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Exercise intervention for prevention, management of and rehabilitation from COVID-19

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Exercise intervention for prevention, management of and rehabilitation from COVID-19

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Editorial: Exercise intervention for prevention, management of and rehabilitation from COVID-19

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Editorial on the Research Topic
Exercise intervention for prevention, management of and rehabilitation from COVID-19

Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus disease 2019 (COVID-19) pandemic has greatly stimulated health research with numerous benefits for patient care, ranging from the development of new vaccines to the identification of at-risk populations and the recognition of the value of physical exercise interventions as an effective method of prevention, management, and rehabilitation of patients. In this Research Topic "*Exercise intervention for Prevention, Management of and Rehabilitation from COVID-19*", studies explore the effects of physical activity on COVID-19 illness and mortality, the impact of rehabilitation programs on different populations of COVID-19 patients, and characterize difficulties and needs of patients or athletes with disabilities during COVID-19 lockdown.

An increase in mortality among hospitalized COVID-19 patients with previous sedentary lifestyles has been shown in many studies. Conversely, the beneficial effects of physical activity on COVID-19 outcomes and disease severity have been suggested. Recently, a meta-analysis involving one million patients assessed the hospitalization, intensive care unit (ICU) admissions, and mortality rates of COVID-19 patients with a history of physical activity involvement before the beginning of the pandemic (Rahmati et al., 2022). Interestingly, the types of exercises were also studied. Resistance exercise and combined aerobic and muscle strength training were significantly associated with reductions in COVID-19 hospitalizations, and COVID-19 ICU admissions, respectively. The authors reported a positive association between endurance exercise and reduction in COVID-19 mortality. In this Research Topic, a Mendelian randomization study assessed the causal influence of light and moderate-to-vigorous physical activity on COVID-19 susceptibility, hospitalization and severity (Zhang et al.). No significant effects were found for moderate to vigorous physical activity on COVID-19 outcomes. However, light physical activity reduced the risk of COVID-19 hospitalization and severe complications. Another review and meta-analysis assessed the association between physical activity before COVID-19 and the severity of illness and mortality in COVID-19 patients (Sittichai et al.). Subgroup analysis showed that physical activity for ≥150 min/week at a moderate intensity or ≥75 min/week at a vigorous intensity reduced the risks of severity and mortality. Vigorous PA reduced mortality risk, whereas moderate to vigorous PA reduced the risks of severity and mortality. Although the heterogeneity in physical activity patterns and severity definition constitutes a limitation of these meta-analysis studies, engaging in regular physical activity was shown to decrease the severity and mortality of COVID-19 patients. Several studies suggest that exercise intervention improves the functional capacities and psychological health status of COVID-19 patients who were discharged from the hospital. Focusing on the management and rehabilitation of post-COVID-19 Tunisian patients, Toulgui et al. assessed the effect of 4-week cardiorespiratory rehabilitation program including aerobic cycle endurance, strength training, and educational sessions. The authors reported significant improvements in dyspnea, lung function, 6-min walk work, and resting heart rate and diastolic blood pressure in 14 moderate to severe COVID-19 patients (Toulgui et al.). Another clinical trial showed that an 8-week multi-professional intervention increased physical fitness, reduced biomarkers of inflammation, and improved lipid and glucose metabolism in overweight COVID-19 survivors from southern Brazil (Sordi et al.). In a critical scoping review of the literature, Puce et al. evaluated the effects of COVID-19 on athletes with disabilities and para-athletes. Interestingly, the authors highlighted the lack of follow-up studies in these populations and recommended more attention towards their needs. In a case report, Crisafulli et al. highlighted the importance of personalized adapted motor activity in a COVID-19 patient with critical illness polyneuropathy and myopathy. Numerous studies have reported the psychological effects of COVID-19 lockdown. AlMarzooqi et al. found an association between body image perception and demographic factors among physically active individuals during the COVID-19 lockdown in Saudi Arabia. In Malaysia, Washif et al. evaluated the extent of changes in training practices, recovery, mental health, and sleep patterns of athletes during the COVID-19 lockdown. Finally, Wedig et al. discussed the potential interest of blood flow restriction to decrease loss of muscle mass and strength during acute infection, and to mimic high-intensity exercise intervention during convalescence.

The studies published in this Research Topic report promising findings on the beneficial effects of regular physical activity and/or adopting exercise interventions on promoting functional capacities and psychological status in COVID-19 survivors while reducing the severity and mortality of COVID-19 patients. However, most of these studies agreed on the difficulty of adapting a rehabilitation program and finding the optimal levels of physical activity in a given individual.

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Impact of cardiorespiratory rehabilitation program on submaximal exercise capacity of Tunisian male patients with post-COVID19: A pilot study

Emna Toulgui[1†], Wafa Benzarti[2†], Chiraz Rahmani[1], Sana Aissa[2], Ines Ghannouchi[3], Asma Knaz[2], Amani Sayhi[3], Sana Sellami[3], Khaoula Mahmoudi[3], Sonia Jemni[1], Imene Gargouri[2], Abdelaziz Hayouni[2], Walid Ouanes[1], Achraf Ammar[4,5,6*‡] and Helmi Ben saad[3‡]

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Post-COVID19 patients suffer from persistent respiratory, cardiovascular, neurological, and musculoskeletal health complaints such as dyspnea, chest pain/discomfort, and fatigue. In Tunisia, the potential benefits of a cardiorespiratory rehabilitation program (CRRP) after COVID19 remain unclear. The main aim of this study was to evaluate the impact of a CRRP on submaximal exercise capacity, evaluated through the 6-min walk test (6MWT) data in post-COVID19 Tunisian patients. This was a cross-sectional study including 14 moderate to severe COVID19 patients aged from 50 to 70 years. CRRP was performed after the end of patients' hospitalization in COVID19 units for extensive or severe extents of COVID19. Dyspnea (modified medical research council), spirometry data, handgrip strength values, 6MWT data, and 6-min walk work (i.e., 6-min walk distance x weight) were evaluated 1-week pre-CRRP, and 1-week post-CRRP. CRRP included 12 sessions [3 sessions (70 min each)/week for 4 weeks]. Exercise-training included aerobic cycle endurance, strength training, and educational sessions. Comparing pre- and post-CRRP results showed significant improvements in the means±standard deviations of dyspnea by 1.79 ± 0.80 points ($p < 0.001$), forced expiratory volume in one second by 110 ± 180 ml ($p = 0.04$), 6-min walk distance by 35 ± 42 m ($p = 0.01$), 6-min walk work by 2,448 ± 3,925 mkg ($p = 0.048$), resting heart-rate by 7 ± 9 bpm ($p = 0.02$) and resting diastolic blood pressure by 6 ± 10 mmHg ($p = 0.045$). In Tunisia, CRRP seems to improve the submaximal exercise capacity of post-COVID19 patients, mainly the 6-min walk distance and work.

KEYWORDS

handicap, health status, lung function test, SARS-Cov-2, walking, 6MWT

1 Introduction

The coronavirus disease 2019 (COVID19) pandemic has overburdened healthcare systems and it poses a threat to the global economy and social disruption (Bessis, 2020). COVID19 is a respiratory infection with multisystem manifestations, affecting the respiratory, cardiovascular, neurological, and muscular systems (Xie et al., 2022). Several symptoms (e.g., dyspnea, dysrhythmias, stroke, headache, myalgia, and asthenia), and complications (e.g., respiratory failure, acute myocardial injury, thromboembolic events) have been reported for acute-COVID19 (Long et al., 2020; Murk et al., 2021). In post-acute COVID19, 40%–90% of patients continue to manifest symptoms for months, and the disease is named "long-COVID19" (Lopez-Leon et al., 2021). The "long-COVID19," also called "post-acute-COVID19" or "persistent-COVID19 symptoms," has various clinical manifestations affecting several systems, mainly the respiratory, cardiovascular, neurological, and muscular systems (e.g., dyspnea, post-activity polypnea, cough, chest pain/discomfort, resting tachycardia, fatigue), and alters the nutritional status (e.g., weight-loss) (Lopez-Leon et al., 2021; Skjorten et al., 2021; Ali et al., 2022; Ghram et al., 2022). Several studies have reported persistent physical impairments following hospital discharge (e.g., reduced forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (Zhao Y. M. et al., 2020), decreased handgrip strength (HGS) (Cheval et al., 2021), and exertional dyspnea (modified medical research council (mMRC)) (Huang et al., 2021). In one study, the prevalence of musculoskeletal health complaints in "long-COVID19" patients was high at 38.7% (Ali et al., 2022). A reduced 6-min walk distance (6MWD) was reported by Huang et al. (2021), and it seems that 3 months after hospital discharge, one-third of long-COVID19 patients had a peak oxygen consumption <80% (Skjorten et al., 2021). Since survivors of moderate to severe COVID19 are significantly impaired in all activities of daily living (Skjorten et al., 2021), rehabilitation strategies are needed to improve post-COVID19 outcomes in this population. (Demeco et al., 2020; Hermann et al., 2020; Liu K. et al., 2020; Betschart et al., 2021; Bouteleux et al., 2021; Daynes et al., 2021; Gloeckl et al., 2021; Puchner et al., 2021; Spielmanns et al., 2021). The cardiorespiratory rehabilitation program (CRRP) is the cornerstone in the management of chronic cardiorespiratory diseases, and its benefits are well demonstrated (Ben Saad et al., 2008; Jenkins et al., 2018; Rezende Barbosa et al., 2018).

In COVID19, CRRP is a new management axis, and studies related to its impact on patients' capacities are scarce (Demeco et al., 2020; Hermann et al., 2020; Liu K. et al., 2020; Betschart et al., 2021; Bouteleux et al., 2021; Daynes et al., 2021; Gloeckl et al., 2021; Puchner et al., 2021; Spielmanns et al., 2021). Two systematic reviews including almost 33 studies demonstrated the feasibility and efficiency of CRRP in the management of post-COVID19 patients (Demeco et al., 2020; Dixit et al., 2021). Almost all 33 retained studies were conducted in specialized rehabilitation units from industrialized countries. In low-income countries, such as Tunisia, the potential benefits of CRRP after COVID19 is unclear. Indeed, in these countries, CRRP centers are rare, no specialized rehabilitation equipment is available, and too few COVID19 patients have access to CRRP.

The objective of the present study, conducted in Tunisia, was to evaluate the impact of an ambulatory CRRP on perceived dyspnea (mMRC), spirometric, HGS, and 6-min walk test (6MWT) data. CRRP will be considered "efficient" if the delta CRRP changes (ΔCRRP = post-CRRP value minus pre-CRRP value) in the 6MWD and dyspnea mMRC scale exceed the recommended minimal clinically important differences (MCIDs) for respiratory chronic diseases [i.e., MCID = 30 m for 6MWD (Singh et al., 2014), MCID = one point for dyspnea (mMRC) (Crisafulli and Clini, 2010)].

2 Patients and methods

This study is part of a project involving two parts. The first part constitutes the aim of this study. The second part will be the evaluation of the impact of CRRP on social disadvantage (i.e., physical activity, psychological data, health-related quality of life). Figure 1 details the present project flowchart.

2.1 Study design

This was a cross-sectional study conducted by a multidisciplinary team, including the following three departments: the department of pulmonology, the department of physiology and functional explorations (Farhat HACHED hospital, Sousse, Tunisia), and the department of physical medicine and rehabilitation (Sahloul hospital, Sousse, Tunisia). This study was approved by the medical and research ethics committee of Farhat HACHED Hospital (Approval number FH2502/2021). Written informed consent was obtained from all patients after receiving an explanation of the study. This study was performed from February 2nd to September 26th 2021, including the Ramadan month (from April 13th to May 13th 2021). The period from February to June

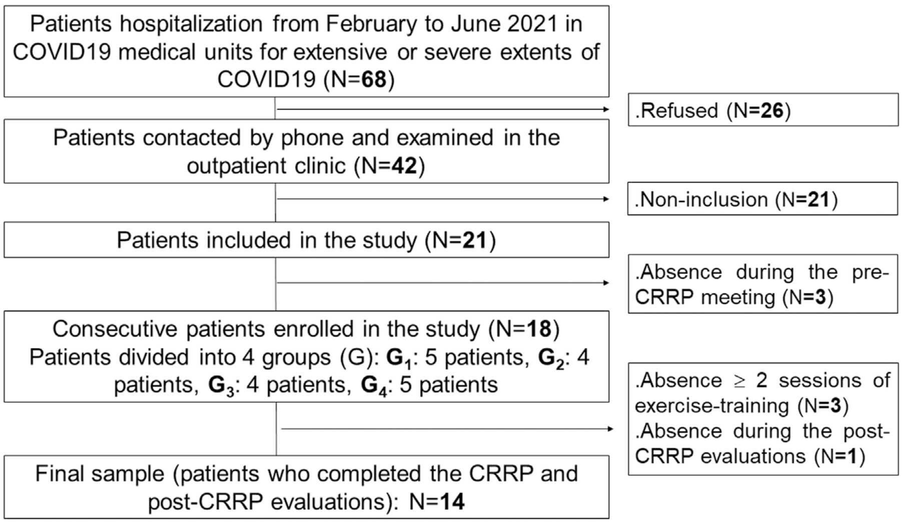

FIGURE 1
Study protocol. COVID19: coronavirus disease 2019. CRRP, cardio-respiratory rehabilitation program.

2021 was reserved for the recruitment of COVID19 patients. The period from April to September 2021 was reserved for the practice of CRRP. The CRRP was performed at least 2 months after the end of the hospitalization in COVID19 units.

During the present study period (i.e., February 2nd to September 26th 2021), Tunisia decided to declare a 1-week nationwide lockdown starting from May 9th to May 16th 2021. During all the study steps, all recommended preventive measures to fight against COVID19 transmission (e.g., physical distancing of at least 1 m, wearing a fitted facemask properly, and cleaning hands frequently with alcohol-based hand rub or soap and water) were applied.

2.2 Study population

The source population was COVID19 patients living in Sousse (Tunisia) who needed hospitalization in a medical facility. The target population was patients hospitalized in COVID19 units of the aforementioned departments of pulmonology and physical medicine from February to June 2021 (Figure 1).

The following inclusion criteria were applied: confirmed diagnosis of COVID19, male patients, age >50 years, and chest computed tomography during the hospitalization period showing an extensive/severe extent of parenchymal lung injury (Revel et al., 2020). The applied exclusion criteria were: 1) COVID19 patients admitted in an intensive care unit; 2) contra-indications to 6MWT (Singh et al., 2014) [e.g., signs of unstable angina or myocardial infarction within the previous month, resting heart-rate ≥ 120 bpm, systolic blood pressure (SBP) ≥ 180 mmHg, diastolic blood pressure (DBP) ≥ 100 mmHg)]; 3) contra-indications to spirometry (Miller et al., 2005); and 4) orthopedic, rheumatologic, or muscular history, which may interfere with walking or HGS. Absence during two or more exercise-training sessions or the post-CRRP evaluation session was applied as an exclusion criterion.

2.3 Sample size

The sample size (N) was calculated according to the following predictive equation (Serhier et al., 2020): $N = (Z_\alpha\ p\ (1\text{-}p))/i^2$, where "$Z_\alpha$" is the normal deviates for type I error (equal to 1.28 for 90% confidence level), "p" is the percentage of improvement of the main outcome (i.e., 6MWD) post-CRRP in COVID19 patients; and «i» is the precision ($i = 0.15$). According to a Chinese study (Liu K. et al., 2020), the 6MWD of trained COVID19 patients ($n = 36$, mean age: 69.4 years) was improved by 30.5% ($p = 0.305$) [went from 163 ± 72 (pre-CRRP) to 212 ± 82 m (post-CRRP)]. The application of the above-mentioned data in the predictive equation gave a sample size of 15 COVID19 patients. Assumption of 10% of absence during the exercise-training sessions or the post-CRRP evaluation session gave a revised sample of 17 COVID19 patients [17 = 15/(1–0.10)].

2.4 Coronavirus disease 2019 diagnosis and extent evaluation

COVID19 diagnosis was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) (Jamil et al., 2020). All patients underwent chest-computed

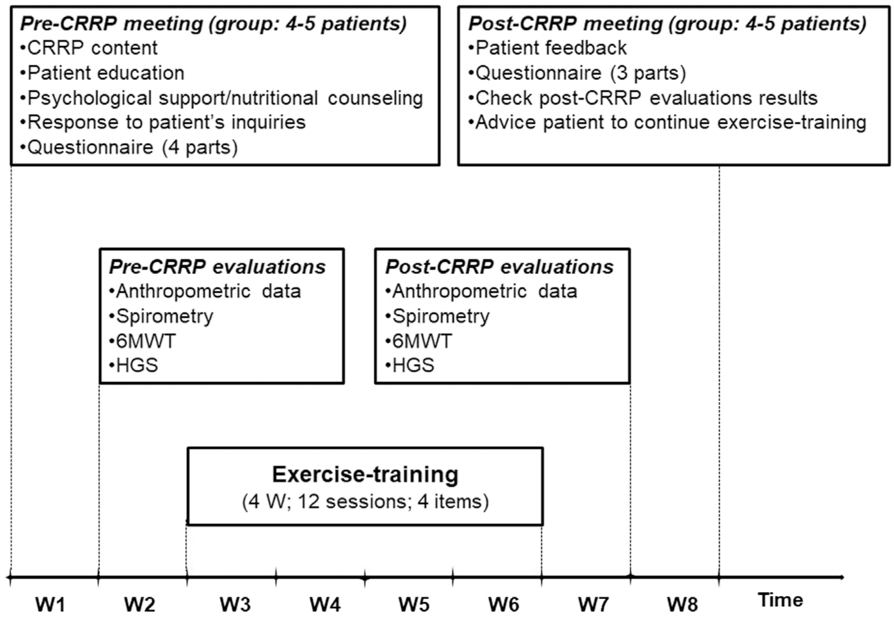

FIGURE 2
Cardiorespiratory rehabilitation program (CRRP). HGS, handgrip strength; W, week; 6MWT, 6-min walk test.

tomography. The following two classifications were applied: 1) chest computed-tomography classification, including the following five levels based on the extent of parenchymal lung injury: *absent* or *minimal* (<10%), *moderate* (10%–25%), *extensive* (25%–50%), *severe* (50%–75%), and *critical* (>75%) (Revel et al., 2020), and 2) clinical classification (WHO, 2021), including the following four levels: *mild*, *moderate*, *severe*, and *critical*.

2.5 Applied protocol

The components of the CRRP were "derived" from previous international recommendations for COVID19 CRRPs (Barker-Davies et al., 2020; Carda et al., 2020; Spruit et al., 2020; Zhao H. M. et al., 2020), and from the American societies of cardiology and sports medicine recommendations for the practice of physical activity in chronically ill patients aged over 50 years (Nelson et al., 2007). Once four to five consecutive patients agreed to participate in the CRRP, they formed one group (Figure 1), perform the recommended tests, and begin the CRRP. Figure 2 summarizes the five steps of the study.

2.5.1 First step: Pre-CRRP meeting

The first step consists of a pre-CRRP meeting between two physicians (*ET* and *WB* in the authors' list) and a group of four to five COVID19 patients. During this step, the following five actions were performed: 1) explanation of the CRRP content and its progress; 2) when applicable, education about how to manage comorbidities (e.g., diabetes-mellitus, arterial-hypertension), and encouraging smoking cessation; 3) psychological support (e.g., management of emotional distress, post-traumatic stress disorder, and strategies for coping with COVID19) (Simpson and Robinson, 2020), and nutritional counseling (Ghram et al., 2022); 4) response to patients' inquiries; and 5) filling in the questionnaire.

The questionnaire was prepared in the local Arabic dialect by two trained physicians (*ET* and *WB* in the authors' list). For each patient, the questionnaire was repeated by the same interviewer pre- and post- CRRP. The duration of the questionnaire was approximately 30 min for each patient. The questionnaire includes four parts. The first part (i.e., a general questionnaire), derived from the American thoracic society questionnaire (Ferris, 1978), was performed only pre-CRRP, and it involved clinical (e.g., lifestyle habits, medical history) and COVID19 (e.g., date of RT-PCR, hospitalization, number of days pre-CRRP, treatment, imaging) data. Cigarette smoking was evaluated in pack-years, and patients were classified into two groups [i.e., non-smoker (<5 pack-years), and smoker (≥5 pack-years)]. Hospital stay is the number of days of hospitalization for COVID19 management. The number of days pre-CRRP represents the number of days between COVID19 diagnosis (day of RT-PCR) and the first day of the onset of exercise-training. Dyspnea was assessed (pre- and post- CRRP) using the mMRC scale (Fletcher et al., 1959). The latter is a self-rating scale that measures the disability caused by breathlessness in daily activities (Mahler and Wells, 1988). This scale ranges from 0 to 4, where "0" is no breathlessness, except on strenuous exercise; and "4" is too breathless to leave the house, or breathless when dressing or undressing (Mahler and Wells, 1988). The remaining three parts of the questionnaire were reserved to explore the level of physical activity, current presence and tendency to anxiety or depression at the time of evaluation, and health-related quality of life. The data of the last three parts of the questionnaire will be explored in the second part of the project.

2.5.2 Second step: Pre-CRRP evaluations

During this step, the following four evaluations/tests were performed on the same day in the morning, and in the following order: anthropometric data, spirometry test, 6MWT, and HGS. The 6MWT and the HGS were performed on patients not wearing facemask.

Anthropometric data e.g., age, height (cm), weight (kg), and body mass index (BMI, kg/m^2) were determined. The obesity status [underweight (BMI <18.5 kg/m^2), normal weight (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25.0–29.9 kg/m^2), and obesity (BMI ≥30.0 kg/m^2)] was noted (Tsai and Wadden, 2013).

The spirometry test was performed by an experiment technician using a portable spirometer (SpirobankG MIR, delMaggiolino 12500155 Roma, Italy), according to international guidelines (Miller et al., 2005). The collected spirometric data [i.e., (FVC, L), (FEV_1, L), maximal mid-expiratory flow (L/s), and FEV_1/FVC ratio (absolute value)] were expressed as absolute values and as percentages of predicted local values (Ben Saad et al., 2013).

The 6MWT was performed outdoors in the morning by one physician (*HBS* in the authors' list), according to the international guidelines (Singh et al., 2014). The 6MWT was performed along a flat, straight corridor with a hard surface that is seldom traveled by others (40 m long, marked every 1 m with cones to indicate turnaround points). During the 6MWT, some data were measured at rest ($_{Rest}$) and at the end ($_{End}$) of the walk [e.g., dyspnea (visual analogue scale (VAS)), heart-rate, oxyhemoglobin saturation (SpO_2, %); SBP and DBP (mmHg)], and the 6MWD (m, % of predicted value), and the number of stops were noted. For some 6MWT data, delta exercise changes (ΔExercise = $6MWT_{End}$ value minus $6MWT_{rest}$ value) were calculated [e.g., ΔSpO_2, Δheart-rate, ΔDBP, ΔSBP, Δdyspnea (VAS)]. The test instructions given to the patients were those recommended by the international guidelines (Singh et al., 2014). Heart-rate was expressed as absolute value (bpm) and as percentage of the predicted maximal heart-rate [predicted maximal heart-rate (bpm) = 208—(0.7 x Age)] (Tanaka et al., 2001). Heart-rate and SpO_2 were measured *via* a finger pulse oximeter (Nonin Medical, Minneapolis, MN). The heart-$rate_{End}$ (bpm) was considered as heart-rate target for lower limb exercise-training (Fabre et al., 2017). The predicted 6MWD and the lower limit of normal (LLN) were calculated according to local norms (Ben Saad et al., 2009). The 6-min walk work (i.e., the product of 6MWD and weight (Chuang et al., 2001; Carter et al., 2003)) was calculated. The VAS is an open line segment with the two extremities representing the absence of shortness of breath and the maximum shortness of breath (Sergysels and Hayot, 1997). Dyspnea (VAS) is evaluated by the physician from 0 (no shortness of breath) to 10 (maximum shortness of breath) (Sergysels and Hayot, 1997).

The HGS test measures the maximum-voluntary upper-limb muscle strength using an adjustable handgrip dynamometer (TKK5401®, Takei Scientific Instruments Co., Ltd., Niigata, Japan). The latter is a valid and reliable measure having a range of 5–100 kg of force, with increments of 1 kg (Cadenas-Sanchez et al., 2016). A brief demonstration and verbal instructions for the test were given to patients, and if necessary, the dynamometer was adjusted to the size of the hand. The measurements were taken in a standing position with the shoulder adducted and in neutral rotation, and the arms parallel but not in contact with the body. Participants were asked to tighten the dynamometer as hard as possible while exhaling. The test was repeated three times on each hand. The highest value of the three trials of the dominant hand was retained (Haidar et al., 2004), and it was expressed as absolute (kg) and relative (i.e., divided by weight) values.

2.5.3 Third step: Exercise-training

Exercise-training consists of 12 sessions (i.e., three sessions/week for 4 weeks).

The duration of each session was 70 min. Exercise-training was performed in four groups of four or five patients. The typical exercise-training session included the following five items (Figure 3): warming-up for 5 minutes, lower limbs strengthening for 45 min, upper limbs strengthening for 10 min, balance posture and proprioception exercises for 5 minutes, and relaxation session for 5 minutes. During the *first item* (i.e., warming-up), light exercises were performed (i.e., walking slowly; mobilization of cervical, lumbar spine, and peripheral joints). During the *second item* (i.e., lower limbs strengthening), aerobic training on ergocycle was performed. The cycling intensity was standardized and personalized using a heart-rate monitor. As done in one previous similar study (Hermann et al., 2020), the heart-rate target was the heart-$rate_{End}$ ± 5 bpm determined during the 6MWT. In patients with chronic respiratory conditions, the heart-rate at the first ventilatory threshold measured during a cardiopulmonary exercise test was comparable and correlated to the heart-rate determined at the end of the 6MWT (Fabre et al., 2017). The latter heart-rate target (i.e., heart-$rate_{End}$) allows individualizing the training intensity for each patient, and therefore optimizing the physical and physiological benefits of the CRRP (Fabre et al., 2017). The heart-rate monitor alarms were set around the heart-rate target. The patients were asked to gradually reach their heart-rate targets during the first 5 minutes and to maintain pedaling for 10 min at this intensity. Then, they were asked to return to empty pedaling or walking at their own pace for 5 minutes. They were again asked to complete one cycle of 10 min of target heart-rate training and 5 minutes of active recovery (e.g., empty pedaling or walking at their own pace), then to complete the last cycle of 7 minutes of target heart-rate training and 3 minutes of active recovery. During the *third item* (i.e., upper limbs strengthening), various muscle groups of the upper limbs were performed in sets of ten repetitions (e.g., raising and lowering shoulders, shoulder blade stabilization, bending and straightening elbows, raising arms). These exercises were performed without load during the first exercise-training sessions, then with dumbbells of increasing weights along exercise-training (Ben Saad and Ben Abdelkrim, 2005). During the *fourth item*, several exercises were performed to improve balance posture, proprioception, coordination, and stability. Positions exercises (i.e., floor exercises, seated, and standing exercises) were varied between sessions. Exercises of increasing difficulty on a mat, static and dynamic standing and walking, bipodal, and then unipodal exercises on an unstable platform were performed along the exercise-training (Ben Saad and Ben Abdelkrim, 2005). During the *fifth item* (i.e., relaxation), several exercises involving spine and limbs stretching (e.g., standing stretch, cat back exercises, sphinx position) and breathing exercises (e.g., controlled diaphragmatic breathing, coordination between inspiratory and expiratory times) were performed (Ben Saad and Ben Abdelkrim, 2005). During each exercise-training session, therapeutic education was carried out to strengthen the patients' adherence to the lifestyle counseling provided during the pre-CRRP meeting (e.g., management of comorbidities and encouraging smoking cessation when applicable, psychological support, and nutritional counseling) (Ghram et al., 2022). All exercise-training items were performed on patients not wearing the facemask.

2.5.4 Fourth step: Post-CRRP evaluation

During this step, similar evaluations/tests to the second step were performed.

2.5.5 Fifth step: Post-CRRP meeting

During this step, the following issues were tackled: patients' feedback, questionnaire (as conducted during the first step, except the general questionnaire), checking the results of post-CRRP evaluations, and advising patients to continue exercise-training.

2.6 Applied definitions for the submaximal exercise data

1) Abnormal 6MWD: 6MWD < LLN (Singh et al., 2014);

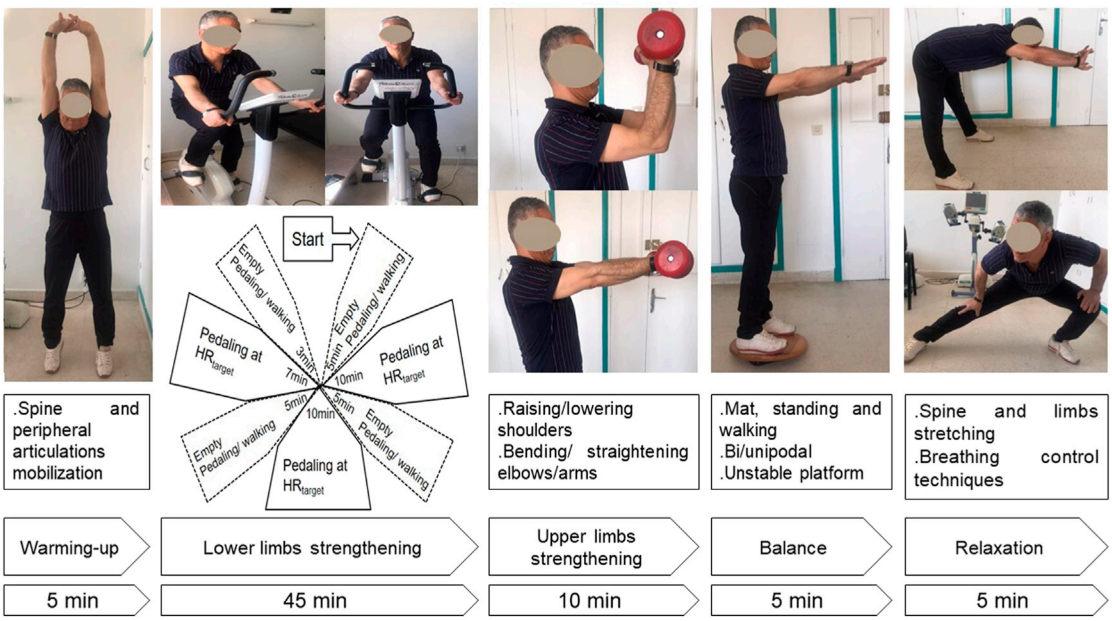

FIGURE 3
Description of an exercise training session. HR, heart-rate.

TABLE 1 Initial descriptive data of patients with coronavirus disease 2019 (COVID19) (n = 14).

Data	Unit	Value
Anthropometric and medical data		
Age	Year	61 ± 4 (59–64)
Height	cm	170 ± 4 (167–172)
Weight	kg	89 ± 16 (80–99)
Body mass index	kg/m^2	31.0 ± 5.2 (28.0–34.0)
Obesity status	Normal	1 (7)
	Overweight	7 (50)
	Obesity	6 (43)
Smoking status and data	Yes	9 (64)
	Pack-year	24 ± 18 (8–39)
Medical history	Diabetes-mellitus	8 (57)
	Arterial-hypertension	6 (43)
	Chronic obstructive pulmonary disease	5 (36)
	Dyslipidemia	3 (21)
	Dysthyroidism	1 (7)
	Coronary heart-disease	0 (0)
COVID19 data and severity classification		
Period before the cardiorespiratory rehabilitation program	Days	83 ± 30 (65–100)
Hospital stay	Days	17 ± 7 (10–17)
Chest computed-tomography severity classification	Extensive	4 (29)
	Severe	10 (71)
Clinical severity classification	Moderate	3 (21)
	Severe	11 (79)

Quantitative and categorical data were mean ± standard deviation (95% confidence interval) and number (%), respectively.

2) Clinically significant desaturation: $\Delta SpO_2 > 5$ point (Ben Saad et al., 2009; Ben Saad et al., 2014; Ben Saad et al., 2015; Ben Saad, 2020);

3) Walk intolerance signs: clinically significant dyspnea [i.e., $dyspnea_{End}$ (VAS) > 5/10] (Sergysels and Hayot, 1997; Ben Saad et al., 2014), and/or stopping during the 6MWT (Ben Saad et al., 2009; Ben Saad et al., 2014; Ben Saad et al., 2015; Ben Saad, 2020).

2.7 Statistical analysis

Quantitative and categorical data were presented as means ± standard deviation (95% confidence interval) and number (%), respectively. For each quantitative data (i.e., dyspnea (mMRC and VAS), weight, BMI, HGS, 6MWD, 6-min walk work, heart-rate, SpO_2, SBP, DBP, and ΔExercise), a ΔCRRP was calculated. The Wilcoxon matched pairs test and the one-sided chi-2 test were used to compare the quantitative and categorical data pre- and post- CRRP, respectively. CRRP was considered "efficient" if the means of ΔCRRP for 6MWD and dyspnea (mMRC) exceeded the recommended MCIDs [i.e., 30 m for 6MWD (Singh et al., 2014)) and one point for dyspnea (Crisafulli and Clini, 2010)]. All statistical procedures were performed using statistical software (StatSoft, Inc. (2011). STATISTICA, version 12). The significance level was set at $p < 0.05$.

3 Results

An initial sample of 68 patients was recruited. After the application of the inclusion/non-inclusion criteria, 18 patients were retained. Four patients withdrew during CRRP. Fourteen patients (age: 61 ± 4 years) completed the full CRRP and tests evaluations (Figure 1).

Table 1 details the patients' characteristics. The profile of COVID19 patients was characterized by high frequencies of overweight and obesity (n = 13/14; 93%), level-2 chest computed-tomography at admission (n = 10/14; 71%), and smoking (n = 9/14; 64%). The two most frequent medical comorbidities were diabetes-mellitus and arterial-hypertension.

Table 2 illustrates the impact of CRRP on dyspnea, anthropometric, spirometric, and HGS data. Dyspnea

TABLE 2 Impact of CRRP on dyspnea, and anthropometric, spirometric and HGS data of patients with coronavirus disease 2019 (n = 14).

Data	Unit/Category	Pre-CRRP	Post-CRRP	ΔCRRP	p-value
Dyspnea	mMRC, point	2.07 ± 0.73 (1.65–2.49)	0.29 ± 0.47 (0.02–0.56)	−1.79 ± 0.80 (−2.25 to −1.32)	0.0009*
Weight	kg	89 ± 16 (80–99)	89 ± 16 (79–98)	−0.79 ± 2.19 (−2.05 to 0.48)	0.2845
BMI	kg/m^2	31.0 ± 5.2 (28.0–34.0)	30.7 ± 5.2 (27.7–33.7)	−0.27 ± 0.78 (−0.72 to 0.18)	0.2845
Obesity status	Normal	1 (7)	0 (0)	—	0.3086
	Overweight	7 (50)	8 (57)	—	0.7049
	Obesity	6 (43)	6 (43)	—	—
FEV_1	l	2.89 ± 0.64 (2.52–3.26)	3.01 ± 0.71 (2.60–3.42)	0.11 ± 0.18 (0.01–0.22)	0.0354*
	%	81 ± 17 (71–90)	84 ± 19 (73–95)	3.29 ± 4.97 (0.42–6.15)	0.0280*
FVC	l	3.68 ± 0.55 (3.36–3.99)	3.85 ± 0.74 (3.42–4.28)	0.17 ± 0.33 (−0.02–0.37)	0.0652
	%	88 ± 12 (81–94)	92 ± 16 (82–101)	4.00 ± 7.96 (-0.60–8.60)	0.0652
FEV_1/FVC	Absolute value	0.78 ± 0.10 (0.72–0.83)	0.77 ± 0.10 (0.71–0.83)	−0.01 ± 0.03 (−0.02 to 0.01)	0.2787
MMEF	l/s	3.11 ± 1.33 (2.35–3.88)	3.17 ± 1.42 (2.35–3.98)	0.05 ± 0.34 (−0.15–0.25)	0.6832
	%	65 ± 27 (49–80)	66 ± 29 (49–82)	1.00 ± 7.21 (−3.16–5.16)	0.6378
HGS	Absolute value (kg)	36 ± 6 (33–40)	39 ± 6 (35–42)	2.35 ± 8.01 (−2.028–6.98)	0.6377
	Relative value	0.41 ± 0.08 (0.37–0.46)	0.45 ± 0.10 (0.39–0.50)	0.03 ± 0.10 (−0.02–0.09)	0.7298

BMI, body mass index; CRRP, cardiorespiratory rehabilitation program; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HGS, handgrip-strength; MMEF, maximal mid expiratory flow; mMRC, modified medical research council; %, percentage of predicted value. ΔCRRP, post-CRRP, value minus pre-CRRP, value. Quantitative and categorical data were mean ± standard deviation (95% confidence interval) and number (%), respectively. *p-value <0.05 (Wilcoxon matched pairs test or one-sided chi-2, test): pre-CRRP, vs. post-CRRP.

(mMRC) was improved by 1.79 points, which exceeds the MCID of one point. FEV_1 was improved by 110 ml (3.29%).

Table 3 illustrates the impact of CRRP on submaximal exercise data. The 6MWD increased by 35 m, which is higher than the MCID of 30 m. Nine patients (64.3%) increased their 6MWD by more than 35 m, and the number (%) of COVID19 patients with abnormal 6MWD decreased from 3 (21%) to 0 (0%). The 6-min walk work increased by 2,448 mkg. The heart-rate$_{Rest}$ (bpm, %) decreased by seven bpm (5%), and DBP$_{Rest}$ decreased by 6 mmHg.

4 Discussion

The present Tunisian study demonstrated that the CRRP improves the submaximal exercise capacity of post-COVID19 patients. For instance, the 6MWD improved by 35 m, which exceeds the MCID of 30 m, and the dyspnea (mMRC) improved by 1.78 point, which exceeds the MCID of one point. To the best of the authors' knowledge, this is the first North-African study investigating the impact of CRRP on post-COVID19 patients. The methodology and main outcomes of some similar studies including a single group of COVID19 patients (Hermann et al., 2020; Betschart et al., 2021; Bouteleux et al., 2021; Daynes et al., 2021; Gloeckl et al., 2021; Piquet et al., 2021; Puchner et al., 2021), and case-control studies (Liu K. et al., 2020; Spielmanns et al., 2021) are detailed in Tables 4, 5, respectively.

4.1 Discussion of results

In this study, the increase in the main outcome (i.e., 6MWD) was both "statistically" and "clinically" significant (mean of 35 m, which exceeds the MCID of 30 m (Singh et al., 2014)). At the end of CRRP, no COVID19 patients had an abnormal 6MWD, and the heart-rate$_{Rest}$ and DBP$_{Rest}$ decreased by seven bpm (5%) and 6 mmHg, respectively (Table 3).

The mean increase in 6MWD reported in this study was intermediate with the values reported in the literature (Liu K. et al., 2020; Betschart et al., 2021; Gloeckl et al., 2021) (Tables 4, 5). The 35-m 6MWD mean was closer to these reported in some studies [e.g., 48 m for mild/moderate patients (Gloeckl et al., 2021), 50 m (Liu K. et al., 2020)], but it was lower than the values reported in some other studies [e.g., 88 m (Betschart et al., 2021), 124 m for severe/critical patients (Gloeckl et al., 2021), 130 m (Hermann et al., 2020), 176 m mean (Puchner et al., 2021)]. Similar to some studies (Hermann et al., 2020; Betschart et al., 2021; Gloeckl et al., 2021), the improvement in 6MWD noted in this study was "clinically significant." Indeed, before CRRP, three patients had an abnormal 6MWD; and after CRRP, all patients had normal 6MWD (p = 0.03) (Table 3). This finding is inconsistent with the one reported in a German study (Gloeckl et al., 2021), where 79% of mild/moderate patients had an abnormal 6MWD after 3 weeks of inpatient rehabilitation. Because weight directly affects the work/energy required to perform the 6MWT (Holland et al., 2014; Singh et al., 2014), the 6-min walk work was calculated. The latter,

TABLE 3 Impact of CRRP on submaximal exercise data of patients with coronavirus disease 2019 (n = 14).

Data	Unit/Category	Pre-CRRP	Post-CRRP	ΔCRRP	p-value
6-min walk distance	m	571 ± 53 (540–602)	606 ± 44 (581–631)	35 ± 42 (11–60)	0.0131*
	%	95 ± 9 (90–100)	102 ± 7 (98–106)	7 ± 8 (3–11)	0.0088*
	< LLN	3 (21)	0 (0)	—	0.0350*
6-min walk work	mkg	50,974 ± 10,052 (45,170–56,778)	53,442 ± 8,406 (48,569–58,276)	2,448 ± 3,925 (182–4,715)	0.0480*
HR (bpm)	HR_{Rest}	78 ± 10 (72–84)	71 ± 12 (64–78)	−7 ± 9 (−13 to −2)	0.0175*
	HR_{End}	118 ± 27 (103–134)	118 ± 27 (102–133)	−1 ± 32 (−19 to 18)	0.9250
	ΔExercise	40 ± 26 (25–55)	47 ± 22 (34–60)	6 ± 30 (−11–24)	0.4512
HR (%)	HR_{Rest}	46 ± 6 (42–49)	41 ± 6 (37–45)	−5 ± 5 (−8 to −2)	0.0068*
	HR_{End}	69 ± 16 (60–78)	69 ± 15 (60–78)	−1 ± 19 (−12 to 10)	0.8506
	ΔExercise	24 ± 15 (15–32)	28 ± 13 (20–35)	4 ± 18 (-6–14)	0.4326
SpO_2 (%)	SpO_{2Rest}	96 ± 2 (95–97)	96 ± 2 (94–97)	−0 ± 3 (−2 to 1)	0.3882
	SpO_{2End}	94 ± 5 (91–97)	94 ± 8 (89–99)	-0 ± 4 (-3 to 2)	0.7897
	ΔExercise	−2 ± 5 (−5 to 1)	−2 ± 7 (−6 to 3)	0 ± 5 (−3 to 3)	0.6566
	Desaturation	2 (14)	1 (7)	—	0.2729
Dyspnea (VAS)	$Dyspnea_{Rest}$	1 ± 2 (0–2)	1 ± 1 (0–2)	−0 ± 2 (−1 to 1)	0.7353
	$Dyspnea_{End}$	3 ± 1 (2–3)	3 ± 2 (1–4)	0 ± 2 (-1 to 1)	0.9291
	ΔExercise	1 ± 1 (1–2)	2 ± 1 (1–3)	0 ± 2 (−1 to 1)	0.7221
	$Dyspnea_{End}$ > 5	0 (0)	1 (7)	–	0.1568
SBP (mmHg)	SBP_{Rest}	139 ± 14 (131–147)	134 ± 11 (127–140)	−6 ± 14 (−14 to 2)	0.1535
	SBP_{End}	155 ± 16 (146–165)	151 ± 13 (144–159)	−4 ± 14 (−12 to 4)	0.3590
	ΔExercise	16 ± 11 (9–23)	18 ± 11 (11–24)	2 ± 12 (−5–9)	0.6784
DBP (mmHg)	DBP_{Rest}	85 ± 8 (80–89)	79 ± 9 (73–84)	−6 ± 10 (−12 to −0)	0.0454*
	DBP_{End}	84 ± 12 (77–90)	84 ± 11 (77–90)	0 ± 11 (−6 to 6)	0.9165
	ΔExercise	−1 ± 9 (−6 to 4)	5 ± 13 (-3–13)	6 ± 17 (−4–16)	0.2635

CRRP, cardiorespiratory rehabilitation program; DBP, diastolic blood pressure; $_{End}$, at the end of the 6-min walk test (6MWT); HR, heart-rate; LLN, lower limit of normal; $_{Rest}$, at rest before the 6MWT; SBP, systolic blood pressure; SpO_2, oxyhemoglobin saturation; VAS, visual analog scale; 6MWD, 6-min walk distance; %, percentage of predicted value. ΔCRRP, post-CRRP, value minus pre-CRRP, value. ΔExercise = $_{End}$ of exercise value minus $_{Rest}$ value. Quantitative and categorical data were mean ± standard deviation (95% confidence interval) and number (%), respectively. *p-value<0.05 (Wilcoxon matched pairs test or one-sided chi-2, test): pre-CRRP, vs. post-CRRP.

which is the product of 6MWD and weight, provides a better estimate of the work required to perform the 6MWD than distance alone (Holland et al., 2014; Singh et al., 2014). In this study, since the 6-min walk work increased significantly (Table 3), and since there were no statistically significant changes in patients' weight or BMI (Table 2), these confirm that the 6MWD improve is independent of changes in weight or BMI. To the best of the authors' knowledge, no previous study investigated the change of the 6-min walk work before/after a CRRP in COVID19 patients. Additional studies are needed to better characterize the utility of 6-min walk work in rehabilitation programs of COVID19 patients.

The decrease in heart-$rate_{Rest}$ and DBP_{Rest} noted in this study (Table 3) could have some clinical importance. It appears that increased heart-$rate_{Rest}$ (after adjustment for fitness) is an independent risk factor for all-cause mortality in males (Aladin et al., 2014), and a previous report indicated that a 10-bpm increase in heart-$rate_{Rest}$ may increase all-cause mortality by 17% (Aune et al., 2017). High blood pressure is among the most important modifiable risk factors for cardiovascular disease and death (Williams et al., 2018). After the CRRP, the mean DBP_{Rest} decreased from 85 to 79 mmHg, which is an interesting outcome since the 2018 European society of cardiology recommends an optimal DBP_{Rest} target between 70 and 80 mmHg for patients with all risk levels (Williams et al., 2018). The present decrease in heart-$rate_{Rest}$ is comparable to previously reported findings in older adults indicating a beneficial effect for endurance-based exercise-training (Schmidt et al., 2014; Akwa et al., 2017) as well as combined exercise-training (Delecluse et al., 2004; Ammar et al., 2021) with a significant reduction of heart-$rate_{Rest}$ ranging from 4.5 to eight bpm. Presumably, the present beneficial cardiac effects of twelve-CRRP sessions could be the result of an enhancement of the cardiovascular autonomic control, with possible modification in the sympathovagal balance (Gamelin et al., 2007; Ammar et al., 2021). However, the exact mechanisms require further investigation. Additionally, the reduced values of both heart-$rate_{Rest}$ and DBP_{Rest} at post-CRRP could be explained by the improvement in fitness (Greenland et al., 1999), and/or sleep quality (Soler et al., 2013; Yuksel et al., 2014), and/or nutritional

TABLE 4 Methodology and main outcomes of some studies including a single group of COVID19 patients, and aiming at evaluating the impacts of CRRP on COVID19 patients.

1st author (Yr) [country]	a. Study design (type CRRP) b. Participants, N (male) c. Age (Yr)	Comorbidities (%)	Characteristics of CRRP program		Main outcomes	Summary of findings
			Components	a. Frequency b. Duration c. Period between the COVID19 diagnosis and CRRP starting (D) d. Other details		
Hermann et al. (2020), [Switzerland]	a. Interventional study (rehabilitation unit). b. 28 (14), Ventilated: 12, Not ventilated:16. c. Ventilated: 64 ± 9[a], Not ventilated: 67 ± 10[a]	Ventilated: AH: 41.7, DM: 33.3, CKD: 25, dyslipidemia: 16.7, CHD: 8.3. Not ventilated: AH: 56.3, COPD: 37.5, dyslipidemia: 25, CHD: 18.8, DM: 18.8, CKD: 12.5, stroke: 6.3	**ET**. ACE (walking/ cycling). Strength training. **Education**. Coping skills. Nutrition interventions. Activities of daily living	a. 5–6 D/W b. 25–30 sessions c. NR d. 2 D after being asymptomatic and 10 D after onset of infection	Spirometry, 6MWT	Improve in 6MWD*
Betschart et al. (2021), [Switzerland]	a. Pilot study (outpatient) b. 12 (8) c. 61 (26-84)[b]	CHD: 50, CKD: 42, AH: 25, malignancy: 25, CLuD: 16, internal disease: 16, DM: 8, obesity: 8, polyneuropathia: 8	**ET**. ACE training: 30 min RT: 30–40 min. **Education and physical activity coaching**	a. 2 D/W b. Minimum number of sessions = 16 c. 41.5 (21–73)[b]	6MWT	Improve in 6MWD*
Gloeckl et al. (2021), [Germany]	a. Prospective observational cohort study (rehabilitation unit) b. 50 (22), Mild/ moderate: 24 (4), Severe/critical: 26 (18) c. Mild/ moderate: 52 (47-56)[c], Severe/critical: 66 (60-71)[c]	Mild/moderate: OSA:38, CLuD:30, AH:21, obesity:21, dyslipidaemia:13, CHD: 5, DM:5 Severe/critical: AH:62, dyslipidaemia: 38, OSA: 35, CHD:27, DM:23, CRD:23, obesity: 19, CLuD:19, stroke:4	**ET**. ACE: 10–20 min. Strength training: 30 min. **Education** Respiratory physiotherapy. Activities of daily living training. Relaxation techniques. Occupational therapy. Psychological support. Nutritional counselling	a. 5 D/W. b. 3 W. c. Mild/ moderate: 178 (127-217)[c], Severe/critical: 61 (40–108)	mMRC, spirometry, DLCO, HGS, 6MWT, ESWT, 5rep STST	Mild/moderate: improve in FVC[α], FEV_1[α], 6MWD[α]. Severe/critical: improve in HGS[β], mMRC[β], FVC[β¥], FEV_1[β¥]. 6MWD[β¥], ESWT[β]. 5rep STST[β]
Daynes et al. (2021), [United Kingdom]	a. Observational study (outpatient). b. 30 (16). c. 58 ± 16[a]	Asthma: 10, COPD: 3	**ET**. Aerobic exercise (walking/treadmill based). Strength training. **Education**. .educational discussions with handouts	a. 2 D/W. b. 6 W. c. 125 ± 54[a]	CAT, ISWT, ESWT	Improve in CAT*. Improve in ISWT* and ESWT*
Puchner et al. (2021), [Austria]	a. Observational multicenter study (rehabilitation unit). b. 23 (16). c. 57 ± 10[a]	CHD:48, endocrine disease: 48, AH:39, DM: 26, CLuD:22, CKD: 13, asthma: 13, malignancy: 13, immunodeficiency: 13, CLiD: 9, hypercholesterolemia: 9, COPD: 4	**ET**. (25–50 min each session). Respiratory muscle training. Endurance and strength training. Passive therapy session (e.g., massages). Mobilization and breathing perception therapy. **Education**. Speech therapy and swallow evaluation. Occupational herapy . Neuropsychological therapy. Nutritional counseling	a. At least 3 W. b. 24 ± 5[a]D. c. 44 (13)[c]	Plethysmography, DLCO, MIP, 6MWT	Improve in FVC*, FEV_1*, TLC*, DLCO*, MIP*. Improve in 6MWD*

(Continued on following page)

TABLE 4 (*Continued*) Methodology and main outcomes of some studies including a single group of COVID19 patients, and aiming at evaluating the impacts of CRRP on COVID19 patients.

1st author (Yr) [country]	a. Study design (type CRRP) b. Participants, N (male) c. Age (Yr)	Comorbidities (%)	Characteristics of CRRP program		Main outcomes	Summary of findings
			Components	a. Frequency b. Duration c. Period between the COVID19 diagnosis and CRRP starting (D) d. Other details		
Bouteleux et al. (2021), [France]	a. Observational longitudinal study (outpatient). b. 39 (17), PFS: 29 (11), NPFS: 10 (6). c. 48 ± 15[a]	No comorbidities	**ET**. (90 min each session). Aerobic exercise. Strength training. Specific controlled ventilation techniques	a. 3/W. b. 66 (26-110)[c] D. c. 73 (34-178)[c]	mMRC, spirometry, hyperventitlation syndrome provocation test, Nijmegen score, 6MWT, 3min-STS	Improve in mMRC* and FVC*. Improve in 6MWD* and 3min-STS*
Piquet et al. (2021), [France]	a. Retrospective study (rehabilitation unit). b. 100 (66). c. 66 ± 22[c]	AH: 48, DM: 29, obesity: 17, CKD: 13, stroke: 9, immunodeficiency: 3, CHD: 1	**Respiratory rehabilitation**. Controlled diaphragmatic breathing. **ET**. ACE (bicycle ergometer). Motor strengthening (body weight exercises, elastics, weights). **Education**. Occupational therapy. Speech therapy. Psychological therapy. Nutritional counseling	a. 2sessions/D. b. 5 D/W, 10 ± 5[a] D. c. 20 ± 10[c]	HGS, 10full-STS	Improve in HGS*. Improve in 10full-STS*

ACE, aerobic cycle endurance; AH, arterial-hypertension; BI, barthel index dyspnea; CAT, COPD, assessment test; CHD, coronary heart disease; CKD, chronic kidney disease; CLiD, chronic liver disease; CLuD, chronic lung disease; COPD, chronic obstructive pulmonary disease; COVID19, coronavirus disease 2019; CRRP, cardiorespiratory rehabilitation; D, day; DLCO, diffusing capacity of the lung for carbon monoxide; DM, diabetes-mellitus; ESWT, endurance shuttle walk test; ET, exercise-training; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HGS, handgrip strength; Min, minute; MIP, maximal inspiratory pressure; mMRC, modified medical research council dyspnea scale; N, number; NA, not-applied; NPFS, no prolonged functional sequelae; NR, not-reported; OSA, obstructive sleep apnea; PFS, prolonged functional sequelae; RT, resistance training; TLC, total lung capacity; VAS, visual analogue scale; W, week; Yr, year; 3min-STS, 3 min sit-to-stand test; 5rep-STST, five repetitions sit-to-stand test; 10full-STS, 10 full sit-to-stands test; 6MWT, 6-min walk test; 6MWD, 6-min walk distance; Data were: [a]Mean ±SD; [b]Median (minimum-maximum); [c]Median (interquartile range). *$p < 0.05$: pre-CRRPvs. after CRRP. For the study of Gloeckl et al. (2021): [α]p<0.05 pre-CRRP, vs. post-CRRP, for the same group mild/moderate; [β]p<0.05 pre-CRRP, vs. post-CRRP, for the same group severe/critical. [¥]$p < 0.05$ between-group difference mild/moderate vs. severe/critical for the same period.

status (Singh et al., 2000). The aforementioned results have not been discussed in previous studies evaluating the effects of CRRP on 6MWT data in COVID19 patients (Table 4, 5).

In our study, while dyspnea (mMRC) and FEV_1 were improved by 1.79 points and 110 ml, respectively, HGS remained unchanged (Table 2). The finding related to dyspnea is in line with previous reports (Table 4) indicating that CRRP improves perceived dyspnea [whatever its mode of evaluation; e.g., mMRC (Bouteleux et al., 2021; Gloeckl et al., 2021), chronic obstructive pulmonary disease assessment test (Daynes et al., 2021)], even in severe/critical COVID19 patients (Gloeckl et al., 2021). In our study, mMRC improvement was higher than the one point MCID (Crisafulli and Clini, 2010). To the best of the authors' knowledge, this is the first study investigating MCID dyspnea after a CRRP in post-COVID19 patients. In these patients, improvement in perceived dyspnea is capital since dyspnea is significantly associated with higher mortality (Shi et al., 2020), and it is a predictive factor of reduced functional capacity (Wong et al., 2021).

Our results concerning spirometry data are comparable with those investigating the impact of CRRP on lung function data (Liu K. et al., 2020; Bouteleux et al., 2021; Gloeckl et al., 2021; Puchner et al., 2021) (Tables 4, 5). In the latter studies, at least one lung function parameter was improved [FEV_1 (Liu K. et al., 2020; Gloeckl et al., 2021; Puchner et al., 2021), FVC (Liu K. et al., 2020; Bouteleux et al., 2021; Gloeckl et al., 2021; Puchner et al., 2021), total lung capacity (Puchner et al., 2021), diffusing lung capacity for carbon monoxide (DLCO) (Liu K. et al., 2020; Puchner et al., 2021)]. Concerning the improvement in FEV_1, the 110-ml increase observed in our study was lower than the values reported in the literature [e.g., 200 ml (Puchner et al., 2021), 340 ml (Liu K. et al., 2020)]. The improvement in lung

TABLE 5 Methodology and main outcomes of some case-control studies aiming at evaluating the impact of CRRP on COVID19 patients.

1st author (Yr) [country]	a. Study design (type CRRP). B. Participants, N (male. c. Age (Yr))	Comorbidities (%)	Characteristics of CRRP program		Main outcomes	Summary of findings: Comparison
			Components	a. Frequency. b. Duration. c. Period between the COVID19 diagnosis and CRRP starting (D)		
Liu K. et al. (2020), [China]	a. Randomized controlled trial (outpatient). **b.** 72 (49), Intervention: 36 (24), Control: 36 (25). **c.** Intervention: 69 ± 8[a], Controls: 69 ± 8[a]	**Intervention:** AH: 28, DM: 25, osteoporosis: 22. **Controls:** DM: 25, AH: 22, osteoporosis: 17	**ET**. 0.10 min. Respiratory muscle training. Cough exercise. Diaphragmatic training. Stretching exercise. Home exercise	a. 2 D/W. **b.** 6 W. c. NR	.Spirometry, DLCO, 6MWT	**Intervention group:** Improve in $FEV_1^{\alpha¥}$, FVC$^{\alpha¥}$, DLCO$^{\alpha¥}$, 6MWD$^{\alpha¥}$. **Controls:** No impact
Spielmanns et al. (2021), [Switzerland]	a. Interventional study (rehabilitation unit). b. 518 (263), PG:99 (57), LG:419 (206. c. PG: 68 ± 10[a], LG: 69 ± 11[a])	**PG:** AH:54, obesity:25, MSD:25, dyslipidemia: 20, ND:20, CKD:19, CHD:18, malignancy:15, COPD:11. **LG:** NR	**ET**. ACE (cycling/ treadmill): 10–30 min. Gymnastics: 45 min. Outdoor walking: 45 min.Strength training: 30 min. **Education**. Relaxation: 45 min . Respiratory therapy: 30 min	a. 5-6 D/W. b. 3 W, 25–30 sessions. c. 2 D after being asymptomatic and 10 D after onset of infection	Spirometry, 6MWT	**PG:** Improve in 6MWD$^{\Delta£}$. **LG:** Improve in 6MWD$^{\delta}$

ACE, aerobic cycle endurance; AH, arterial-hypertension; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID19, coronavirus disease 2019; CRRP, cardiorespiratory rehabilitation; D, day; DLCO, diffusing capacity of the lung for carbon monoxide; DM, diabetes-mellitus; ET, exercise-training; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LG, lung diseases group; Min, minute; MSD, musculoskeletal disease; N, number; NA, not-applied; ND, neurological disease; NR, not-reported; PG, post-COVID19, group; W, week; Yr, year; 6MWD, 6-min walk distance; 6MWT, 6-min walk test; Data were [a]Mean±SD. $^*p < 0.05$. For the study of Liu K. et al. (2020): $^{\alpha}p<0.05$ pre-CRRP, vs. post-CRRP, for the same group cases; $^{¥}p < 0.05$ between-group difference cases vs. controls for the same period. For the study of Spielmanns et al. (2021): $^{\Delta}p<0.05$ pre-CRRP, vs. post-CRRP, for the PG, group; $^{\delta}p<0.05$ pre-CRRP, vs. post-CRRP, for the LG, group. $^{£}p < 0.05$ between-group difference PG, vs. LG, for the same period.

function data could be explained by the breathing exercises and the respiratory muscle training applied during CRRP (Liu K. et al., 2020; Gloeckl et al., 2021; Puchner et al., 2021). Improvement in lung function data, such as FVC and FEV_1, is useful to improve risk stratification in patients with intermediate coronary heart disease (Lee et al., 2010). FVC is implicated in predicting cardiovascular events and thus mortality (Lee et al., 2010). In addition, even in healthy people, there is a positive correlation between spirometric data (e.g., FEV_1 and FVC) and 6MWD (Ben Saad et al., 2009).

In our study, the HGS remained unchanged (Table 2). Our findings were inconsistent with those reported by two previous studies, where HGS improved by 3 kg (i.e., from 18 to 21 kg) (Piquet et al., 2021) or 5 kg (from 25 to 30 kg) (Gloeckl et al., 2021) (Table 4). The absence of improvement in HGS could be explained by the fact that the pre-CRRP HGS value (i.e., 37 kg) was in the norms [i.e., >27 kg (Cruz-Jentoft et al., 2019)], and by the inclusion of moderate to severe COVID19 patients (Table 1). In the two above-cited studies reporting improvement in HGS, patients were classified as severe or critical (Gloeckl et al., 2021), and both the pre- and the post- CRRP HGS values were below the norms (Piquet et al., 2021). HGS measurement is important since it is associated with frailty and with an increased risk of mortality (Cheval et al., 2021). Indeed, COVID19 survivors have an increased risk of acute sarcopenia (Welch et al., 2020) due to the loss of muscle mass, fiber denervation, neuromuscular junction damage, and upregulation of protein breakdown (Puthucheary et al., 2010).

4.2 Discussion of methods

The discrepancies noted between our results and these of some similar studies (Tables 4, 5) could be explained by at least seven points related to differences in:

1) Study designs: prospective observational cohort (Gloeckl et al., 2021) vs. case control (Liu K. et al., 2020) studies;
2) CRRP locations: outpatient (Betschart et al., 2021) vs. inpatient (Puchner et al., 2021) rehabilitation;
3) Some inclusion criteria such as inclusion of both males and females (Bouteleux et al., 2021; Daynes et al., 2021), which could have influenced the findings since COVID19 clinical data are sex-dependent (Marik et al.,

2021); or inclusion of COVID19 patients having different ages (e.g., elderly (≥65 years) (Liu K. et al., 2020) vs. middle-aged (48 ± 15 years) (Bouteleux et al., 2021)) which could have influenced the findings (Liu Y. et al., 2020);
4) COVID19 patients' profiles (e.g., no (Bouteleux et al., 2021), vs. several (Betschart et al., 2021; Gloeckl et al., 2021) comorbidities) and/or in the disease severity stages (e.g., mild/moderate vs. severe/critical) (Gloeckl et al., 2021);
5) CRRP' components (e.g., exercise-training and education (Hermann et al., 2020; Betschart et al., 2021) vs. exercise-training alone (Bouteleux et al., 2021));
6) Durations and/or frequencies of CRRP (e.g., two sessions/week and 16 sessions (Betschart et al., 2021) vs. five sessions/week and three sessions (Gloeckl et al., 2021)); and
7) Time periods' between the diagnosis of COVID19 and the start of CRRP [e.g., early rehabilitation for acute COVID19 (Puchner et al., 2021) vs. late rehabilitation for long-COVID19 (Daynes et al., 2021)].

4.3 Strengths and limitations

This study has three strong points. First, our study was conducted in an outpatient unit in a low-income country (e.g., Tunisia) and the different components were performed (i.e., exercise-training, education, and nutritional counseling). Second, our sample size was calculated according to a predictive equation (Serhier et al., 2020). Determination of the finest size is a central topic since it helps in avoiding an inadequate power to distinguish statistical effects (Mascha and Vetter, 2018), and it guarantees a representative sample to differentiate statistical significance (Serhier et al., 2020). Huge sample size is costly and exposes more participants to measures (Mascha and Vetter, 2018), but using insufficient participants may lead to lower "precision" in results. Third, both statistically and clinically significant approaches were applied. Nowadays, the statistically significant approach, with a "*p*-value" < 0.05 being considered significant, is disapproved (Yaddanapudi, 2016). The MCID of 30 m for the 6MWD (Singh et al., 2014) and one point for dyspnea (mMRC) were introduced (Crisafulli and Clini, 2010). For instance, in a German study (Gloeckl et al., 2021) (Table 4), it was demonstrated that post-CRRP dyspnea median (interquartile) value is significantly lower than the one measured pre-CRRP [2 (2-2) vs. 2 (1–2), $p < 0.003$]; but the zero mean difference between the two periods does not exceed the MCID of one point (Crisafulli and Clini, 2010).

The present study has two limitations. First, the lack of a control group is a major limitation. Indeed, the inclusion of a control group was reported only in few studies (Liu K. et al., 2020; Spielmanns et al., 2021) (Table 5). Several studies (Hermann et al., 2020; Betschart et al., 2021; Bouteleux et al., 2021; Daynes et al., 2021; Gloeckl et al., 2021; Piquet et al., 2021; Puchner et al., 2021) have included only one group (Table 4) and it was difficult to include a control group due to ethical considerations during the COVID19 pandemic. The lack of a control group did not allow us to "affirm" that our results are only attributable to CRRP. Indeed, one study reported that lung function data of most COVID19 patients improve spontaneously over 3-month period (Wu et al., 2021). Second, it would have been more interesting to explore the respiratory function using additional tests, such as plethysmography (Puchner et al., 2021), DLCO (Liu K. et al., 2020; Gloeckl et al., 2021; Puchner et al., 2021), and maximal inspiratory pressure (Puchner et al., 2021), and exercise data using a cardiopulmonary exercise test in order to determine the first ventilatory threshold. In COVID19 patients, the most frequent lung function impairment is altered DLCO (39%) (Torres-Castro et al., 2021). Due to the unavailability of equipment in our public health hospital, these examinations were not performed.

5 Conclusion

A 4-week CRRP in post-COVID19 patients improved dyspnea (mMRC), FEV_1, 6MWD, 6-min walk work, resting heart-rate and DBP. CRRP has imposed itself as a standard of care for the treatment of post-COVID19 patients.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Farhat HACHED Hospital medical and research ethics committee (Approval number FH 2502/2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ET conceived the study, participated in its design, the statistical analysis, performed the questionnaires and the exercise training and helped to draft the manuscript. WB conceived the study, participated in its design, the statistical analysis, performed the questionnaires and helped to draft the manuscript. CR helped to draft the manuscript. SA helped to draft the manuscript. InG performed the spirometry, HGS and 6MWT tests, and helped to draft the manuscript. AK helped to draft the manuscript. AS performed the spirometry, HGS and

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6MWT tests, and helped to draft the manuscript. SS performed the spirometry, HGS and 6MWT tests, and helped to draft the manuscript. KM performed the spirometry, HGS and 6MWT tests, and helped to draft the manuscript. SJ helped to draft the manuscript. ImG helped to draft the manuscript. AH helped to draft the manuscript. WO helped to draft the manuscript. AA helped to draft the manuscript and coordinated the study. HBS conceived the study, participated in its design, performed the spirometry, HGS and 6MWT tests, performed the statistical analysis, helped to draft the manuscript and coordinated the study. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer IL declared to the handling editor a shared affiliation with all authors besides AA at the time of review.

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Association between body image perception with demographic characteristics of physically active individuals during COVID-19 lockdown in Saudi Arabia

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Objective: This study aimed to determine the relationship between body image perception and demographic factors among physically active (men and women) during the COVID-19 lockdown in Saudi Arabia.

Methods: A descriptive cross-sectional survey was employed among physically active individuals in Saudi Arabia between June and July 2020. Eligible participants completed a 19-item self-administered questionnaire that covered three areas: demographic questions, reasons for physical activity, and role or perceptions of body image during the COVID-19 pandemic quarantine.

Results: A total of 323 physically active individuals participated in this study. The majority of the participants were female (N=217, 72.7%), were married (66.6%), and living in the Middle region of Saudi Arabia (N= 268, 83%). The analysis shows that majority of the participants were dissatisfied with their current body shape. The analysis also showed a significant association between participants' educational attainment and BMI and body dissatisfaction (p= 0.001). The strongest predictor was BMI level, recording an odds ratio (OR) of 5.99 (CI: 2.15 – 10.54, p=0.001) in obese and an OR of 4.55 (CI: 1.31 – 9.35, p=0.001) in overweight, indicating that compared with normal weight, obese and overweight participants were more likely to be dissatisfied by five and four times, respectively.

Conclusion: This study indicates that physically active individuals are greatly influenced by the confinement period. Programs that promote physical activity in their house or during lockdown may help to encourage, lessen their anxiety, and maintain their health. This may also decrease the anxiety of individuals, particularly those active ones.

KEYWORDS

body image, body image dissatisfaction, COVID-19, physically active, Saudi Arabia

Introduction

Saudi Arabia reported the first coronavirus disease 2019 (COVID-19) case on 2 March 2020. The rapid increase of COVID-19 cases and deaths has caused a global public health concern. Different countries implemented nonpharmaceutical interventions (NPIs) to mitigate the spread of COVID-19. The Ministry of Health implemented NPIs such as suspension of all classes, 14 days of isolation for travelers, mask-wearing, physical distancing, the shutdown of nonessential businesses (e.g., coffee shops, sports clubs, schools, and fitness gyms), and a nationwide curfew between 2 p.m. and 6 a.m. (1). In addition, the Islamic pilgrimage called "Umrah," performed by thousands of Muslims in Mecca, was also suspended to contain the COVID-19 outbreak. Due to the unprecedented measures placed on people's movements may significantly influence their habits and behaviors and consequently increase the risk of anxiety and emotional distress (2).

Several studies have expressed concern about the potential health risk for NPIs, particularly lockdown measures that increase sedentary behaviors and irregular eating patterns in the general population (3–6). In addition, collective anxiety about weight gain during the lockdown and stigmatizing media messages about the dangers of higher body weight might contribute to increased body shame and levels of disordered eating (2). A global study shows that home confinement had a negative effect on the intensity of physical activity of individuals and increased the number of sitting time (7). Other studies also revealed the negative effect of home confinement on the emotional wellbeing of individuals (8, 9).

Physical inactivity increases the risk of many chronic diseases, such as hypertension, coronary heart disease, stroke, diabetes, depression, and risk of falls (10). Previous studies have shown that proper or regular physical activity helps maintain a healthy weight, reduces the risk of developing obesity, and strengthens the immune system (10, 11). Considering the health benefits of regular physical activity, the WHO recommends that individuals, mainly adults, undertake 150–300 min of moderate-intensity, or 75–150 min of vigorous-intensity physical activity, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity per week (12).

To individuals who are physically active and involved in sports disciplines and where appearance, including body shape and mass, is essential, the effects of lockdown measures can increase the level of anxiety from undertaking physical activity. Furthermore, individuals who exercise regularly can be expected to differ in the impact of NPIs because it tends to be more concerned and dissatisfied with their appearance compared with those who are physically inactive. Body image dissatisfaction is defined as negative thoughts, feelings, and perceptions about one's body (13). Body image is a multidimensional concept of individual perception, affection, and behaviors (e.g., satisfaction or dissatisfaction with body image and evaluation of body size) (14, 15). Body image involves different aspects, such as cognitive, emotional, social, and cultural, in addition to dissatisfaction with own body (14). A popular belief about body image is that social media and society with lean anthropometric profiles are beauty standards (16, 17). Moreover, physical activity is regarded as a critical component of a healthy lifestyle and disease prevention (18). A previous study has shown that a negative body image may work as both a motivation and a barrier to exercise participation (19).

Several studies revealed that body weight concerns and body dissatisfaction are prevalent in Arab countries, particularly among women. A survey conducted in five Arab countries (Syria, Bahrain, Jordan, Oman, and Egypt) shows that 33% of Arab women were dissatisfied with their body weight (20). In Saudi Arabia, 21.4% of men and 33.5% of women reported body image dissatisfaction (21). Another study among Saudi females attending fitness centers revealed that 87% were dissatisfied with their body image, including those of normal weight (22). Such findings may call the attention that the COVID-19 and NPIs will have negative implications for those individuals, particularly those who are physically active.

Accordingly, it is necessary to identify the perceived changes to their body image behaviors during this period considering the effects of the COVID-19 lockdown. We hypothesized that social isolation, lockdown, and quarantine in Saudi Arabia may have adversely impacted the perception of body image of physically active individuals. Thus, we aimed to assess the body dissatisfaction of physically active (men and women) during the COVID-19 lockdown in Saudi Arabia and determined the possible associated factors that can serve as a baseline for future policies and health programs.

Materials and methods

Design and participants

This descriptive cross-sectional study employed a total of 323 physically active individuals who were living in Saudi Arabia during the COVID-19 pandemic. The participants' inclusion criteria were as follows: aged 18 years and above, Saudi nationals, physically active individuals exercising equal to or more than 150–300 min of moderate activity for 1 week, and member of a sports club. The participants were also asked to describe themselves as somehow active, amateur, and athletes for the classification of physical activity. A convenience sampling method was used due to the pandemic situation. A 5% margin of error, a confidence level of 95%, and a significance value of 0.05 were used as statistical parameters. Ethical approval for this study was approved by the King Saud University Ethics Research Committee. All participants provided informed consent prior to participating in this study.

Instrument

An instrument was developed which covered the following three areas: demographic questions, role and perception of body image, and reasons for physical activity during the COVID-19 quarantine. The demographic section includes age, sex, marital status, educational level, and body mass index (BMI). The Stunkard Figure Rating Scale (FRS) images were used to assess the perception of the body image of the participants. This questionnaire consists of two diagrams in which the first diagram ranks their actual body image based on the nine silhouette figures, while the second diagram ranks their desires to look like from the same nine figure images. A corresponding rating score of each figure is from 1 to 9, with nine representing the most obese figure and one the thinnest (23). The discrepancy between perceived and desired body image scores was calculated. Body dissatisfaction occurred when the desired silhouette was smaller than the self-evaluated and dissatisfaction with slimness when the desired shape was larger than the self-evaluated (23).

The International Physical Activity Questionnaire (IPAQ) was used to assess participants' physical activity levels. The participants were asked how often (the number of days per week) and for how long (the average time in minutes) they had been active at light, moderate, and vigorous intensities during the last 7 days. The intensities of physical activity were assigned to an average Metabolic Equivalent Time (MET) to yield MET-minutes (MET-min) per week. We based the overall MET value on the average MET value for each intensity in the MET compendium (24, 25). Light activity was 3.3 MET, moderate 4.0 MET, and vigorous 8.0 MET. All scored data were according to the IPAQ scoring protocol, version 2.0. All participants in one or more intensity levels had reported days (frequency) and time (duration) of physical activity or vice versa and were included in the analysis by summing up the frequency and duration of activity. A draft questionnaire was piloted and revised to a final survey of 19 items related to electronic survey response and demographic variables, which took approximately 15 min to complete. All the participants' responses were recorded *via* the platform of the study survey and downloaded by a trained researcher.

Data gathering procedure

All participants were recruited online through a sports club group. All eligible participants received an invitation, including a link to an online survey. The survey questionnaire includes participants' consent information, which explains the rationale for the study, and all participants' information is confidential and anonymous. All participants entered and completed the survey between June and July 2020.

Statistical analysis

Statistical analysis was performed using SPSS (version 23.0). Microsoft Excel was used for data entry, editing, and sorting. Continuous data were presented as mean and standard deviation (SD), and categorical data as frequency and percentage. The classifications of physical activity were categorized into three based on the guidelines and recommendations of the International Physical Activity Questionnaire Research Committee (IPAQ Research Committee, 2005). The proposed levels of physical activity are [i] inactive (low), [ii] minimally active (moderate), and [iii] health-enhancing physical activity, or a high active category (IPAQ Research Committee, 2005). Furthermore, the level of physical activity was dichotomized into moderate activity, which has >1,680 MET-min/week, and vigorous activity, whose MET-min/week was <1,680 (24–26). The association between body image and physical activity was examined using the chi-square test analysis. To assess the predictors associated with body dissatisfaction, we performed a multiple logistic regression model, and the odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. The dependent variable was body image, and the reference category was "Satisfied". Statistical significance was set at $p < 0.05$.

Results

The composition of the study sample with age category shows that 29.1% were aged 18–24, 24.5% were aged 25–29 years, 17.3% were aged 30–34 years, 16.4% (26–30), and 12.7% were aged 40 years and above (Table 1). The majority of the participants were female ($N = 217$, 72.7%), were married (66.6%), and living in the Middle region of Saudi Arabia ($N =$ 268, 83%). Sixty percent of the participants were of university education level, where a small sample had a high school/diploma (18.6%) or <high school (0.6%). Most of the respondents were amateurs ($N = 220$, 68.1%), and 26% ($N = 85$) were athletes in the club or the school. More than half of the participants had normal BMI levels ($N = 204$, 63%), 27.9% ($N = 90$) were overweight, and 9% of the participants were obese ($N = 29$). Notably, 31% of the participants had higher energy expenditure in MET-min/week of vigorous based on the 1,680 MET-min/week cutoff. The majority of the participants were dissatisfied with their current body shape or desired a smaller shape ($N = 276$, 85.5).

Table 2 displays the demographic characteristics of physically active individuals who were satisfied and dissatisfied with their body shape. The analysis shows that majority of the participants were dissatisfied and desired a smaller shape. The chi-square test analysis also indicated a significant association of participants' educational attainment and BMI with body dissatisfaction ($p = 0.001$). The proportion of physically active individuals with body dissatisfaction

TABLE 1 Demographic characteristics of the participants.

Variable	$N = 323$	%
Age		
18–24	94	29.1
25–29	79	24.5
30–34	56	17.3
35–39	53	16.4
40 and above	41	12.7
Gender		
Male	66	27.3
Female	217	72.7
Marital status		
Single	108	33.4
Married	215	66.6
Educational level		
<high school	2	0.6
High school/diploma	60	18.6
Bachelor's degree	196	60.7
High education degree	65	20.1
Region		
Middle region	268	83
Eastern and Western region	47	14.5
Northern and Southern Western	8	2.5
BMI		
Normal	204	63.1
Overweight	90	27.9
Obese	29	9
Classification of physical activity		
I am not always active	18	5.6
Amateur	220	68.1
Athletes in the club or school	85	26.3
Level of physical activity		
METs-min/week from moderate activity < 1,680	222	68.1
METs-min/week from vigorous activity > 1,680 METs-min/week	103	31.9
Body dissatisfaction		
Satisfied	47	14.5
Dissatisfied	276	85.5

across educational attainment increased significantly (high school/diploma—77.4%, Bachelor's degree—85.7%, and Postgraduate or High education degree—92.3%, $p < 0.05$). Body dissatisfaction was also significantly associated with participants' BMI in which the majority of the participants who were overweight ($N = 65$, 72%) and obese ($N = 23$, 79.3%) were dissatisfied with their actual BMI ($p = 0.001$). The analysis also shows that 92.2% who had normal BMI were dissatisfied or desired a smaller shape than their actual BMI ($p = 0.001$).

Multiple logistic regression was performed to assess the predictors of body dissatisfaction of physically active individuals. The model contained eight independent variables (age, gender, marital status, educational level, region, BMI level, classification of physical activity, and level of physical activity). As shown in Table 3, only one variable emerged as a significant predictor of body dissatisfaction of physically active individuals. The strongest predictor was BMI level, recording an OR of 5.99 (CI: 2.15–10.54, $p = 0.001$) in obese and an OR of 4.55 (CI: 1.3– 9.35, $p = 0.001$) in overweight, indicating that compared with normal weight, obese and overweight participants were more likely to be dissatisfied by five and four times, respectively.

Discussion

This study intended to assess the body dissatisfaction of physically active (men and women) during the COVID-19 lockdown in Saudi Arabia. The analysis shows that majority of the participants were dissatisfied with their body image or desired a smaller shape. The findings were parallel with previous research among Saudi females attending fitness clubs and those adolescents in Brazil (14, 22). The less altered body image dissatisfaction of the participants was possibly driven by the concerns during a lockdown of not engaging in their usual physical activity routine. A previous study concurred that body dissatisfaction is associated with disordered eating (19). Behavior theory suggests that a common emotional response to a pandemic is an exaggerated feeling of fear or anxiety (31, 32). Therefore, these findings may support concerns that the COVID-19 lockdown is a factor in developing these complex health conditions.

Our results also highlight that educational attainment and BMI level were significantly associated with body dissatisfaction. These results confirm that body shape dissatisfaction was higher than those with higher education, as previously stated in other literature (33). With regards to body dissatisfaction between BMI levels, it was noted that the majority of participants with normal BMI levels were dissatisfied or desired a smaller shape than their actual BMI. Similar findings were found among Spanish adults and in the USA (34, 35). Our findings were also parallel to a study in Hong Kong in which the majority of the participants with normal weight status desired a leaner or slimmer body (33). The results are not surprising that a relatively high proportion of individuals with normal BMI levels misperceived their body image since our participants were physically active individuals. This mismatch could also have been perceived by the desire for an ideal body shape influenced by norms, media, and society (33). The findings indicate a signal of a feeling of distress and the development of anxiety among

TABLE 2 Association of body image dissatisfaction with demographic characteristics of the participants.

Variable	$N = 323$	Body Image		P-value
		Satisfied ($N = 47$)	Dissatisfied ($N = 276$)	
Age				0.568
18–29	173 (53.6)	23 (13.3)	150 (86.7)	
30–39	109 (33.7)	19 (82.6)	19 (17.4)	
40 and above	41 (12.7)	5 (87.8)	36 (12.2)	
Gender				0.175
Male	66 (27.3)	19 (17.6)	89 (82.4)	
Female	217 (72.7)	28 (13)	187 (87)	
Marital status				0.211
Single	108 (33.4)	18 (16.7)	90 (83.3)	
Married	215 (66.6)	29 (13.5)	186 (86.5)	
Educational level				0.050
High school/diploma	62 (19.2)	14 (22.6)	48 (77.4)	
Bachelor's degree	196 (60.7)	28 (14.3)	168 (85.7)	
High education degree	65 (20.1)	5 (7.7)	60 (92.3)	
Region				0.091
Middle region	268 (83)	44 (16.4)	224 (83.6)	
Eastern and Western region	47 (14.5)	2 (4.3)	45 (95.7)	
Northern and Southern Western	8 (2.5)	1 (12.5)	7 (87.5)	
BMI				0.001
Normal	204 (63.2)	16 (7.8)	188 (92.2)	
Overweight	90 (27.9)	25 (27.8)	65 (72.2)	
Obese	29 (9)	6 (20.7)	23 (79.3)	
Classification of physical activity				0.094
I am not always active	18 (5.6)	4 (22.2)	14 (77.8)	
Amateur	220 (68.1)	32 (14.5)	182 (85.5)	
Athletes in the club or school	85 (26.3)	11 (12.9)	74 (87.1)	
Level of physical activity				0.311
METs-min/week from moderate activity < 1,680	222 (68.1)	34 (15.5)	186 (84.5)	
METs-min/week from vigorous activity > 1,680 METs-min/week	103 (31.9)	13 (12.6)	90 (87.4)	

Chi-square tests for the differences in proportions; significance level at <0.05.

the participants. In addition, misperception of body shape is common, particularly among adolescents and adults (36–38).

Another result worth emphasizing was BMI levels as a predictor associated with the body dissatisfaction of the participants. The analysis indicated that the strongest predictor was obesity, followed by overweight participants in the BMI level. The research reflects the difference between BMI levels and body image perception of physically active individuals during the COVID-19 pandemic. These findings were consistent with previous research in Brazil (14, 17). A previous study suggests that promoting exercise needs to deemphasize weight loss and appearance for positive body image (27, 39). These findings demonstrated the importance of physical activity behavior as a potential mechanism to develop body image positivity. Considering the benefits of physical activity during quarantine and in relation to body image, it is necessary to identify ways and promote exercise during the isolation period. Similarly, physical activity could be recommended to reduce the negative emotional effect during the periods of lockdown and quarantine (2, 28). In addition, digital health solutions such as exergames or the development of virtual coaches can allow easy and accurate interventions as well as recommendations to improve physical activity during the quarantine and pandemic (29).

The findings of this study present some limitations. First, the cross-sectional design of this study limits the causality. Second, the small sample size and the use of convenience sampling may result in bias and may not be able to generalize the entire population. However, the results are comparable with the previously conducted study. In addition, it produced information about body image perception (body dissatisfaction) and its association with the demographic characteristics of physically active individuals during the COVID-19 lockdown in Saudi Arabia.

TABLE 3 Predictors associated with body dissatisfaction among physically active individuals.

	OR (95 % CI)	*P*-value
Variable	*N* = 323	
Age		0.820
18–29	1	
30–39	1.11 (0.45–2.74)	
40 and above	0.36 (0.08–1.49)	
Gender		0.649
Male	1	
Female	0.84 (0.08–1.49)	
Marital status		
Single	1	
Married	1.36 (0.53–3.48)	
Educational level		0.099
High school/diploma	1	
Bachelor's degree	0.57 (0.25–1.29)	
High education degree	0.26 (0.07–0.90)	
Region		
Middle region	1	0.094
Eastern and Western region	0.18 (0.04–0.84)	
Northern and Southern Western	0.94 (0.09–9.30)	
BMI		0.001
Normal	1	
Overweight	4.55 (2.22–9.35)	
Obese	5.99 (2.15–10.54)	
Classification of physical activity		
I am not always active	1	0.819
Amateur	0.77 (0.21–2.79)	
Athletes in the club or school	0.64 (0.15–2.70)	
Level of physical activity		
METs-min/week from moderate activity <1680	1	0.92
METs-min/week from vigorous activity >1680	0.96 (0.45–2.20)	

CI, confidence interval for odds ratio (OR); dependent variable "body image" and the reference category "Satisfied"; significance level at <0.05.

Conclusion

This study identified that the majority of the participants were dissatisfied with their current body shape. The analysis also found that the proportion of physically active individuals with body dissatisfaction increased significantly across educational attainment. In addition, the findings indicate a trend of increased body dissatisfaction from normal weight to overweight and then decreased likelihood of obese participants. This study indicates that confinement greatly influences physically active individuals. The findings of this study provide important insights into the effect of COVID-19 and NPIs among physically active individuals during the COVID-19 pandemic. The present results need to be interpreted with caution due to these limitations. The present findings have potential implications that could aid in developing interventions to mitigate the effect of the COVID-19 pandemic, particularly among these individuals. We recommend programs that promote physical activity in their house or during lockdown which may help to encourage, lessen their anxiety, and maintain their health. This may also decrease the feeling of distress of physically active individuals.

Data availability statement

The data that support the findings of this study are available at the Department of Community Health Sciences, College of Applied Medical Science King Saud University, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request.

Ethics statement

Institutional Review Board Committee at King Saud University approved the study prior to enrollment in this study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MA contributed to data analysis, interpretation of results, drafting, or revising the manuscript, agreed to be accountable for all aspects of the study, and approved the final version of the manuscript.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of physical activity on the severity of illness and mortality in COVID-19 patients: A systematic review and meta-analysis

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Purpose: This systematic review and meta-analysis investigated the association between Physical activity (PA) before Coronavirus Disease 2019 (COVID-19) infection and the severity of illness and mortality in COVID-19 patients.

Methods: A comprehensive search was undertaken to identify retrospective and nonrandomized controlled trial studies comparing the severity and mortality of COVID-19 infection among COVID-19 patients who had previously reported their participation in PA with those who had not. The databases searched were PubMed, Cochrane Library, Scopus, Science Direct, EMBASE, OPENGREY.EU, and ClinicalTrials.gov. The risk of bias was assessed using the Newcastle-Ottawa Scale. A random-effects model was used for determining pairwise meta-analyses. The protocol was registered with PROSPERO (CRD42021262548).

Results: Eighteen studies met the inclusion criteria (5 cross-sectional, 12 cohort, and 1 case-control studies). All 1 618 680 subjects were adults. PA significantly decreased the risk of death in COVID-19 patients (odds ratio [OR] 0.34; 95% confidence interval [CI], 0.19–0.62; $p < 0.001$) and the risk of severe outcomes (OR 0.60; 95% CI, 0.48–0.76; $p < 0.001$). Subgroup analysis showed that PA for ≥150 min/wk at a moderate intensity or ≥75 min/wk at a vigorous intensity reduced the risks of severity and mortality. Vigorous PA reduced mortality risk, whereas moderate to vigorous PA reduced the risks of severity and mortality.

Conclusion: PA before infection might reduce severity and mortality in COVID-19 patients, especially PA ≥ 150 min/wk of moderate activity or ≥75 min/wk of vigorous activity. However, careful interpretations should be considered due to the difference in PA patterns and severity definitions among included studies. This finding implies that engaging in regular PA, even in different patterns, has beneficial effects on the severity and mortality of COVID-19 patients.

KEYWORDS

exercise, physical activity, SARS-CoV-2, coronavirus, severity, mortality

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lai et al., 2020). The World Health Organization declared COVID-19 a global pandemic on March 11, 2020 (World Health Organization, 2020). As at September 2022, over 600 million confirmed cases and over six million deaths were attributed to the virus worldwide (World Health Organization, 2022a). Transmission of the virus can occur through direct contact with the respiratory droplets of an infected person (generated through coughing and sneezing). Individuals can also be infected by touching surfaces contaminated with the virus and then touching their face (eg, the eyes, nose, or mouth) (Halperin, 2021). Approximately 80% of cases are asymptomatic or have mild symptoms, whereas the remainder can be severe and critical, leading to death (Verity et al., 2020) or persistent long COVID (Fahriani et al., 2021; Fajar et al., 2021). During the virus's rapid spread in the absence of a COVID-19 vaccine, many countries implemented restrictive policies (eg, stay-at-home orders and the closures of parks, gymnasiums, and recreation centers). These policies were highly influential in containing the number of COVID-19 infections and preventing healthcare systems from being overwhelmed (Kharroubi and Saleh, 2020). However, the policies led to a significant increase in physical inactivity (PiA) (Stockwell et al., 2021), which has been considered a risk factor for developing COVID-19 severity and mortality (Centers for Disease Control and Prevention, 2020).

Physical activity (PA) has been defined as any bodily movement produced by skeletal muscle function resulting in energy expenditure (Caspersen et al., 1985). PA in daily life can be categorized as structured and incidental activities (Strath et al., 2013). Structured activities are bodily movements that usually occur during free time to promote health and fitness, such as weight training, jogging, and swimming (Strath et al., 2013). Incidental activities are bodily movements that occur during daily living, such as walking to school, gardening, and washing a car (Strath et al., 2013). The PA Guidelines for Americans recommend that all adults between 18 and 65 years of age engage in at least 30 min of moderate-intensity aerobic PA a day for 5 days a week or at least 20 min of high-intensity aerobic PA a day for 3 days a week (Piercy et al., 2018). Regular PA is recommended as a supplement to help strengthen the immune system to defend against COVID-19 infection (da Silveira et al., 2020). In addition, PA counteracts some noncommunicable diseases, such as obesity, diabetes mellitus, and arterial hypertension that increase the likelihood of COVID-19 patients experiencing severe outcomes (Chandrasekaran and Ganesan, 2020). However, there is insufficient scientific evidence supporting the recommendations of the PA Guidelines for Americans. A previous systematic review and meta-analysis of Rahmati et al. (2022) reported that PA decreased hospitalization, intensive care unit (ICU) admissions, and mortality rates of patients with COVID-19 in all study types. COVID-19 patients with a history of resistance and endurance exercises experience a lower rate of hospitalization and mortality, respectively. Meta-analysis results from a few studies showed lower mortality in low and moderate-vigorous PA (Rahmati et al., 2022). Only one study (Lee et al., 2021) was included to analyze the effects of PA level on ICU admission. It is suggested that further study should be recommended due to the limited number of studies.

The present study aimed to systematically review all available evidence and pooled odds ratios (ORs) adjusted by confounding factors to determine whether regular PA before COVID-19 infection affects the severity of illness and mortality in COVID-19 patients.

Methods

Protocol and registration

This investigation was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for healthcare applications (Page et al., 2021). The protocol was prospectively registered with PROSPERO (www.crd.york.ac.uk/PROSPERO; reference CRD42021262548).

Information sources and search strategy

The PubMed, Cochrane Library, Scopus, Science Direct, and EMBASE databases were systematically searched through 15 June 2022. The search keywords were "COVID*," "exercise," "physical activity," "mortality," and "severity" (Supplementary Table S1). In addition, grey literature was searched in OPENGREY.EU and ClinicalTrials.gov through 18 September 2022. No language restrictions were applied. Reference lists were also manually reviewed to find citations for additional pertinent meta-analyses and reviews.

Eligibility criteria

Each study identified by the search was reviewed (by NS, NK, and KP in the authors' list) to determine if it had information on the PA or exercise habits of COVID-19 patients before their infection. The PA definition follows WHO (World Health Organization, 2022b), such as regular movement during leisure time, moderate- and vigorous-intensity PA, and active activity (i.e., walking, cycling, wheeling, sports, active recreation, and play). The comparators (physical inactivity; PiA) were activities or habits that were not classified as PA definition of WHO. The primary outcomes of interest were the severity and mortality of COVID-19. Severe COVID-19 follows WHO severity definitions (World Health Organization, 2022c), including severe and critical COVID-19. Articles that reported ORs of severely symptomatic patients admitted to a hospital under treatment (in the general ward and ICU) were included in this study. Non-severe COVID-19 was patients who had an absence of any sign of severe or critical COVID-19. Mortality was confirmed deaths from COVID-19, both inpatient and outpatient, reported in included studies. Moreover, case reports, case series, letters, and studies without interesting outcomes or group comparisons were excluded.

Study selection

Two investigators (NK and KP in the authors' list) independently screened the titles and abstracts of the retrieved studies. Full texts were reviewed as necessary. Trials were determined to be eligible for this study based on the inclusion and exclusion criteria mentioned above. A third investigator (MP in the authors' list) resolved disagreements.

Data extraction

Two investigators (NS and KP in the authors' list) independently extracted details from the selected studies and recorded them in a Microsoft Excel spreadsheet. A third investigator (MP in the authors' list) resolved disagreements. The data extracted were related to the setting, study design, sample size, patient demographics, PA or exercise details, comparators, number of mortalities, and number of patients at each severity level. The authors of the retrieved studies were contacted for missing data by email.

Risk of bias assessment

Two investigators (NP and MP in the authors' list) independently evaluated the risk of bias in the included cohort, cross-sectional, and case-control studies using the Newcastle-Ottawa Scale (NOS) (Stang, 2010). A third investigator (SK in the authors' list) resolved disagreements. The NOS contains three domains: quality of selection, comparability, and outcome. Each study was defined as low, moderate, and high quality when scores were 0–3, 4–6, and 7–10, respectively.

Quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates (Guyatt et al., 2008). This study used GRADE to determine the quality of evidence for outcome according to five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The levels of evidence can be categorized into four levels: high, moderate, low, and very low.

Data synthesis and analysis

Analyses were conducted using Stata Statistical Software, release 14.1 (StataCorp LLC, College Station, TX, United States). A random-effects model was used for determining pairwise meta-analyses. The results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity in each pairwise comparison was estimated using the I^2 statistic. Publication bias was assessed using a funnel plot, and Egger's tests were employed to assess the funnel plot asymmetry. Sensitivity analysis and subgroup analysis by level of PA were performed to evaluate the robustness of the results in determining the severity and mortality of illness in COVID-19 patients.

Results

General information

The literature search process is illustrated in Figure 1. The search strategies identified 11 418 articles from five databases and one article from two grey literature databases. Duplicates accounted for 1131 articles and were eliminated. After screening the titles and abstracts, an additional 10 246 articles were excluded for various reasons. Twenty-five articles were excluded from the study after assessment for eligibility

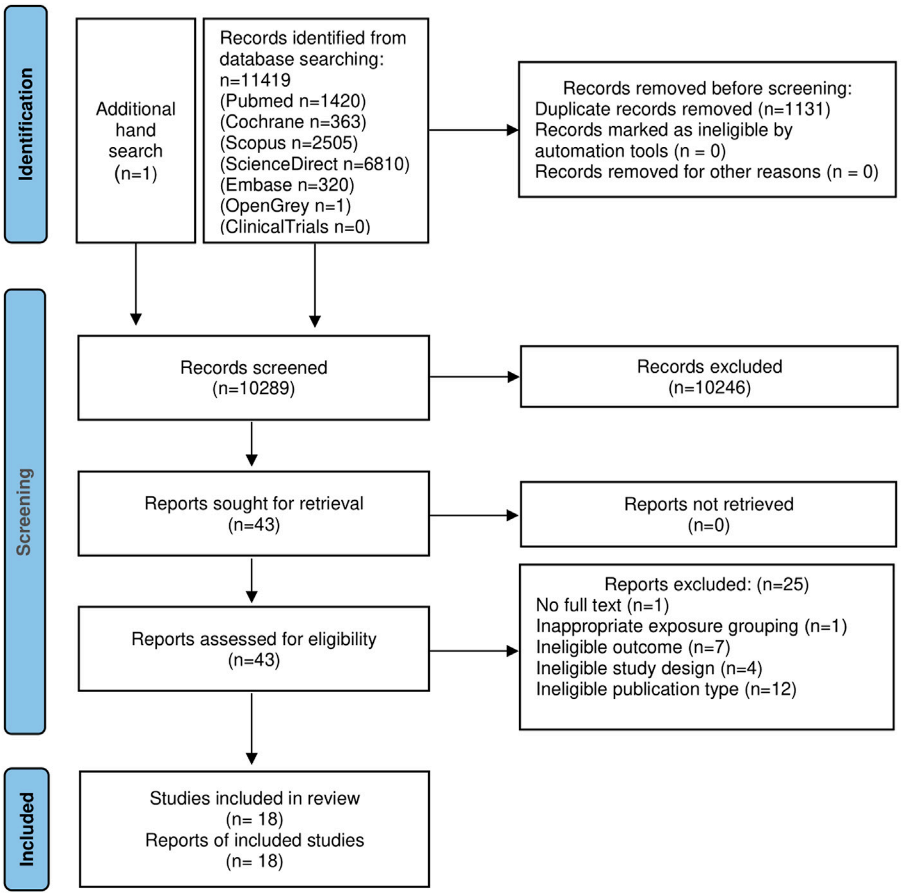

FIGURE 1
Flow diagram of the literature search in this meta-analysis.

(Supplementary Table S2). The meta-analysis was carried out on the remaining 18 eligible original articles.

Table 1 summarizes the core characteristics and outcomes of the selected studies. In all, 1 618 680 subjects were adults. Five studies used cross-sectional designs (Halabchi et al., 2021; Tavakol et al., 2021; Yuan et al., 2021; Tret'yakov et al., 2020; Latorre-Román et al., 2021), 12 had cohort study designs (Sallis et al., 2021; Cho et al., 2021; Lee et al., 2021; Hamrouni et al., 2021; Ahmadi et al., 2021; Hamer et al., 2020; Maltagliati et al., 2021; Malisoux et al., 2022; Baynouna Alketbi et al., 2021; Rowlands et al., 2021; Salgado-Aranda et al., 2021; Pinto et al., 2021), and only one employed a case-control design (Ekblom-Bak et al., 2021). We discovered four studies in the United Kingdom: Hamrouni et al., 2021; Ahmadi et al., 2021; Hamer et al., 2020; and Rowlands et al., 2021. Meanwhile, four studies were conducted in Europe: Latorre-Román et al., 2021; Salgado-Aranda et al., 2021; Ekblom-Bak et al., 2021; and Malisoux et al., 2022. In the meantime, six studies were carried out in Asia (Halabchi et al., 2021; Tavakol et al., 2021; Cho et al., 2021; Lee et al., 2021; Yuan et al., 2021; Baynouna AlKetbi et al., 2021). Besides that, three studies were discovered in the United States (Sallis et al., 2021), Brazil (Pinto et al., 2021), and Russia (Tret'yakov et al., 2020).

In terms of focus, 10 studies investigated the impacts of PA on mortality (Ahmadi et al., 2021; Baynouna AlKetbi et al., 2021; Cho et al., 2021; Ekblom-Bak et al., 2021; Halabchi et al., 2021; Hamrouni et al., 2021; Lee et al., 2021; Pinto et al., 2021; Sallis et al., 2021; Yuan et al., 2021), and 14 studies reported the severity of the disease (Tavakol et al., 2021; Yuan et al., 2021; Tret'yakov et al., 2020; Sallis et al., 2021; Lee et al., 2021; Hamer et al., 2020; Maltagliati et al., 2021; Latorre-Román et al., 2021; Malisoux et al., 2022; Ekblom-Bak et al., 2021; Baynouna AlKetbi et al., 2021; Rowlands et al., 2021; Salgado-Aranda et al., 2021; Pinto et al., 2021). Variations in PA or exercise intervention were observed across the 18 studies. Fourteen studies involved PA. In 1 of these 14 studies, one group of participants performed inconsistent activity for between 11 and 149 min/wk, while another group undertook

TABLE 1 Characteristics of the included studies.

Author (year)	Characteristics						
	Setting	Study design	Sample size	Age	Interventions	Comparison	Outcome measure
Halabchi et al. (2021)	Iran	Cross-sectional study	4694	Mean (SD) 42.31 (11.9)	Regular sport (athletes) (Fitness and bodybuilding = 47.8%; Team sport = 16.5%; Combat sports = 19.7%; Individual sports = 16.1%)	Without regular sport (nonathletes)	Death
Sallis et al. (2021)	The United States of America	Cohort study (Retrospective observational study)	48439	Mean (SD) 47.5 (16.97)	Inconsistency active (11–149 min/week) Consistency active (>150 min/week)	Consistency inactive	Death, Severity
Cho et al. (2021)	Korea	Cohort study (Retrospective, nationwide study)	6288	Mean (SD) 50.7 (14.3)	Physical activity moderate to vigorous (using questionnaire comprised three parameters to determine frequency, intensity and metabolic equivalent of task)	Physically inactive	Death
Tavakol et al. (2021)	Iran	Cross-sectional study	206	Mean (SD) 40.9 (11.6)	Moderate to high physical activity level (according by global physical activity questionnaire)	low physical activity level	Severity (Based on the result of symptoms, clinical examinations, and chest radiology) according to clinical classification of COVID-19 released by National Health Commission of China
Tret'yakov et al. (2020)	Russia	Cross-sectional study	298	Median (IQR) 54.5 (44–65	Aerobic exercise during previous 12 months (e.g., running, stationary bike exercise)	Without regular aerobic exercise	Severity
Yuan et al. (2021)	China	Cross-sectional study	164	Mean (SD) 61.8 (13.6)	Based on exercise Vital sign evaluation method (>150 min/week of moderate activity)	Inactivity (<150 min/week of moderate activity or <75 min/week of vigorous activity)	Death, Severity (fever or respiratory infection, plus one of: respiratory rate >30 breaths/min; severe respiratory distress; peripheral capillary oxygen saturation, 93%)
Lee et al. (2021)	South Korea	Cohort study	76395	Not mention	Muscular strengthening >2 times/week or/and Aerobic physical activity. 150 min/week of moderate intensity or >75 min/week of vigorous intensity activity	Insufficient muscle strengthening activity (<2 times/week) and Insufficient aerobic physical activity (<150 min/week of moderate intensity activity, <75 min/week of vigorous intensity activity and less than an equivalent combination)	Death, Severity
Hamrouni et al. (2021)	The United Kingdom	Cohort study	259397	Median (IQR) Individual who did not covid -19; 68 (61–74) and individual did covid-19; 76 (72–78)	High and moderate physical activity level based on International Physical Activity Questionnaire (IPQA)	Low physical activity level based on IPQA	Death

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of the included studies.

Author (year)	Characteristics						
	Setting	Study design	Sample size	Age	Interventions	Comparison	Outcome measure
Ahmadi et al. (2021)	The United Kingdom	Cohort study	468569	Minimum-maximum 40–69	Sufficient physical activity using IPAQ-short form (reported by MET-min/week	Sedentary behavior (low, moderate, high)	Death
Hamer et al. (2020)	The United Kingdom	Cohort study	387109	Mean (SD) 56.2 (8.0)	Sufficient physical activity using IPAQ-short form	Sufficient physical activity	Severity (hospital admission)
Ekblom-bak et al. (2021)	Sweden	Case-control study	279455	Mean (SD) 49.9 (10.7)	Exercise habits (1–2 or >3 times/week)	Exercise habits (never or irregular)	Death, Severity (hospital admission, admission to ICU)
Baynouna Alketbi et al. (2021)	Abu Dhabi (The united Arab Emirates)	a mix retrospective cohort study and case-control study	641	Not mention	Physical activity (times per week)		Death, Severity (ICU admission)
Maltagliati et al. (2021)	European countries	Cohort study	3139	Mean (SD) 69.3 (8.5)	Vigorous physical activity	Low to moderate physical activity	Severity (COVID-19 hospitalization)
Latorre-Roman et al. (2021)	Spain	Cross-sectional study	420	Median (IQR) 33 (20–54)	Moderate physical activity	None physical activity	Severity
Malisoux et al. (2022)	Denmark	Cohort study	452	Median (IQR) 42 (31–51)	Physical active (MET-hour/week)	Sedentary behavior	Severity
Rowlands et al. (2021)	The United Kingdom	Cohort study	82,253	Minimum-maximum 63–68	Moderate to vigorous physical activity (MVPA)		Severity
Salgado-Aranda et al. (2021)	Spain	Cohort study	552	Not mention	Adequate regular exercise (MVPA)	Sedentary or light physical activity	Severity
Pinto et al. (2021)	Brazil	Cohort study	209	Mean (SD) 54.9 (14.5)	Physical activity level consists of 3 sections (work, sport, and leisure-time activity) using the Baecke questionnaire		Severity and death

consistent PA for at least 150 min/wk (Sallis et al., 2021). The participants in the 13 other studies engaged in a moderate to high PA level (Hamer et al., 2020; Ahmadi et al., 2021; Baynouna AlKetbi et al., 2021; Cho et al., 2021; Ekblom-Bak et al., 2021; Hamrouni et al., 2021; Latorre-Román et al., 2021; Maltagliati et al., 2021; Pinto et al., 2021; Rowlands et al., 2021; Salgado-Aranda et al., 2021; Tavakol et al., 2021; Malisoux et al., 2022). As for the type of PA, one study reported regular sports, including bodybuilding, team sports, combat sports, and individual sports (Halabchi et al., 2021). However, only three studies showed exercise intervention, including aerobic and muscle strengthening (Yuan et al., 2021; Tret'yakov et al., 2020; Lee et al., 2021).

Quality assessment

According to the NOS, all studies were rated between 7 and 10 stars. Therefore, all studies were high quality (Table 2). However, the incomplete comparability data in six studies were inadequately explained and not appropriately addressed.

Effect of physical activity on severity and mortality

A pooled OR model was used to evaluate two sets of studies. One set investigated the effects of PA on mortality, and the other set explored PA's impact on the severity of illness in COVID-19 patients (Figure 2).

Regarding the mortality outcome, 10 studies were meta-analyzed (Ahmadi et al., 2021; Cho et al., 2021; Ekblom-Bak et al., 2021; Halabchi et al., 2021; Hamrouni et al., 2021; Lee et al., 2021; Pinto et al., 2021; Salgado-Aranda et al., 2021; Sallis et al., 2021; Yuan et al., 2021). Significant heterogeneity was found among these articles (I^2 = 85%; p < 0.001). The effects shown as pooled ORs suggested that PA significantly reduced the risk of death in COVID-19 patients compared with PiA (OR 0.34; 95% CI, 0.19–0.62; p < 0.001) (Figure 2). A

TABLE 2 Assessment of quality using the Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			Score
	1	2	3	4	1	1	2	3	
Cross-sectional study									
Halabchi et al. (2021)	*	*	*	**	*	**	*	-	9
Tavakol et al. (2021)	*	*	*	**	**	**	*	-	10
Tret'yakov et al. (2020)	*	*	*	**	*	**	*	-	9
Yuan et al. (2021)	*	*	*	**	**	**	*	-	10
Latorre-Roman et al. (2021)	*		*	**	**	**	*	-	9
Cohort study									
Sallis et al. (2021)	*	*	*	*	**	*	*	*	9
Cho et al. (2021)	*	*	*	*	**	*	*	*	9
Lee et al. (2021)	*	*	*	*	**	*	*	*	9
Hamrouni et al. (2021)	*	*	*	*	**	*	*	*	9
Ahmadi et al. (2021)	*	*	*	*	*	*	*	*	8
Hamer et al. (2020)	*	*	*	*	*	*	*	*	8
Maltagliati et al. (2021)	*	*	*	*	**	*	*	*	9
Salgado-Aranda et al. (2021)	*	*	*	*	*	*	*	*	8
Malisoux et al. (2022)	*	*	*		*	*	*	*	7
Rowlands et al. (2021)	*	*	*	*	**	*	*	*	9
Pinto et al. (2021)	*	*	*	*	*	*	*	*	8
Baynouna Alketbi et al. (2021)	*	*	*	*	**	*	*	*	9
Case control study									
Ekblom-bak et al. (2021)	*	*	*	*	**	*	*	*	9

statistical study of the publication bias showed no obvious bias or significant difference in the publications, which was confirmed by a funnel plot (Supplementary Figure S1). The evidence of Egger's test for bias showed $p = 0.083$ (Supplementary Figure S2).

As for the severity outcome, 14 studies estimated the effects of PA on the severity of disease in patients with COVID-19 (Halabchi et al., 2021; Tavakol et al., 2021; Yuan et al., 2021; Tret'yakov et al., 2020; Sallis et al., 2021; Lee et al., 2021; Hamer et al., 2020; Maltagliati et al., 2021; Latorre-Román et al., 2021; Malisoux et al., 2022; Ekblom-Bak et al., 2021; Baynouna AlKetbi et al., 2021; Rowlands et al., 2021; Pinto et al., 2021). Significant heterogeneity was observed among these articles ($I^2 = 86\%$; $p < 0.001$). The overall effects of the pooled ORs demonstrated a significantly decreased risk of severe disease in COVID-19 patients with PA compared with PiA (OR 0.60; 95% CI, 0.48–0.76; $p < 0.001$) (Figure 2). As assessed by the funnel plot (Supplementary Figure S1), there was no apparent systematic bias (Egger's test for bias: $p = 0.472$; Supplementary Figure S2).

Assessment of quality of evidence

The quality of evidence of the observational studies included in the meta-analysis is determined in Table 3. For each outcome, the observational studies were rated very low on the GRADE scale. Since the included studies were noted to have high heterogeneity, we decided to rate down for the inconsistency. The interventions were delivered in different activities among these studies. Thus, we downgraded the rating of indirectness.

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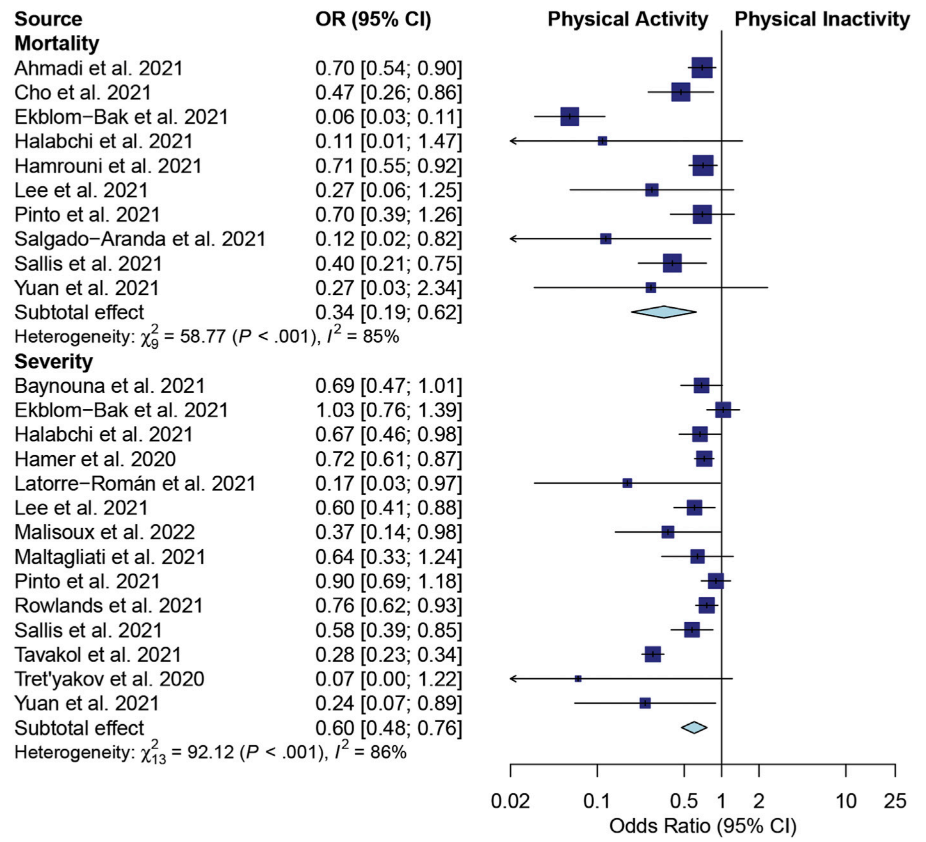

FIGURE 2
A forest plot of the association between physical activity and mortality and severity in COVID-19 patients.

TABLE 3 The quality of evidence of the observational studies included for meta-analysis.

Outcome	Quality assessment							Odds ratio (95% CI)	Quality
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Mortality	10	Observational studies	Not serious[a]	Serious[b]	Serious[c]	Not serious[d]	None[e]	0.34 (0.19–0.62)	⊕ O O O Very low
Severity	14	Observational studies	Not serious[a]	Serious[b]	Serious[c]	Not serious[d]	None[e]	0.60 (0.48–0.76)	⊕ O O O Very low

[a]Studies were low risk of bias; Newcastle-Ottawa Scale ≥7.
[b]Inconsistency explained by I^2 value as more 75%; high heterogeneity; serious.
[c]The interventions were delivered in different activity among these studies.
[d]The confidence interval includes benefit from intervention.
[e]Publication bias is not likely.

Sensitivity and subgroup analyses

A sensitivity analysis was undertaken to investigate the robustness of the effect estimates. The different models (fixed-effects and random-effects) did not significantly modify the pooled ORs for all outcomes. However, as there were studies on PA at different intensity levels, we performed a subgroup analysis by moderate and high/vigorous intensity. Moreover,

TABLE 4 Subgroup analyses of the included studies.

Subgroup analysis by	Number of study	OR (95%CI)	Heterogeneity I^2 (p-value)	Z (p-value)	List of studies
Mortality					
Moderate to high/vigorous PA	2	0.28 (-0.06–0.63)	44.4% (0.180)	1.84 (0.066)	Cho et al. (2021) Salgado-Aranda et al. (2021)
High/vigorous PA	2	0.57 (0.25–0.89)	36.4% (0.210)	2.43 (0.015)	Cho et al. (2021) Hamrouni et al. (2021)
Sufficient PA	3	0.56 (0.31–0.81)	37.2% (0.204)	2.50 (0.012)	Sallis et al. (2021) Ahmadi et al. (2021) Yuan et al. (2021)
Severity					
Moderate to high/vigorous PA	5	0.54 (0.21–0.87)	94.3% (<0.001)	2.10 (0.036)	Latorre-Román et al. (2021) Ekblom-Bak et al. (2021) Rowlands et al. (2021) Tavakol et al. (2021) Malisoux et al. (2022)
Sufficient PA	5	0.45 (0.21–0.70)	52.9% (0.075)	2.90 (0.004)	Hamer et al. (2020) Tret'yakov et al. (2020) Yuan et al. (2021) Latorre-Román et al. (2021) Sallis et al. (2021)

"Sufficient PA" is defined as the performance of PA for ≥150 min/wk of moderate activity or ≥75 min/wk of vigorous activity. Abbreviations: CI, confidence interval; OR, odds ratio; PA, physical activity.

some studies identified a sufficient PA level as a PA of ≥150 min/wk of moderate activity or ≥75 min/wk of vigorous activity (Table 4). A subgroup analysis was therefore performed by using sufficient PA. The results showed that PA for ≥150 min/wk at a moderate intensity or ≥75 min/wk at a vigorous intensity reduced the risks of severity and mortality. High or vigorous PA levels reduced the mortality risk, whereas moderate to high/vigorous PA reduced the risks of severity and mortality in COVID-19 patients.

Discussion

This systematic review and meta-analysis revealed an association between regular PA and severity and mortality in COVID-19 patients. We included adjusted ORs that considered confounding factors possibly related to the outcomes. The major finding was that regular PA reduced patients' risks of severity and mortality.

SARS-CoV-2 enters the host cell *via* the angiotensin-converting enzyme (ACE) two receptor. The targeted cells, especially lung parenchyma, have an off-balance between the ACE2/Ang (1–7)/Mas axis and ACE/AngII/AT1R axis that aggravates tissue injury (Yan et al., 2020). Previous studies reported that treatments with ACE inhibitors and angiotensin II receptor blockers were associated with a lower risk of death in COVID-19 patients (Kai and Kai, 2020; Yan et al., 2020; Zhang et al., 2020). Tavakol et al. (2021) reported a reverse correlation between increased PA and COVID-19 disease severity. Our study found a significantly lower risk of mortality with high levels of PA than with PiA. Moderate to high intensity tended to reduce the risk. Cho et al. (2021) reported that dose-dependent exercise reduced infection risk and mortality in COVID-19 patients. They found that vigorous and moderate intensities of exercise training (>1000 metabolic equivalent of task (MET)-min/wk) could reduce the risk of COVID-19 infection and mortality (Cho et al., 2021).

However, excessive exercise has been reported to increase the risk of respiratory infection. Long-term hyperventilation in untrained subjects may involve physical damage to bronchial and alveolar epithelial cells (Nieman, 2000; Murphy et al., 2008). The soluble ACE2 (sACE2) and the transmembrane ACE2 (tACE2) competitively bind with the SARS-CoV-2 virus. Therefore, the probability of a virus entering the targeted cells may be reduced (Yan et al., 2020). However, COVID-19 severity has an opposite response to moderate- and high-intensity exercise. Moderate-intensity exercise increases sACE2, whereas high-intensity exercise increases tACE2 (Hagiu, 2021). Our study found a reduced severity risk in patients who previously had sufficient PA (≥150 min/wk of moderate activity or ≥75 min/wk of vigorous activity) or moderate to high-intensity PA.

Regular exercise can improve the systemic immune response and reduce infection. The ratio of natural killer (NK) cells is modified, and changes in T helper cell expression and function due to exercise may improve the body's resistance to respiratory infections (Timmons and Cieslak, 2008; Nieman and Wentz, 2019). Moderate exercise increases NK-cell activity (Nieman et al., 1990; Nieman, 2000). In addition, T helper (Th) cells (Th1 and Th2) and T-cell function in the upper respiratory tract mucosa are improved (Timmons and Cieslak, 2008; Nieman and Wentz, 2019). Moreover, McFarlin et al. (2005) reported that exercise training improves NK-cell activity. PA might reduce the cytokine storm following infection with SARS-CoV-2. Regular PA or exercise facilitates the release of anti-inflammatory myokines (Marino et al., 2022); reduces chemokines, pro-inflammatory cytokines, and the pathogen load (Lowder et al., 2006; Sim et al., 2009; Warren et al., 2015); and promotes the balance of pro- and anti-inflammatory cytokines *via* renin-angiotensin system (RAS) modulation (Agarwal et al., 2011). Increased vagal tone resulting from high levels of PA also reduces pro-inflammatory cytokines (Tracey, 2009). In addition, aerobic exercise training decreases tissue inflammation by increasing antioxidant enzyme levels (superoxide dismutase and glutathione peroxidase) and mitochondrial biogenesis (Toledo et al., 2012).

COVID-19 patients had changes in the alveolar-capillary membrane (ACM) (Yan et al., 2020), resulting in an impairment of the diffusion capacity of the lungs (Yan et al., 2020). Aerobic exercise training improves the diffusing capacity for carbon monoxide during resting and exercise by modifying the ACM. Enhancing the density and affinity of adrenoreceptors in respiratory muscles through aerobic exercise may improve respiratory muscle function, bronchodilation, and airway secretion production, thereby improving lung function (Tret'yakov et al., 2020). The more preserved lung function and the sparing use of respiratory regulatory elements during stress increase the ability to mobilize efficiently when needed.

A strategy for COVID-19 treatment may be attenuating the risk of comorbidities associated with severity and mortality, such as obesity, diabetes mellitus, stroke, and coronary artery disease. Regular exercise increases maximal oxygen uptake, shifting high-risk patients into low-risk patients (Ahmed, 2020). The metabolic dysfunction, impaired immune response, and increased adipose-tissue inflammatory cytokine secretion associated with obesity can increase the risk of severe pneumonia in COVID-19 patients (Cai et al., 2020; Popkin et al., 2020). Aerobic exercise improves metabolic function and the immune response and decreases obesity, especially central obesity. Disruptions of the ACM in the lung tissues of obese and diabetic patients were observed (Foster et al., 2010). The increased thickness and lowered elasticity of the ACM impaired the diffusion capacity of the lungs (Foster et al., 2010). Reducing the risk factors associated with COVID-19 infection and severity may reduce mortality.

This study has several strengths. First, the systematic review and meta-analysis followed a standard protocol (Page et al., 2021). Second, the included studies were of high quality, denoted by their high NOS scores for quality assessment. Third, the included factors' adjusted ORs are likely to be involved in the severity and mortality of infection in COVID-19 patients, for example, demographic variables, comorbidities, medical history, smoking status, and alcohol consumption.

There are some limitations to this study. First, it included only retrospective, cross-sectional, case-control, and nonrandomized controlled trials. Because COVID-19 is a newly emerging disease, studying the effects of regular PA requires long-term monitoring. Moreover, using a randomized controlled trial may be ethically inappropriate. Second, severity definitions were different among studies. Some included studies did not mention, some defined patients admitted to ICU and some represented hospitalization. Third, there are different patterns of PA, and exercise training was observed. Some of the included studies failed to report full details of the PA or exercise, for example, type, intensity, frequency, and time to perform an activity. This may be the source of the high heterogeneity in severity (I^2 = 86%) and mortality (I^2 = 85.0%) found in our study.

On the other hand, the forest plots showed that the studies agreed that PA might induce less severe illness and lower mortality in COVID-19 patients than PiA. This finding implies that engaging in regular PA, even in different patterns, has beneficial effects on the severity and mortality of COVID-19 patients. More studies on the impact of regular PA or exercise training are needed to draw definitive conclusions. Finally, the levels of PA and exercise were evaluated by self-reporting questionnaires, which may not directly reflect the actual performance of the patients. Therefore, for clinical application, the results should be carefully interpreted. Nevertheless, this study provided knowledge and understanding to medical professionals about the effects of regular PA on severity and mortality in COVID-19 patients.

A previous meta-analysis from a few studies showed that low and moderate-vigorous PA lowered mortality in COVID-19 patients (Rahmati et al., 2022). However, only one study (Lee et al., 2021) was included to show the lower ICU admission. The researchers suggested that levels of PA should be recommended. A recent study of pooled ORs adjusted by confounding factors concluded that PA ≥ 150 min/wk of moderate activity or ≥75 min/wk of vigorous activity showed a reduction in severity and mortality risk in COVID-19 patients. A strategy for COVID-19 treatment has been reported to prevent infection by SARS-CoV-2. The strategy involves preventing viruses from entering the body; blocking the binding between the virus and host cells; preventing new viral replication; and improving the immune response, anti-inflammation, antioxidants, and body functions. Possible explanations for why PA and exercise training reduce severity and mortality in COVID-19 patients include improvements in the systemic immune response, inflammatory cytokines, antioxidants, and lung function. Moreover, PA may reduce viruses entering the cells and lower some risk factors (eg, obesity, diabetes mellitus, and arterial hypertension) associated with severe outcomes for COVID-19 patients. However, lockdowns and restrictions due to the COVID-19 pandemic might increase barriers to engaging in regular PA. A tele-exercise program may be a strategy for promoting PA to prevent infection and reduce the severity and mortality of illness in COVID-19 patients.

Conclusion

Regular PA can reduce the severity and mortality risk of COVID-19 patients, especially with ≥150 min/wk of moderate activity or ≥75 min/wk of vigorous activity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

NS, NP, SS, NK, KP, MP, and PP took part in designing the study, the selection process, and the writing of the first manuscript draft; NS, NP, SS, and MP took part in designing the study; NS, NP, SS, SK, NK, KP, and MP took part in the selection process and statistical analyses; NS, NP, NK, KP, MP, and PP wrote sections of the manuscript; all authors read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.1030568/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Assessing publication bias by funnel plot: **(A)** effects of physical activity on mortality; **(B)** effects of physical activity on severity.

SUPPLEMENTARY FIGURE S2
Assessing publication bias by Egger's test: **(A)** effects of physical activity on mortality; **(B)** effects of physical activity on severity. Abbreviations: CI, confidence interval; SND, standard.

SUPPLEMENTARY TABLE S1
Data search algorithm.

SUPPLEMENTARY TABLE S2
Excluded studies after assessment for eligibility.

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A tale of two stories: COVID-19 and disability. A critical scoping review of the literature on the effects of the pandemic among athletes with disabilities and para-athletes

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The still ongoing COVID-19 pandemic has dramatically impacted athletes, and, in particular, para-athletes and athletes with disabilities. However, there is no scholarly appraisal on this topic. Therefore, a critical scoping review of the literature was conducted. We were able to retrieve sixteen relevant studies. The sample size ranged from 4 to 183. Most studies were observational, cross-sectional, and questionnaire-based surveys, two studies were interventional, and two were longitudinal. One study was a technical feasibility study. Almost all studies were conducted as single-country studies, with the exception of one multi-country investigation. Five major topics/themes could be identified: namely, 1) impact of COVID-19-induced confinement on training and lifestyles in athletes with disabilities/para-athletes; 2) impact of COVID-19-induced confinement on mental health in athletes with disabilities/para-athletes; 3) impact of COVID-19-induced confinement on performance outcomes in athletes with disabilities/para-athletes; 4) risk of contracting COVID-19 among athletes with disabilities/para-athletes; and, finally, 5) impact of COVID-19 infection on athletes with disabilities/para-athletes. The scholarly literature assessed was highly heterogeneous, with contrasting findings, and various methodological limitations. Based on our considerations, we recommend that standardized, reliable tools should be utilized and new, specific questionnaires should be created, tested for reliability, and validated. High-quality, multi-center, cross-countries, longitudinal surveys should be conducted to overcome current shortcomings. Involving all relevant actors and stakeholders, including various national and international Paralympic Committees, as a few studies have done, is fundamental: community-led, participatory research can help identify gaps in the current knowledge about sports-related practices among the population of athletes with disabilities during an unprecedented period of measures undertaken that have significantly affected everyday life. Moreover, this could advance the field, by capturing the needs of para-athletes and athletes with disabilities and enabling the design of a truly "disability-inclusive response" to COVID-19 and similar future conditions/situations. Furthermore, follow-up studies on COVID-19-infected para-athletes and athletes with disabilities should be conducted. Evidence of long-term effects of COVID-19 is available only for able-bodied athletes, for whom cardiorespiratory residual alterations and mental health issues a long time after COVID-19 have been described.

KEYWORDS

COVID-19, para athletes, disability in sport, scoping review, critical review, research methodology

Introduction

The still ongoing "Coronavirus Disease 2019" (COVID-19) outbreak, caused by an emerging infectious agent, termed "Severe Acute Respiratory Syndrome Coronavirus type 2" (SARS-CoV-2) (Sharma et al., 2021), has been affecting more than 200 countries since early 2020. Initially declared by the World Health Organization (WHO) a "Public Health Emergency of International Concern" (PHEIC), at the end of January 2020, and, subsequently, a pandemic, it has significantly overwhelmed healthcare infrastructure worldwide (Singhal, 2020; Bernacki et al., 2021). Given the initial lack of availability of effective drugs and vaccines, in order to control and contain the pandemic, governments and authorities have had to implement a package of public health interventions, such as social/physical distancing, hygiene/sanitation protocols (hand washing, use of masks and other personal protective equipment, PPE, devices), and self-isolation (safer-at-home, stay-at-home, shelter-in-place, quarantine, and even lockdown), collectively known as non-pharmaceutical interventions (NPIs), the stringency of which has significantly varied across the world (Perra, 2021). In some countries (such as Italy), NPIs have included the ban of any kind of inter-household mingling and/or outdoor activities, including sports and physical activity. In contrast, in other countries (like the United Kingdom, Germany, or Poland), certain types of activities were allowed. Other countries, like Sweden, have, instead, avoided the implementation of stringent protocols and have only recommended precautionary measures (Seale et al., 2020; Urbański et al., 2021).

All this has dramatically impacted the physical level of entire populations, especially affecting socially vulnerable communities, such as populations with disabilities (Jesus et al., 2020; Jesus et al., 2021a; Jesus et al., 2021b; Kamalakannan et al., 2021), who presented greater infection risks due to multiple, intersecting mediators (i.e., lack of accessible evidence-based information, structural barriers, difficulties in complying with COVID-19 induced restrictions, institutional ableism in health care and unethical disadvantages in the rationing of the delivery of lifesaving and critical care provisions), as well as psychological distress and trauma (due to the fear of COVID-19, isolation, loneliness, deaths and illnesses of loved ones and community members, retaliation, and interpersonal violence, among others) (Jesus et al., 2020; Lund, 2020; Lund et al., 2020; Jesus et al., 2021a; Jesus et al., 2021b; Kamalakannan et al., 2021; Goddard et al., 2022).

On the one hand, physical activity and exercise could counteract or, at least partially, mitigate against this burden (Chtourou et al., 2020; Ghram et al., 2021), especially in people living with disabilities. An accumulating body of evidence has, indeed, shown that regularly practicing sports can promote rehabilitation, and improve physical and mental health and wellbeing, resulting in better self-confidence, self-esteem, psychological balance, self-acceptance, social inclusion, and integration, as well as enhanced quality of life (Puce et al., 2017; Puce et al., 2019; Brancher et al., 2021). On the other hand, COVID-19 has affected the sports world as well, disrupting the training and preparation of athletes, causing, in some cases, reduced opportunities to access gyms, fitness centers, and other sports infrastructure, and resulting in confinement-induced detraining in several cardio-pulmonary (i.e., cardiac output, VO_{2max}, maximal stroke volume, and artero-venous O_2 difference) and musculoskeletal (muscle mass, strength, and power) variables (Cavaggioni et al., 2022). Moreover, access to high-quality food, which is of paramount importance for elite athletes, has been particularly challenging, with many athletes experiencing "food insecurity" (Roberts et al., 2020; Abbey et al., 2022). Furthermore, athletes have had to cope with an unprecedented situation, characterized by the loss of daily routine (consisting of scheduled training appointments, and matches), and the postponement or even cancellation of major national and international sports events (like national championships and the Tokyo 2020 Olympic and Paralympic Games), with subsequent career and financial insecurity (Håkansson et al., 2020; Dehghansai et al., 2021; Busch et al., 2022). All this uncertainty, along with the necessity to set new goals, has contributed to psychological distress and feelings of depression and anxiety (Busch et al., 2022).

If the impact of COVID-19 on athletes has been investigated (Clemente-Suárez et al., 2020; Tomovic and Krzman, 2020; Harangi-Rákos et al., 2022; Romdhani et al., 2022), there is a dearth of data concerning the effects of the pandemic on para-athletes and athletes with disabilities. Therefore, to fill in this gap in knowledge, we carried out the present scoping review.

Material and methods

Study design choice and strategy

Given the breadth (rather than the width) of our research questions and the complex, intersectional nature of our study (situated at the intersection of sport, disability, and COVID-19), we opted for a scoping review (rather than for a systematic review). A scoping review represents an emerging technique for synthesizing the existing scholarly literature on a given topic (Moher et al., 2015; Khalil and Tricco, 2022; Munn et al., 2022). Scoping studies or scoping reviews "aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available, and can be undertaken as stand-alone projects in their own right, especially where an area is complex or has not been reviewed comprehensively before" (Arksey and O'Malley, 2005). We leveraged Arksey and O'Malley (2005), Levac et al. (2010), Colquhoun et al. (2014), Peters et al. (2015), and Tricco et al. (2016) working definitions and frameworks of scoping reviews. In particular, Arksey and O'Malley (2005) recommend a six-stage approach. The steps and the iterative processes followed and implemented in the present scoping study are briefly overviewed in the following sub-sections.

Stage 1: Identification of the research question(s) and team building and development

The "population/participants-concepts-context" (PCC) mnemonic was utilized to generate a preliminary search strategy, ensuring both breadth and relevance of coverage, as recommended by the Joanna Briggs Institute for scoping reviews (2015). "Population/participants" were para-athletes and athletes with disabilities, the main "concept" was the impact of COVID-19 on this specific population; and, the "context" was worldwide (we did not restrain our search to a particular territory/geographic location).

More precisely, concerning the population of our study, we note that terms, such as "adapted sport," "disability sport," "Paralympic sport," and "Para sport," are words commonly used in an interchangeable fashion to indicate sports disciplines that accommodate people with any kind of disability, including physical/motor, sensory and intellectual/relational/developmental disabilities, practicing sports as a recreational physical activity or participating in organized competitions (Brancher et al., 2021). On the other hand, "Paralympic sport" is often utilized as a term to specifically describe sports disciplines that compete in Paralympic events, such as the Paralympic Games (Brittain, 2016; Townsend et al., 2018), organized under the auspices of the "International Paralympic Committee" (IPC), the global governing body responsible for the development of Para sport and, more generally speaking, a more socially just and inclusive sports world.

After rapidly scanning and familiarizing ourselves with the existing scholarly literature, we were able to specify and formulate our research questions: "What is the impact of the still ongoing COVID-19 pandemic on para-athletes and athletes with disabilities, in terms of health risks of contracting the virus and developing the infection, and disruptive effects, if any, posed by COVID-19 on training and performance outcomes, physical and mental health and well-being? Which strategies can be adopted and implemented to protect para-athletes and athletes with disabilities against the health risks imposed by COVID-19? Which interventions can be applied to counteract/minimize the effects of detraining and optimize training protocols and conditioning programs among para-athletes and athletes with disabilities?".

Then, we assembled our interdisciplinary team. Given the complex, intersectional nature of the topic and the different competencies and skills required, our team consisted of specialists from different disciplines: public and global health, epidemiology, biostatistics and research methodology, infectious diseases, microbiology, and, in particular, virology, sports sciences, orthopedics, sports and exercise medicine, rehabilitation medicine, and physical therapy.

Subsequently, a team leader was identified and formally designated. Given *their* multidisciplinary skills, NLB were indicated as the team coordinator: NLB are a queer, gender-diverse scientist and medical doctor, with a specialization in public health, epidemiology, and biostatistics, and are strongly

TABLE 1 Search strategy adopted in the present review.

Search strategy item	Details
Databases searched	PubMed/MEDLINE, Scopus
Keywords	(SARS-CoV-2 OR COVID-19 OR "novel emerging coronavirus") AND ("disabled athletes" OR "athletes with disabilities" OR "para-athletes" OR "paralympic" OR "wheelchair sport" OR "amputee athletes" OR "athletes with limb deficiency" OR "athletes with visual impairment" OR "athletes with sensory impairment" OR "athletes with motor impairment" OR "athletes with cerebral palsy" OR "athletes with spinal cord injury" OR "disabled players" OR "players with disabilities" OR "players with cerebral palsy")
Inclusion criteria	P: athletes with disabilities/para-athletes E: potentially exposed to the novel emerging coronavirus C: among different para-sport disciplines; against the general population O: the risk of contracting the virus; the impact of the pandemic on training, mental health S: any study design (quantitative, qualitative, retrospective, prospective; cross-sectional, longitudinal; observational, interventional)
Exclusion criteria	P: people with disabilities practicing sports and physical activities E: non-potentially exposed to SARS-CoV-2 O: any other outcome
Time filter	Since the inception of the infectious outbreak
Language restriction	None applied
Hand-searched target journals	Disabil Health J; Front Sports Act Living; Int J Environ Res Public Health; J Sports Med Phys Fitness

passionate about equity, diversity, and inclusion (EDI) principles. NLB also act as the main contact author/corresponding author of the present study.

We devised an *a priori* protocol, as recommended. This can be accessed upon written request to the corresponding author.

Stage 2: Identification of relevant literature and literature search strategy

Two major scholarly electronic databases were consulted: namely, MEDLINE (accessed *via* PubMed's freely available interface) and Scopus (Elsevier). They were mined since the inception of the infectious outbreak, with no language restrictions. The search string consisted of two major components: para-athletes/athletes with disabilities and COVID-19, with synonyms/variants properly linked by using Boolean operators. "Medical subject headings" (MeSH) terms and wild-card (truncated words) options were used when appropriate. The full search string is reported in Table 1. Extensive cross-referencing was applied: reference lists of eligible studies were scanned for getting further relevant articles not returned by the keyword-based search. This was done iteratively until "search saturation", that is to say, no new relevant articles could be found. Existing reviews on similar or related topics, if existing (Alcaraz-Rodríguez et al., 2021), were scanned to increase the chance of including all relevant studies. Further, specific target journals were hand-searched for relevant studies. Finally, also gray literature was consulted, by mining the "Directory of Open Access Journals" (DOAJ) and Google Scholar.

Stage 3: Selection of the studies

Studies were selected for inclusion based on pre-specified inclusion and exclusion criteria, which were devised and formulated based both on the PCC mnemonic and the "population/participants-intervention-comparator/comparison-outcome-study design" (PICOS)/"population/participants-exposure-comparator/comparison-outcome-study design" (PECOS) components.

Studies were included if focusing on a population of para-athletes/athletes with disabilities (P), potentially exposed to the novel emerging coronavirus (E), or observing the COVID-19 restrictions (practicing social/physical distancing, quarantine, wearing masks, etc.) and/or undergoing personalized, adapted/modified training protocols during the pandemic (I). Studies could be included if comparing different para-sport disciplines; against the general population, and/or able-bodied athletes. Other comparisons of interest included sex/gender- and age-specific comparisons (C). Outcomes of interest were the quantification of the risk of contracting the virus; the rate of infection among para-athletes/athletes with disabilities; the impact of the pandemic on lifestyles, training, and performance outcomes, and physical and mental health/well-being (O). Any study design was eligible for inclusion: retrospective, prospective, questionnaire- or test-based, quantitative, qualitative, or mixed-method studies (S).

Stage 4: Mapping out the data, data charting, and extraction

An Excel spreadsheet contained information on how and which relevant data to extract. Then, we utilized the "Research Electronic Data Capture" (REDCap) software to store the retrieved articles (both deemed eligible for inclusion and those finally included in the present scoping review) and assist/facilitate data extraction. REDCap is a secure, web-based platform that efficiently supports and enhances data capture for research purposes (Westphaln et al., 2021). Moreover, since our team is highly multidisciplinary and diverse, REDCap allows the inclusion of multiple users within projects. Further, it can accommodate multiple types of data, which, in our case, were rather heterogeneous. It provides audit trails and quality checks for tracking and monitoring data manipulation and exportation. Also, REDCap supports and facilitates data exportation into many types of statistical software for their further processing and analysis (Westphaln et al., 2021). These functions allow REDCap to properly accommodate all the processes of full-text review and data extraction/manipulation for large and diverse research teams.

Data extraction quality was checked by computing the pooled kappa statistics as a quantitative measure of the inter-rater reliability/agreement, as recommended by Tricco et al. (2015).

Stage 5: Data collating, summary, synthesis, and reporting

Data extracted were tabulated and synthesized in a narrative fashion. Major topics/themes were identified by means of thematic analysis and overviewed qualitatively. Furthermore, we followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) extension for scoping reviews (PRISMA-Scr) (Tricco et al., 2018).

Stage 6: Expert consultation/"consultation exercise"

Our team identified experts on the topic of sports and disability, as well as on the topic of COVID-19. For this, we used cues from the identified literature, as well as cues from electronic databases (such as Scopus) which enable the visualization of a list of the top-cited and most productive scholars on a given topic. Some of these experts were consulted during the preparation of the manuscript to provide critical feedback on our work.

Quality assessment

A thorough, formal quality appraisal was not conducted given that is not a mandatory component of scoping reviews, while an informal assessment was carried out, by noting down the methodological limitations of each study and providing an overall qualitative synthesis of the shortcomings. This rapid, informal assessment was instrumental to the recommendations we were able to formulate.

Results

Outcomes of the literature search strategy

The initial literature search yielded a pool of 123 items, by searching PubMed/MEDLINE and Scopus. After removing duplicates, seventy items were examined and 54 items were further discarded based on title and/or abstract. Sixteen studies were considered potentially eligible and were read in full text. Two studies were subsequently discarded with reason: one because it did not contain any original data concerning para-athletes (Håkansson et al., 2020), and one because the population did not meet inclusion criteria (people with disabilities, but not athletes with disabilities) (Kamyuka et al., 2020). Subsequently, fourteen articles were retained in the present scoping review. Two further studies were retrieved by searching Google Scholar. The final number of included studies was sixteen. Their major characteristics and findings are summarized in Table 2, to which the reader is referred.

Features of studies included

The sample size ranged from 4 to 183. Most studies were observational, cross-sectional, and questionnaire-based surveys, two studies were interventional (Cavaggioni et al., 2022; Peña-González et al., 2022), two were longitudinal (Busch et al., 2022; Cavaggioni et al., 2022). One study was a technical feasibility study (Muti et al., 2022). Almost all studies were conducted as single-country studies, with the exception of the multi-country investigation by Shaw et al. (2021). Five major topics/themes could be identified: namely, 1) impact of COVID-19-induced confinement on training and lifestyles in para-athletes/athletes with disabilities; 2) impact of COVID-19-induced confinement on mental health in para-athletes/athletes with disabilities; 3) impact of COVID-19-induced confinement on performance outcomes in para-athletes/athletes with disabilities; 4) risk of contracting COVID-19 among para-athletes/athletes with disabilities; and, finally, 5) impact of COVID-19 infection on para-athletes/athletes with disabilities.

Impact of COVID-19-induced confinement on training and lifestyles in para-athletes/athletes with disabilities

Six studies (Shaw et al., 2021; Urbański et al., 2021; Cavaggioni et al., 2022; Peña-González et al., 2022; Schipman et al., 2022; Trigo et al., 2022) have assessed the impact of COVID-19 on training and lifestyles in para-athletes/athletes with disabilities. Shaw et al. (2021) conducted a survey concerning the impact of the pandemic on diet, fitness, and sedentary behaviors in a sample of 25 elite national and international (from Canada, the United Kinggdom, Australia, United States, South Africa, and Belgium) para cyclists and para triathletes recruited in the period from early May to mid-June 2020.15 were females, and 10 were males. Age ranged from 21 to 60 years. Ramp exercise test duration varied significantly between pre- (27.3 ± 5.8 min) and post-pandemic (28.0 ± 6.4), suggesting an improving trend, but no effects in terms of average and maximum power, as well as average and maximum heart rate, could be found. The authors concluded that, overall, COVID-19 did not impact the training volume or intensity or the

TABLE 2 Main features of included studies. Abbreviations: BFPI, Big Five Personality Inventory; CAS, coronavirus anxiety; CMJ, countermovement jump; FFQ, Food Frequency Questionnaire; MAT, modified agility *t*-test; NA, not available; 1RM, one repetition maximum; PHQ-4, Patient Health Questionnaire 4; PSS, Perceived Stress Scale; RPE, rating of perceived exertion; STAI, State-Trait Anxiety Inventory; TSS, Training Stress Score.

References	Study design	Country/ countries	Study period	Sample size, sex/ gender, and mean age	Para-sport	Measures	Main findings
Busch et al. (2022)	Longitudinal study	Germany	March 2020-April 2021: eight time points (March 27 to 6 April 2020, April 24 to 4 May 2020, May 15 to 25 May 2020, June 5 to 15 June 2020, September 25 to 5 October 2020, October 23 to 2 November 2020, January 1 to 11 January 2021, and March 26 to 5 April 2021)	78; 40 F, 38 M; 29.8 ± 11.4 years	Paralympic athletes	PHQ-4	↓ PHQ-4 scores
Cavaggioni et al. (2022)	Longitudinal case series/ interventional study with a pre-post assessment	Italy	Three time points: end of February 2020 (2 weeks prior to COVID-19 lockdown), March 2020-September 2020, and 16 weeks after returning to a regular gym-training	4; 1 F, 3 M; 24.3 ± 3.8 years	Para swimmers	Upper-body muscular strength and power—1RM, mean propulsive velocity of the barbell, mean propulsive velocity close to 1RM, and mean relative propulsive power (lat pull-down and bench press exercises)	↓ muscular strength and power
Clemente-Suárez et al. (2020)	Online questionnaire-based study	Spain	From March 24 to 12 April 2020	39 (vs. 175 Olympic athletes); 31.8 ± 9.3 years	Paralympic athletes; athletics n = 8, basketball n = 6, canoe n = 1, cycling n = 4, football n = 1, judo n = 1, swimming n = 9, table tennis n = 5, taekwondo n = 1, triathlon n = 2, weightlifting n = 1	Individual perceptions about the COVID-19 crisis; psychological profile (BFPI, UCLA Loneliness Scale, Acceptance and Action Questionnaire-II, STAI)	↑ importance placed on the confinement ↑ perceived support from public institutions ↑ conscientiousness
Denerel and Lima, (2022)	Online questionnaire-based study	Turkey	Between 15 June 2021 and 15 July 2021	362 (183 with disabilities)	Athletes with disabilities	Depression, anxiety, stress, CAS, and nonspecific psychological distress	↑ higher depression, anxiety, and CAS scores

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TABLE 2 (*Continued*) Main features of included studies. Abbreviations: BFPI, Big Five Personality Inventory; CAS, coronavirus anxiety; CMJ, countermovement jump; FFQ, Food Frequency Questionnaire; MAT, modified agility *t*-test; NA, not available; 1RM, one repetition maximum; PHQ-4, Patient Health Questionnaire 4; PSS, Perceived Stress Scale; RPE, rating of perceived exertion; STAI, State-Trait Anxiety Inventory; TSS, Training Stress Score.

References	Study design	Country/ countries	Study period	Sample size, sex/ gender, and mean age	Para-sport	Measures	Main findings
Fiorilli et al. (2021)	Questionnaire-based, case-control study	Italy	From 12 March 2020, to 3 May 2020	146 (73 with disabilities, 73 able-bodied); 42.11 ± 13.70 years (with disabilities), 40.23 ± 13.73 years (able-bodied)	Athletes with disabilities (blind, 52%, with mobility impairment, 34%, such as limb amputation, and deaf, 14%)	Psychological distress	↓ subjective distress
Hu et al. (2021)	Qualitative study (in-depth, semistructured interviews)	United States	NA	29; 18 F, 11 M; 18–62 years	Thirteen different Paralympic sports (boccia, cycling, equestrian, fencing, goalball, paracanoeing, powerlifting, rugby, sitting volleyball, swimming, taekwondo, wheelchair racer, and wheelchair tennis)	Athletic identity (Disability Sport Athletic Identity)	↑ multiplicity of roles ↑ mental adaptation
Kaneda et al. (2021)	Questionnaire-based study	Japan	From 16 April to 24 May 2020	39 (20 with disabilities; 19 able-bodied); 8 F, 11 M	Para swimmers	Mental health and apathy	↑ mental health ↑ apathy
Kaneda et al. (2022)	Databased-based epidemiological survey	Japan	From August 17 to September 5 and from July 13 to August 8	NA	Paralympic athletes (*versus* Olympic athletes)	COVID-19 infection rate	↑ than able-bodied athletes
Kubosch et al. (2021)	Cross-sectional, questionnaire-based study	Germany	From May 17 to 30 August 2020	109; 57 F, 52 M; 29.2 ± 10.4 years	Paralympic athletes	Well-being Satisfaction with training Financial preoccupations	↓ well-being ↓ satisfaction with training ↑ financial preoccupations
Martínez-Patiño et al. (2021)	Questionnaire-based study	Spain	Recruitment from 2 to 22 September 2020	511 (64 with disabilities, 447 able-bodied); NA; 28.44 ± 10.50 years	Paralympic athletes from athletics, basketball, cycling, weightlifting, horse riding, judo, swimming, canoeing, taekwondo, tennis, table tennis, archery, Olympic shooting, and triathlon	Perception of threat, stress (PSS-10), state of mind, and training patterns	↑ coping with personal problems ↓ feelings of being lonely ↑ approval of confinement
Muti et al. (2022)	Technical feasibility study	Italy (Piediluco, Umbria, at the Center for preparation of the Olympic and Paralympic National Italian Rowing team; Varese, and Gavirate)	During each retreat of the Italian Paralympic rowing team and during National and International rowing competitions Each retreat lasted 7–14 days; for a total of 11 retreats Duration of the study 10 months, from November 2020 to August 2021	23 (16 athletes, 5 coaches, and 2 staff members; 12 at the follow-up); 9 F, 7 M; 18–55 years (35.38 ± 12.88 years)	Rowing para-athletes	Risk of contracting the coronavirus	No clusters of coronavirus

(Continued on following page)

TABLE 2 (*Continued*) Main features of included studies. Abbreviations: BFPI, Big Five Personality Inventory; CAS, coronavirus anxiety; CMJ, countermovement jump; FFQ, Food Frequency Questionnaire; MAT, modified agility *t*-test; NA, not available; 1RM, one repetition maximum; PHQ-4, Patient Health Questionnaire 4; PSS, Perceived Stress Scale; RPE, rating of perceived exertion; STAI, State-Trait Anxiety Inventory; TSS, Training Stress Score.

References	Study design	Country/ countries	Study period	Sample size, sex/ gender, and mean age	Para-sport	Measures	Main findings
Peña-González et al. (2022)	Interventional study with a pre-post assessment	Spain	Testing session before commencement of the lockdown and second timepoint 12 weeks after	15; 15 M; 18 [21–30] years	Football players with cerebral palsy	Fitness (free CMJ, 5-, 10-, 20-m sprint, MAT, dribbling test)	= fitness (↑ CMJ)
Schipman et al. (2022)	Case-control study	Germany	255 Paralympic events	NA	Paralympic athletes taking part in 255 Paralympic events since 2010	Performance outcomes	↓ performance outcomes
Shaw et al. (2021)	Questionnaire-based retrospective, pre-post study	Canada, United Kingdom, Australia, South Africa, Belgium	Recruitment during May-mid June 2020; four time-points (February, March, April, and May)	25; 15 F, 10 M; 21–60 years	Para-cyclists and para triathletes	Training (TSS) Caloric intake (FFQ) Fitness (ramp exercise test) Time spent engaging in sedentary screen time activities	= training volume and intensity = caloric intake = fitness (↑ duration time, = average power, = maximum power, = average heart rate, = max heart rate) ↑ sedentary behavior
Trigo et al. (2022)	Cross-sectional, questionnaire-based study	Brazil	May 2020	180; 72 F, 107 M; 33.85 ± 9.41 years	Athletes from 22 different para-sports with several types of impairment (visual impairment, intellectual impairment, limb deficiency, short stature, leg length difference, impaired muscle power, impaired passive range of movement, coordination impairment—hypertonia, ataxia, and athetosis). Para sports were divided into Individual sports (athletics, boccia, cycling, powerlifting, rowing, swimming, triathlon); individual sports with opposition (badminton, judo, Table tennis, taekwondo, wheelchair fencing, and wheelchair tennis); and team sports (football 5-a-side, goalball, sitting volleyball, wheelchair basketball, wheelchair rugby)	Hours of training, number of sessions, and RPE	↓ hours of training, number of sessions, and RPE = life satisfaction ↓ perceptions on the impact of COVID-19 on performance outcomes and career
Urbański et al. (2021)	Cross-sectional questionnaire-based study	Poland	Recruitment from May to June 2020 Questionnaire period from May 20 to 30 April 2020	166; 66 F, 100 M; 33 ± 11.7 years	Athletes with disabilities (spinal cord injury and limb amputation/ deficiency) from 15 different sports disciplines	Access to sports infrastructures and weekly training time Satisfaction with training	↓ access to infrastructure ↓ weekly training time ↓ satisfaction with training

fitness of para cyclists, also when comparing data between February and May 2020 (where the motivation levels and other psychological parameters were expected to be low). Sex- and gender-specific differences could be computed in dietary uptake concerning several parameters and macro- and micronutrients (namely, energy, carbohydrates, sugar, protein, total fat, saturated, monounsaturated, and polyunsaturated fat, folate, iron, potassium, sodium, vitamins B1, B12, B3, B6, and D, and zinc), with lower intakes in females. However, dietary uptake did not differ between pre- and post-pandemic. Furthermore, the authors found that, whereas no temporal differences could be detected concerning energy intake and exercise expenditure, the latter parameter could be decreased, due to an increase in sedentary screen time (from 4.5 ± 1.9 h per day to 6.1 ± 1.5 h per day, $p = 0.001$), leading to a net caloric imbalance, which, however, is unlikely to have any consequences in a sample of highly trained, elite athletes and, being short-lived, may quickly restore, returning to the baseline levels prior to the pandemic, once COVID-19 induced strictures are lifted.

Similarly, Peña-González et al. (2022), performing a 12-week interventional study in an ecological environment with a pre-post assessment, found that international football players with cerebral palsy were able to maintain adequate levels of self-training (which consisted of combined strength, and resistance exercises, four training sessions per week) during the COVID-19 pandemic, thus preserving their fitness. An improvement in free countermovement jump (CMJ) was computed (from 28.60 ± 6.18 cm to 32.79 ± 6.69 cm, p-value <0.001, with an increase of 4.19 [95%CI 2.46–5.93] cm), whereas the other fitness variables (5-m, 10-m, and 20-m sprints, the modified agility t-test or MAT, and the dribbling test) remained stable. Differences between sports classes (severe impairment or FT1, moderate impairment or FT2, and mild impairment or FT3) could not be found. Finally, the authors speculated that the increase in free CMJ could be due to the fact that in the modified training protocol there was an over-representation of vertical, rather than horizontal, exercises.

Contrasting findings were, instead, obtained by Cavaggioni et al. (2022), who retrospectively analyzed a case series consisting of four para swimmers. One had cerebral palsy and belonged to the S5 para-swimming functional class, one had a hereditary spastic paraparesis (S6 class), one had a lower limb deficiency (S9 class), and one had lower limb amputation (S8 class). The authors evaluated the effectiveness of muscular strength and power, dry-land home training, and found a very likely/substantial decrement in one-repetition maximum, mean propulsive velocity, and mean relative propulsive power during the lockdown period, which was reverted when COVID-19-induced restrictions were lifted and para-athletes could return to a regular gym-training program. The decrease in neuromuscular variables (including motor unit recruitment, and firing rate) was potentially due to the fact that equipment available at home (weights, and elastic band), while, on the one hand, ensuring a certain degree of continuity in training, was not enough, on the other hand, to enable the execution of moderate-to high-intensity resistance exercises.

In line with Cavaggioni et al. (2022), Trigo et al. (2022), in a cross-sectional, questionnaire-based survey in Brazil, obtained comparable results. The authors had recruited participants with 9.83 ± 5.73 years and 7.49 ± 5.26 years of practice since the first national and international competition, respectively. In terms of performance level, there were 59 (35.75% of the sample) medal winners in the Paralympic Games or World Championships, and 106 (64.24%) participants competed at the Paralympic Games. The authors found that hours of training, the number of sessions, and the rate of perceived exertion (RPE) decreased significantly during the COVID-19-induced confinement. More specifically, hours of training decreased from 9.3 ± 4.3 to 5.5 ± 3.7, sessions reduced from 6.5 ± 3.1 to 4.6 ± 2.7 and RPE decreased from 5.0 ± 2.0 to 4.0 ± 2.0. Approximately 55% of the participants perceived that this reduction in training load along with the postponement of the Tokyo 2022 Paralympics Games would have been damaging and would have interfered with their careers. Particularly negative feelings were expressed by para-athletes of individual para-sports with opposition. This detrimental impact was greater among para-athletes with spinal cord injury and limb deficiency, when compared with other types of disability (visual, coordination, and peripheral impairment) and their able-bodied counterparts, and those taking part in team para-sports, when compared with individual sports.

Similarly, Urbański et al. (2021), conducting a questionnaire-based survey in Poland, recruited a sample of athletes with disabilities from 15 Paralympic sports disciplines, mainly suffering from spinal cord injury (paraplegia and tetraplegia, 25.9%), and limb amputation/deficiency (22.2%). The average time from diagnosis or injury was 20 ± 12.5 years, whereas the mean training experience was 10 ± 7 years. The authors found that most athletes with disabilities had to train at home (88.6%), while 60.2% of them could train outdoors. However, 12% of the interviewees had to suspend their training regimens, with only 5.4% of athletes with disabilities having some access to sports facilities and infrastructure. This resulted in a significant reduction in weekly training time (from 9.4 h/week *versus* 5.3 h/week, p-value <0.001). 60.8% of study participants reported difficulties and perceived barriers due to insufficient contact with assistants/caregivers or lack of access to assistive training devices. Finally, a significant majority of participants (more than 74%) were not satisfied with their training.

Impact of COVID-19-induced confinement on mental health in para-athletes/athletes with disabilities

Eight studies have dealt with the impact of COVID-19 on mental health and psychological variables among para-athletes/

athletes with disabilities (Clemente-Suárez et al., 2020; Dehghansai et al., 2021; Fiorilli et al., 2021; Hu et al., 2021; Kaneda et al., 2021; Kubosch et al., 2021; Martínez-Patiño et al., 2021; Busch et al., 2022). These populations have had to experience unique challenges during the COVID-19 pandemic, which has been "a tale of two stories": the infectious outbreak and disability. Living with disabilities, these populations are at higher risk for contracting the emerging coronavirus compared with the general population, besides facing psychological distress (Busch et al., 2022; Dehghansai et al., 2021; Hu et al., 2021; Kaneda et al., 2021), due to several, intersecting mediators (Jesus et al., 2020; Lund, 2020; Lund et al., 2020; Jesus et al., 2021a; Jesus et al., 2021b; Kamalakannan et al., 2021; Goddard et al., 2022), as mentioned before. Dehghansai et al. (2021) performed a qualitative study interviewing seven Australian para-athletes, in order to capture the unique challenges of athletes with disabilities during the outbreak. The authors found high psychological distress levels among the participants who had to cope with their impairments during the pandemic, facing future uncertainty, budgetary constraints, and decentralized experiences. The athletes had to deploy two major strategies: namely, "anticipate and prepare" and "manage expectations".

Hu et al. (2021) conducted a qualitative study (in-depth, semistructured interviews) and recruited a sample of para-athletes. They suffered from neurological disabilities (cerebral palsy, Wyburn-Mason syndrome, brain stem cerebellar injury, primary cerebellar degeneration, multiple sclerosis, spinal cord injury, spina bifida, transverse myelitis, and brachial plexus), limb deficiency (amputation, fibular hemimelia), visual disabilities (congenital glaucoma, retinitis pigmentosa, and other forms of visual impairment), and other complex, congenital syndromes (neuroblastoma, and Ehlers-Danlos syndrome). The authors found that the pandemic profoundly challenged their athletic identity, which is an important component of athletes' self-concept and is closely related to health- and performance outcomes. More specifically, being highly challenged by the unprecedented situation, para-athletes had to re-structure their "Disability Sport Athletic Identity" (DSAI), and perceived the multiplicity rather than the exclusivity of their roles, to mentally adapt to the COVID-19-induced restriction and loss of physical participation in sport.

Kaneda et al. (2021) conducted a questionnaire-based, pre-post survey in Japan among a sample of 39 competitive athletes, including 20 para swimmers (8 females, 11 males) suffering from cerebral palsy, amputation, visual impairment, hemiplegia, spinal cord injury, osteoarthritis, and multiple sclerosis, and 19 able-bodied athletes. The authors found that female para-athletes reported worsening mental health, with higher apathy values than their able-bodied counterparts. Also, their male counterparts did not experience the same worsening mental health.

Kubosch et al. (2021) sampled the German paralympic athlete population. The authors found that 70% of the athletes felt that, during the COVID-19 pandemic, organizing their training was difficult, and two-thirds of the athletes trained less than before the pandemic period. Half of the participants worried about their own well-being, 25% about their career, and only 8% had economical-financial preoccupations. Similar results were reported by the same author group in another investigation (Busch et al., 2022), where seventy-eight paralympic athletes (40 women, 38 men, mean age 29.8 ± 11.4 years) were recruited and matched against the general population (mean age 30.5 ± 10.9 years). The para-athletes reported significantly lower scores on the "Patient Health Questionnaire 4" (PHQ-4) scale at each measurement time point compared to the matched control group. No age nor sex- and gender-specific effects could be detected.

Contrasting findings were obtained by Martínez-Patiño et al. (2021), who performed a cross-sectional, questionnaire-based survey in Spain and analyzed a sample of 64 Paralympic athletes (aged 28.4 ± 10.5 years old) *versus* 447 Olympic athletes (aged 26.0 ± 7.5 years), both nationally ranked or in the process of taking part into the Tokyo 2020 Olympic and Paralympic Games. The para-athletes were from the following disciplines: athletics, basketball, cycling, weightlifting, horse riding, judo, swimming, canoeing, taekwondo, tennis, table tennis, archery, Olympic shooting, and triathlon. The authors found that para-athletes were significantly differentially impacted by COVID-19 compared to their Olympic counterparts. More specifically, in the previous month, the former were more able to cope with their personal problems ($r = 0.09$, small effect size, p-value <0.010), reported fewer feelings of being lonely ($r = 0.12$, small effect size, p-value <0.047), and were more accepting of confinement measures (79.7% *versus* 59.9%). The authors suggested that the particular challenges and the unique psychological profile of the Paralympic athletes may have favored a psychological adaptation to the adverse situation. Furthermore, in another study conducted in Spain (Clemente-Suárez et al., 2020), recruiting 175 Olympic and 39 Paralympic athletes (aged 31.8 ± 9.3 years, competing in athletics, basketball, canoe, cycling, football, judo, swimming, table tennis, taekwondo, triathlon, weightlifting), para-athletes reported greater importance placed on the confinement, more perceived support from public institutions, and greater conscientiousness levels.

Finally, in line with Martínez-Patiño et al. (2021), Fiorilli et al. (2021) conducted a questionnaire-based, case-control study in Italy and recruited a sample of 146 athletes (73 without and 73 with disabilities, aged 42.11 ± 13.70 years). The authors found a lower subjective distress level among athletes with disabilities compared to their able-bodied counterparts (8.22% *versus* 30.14%, respectively). Overall, psychological distress was reported by 19.18% of the participants. Within the population of athletes with disabilities, age- and sports discipline-specific effects could be found with increasing age and individual sports participants displaying higher stress levels. No sex- and gender- or technical-level-specific effect could be computed.

Impact of COVID-19-induced confinement on performance outcomes in para-athletes/athletes with disabilities

One study (Schipman et al., 2022) has investigated the impact of COVID-19-induced confinement on performance outcomes in para-athletes/athletes with disabilities. The authors conducted a data mining-based study, collecting data from 255 Paralympic events since 2010 and using the 4-year moving average, the slope of which was quantitatively assessed to evaluate changes in the temporal trend. The authors were able to find a dramatically detrimental and highly disrupting impact of COVID-19.

Risk of contracting COVID-19 among para-athletes/athletes with disabilities

Only four studies assessed the risk of contracting the virus among para-athletes/athletes with disabilities and/or reported statistical figures on the COVID-19 rate in this specific athlete population (Urbański et al., 2021; Denerel and Lima, 2022; Kaneda et al., 2022; Muti et al., 2022). One of these investigations is a technical report on the feasibility of implementing a protocol aimed at protecting the health of paralympic athletes, named the "bubble scheme", consisting of daily antigen testing, isolation, and avoidance of contact with the general public (Muti et al., 2022). The protocol was devised involving different skills and competencies, ranging from epidemiology and biostatistics, microbiology, sport and exercise medicine, and global and public health. The initial sample size of para-athletes was 23, with 12 followed up until the end of the study. The final para-rowing team consisted of 7 athletes, 3 coaches, and 2 team managers. No COVID-19 cases were found among this specific population: an aggressive testing strategy (552 polymerase chain reaction, PCR, tests, and 298 antigen-based tests) was carried out for an average number of 42 tests per athlete, showing that it is possible to create an "anti-COVID-19 protection bubble", enabling para-athletes to compete in safe conditions. Slightly different results were found by Kaneda et al. (2022) and by Urbański et al. (2021). The former is a database-based epidemiological survey, in which the authors mined the website of the Japan Broadcasting Corporation NHK and the Tokyo Metropolitan Government. The COVID-19 infection rates in Tokyo during the Paralympic and Olympic Games were computed at 0.54% and 0.48%, respectively, while those among para-athletes and athletes were 0.30% and 0.25%, respectively. The infection rate was 1.13–1.20-times higher among para-athletes than among their able-bodied counterparts. In Poland, Urbański et al. (2021) reported that only 9% of the para-athletes of the study were quarantined and 1.8% of para-athletes and 0.6% of coaches contracted COVID-19. Finally, in Turkey, Denerel and Lima (2022) computed a slightly higher infection rate among able-bodied athletes (24.6%, $n = 44$) *versus* 23% ($n = 42$) among athletes with disabilities.

Impact of COVID-19 infection on para-athletes/athletes with disabilities

Only one study (Denerel and Lima, 2022) investigated the impact of COVID-19 infection among para-athletes/athletes with disabilities. In particular, Denerel and Lima (2022) found that athletes with disabilities infected with SARS-CoV-2 displayed higher depression, anxiety, and coronavirus-related anxiety (CAS) scores than athletes with disabilities not infected with SARS-CoV-2. Sex- and gender-specific differences could be found, with females reporting higher scores. Athletes with disabilities competing in individual sports also reported higher scores than those participating in team sports.

Discussion

Impact of COVID-19-induced confinement on training and lifestyles in para-athletes/athletes with disabilities

The still ongoing COVID-19 pandemic has dramatically impacted athletes' daily routines, by reducing training opportunities. This is particularly relevant for elite athletes, for whom regular training is highly recommended to preserve adequate muscular, and postural parameters (Alvurdu et al., 2022). As such, home-based training has been proposed as a valid strategy to counteract or, at least, partially mitigate against confinement-induced detraining, which can be further worsened by COVID-19-induced alterations (at the metabolic-respiratory, muscular, cardiac, and neurological levels) (Córdova-Martínez et al., 2022). However, athletes with disabilities and para-athletes may encounter difficulties in meeting with these recommendations, as they struggle more to train alone with respect to their able-bodied counterparts, and need consistent and appropriately trained help/personnel and specialized sports infrastructure (Cavaggioni et al., 2022).

Detraining has been studied among able-bodied athletes and is relatively overlooked among para-athletes/athletes with disabilities. There are a few studies that have explored detraining among people with disabilities (older adults aged ≥ 65 years with moderate mobility disability) in terms of alterations of mobility and gait biomechanics (Beijersbergen et al., 2016; Beijersbergen et al., 2017), showing changes in gait velocity, hip, ankle, and knee work.

Impact of COVID-19-induced confinement on mental health in para-athletes/athletes with disabilities

The existing scholarly literature on the topic of athletes with disabilities and mental health has shown a higher burden in this specific population. For instance, Nabhan et al. (2021) found that, when compared with their able-bodied counterparts, athletes training for the Paralympics had a significantly higher percentage of positive screens for anxiety, depression, poor sleep quality, and sleep apnoea risk. Sport can have a buffering effect in terms of impact on mental health and well-being (Malm et al., 2019). It can promote resilience, improve emotional intelligence, strengthen other competencies, and increase self-esteem, self-perception, self-acceptance, and personal growth. All this significantly enhances the quality of life, and, more generally speaking, mental well-being. By means of sport, athletes with disabilities can build a "strong athletic *persona* (identity)," overcoming the social marginalization they can usually experience (Hu et al., 2021). Differential effects of type of sports discipline (individual versus team para-sport) were detected, suggesting that interactions and communications among peers can relieve and alleviate mental suffering, anxiety, and loneliness, enabling to react to adversities and challenging situations (Fiorilli et al., 2021). Moreover, athletes with disabilities can adopt particular coping strategies, such as avoidance, which is especially common among young para-athletes and athletes with disabilities, who are more likely to deny the implications and effects of COVID-19 and escape from negative emotions/feelings (Fiorilli et al., 2021). In conclusion, regarding confinement and mental health, a few of the studies included in the present scoping review found athletes with disabilities were better able to cope than athletes without an impairment, potentially due to the positive coping skills athletes with a disability may have (Martin, 2012; Dehghansai et al., 2021).

Risk of contracting COVID-19 among para-athletes/athletes with disabilities

Exercise immunology among athletes with disabilities and para-athletes is a relatively underdeveloped and overlooked research field with respect to behavioral/environmental immunological studies conducted among their able-bodied counterparts. However, available scholarly evidence along with clinical experience shows that the unique underlying medical conditions in this specific population make them highly likely to develop an illness (Akashi et al., 2022). According to statistical figures, the incidence rate of illness is rather high in the Summer (10.0–13.2 episodes per 1,000 athlete-days) and Winter (18.7 episodes per 1,000 athlete-days) Paralympic Games (Janse Van Rensburg et al., 2018; Nieman and Wentz, 2019). Moreover, besides these underlying conditions, it is difficult for people with disabilities to adhere to and maintain strict precautions and public health measures of social distancing to avoid COVID-19 infection, especially among people with visual and motor limitations (Muti et al., 2022). Whereas one study did not find any COVID-19 cases among para-athletes/athletes with disabilities (Muti et al., 2022), other studies found an infection rate ranging from 0.3% to 1.8% (Urbański et al., 2021; Kaneda et al., 2022). The "bubble scheme" seems to be quite effective, even though a residual risk for COVID-19 remains, and is higher among para-athletes/athletes with disabilities than among able-bodied athletes or coaches/sports managers, being 1.13–3 time-higher (Urbański et al., 2021; Kaneda et al., 2022) in the Paralympic vs. Olympic Games. This suggests that more bespoke measures should be undertaken and interventions should be implemented to protect para-athletes/athletes with disabilities against COVID-19 like enhancing ventilation, providing free at-home testing kits, and improving tele-medicine, tele-rehabilitation, and other forms of remote support from healthcare workers and providers (Kaneda et al., 2022).

Impact of COVID-19 infection on para-athletes/athletes with disabilities

The scholarly literature on the impact of COVID-19 infection on para-athletes/athletes with disabilities is very scarce. We were able, indeed, to retrieve only one relevant study. Moreover, to the best of our knowledge, data concerning the follow-up and the long-term effects of COVID-19 infection are lacking. A recently published systematic review found that approximately 94% of infected athletes displayed mild or no acute symptoms, with a small percentage of athletes experiencing persistent, long-term symptoms. COVID-19 is generally mostly mild in nature, but it can affect both return-to-play decisions and timing (Lemes et al., 2022). However, no data and recommendations could be given for athletes with disabilities, which warrants further research.

Strengths and shortcomings of the present study

Our study presents several strengths, including the comprehensive literature search and appraisal, the methodological rigor, and the compliance with existing guidelines and checklists. On the other hand, it has also a number of limitations, that should be properly acknowledged. It was not possible to narrow our research question, given the limited number of available studies, so we preferred to broaden our research scope, also to give a broader overview and perspective on the topics under study. The heterogeneity of the literature and the contrasting findings reported preclude a more quantitative and meta-analytical approach.

Critical considerations, implications, and future prospects

The scholarly literature is highly heterogeneous, with contrasting findings. Several hypotheses could be formulated to explain, at least partially, such discrepancies: differences in the methodology and study design (retrospective versus prospective, case-control with age- and sex-/gender-matched control subjects), country and stringency of the package of NPIs implemented, para-sport studied. Concerning the type of para-sport, some disciplines are unique, such as para-cycling, in that they require minimum outside equipment since there are minimal equipment needs and the equipment is available during the pandemic as it is personal equipment that is used outdoors. This could explain why Shaw et al. (2021) were not able to find any detrimental or disruptive effect of COVID-19 on training among para-athletes, since the outbreak could not influence outdoor activities and training, whereas Martínez-Patiño et al. (2021) and Clemente-Suárez et al. (2020) reported a positive response from Paralympic athletes to the COVID-19 pandemic. On the contrary, Cavaggioni et al. (2022), and Schipman et al. (2022) observed a negative impact of the infectious outbreak.

Differences among studies could also be due to different types of impairment evaluated, even though they are rarely reported: only in the studies by Cavaggioni et al. (2022), Hu et al. (2021), Trigo et al. (2022), and Urbański et al. (2021). Also, the composition/selection of the sample could have an effect. Trigo et al. (2022) noticed that paralympic athletes displayed more negative feelings and perceptions about the impact of COVID-19 on the training and performance outcomes when compared to their able-bodied counterparts. This could depend on the fact that, when the survey was conducted, most para-athletes recruited were still waiting for competition selection to the Paralympic Games and to take part in the international classification process. There was, as such, a great degree of uncertainty about the competition calendar, which translated and reflected in reduced load training. Other studies could have captured different times/moments of the international classification process, and, therefore, its effects in terms of expectations related to performance during the Tokyo 2020 Paralympic Games. The study country could have an impact too in terms of policies and public health intervention implemented: for example, in the investigation by Urbański et al. (2021), carried out in Poland, only 9% of athletes were quarantined and 1.8% of para-athletes and 0.6% of coaches contracted COVID-19.

Included studies exhibit some methodological limitations, like the small sample size, incidental/intentional opinion-type sampling for convenience, and unbalanced recruitment (with imbalance, for instance, in terms of para-sports disciplines), which limits the representativeness of the samples and hinders the generalization of the findings. Often, the design was correlational and univariate analyses were not adjusting for confounding variables, given the limited statistical power and the reduced small sample size. Furthermore, the response rate to the survey was in some cases low (ranging from 31.2–36% for the studies by Denerel and Lima, 2022, and by Clemente-Suárez et al., 2020, respectively, to 65.0% for the study by Busch et al., 2022), whereas in a few cases it was excellent (94% in the study by Urbański et al., 2021). Moreover, several measures have been retrospectively collected, which may lead to a recall bias and inaccuracy/unreliability of the results. Furthermore, a few studies, including Busch et al. (2022), did not properly compare the population of para-athletes/athletes with disabilities to a matched athlete population, but rather to the general population.

Furthermore, most studies did not correct for potential confounders, such as psychological variables (Urbański et al., 2021), nutritional uptake, or sleep quality (Trigo et al., 2022), which have been found to be altered during the COVID-19 pandemic and is known to impact the training schedules and performance outcomes among athletes. Finally, the use of self-designed instruments and tools makes it difficult to compare across different surveys.

Recommendations for future studies

Based on our considerations, we recommend that standardized, reliable tools should be utilized and new, specific questionnaires should be created, tested for reliability, and validated. High-quality, multi-center, cross-countries, longitudinal surveys should be conducted to overcome all these shortcomings. Involving all relevant actors and stakeholders, including various national and international Paralympic Committees, as a few studies have done (Urbański et al., 2021) is fundamental: community-led, participatory research can help identify gaps in the current knowledge about sports-related practices among the population of athletes with disabilities during an unprecedented period of measures undertaken that have significantly affected everyday life. Moreover, this could advance the field, by capturing the needs of para-athletes and athletes with disabilities and enabling the design of a truly "disability-inclusive response" to COVID-19 and similar conditions/situations. Furthermore, follow-up studies on COVID-19-infected para-athletes and athletes with disabilities should be conducted. Evidence of long-term effects of COVID-19 is available only for able-bodied athletes, for whom cardiorespiratory residual alterations and mental health issues a long time after COVID-19 are described (Sala et al., 2020; Modica et al., 2022).

Conclusion

Sport is known to play a key role for persons with disabilities, enhancing their socialization, improving their self-esteem, and increasing their quality of life and independence. Investigating the disruptive effect of COVID-19 is, therefore, essential to devise optimal strategies to counteract the negative effects of the infectious outbreak. However, despite the importance and relevance of this topic, evidence on the impact of COVID-19 on para-athletes is scant and contradictory, even though some discrepancies could be reconciled by taking into account the methodology adopted, the study design, the study country, and the type of para-sport assessed. All this calls for country-, para-sport-specific, data-driven recommendations. Athletes with disabilities and para-athletes have been affected to various extents by the COVID-19 pandemic, especially those who require access to specific training equipment and sports infrastructure, and those who take part in team sports who have lacked the social support of peers and other social networks, with subsequently reduced socializing opportunities. However, given the above-mentioned limitations and shortcomings, further research in the field is urgently warranted.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LP and NLB conceived, designed and wrote the manuscript. KT, AA, GJ, LuM, LaM, JK, ChT, FC, CS, MS, CB, PR, and CaT critically revised the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Personalized adapted motor activity in a COVID-19 patient complicated by critical illness polyneuropathy and myopathy

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Background: COVID-19 may require hospitalization in an intensive care unit (ICU) and is often associated with the onset of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM). Due to the spread of the disease around the world, the identification of new rehabilitation strategies for patients facing this sequence of events is of increasing importance.

Case presentation: We report the clinical presentation and the beneficial effects of a prolonged, supervised adapted motor activity (AMA) program in a highly deconditioned 61-year-old male COVID-19 patient discharged from the ICU and complicated by residual CIP and CIM. The program included aerobic, strength, gait, and balance training (1 h, 2 sessions per week).

Measures: Pulmonary (spirometry), metabolic (indirect calorimetry and bioimpedance), and neuromuscular functions (electromyography) were evaluated at baseline and after 1 year of training.

Results: Relative to baseline, an amelioration of several spirometric parameters such as vital capacity (VC, +40%), total lung capacity (TLC, +25%), and forced expiratory volume in 1 s (FEV1, +28%) was appreciable. Metabolic parameters such as body water (60%–46%), phase angle (3.6°–5.9°), and respiratory quotient (0.92–0.8) returned to the physiological range. Electromyographic parameters were substantially unchanged. The overall amelioration in clinical parameters resulted in a significant improvement of patient autonomy and the quality of life.

Abbreviations: ADL, activities of daily living; AMA, adapted motor activity; BCM, body cellular mass; BW, body water; CIM, critical illness myopathy; CIP, critical illness polyneuropathy; CPAP, continuous positive airway pressure; ECM, extracellular mass; EPSN, external popliteal sciatic nerves; FFM, free fat mass; FM, fat mass; ICU, intensive care unit; MI, Motley index; NCV, nerve conduction velocity; PA, phase angle; PEG, percutaneous endoscopic gastrostomy; RMR, resting metabolic rate; ROM, range of motion; RQ, respiratory quotient; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

Conclusion: Our results highlight the importance of AMA for counteracting respiratory, metabolic, and functional but not neuromuscular impairments in COVID-19 patients with residual CIM and CIP.

KEYWORDS

AMA, post-COVID-19, CIM, CIP, case report

Introduction

The search for effective rehabilitation strategies, following discharge of COVID-19 patients from an intensive care unit (ICU), is of major importance, particularly in the presence of additional complications, such as critical illness polyneuropathy (CIP) and critical illness myopathy (CIM), leading to muscle weakness and failure to wean from the ventilator (Latronico & Bolton, 2011). In a systematic review with meta-analysis (Chang et al., 2021), it was found that in a total of 28 studies comprising 12,437 COVID-19 ICU admissions, 69% of cases needed invasive mechanical ventilation (IMV). In addition, approximately 50% of critically ill patients receiving IMV for more than 7 days develop CIP and/or CIM (Z'Graggen & Tankisi, 2020). Latronico & Bolton (2011) reported that CIP and CIM increase hospital mortality in patients who are critically ill and cause chronic disability in survivors due to structural changes like axonal nerve degeneration, skeletal muscle necrosis, and myosin loss. Hence, these type of patients will not only face the long-term effects of severe COVID-19 (Torres-Castro et al., 2021) but also the symptoms of deconditioning due to CIP and CIM, making the rehabilitation process even more complex (Bagnato et al., 2021).

We present a supervised adapted motor activity (AMA) program in a case of severe COVID-19 requiring hospitalization in the ICU for 47 days, of which 20 days were with mechanical ventilation, complicated by the appearance of CIP and CIM. Before and after AMA, the patient underwent a battery of respiratory, metabolic, and electromyographic tests.

Case description

The patient was a 61-year-old male without a relevant past medical history. At the end of February 2020, he began to show signs of acute rhinitis and very high fever. On March 3, he was admitted to the infectious diseases ward for acute COVID-19 pneumonia, and on March 5, his condition worsened, so a continuous positive airway pressure (CPAP) helmet was used. On March 7, he was transferred to the ICU and subjected to orotracheal intubation and mechanical ventilation. In the ICU, pronation cycles were performed with a gradual improvement and reduction of sedation until the recovery of consciousness. In this phase, the patient was hypotonic, a clinical sign which, together with asthenia, led doctors to hypothesize the diagnosis of CIP and CIM.

On April 22, he was transferred to the COVID pneumo-rehabilitation ward to continue treatment and respiratory weaning. On May 18, he was transferred to the neurorehabilitation ward in a condition of tetraparesis and marked weakness. Upon arrival in the neurorehabilitation ward, the patient presented preserved voluntary motility in the four limbs with severe weakness and hypotrophy, which is more marked in the lower limbs. No obvious issues were noted for the upper limbs, except for the bicep reflex which was bilaterally not elicitable and difficulty in holding in the Mingazzini test. The lower limbs were hypotrophic, with segmental asthenia of the hip flexors, bilaterally absent ankle flexion, and barely evident ankle extension. Furthermore, the Mingazzini II test, which requires the patient to lie on his back with eyes closed, with the hip and knees flexed to about 90° and holding the position for 30 s, was not executable. The trunk was hypotonic with difficulty in reaching the semi-sitting position in the bed, even with arm support.

Diagnostic assessment

Electromyography (EMG) and electroneurography (ENG) identified the underlying myopathy and severe sensory-motor axonal neuropathy, prevalent in the lower limbs, with significant bilateral impairment of the internal (IPSN, stimulation 7 cm above the popliteal fossa crease at the midpoint between the tendons of biceps femoris (laterally) and tendons of semitendinosus and semimembranosus (medially); registration from the abductor hallucis belly below the navicular bony prominence) and external popliteal sciatic nerves (EPSN, stimulation at the tibiofibular joint; registration from the extensor digitorum communis below the external malleolus). Additionally, videofluoroscopy showed reduced swallowing function; therefore, after abdominal ultrasound and gastroenterological evaluation, on June 3, percutaneous endoscopic gastrostomy (PEG) was performed. In addition to global recovery, the rehabilitation process was aimed toward the recovery of the walking ability, oral feeding re-education until total weaning from the PEG (which was removed on August 6), and the improvement of the respiratory function through exercises to strengthen the inspiratory and expiratory muscles. In this phase, various walking support braces were used, including a Peromed brace, Codivilla spring, and finally an Ottobock brace (Ottobock, Budrio, Italy), which the patient currently wears.

TABLE 1 Absolute and percentage changes of the functional parameters measured at the beginning and at the end of the AMA intervention.

Functional test and parameter	T0 evaluation	T1 evaluation	Modification (%)
Spirometry			
Vital capacity (L)	3.45	4.84	+40
Residual volume (L)	1.99	1.95	−2
Total	544	6.79	+25
Lung capacity (L)			
Motley index (%)	37	29	−21
FEV1 (L)	3.18	4.10	+28
FEV1/vital capacity (%)	92	85	−7
DLCO (mmol/min/kPa)	3.23	6.25	+93
Indirect calorimetry RMR			
(kcal/day)	1326	1816	+37
Respiratory quotient	0.92	0.8	−13
Bioimpedance			
Resistance (Ohm)	416	432	+4
Reactance (Ohm)	26	45	+73
Angle phase (°)	3.6	5.9	+63
BW and hydration (%)	60	46	−23
Fat mass (kg, %)	11.6–15	25.1–27	+116
Free fat mass (g, %)	63.9–85	66.4–73	+4
Body cellular mass (kg, %)	24.4–38	35.5–53	+46
Extra cellular mass (kg)	39.5	30.9	−21
Electromyography (IPSN dx/sx)			
Conduction velocity (m/s)	34.3/31.4	30.7/34.6	−10.5/+10.2
Latency (ms)	9.1/4.4	6.6/5.1	−27.5/+15.9
Amplitude (mV)	0.6/0.6	0.4/2.1	−33.3/+250

FEV1, forced expiratory volume in the 1st sec; DLCO, diffusing capacity for carbon monoxide; RMR, resting metabolic rate; BW, body water; IPSN, internal popliteal sciatic nerve.

On August 14, the patient was discharged with the indication to continue rehabilitation. In September, he came to our center to begin motor reconditioning and restoration of activities of daily living (ADL). Upon initial examination, he suffered major functional impairments including early fatigue, loss of muscle mass and strength, balance impairment, and gait disturbances due to bilateral damage of IPSN and EPSN for which he required the continued use of orthoses and the Ottobock braces.

Instrumental evaluation

The patient signed an informed content and underwent a battery test with regard to respiratory, metabolic, and neuromuscular domains. The evaluation of the respiratory function was based on a spirometry examination and included the vital capacity (VC), residual volume (RV), total lung capacity (TLC), Motley index (MI), forced expiratory volume in 1 s (FEV1), FEV1/VC, and diffusing capacity for carbon monoxide (DLCO). The metabolic evaluation was based on indirect calorimetry (QRNG, COSMED, Milano, Italy) and bioimpedance (Akern, Pontassieve, Italy) and included the resting metabolic rate (RMR), respiratory quotient (RQ), resistance (Res), reactance (Rea), phase angle (PA), body water (BW), fat mass (FM), free fat mass (FFM), body cellular mass (BCM), and extracellular mass (ECM). Lastly, the evaluation of the neuromuscular function was based on electromyography and included the nerve conduction velocity (NCV), latency (La), and amplitude (Amp). The pre- and post-treatment values are summarized in Table 1.

Adapted motor activity program

The AMA program required a combination of aerobic, strength, gait, and balance training. All sessions were carried

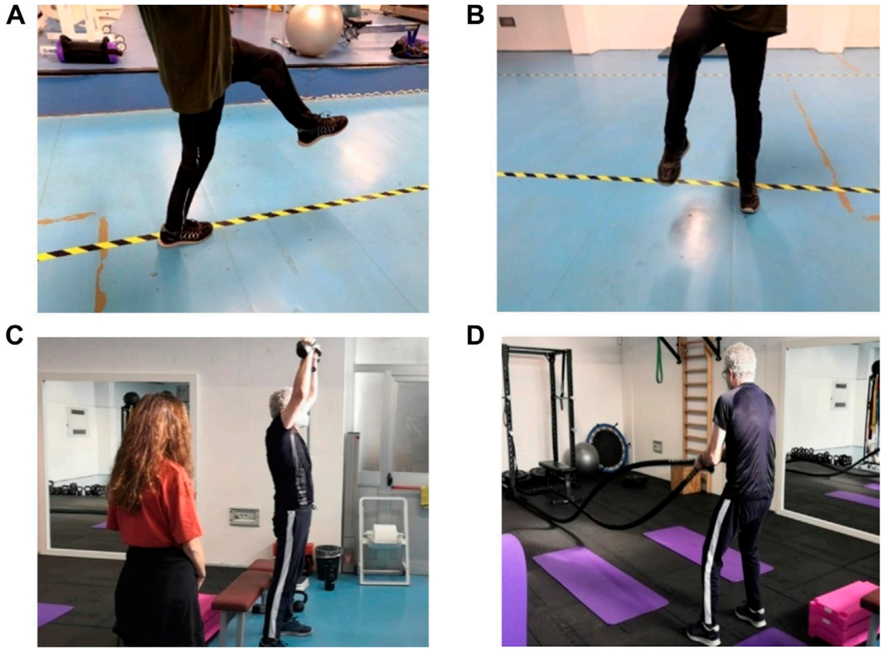

FIGURE 1
Execution of **(A)** frontal walk without sticks or braces; **(B)** side walk without sticks or braces; and **(C)** shoulder press with kettlebell. Next to the patient, an operator supervises the progress of the exercise; **(D)** alternating waves with a rope. All exercises refer to the third phase of the AMA program (with permission from the patient).

out under the supervision of qualified operators (Figure 1). Based on the level of difficulty, modulated according to the patient's observable functional improvement, the program can be divided in three phases.

First phase (September 2020–December 2020): Aerobic training consisted of 10 min of cyclette exercise at a power of 60 W. Strength training consisted of 20 min of exercises performed with low intensity and medium–high repetitions (three sets of 12–15 repetitions): bridge, total body resistance exercise (TRX) traction, step ups, and reinforcement of knee and ankle flexor and extensor muscles with elastic bands and inclined planks (three sets of 20 s). Gait training consisted of 10 min of gait alternating frontal walk, with complete roll of the foot, heel–toe walking, walking only on the toes with possible maintenance of the position at the stop, and side walking. Balance training consisted of 10 min of monopodalic work with support on the ground and bipodalic work on a trampoline, safely carried out with an espalier support. At the end of this phase, the patient gained amplitude in the articular range of motion (ROM), particularly for the ankle. Core strengthening exercises, such as bridge and plank, improved stability and helped make the patient's gait tilt less. The use of sticks was progressively reduced until autonomous walking with braces.

Second phase (January 2021–April 2021): Aerobic training consisted of 10 min of rowing at a power of 80–100 W. Strength training consisted of 20 min of exercises with increasing loads and lower repetitions than the previous phase (three sets of 8–10 repetitions): double support squat with overload, bodyweight split squat, sidewalk with elastic band, and prone push up and plank (three sets of 30 s). Gait training consisted of 10 min of the same exercises of the previous phase, carried out with braces but without sticks. Balance training consisted of 10 min of monopodalic balance on a trampoline and bipodalic balance on unstable surfaces (Skimmy, Navaris) without espalier support. In this phase, for each workout, we measured the saturation level (SpO_2) after the aerobic exercise and the relative recovery time, i.e., the time it takes to return to the SpO_2 level recorded at rest (i.e., 99%). Regarding the mean values of the first 2 months of intervention and those of the last 2 months, it was appreciable that, although the post-exercise SpO_2 values remained almost the same, a clear decrease in the recovery time occurred (Figure 2).

Third phase (May 2021–September 2021): Aerobic work consisted of 12 min of rowing at a power of 110 W. Strength training consisted of 20 min of exercises performed with increasing loads and lower repetitions than the previous phase (three sets of 5–6 repetitions): shoulder press with kettlebells, bench press with barbell or dumbbells, alternating waves with the rope, pull up with the support of elastic bands, double support squat with overload, TRX single leg squat, and plank (three sets of 40 s). Gait training consisted of 10 min of the same exercises of

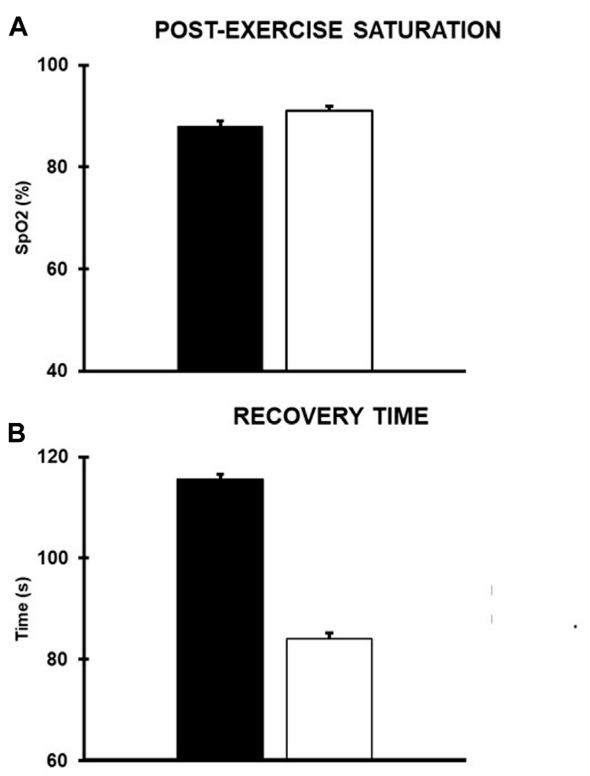

FIGURE 2
Mean values (SD) of the **(A)** post-exercise saturation and **(B)** the mean recovery time. Black and white columns refer to the mean values recorded in the first and last 2 months of the second phase of intervention, respectively.

the previous phase carried out mostly without braces. Balance training consisted of 10 min of complex tasks such as maintaining balance on the trampoline while reaching for an object placed on the ground, and in monopodalic equilibrium, the patient had to touch objects positioned around him with his free limb. At the end of this phase, the patient showed increased autonomy in walking without braces, a noticeable improvement in strength, and good balance even in single stance.

Discussion

Results and considerations

COVID-19 has led to many infections and victims around the world (Pollard et al., 2020). Due to the severity of the disease, a high percentage of these patients require hospitalization in ICU, which is associated with a high risk of developing CIP and CIM (Tsai et al., 2004; Leung et al., 2005; Algahtani et al., 2016). Therefore, given the high number of potential patients, it appears essential to find rehabilitation strategies useful to counteract the long-term effects of both respiratory and neuromuscular diseases. Studies concerning the rehabilitation of CIP and CIM patients are focused on the treatment of the disease in the acute and immediate post-acute phases (Doherty & Steen, 2010; Nordon-Craft et al., 2011; Jang et al., 2019). Available data emphasize the importance of early diagnosis and mobilization and the need to support specific pulmonary rehabilitation in addition to physical therapy (Ydemann et al., 2012; Jang et al., 2019; Cheung et al., 2021). To the best of our knowledge, our study is the first to report the effects of an exercise-based program to contrast the long-term effects of CIP and CIM in a COVID-19 patient discharged from the ICU. After 1 year of training on a twice-weekly basis, we observed significant improvements in gait, balance, metabolism, body composition, and respiratory function but no ameliorations in neuromuscular function.

In particular, regarding the respiratory function, a large improvement in VC was seen (+40% on the initial value). The decrease in RV suggested an improvement in the capacity of air mobilization during maximal exhalation. TLC increased by 25% and the MI, a sign of pulmonary hyperdistension due to broncho-obstruction or pulmonary emphysema, decreased by 21%; FEV1/VC returned to the physiological range. The improvement of lung parameters led to a decrease in the recovery time of the patient after any effort (Figure 2). The DLCO value remained low despite the other volume's improvement, likely due to the presence of fibrotic tissue in the upper and lower lung lobes as observed in a CT scan performed in April 2021. The general amelioration of spirometric parameters seems to confirm the role of aerobic exercise in improving the lung function in post-COVID-19 patients (Araùjo et al., 2022).

Data on metabolism and body composition underpinned a substantial improvement in all parameters. RMR increased by 37%, with a 4% increase in FFM. RQ decreased, approaching the value expected in a healthy subject at rest (Leff et al., 1987). PA, BW, and BCM returned within the physiological ranges. FM, which at T0 was critically low, increased by 116% at T1. Improved body composition and increased muscle mass appear to be in line with literature data, suggesting the role of physical activity as an effective means of treating sarcopenia (for review, see Montero-Fernández & Serra-Rexach, 2013).

Electromyographic parameters were unchanged. The EPSN was bilaterally absent in both evaluations. At T1, left IPSN had a slight improvement in NCV and Amp but a slight worsening in La, while right IPSN had a slight improvement in La but a slight decrease in NCV and Amp. This seems coherent with a follow-up study (sample of 22 subjects) reporting that denervation of muscle consistent with previous CIP can be found up to 5 years after ICU discharge in >90% of these subjects (Fletcher et al., 2003). To the best of our knowledge, the present study is the first to show that AMA does not improve neuropathy in this kind of patients.

The result of the proposed intervention is a clinical and functional improvement which reverberates in an important increase of autonomy during ADL. As mentioned, the use of sticks while walking was gradually reduced until abandonment, and to date, the patient shows good autonomy, albeit not total, in ambulation without braces, without dyspnea or early fatigue. Wintermann et al. (2018) highlighted the disabling impact of fatigue in this population of subjects, showing that patients with CIP and CIM report signs of chronic fatigue even 6 months after ICU discharge. This seems to be in line with the case reported, as at a first evaluation, the subject complained of a markedly premature fatigue. Possibly, its gradual decrease could be linked to the decreased recovery time after an effort (Figure 2). Furthermore, he restored the ability to autonomously carry out some fundamental activities of social life such as driving a car. The good outcomes of the training program could also rely on the constant subject supervision during the activities. This is in line with other studies (Lacroix et al., 2017; Minetama et al., 2019), showing a greater level of effectiveness of supervision compared to unsupervised physical exercise in different populations of subjects.

Limitations

Our data, reported for a single case, cannot be generalized to other patients with CIP and CIM and do not allow us to accurately quantify how much the reported improvements derive from the proposed intervention or from a spontaneous recovery. However, previous follow-up studies focusing on the long-term consequences of CIP and CIM provide conflicting data or are in need of further investigation. Lacomis et al. (1998) have found similar functional outcomes in patients with CIM and CIP. Instead, the study by Guarneri et al. (2008) reports that the presence of CIM alone has generally a good prognosis, while CIP or the simultaneous presence of CIP and CIM is more likely to lead to long-term consequences and suggests that a possible explanation for these different results is that, in the aforementioned study, patients were followed up for only 4 months, when CIM is still prevalent. Finally, a recent scoping review by Intiso et al. (2022) concludes that subjects with intensive care unit-acquired weakness (ICUAW) may show improvements at the follow-up but that due to short follow-ups and the paucity of defined outcome measures, confirmations are required. Certainly, future studies on a large sample and with a control group will be needed to confirm or disprove the results obtained in this study.

Conclusion

This work shows that supervised AMA can be an effective and safe tool to improve respiratory, metabolic, and functional conditions, unlike neuropathy, in this kind of patient.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

OC analyzed and interpreted the data and wrote the first draft of the manuscript; CZ and MB built the personalized adapted motor activity program and supervised each training session and analyzed and interpreted the data. GT provided medical tracking of the patient and contributed to writing and revision of the manuscript for intellectual content; GD developed the concept of the study, interpreted the data, supervised functional measurements, and wrote the first draft and the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Athlete level, sport-type, and gender influences on training, mental health, and sleep during the early COVID-19 lockdown in Malaysia

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Purpose: We evaluated the extent of changes in training practices, recovery, mental health, and sleep patterns of athletes during the early COVID-19 lockdown in a single country-cohort.

Methods: A total of 686 athletes (59% male, 41% female; 9% World Class, 28% International, 29% National, 26% State, 8% Recreational) from 50 sports (45% individual, 55% team) in Malaysia completed an online, survey-based questionnaire study. The questions were related to training practices (including recovery and injury), mental health, and sleep patterns.

Results: Relative to pre-lockdown, training intensity (–34%), frequency (–20%, except World-Class), and duration (–24%–59%, especially International/World-Class) were compromised, by the mandated lockdown. During the lockdown, more space/access (69%) and equipment (69%) were available for cardiorespiratory training, than technical and strength; and these resources favoured World-Class athletes. Most athletes trained for general strength/health (88%) and muscular endurance (71%); and some used innovative/digital training tools (World-Class 48% vs. lower classification-levels ≤34%). More World-Class, International, and National athletes performed strength training, plyometrics, and sport-specific technical skills with proper equipment, than State/Recreational athletes. More females (42%) sourced training materials from social media than males (29%). Some athletes (38%) performed injury prevention exercises; 18% had mild injuries (knees 29%, ankles 26%), and 18% received a medical diagnosis (International 31%). Lower-level athletes (e.g., State 44%) disclosed that they were mentally more vulnerable; and felt more anxious (36% vs. higher-levels 14%–21%). Sleep quality and quantity were "normal" (49% for both), "improved" (35% and 27%), and only 16% and 14% (respectively) stated "worsened" sleep.

Conclusion: Lockdown compromised training-related practices, especially in lower-level athletes. Athletes are in need of assistance with training, and tools to cope with anxiety that should be tailored to individual country requirements during lockdown situations. In particular, goal-driven (even if it is at home) fitness training, psychological, financial, and lifestyle support can be provided to reduce the difficulties associated with lockdowns. Policies and guidelines that facilitate athletes (of all levels) to train regularly during the lockdown should be developed.

KEYWORDS

elite athlete, injury, mental health, periodisation, recovery, remote training

Introduction

Almost as soon as the Coronavirus disease 2019 (COVID-19) pandemic was declared, daily routines of people worldwide including athletes were disrupted. Mandated lockdowns and other measures associated with varying levels of restriction on movement and social interactions (daily living, occupational and physical activity) were imposed across the globe that negatively impacted factors including mental health, sleep patterns, nutritional intake, and fitness levels (Ammar et al., 2020; Trabelsi et al., 2021; Washif et al., 2022b; Romdhani et al., 2022c). Consequently, athletes, from Recreational to World-Class calibre, were forced to alter their training routines (such as training loads and modalities) due to the imposed constraints (Washif et al., 2022e). These constraints necessitated modified training that was often home-based and streamed on the internet (Ammar et al., 2021; Tjønndal, 2022). This online support was especially evident among elite-level athletes (Washif et al., 2022b).

Lockdowns have been reported to be costly for most nations and created a burden for athletes, both physically and mentally. During the lockdown, some countries (such as Sweden) allowed outdoor activities (Carlander et al., 2022); whereas, in contrast, such activity was strictly prohibited in Malaysia (Washif et al., 2021). Thus, athletes in Malaysia, irrespective of their competition classification level (World-Class, International, National, State, Recreational), were confined to training in their homes (Washif et al., 2021). The environmental conditions of the country (hot and humid) may have imposed additional training challenges on the athletes. In addition to these challenges, not all high-level Malaysian athletes received remote training support from their coaches and trainers at the beginning of lockdown training. Logistical constraints and limited resources delayed the implementation of training assistance and athlete support. A large-scale study involving >12,000 athletes with diverse characteristics from 142 countries reported widespread challenges faced by athletes, including disruptions to training and decreased motivation levels among athletes (Washif et al., 2022b). Following this, a study that focused specifically on a sample of elite Malaysian athletes (n = 76) reported negative experiences from mandatory lockdown such as increased mental and emotional stress, fewer nutritional choices, and reduced training motivation (Washif et al., 2021; Washif et al., 2022a). These results are comparable to the conditions faced by South African athletes (Pillay et al., 2020).

Male and female athletes have reported different training experiences during the COVID-19 pandemic. Female athletes are inclined to be involved with online training, while male athletes were more likely to participate in virtual sports competitions (Tjønndal, 2022) in their own homes. Virtual sports are based on simulator platforms (digital technology) or a treadmill/bicycle connected to a computer (with screen monitor) that enables actual and live running/pedaling. The objective is to replicate racing realities, hills, headwinds, drafting effects, and/or even online competition with other athletes. Male athletes also appear to have maintained a higher number of weekly training days and hours, to a greater extent than female athletes (Mon-López et al., 2020). As well as differences between gender, differences between sporting types were identified, with sports requiring specialist facilities such as swimming, shooting, archery, and team sports often unable to carry out technical training at training sites (Washif et al., 2022e). However, some athletes were able to perform specific skills or fitness training such as running for endurance athletes, throwing for shot putters, weight training for weightlifters, and continuance of strength development if possessing training equipment at home (Washif et al., 2022b; Meier et al., 2022; Pagaduan et al., 2022).

Sleep quantity and quality are of paramount importance for recovery and performance of the athletes. Reduced training intensity and fewer training sessions result in circadian interference, which negatively impacts sleep quality (Romdhani et al., 2022b) and could potentially trigger mental health issues (Facer-Childs et al., 2021), such as elevated stress and depression (Facer-Childs et al., 2021; Romdhani et al., 2022b). In this context, high intensity training can promote 1) increased sleep drive contributing to improved sleep (Romdhani et al., 2022b) and 2) activation of endogenous opioid release (inside the brain) resulting in mood elevation and stress reduction (Saanijoki et al., 2018). Unfortunately, mental distress and the athletes' inability to maintain athletic routines have also been associated with an increased injury risk (Wiese-Bjornstal, 2019; Rampinini et al., 2021b). Uncertainty around the resumption of competitions while in lockdown situation, may worsen mood, reduce motivation, and amplify eventual mental health issues (Facer-Childs et al., 2021).

Although some studies have proposed how the lockdown has affected athletes' training practices, injury prevalence, sleep disorder occurrences, and mental-health-related challenges during the lockdown, patterns of discrepancies between gender (male vs. female), and sport-type (individual vs. team-based sports) require clarification. Currently, very few studies have investigated differences due to athlete classification levels (Mon-López et al., 2020; Pillay et al., 2020). Higher classification-level athletes (i.e., World-Class, International) would likely have higher needs for training equipment, frequency, facilities and intensity than lower classification-level athletes (e.g., State).

The aim of this study was to evaluate training and recovery practices, injury prevalence, mental perspectives, and sleep patterns of athletes in Malaysia during the early stages of lockdown, including changes in key training variables with references to athlete classification level, sport type, and gender. This information will elucidate the effects of lockdown among athletes in Malaysia to develop appropriate mitigation approaches for future lockdowns, and/or challenging lockdown-like situations. We expected that athletes from higher classification levels (e.g., World Class), and individual-based sports, would better maintain key training variables compared to athletes from other classification levels and sports.

TABLE 1 Socio-demographic characteristics of the respondents in Malaysia during the 2020 COVID-19 lockdown under a national Movement Control Order (*n* = 686).

	Number	Percentage
Gender		
Male	405	59.0
Female	281	41.0
Age groups, years		
18–29	559	81.7
30–39	94	13.8
>40	31	4.5
Missing	2	(–)
Sports experience, years		
≤3	137	20.8
4–8	309	47.0
9–12	166	25.2
>12	46	7.0
Missing	32	(–)
Residence (state/Federal Territory)		
Sarawak	145	21.1
Selangor	121	17.6
Federal Territory	94	13.7
Penang	66	9.6
Johor	46	6.7
Kedah	40	5.8
Sabah	39	5.7
Negeri Sembilan	32	4.7
Malacca	24	3.5
Terengganu	23	3.4
Pahang	18	2.6
Perak	18	2.6
Kelantan	12	1.8
Perlis	8	1.2
Main sports		
Athletics	83	12.0
Field hockey	61	8.8
Lawn bowls	49	7.1
Badminton	46	6.7
Squash	40	5.8
Soccer	39	5.7
Tenpin bowling	38	5.5
Volleyball	22	3.2
Rugby	21	3.0
Archery	20	2.9
Karate	17	2.5
Pencak silat	16	2.3
Boxing	15	2.2
Sepak takraw	15	2.2
Handball	14	2.0
Judo	14	2.0
Petanque	14	2.0
Swimming	13	1.9
Sailing	12	1.7
Weightlifting	12	1.7
Other sports	125	19

(Continued in next column)

Materials and methods

Design

A within-subject, cross-sectional, questionnaire study was conducted 2 months after the country's announcement of a lockdown, from 17 May–5 July 2020. This study was part of a global survey investigating athletes' training knowledge, beliefs, and practices during the COVID-19 lockdown (Washif et al., 2022b). Overall data and comparisons for differences according to athlete competition classification level (World-Class, International, National, State, and Recreational), sport-type (individual e.g., athletics, badminton, karate vs. team-based sports e.g., hockey, soccer, rugby), and gender (male vs. female) were made. Sport type comparison excluded parasports given a possible confounding factor in the grouping of para-athletes. Athlete classification was based on their highest competition level e.g., Olympic or world championship representatives or similar caliber athletes were grouped as World-Class; participation at other international-, continental-, regional-, and inter-community competitions as International; participation at national-level competition as National; participation at state-level competition as State; and other non-competitive sports participation, usually for leisure, health, or work-related as Recreational (Washif et al., 2022b; Washif et al., 2022e).

Respondents

Participant eligibility is described elsewhere (Washif et al., 2022b). Briefly, only athletes aged 18 years old or above, and who had not missed training for 7 days or more due to illness and/or injury during the lockdown, were allowed to participate in the survey. These participants provided informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki, and approved by the institutional research committee of Institut Sukan Negara, Malaysia (ISNRP004-21).

Sample size

Taking into account the rate of sports participation (two-thirds of the population) in Malaysia (www.iyres.gov.my), a response distribution of 50% (which maximises sample size), a Z-score or standard deviation of 2.6 (for a 99% confidence interval), and the margin of error of ~5%, the sample size requirement of 664 athletes was calculated for the current study. A final sample of 686 consenting athletes was subsequently collected and analysed.

Questionnaires

The survey was developed initially by the first (JAW) and last (KC) authors, then reviewed and revised by the wider authorship team, involving >100 researchers from >60 countries. In the present study, questions were partially taken form the global study of Washif et al., 2022b. The socio-demographic section comprised 7 questions; Table 1; Figure 1 (Washif et al., 2022b). The training practice section comprised 11 questions; Table 2, Figures 2, 3, 4 (Washif

TABLE 1 (*Continued*) Socio-demographic characteristics of the respondents in Malaysia during the 2020 COVID-19 lockdown under a national Movement Control Order (n = 686).

	Number	Percentage
Athlete classification level		
World class	64	9.3
International	187	27.3
National	199	29.0
State	180	26.2
Recreational	56	8.2
Sport classification		
Team sports	193	28.1
Precision sports	132	19.2
Power/Technical sports	104	15.2
Racquet sports	89	13.0
Combat sports	83	12.1
Aquatics sports	41	6.0
Endurance sports	23	3.3
Parasports	21	3.1
Number of household members		
1 (I live alone)	29	4.2
2	94	13.8
3	88	12.9
4	147	21.6
5 or more	324	47.5
Missing	4	(−)

et al., 2022b). Monitoring, recovery, and injury comprised of 8 questions (Table 3; Figure 5). Psychological responses and financial challenge section comprised 5 questions (Table 4; Figure 6). Sleep habits comprised 4 questions (Table 5). These questions involved: 1) selecting one or more predefined answers; 2) comparing related pre-to during-lockdown effects on training practices; 3) yes or no; and 4) sub-questions including a free-text cell to capture details (Washif et al., 2022b). Responses were carefully screened (e.g., exclusion criteria), cleaned (e.g., removal of duplicates), checked for genuinity, and then converted into standardised codes/numbers to facilitate statistical analysis. Test-retest reliability of the survey was rated as good-excellent (ICCs of >.82).

Data collection

The survey was conducted *via* Google Forms, which was disseminated *via* e-mail, personal/group messaging applications (e.g., WhatsApp and Telegram) and social media (e.g., Facebook and Twitter) through networks of the research team. All participants were asked to reflect on their "worst experience" of the lockdown (locally known as Movement Control Order) between March and May 2020.

Statistical analysis

All data were analysed using SPSS v.26 (IBM, Chicago, Illinois, United States). Data are presented using a variety of appropriate descriptive statistics, including frequencies, percentages, and mean ± standard deviation. Mean scores (where related) of two factors (gender, and sport type) or more than two (athlete classification) comparators were compared using an independent t-test and one-way ANOVA with Bonferroni adjusted *post hoc* test, respectively. Contingency tables with Pearson's chi-squared (χ^2) test for independence were utilised to assess the categorical variables. Furthermore, to account for variation due to the sample size (unequal sample size between comparators), adjusted residuals were performed to identify which subsets were significant, or contributed the most (residual greater than 1.96; i.e., significantly higher) or the least (residual less than −1.96; i.e., significantly lower) to the relationships, which corresponds to $p < .05$. A p-value of <.05 was considered statistically significant. Overall data, as well as differences and/or changes before and during lockdown [i.e., ≥10% ($p < .05$), or otherwise noted] in variables are highlighted in the Results section. Visualization of datasets (figures) were made using GraphPad Prism (8.0.1) and Datawrapper (Datawrapper GmbH, Berlin, Germany).

Results

Table 1 shows the demographic characteristics of athletes in Malaysia (n = 686). Most respondents were male (59%), aged 24.2 ± 7.2 years (18–29 years: 82% of the sample), with competitive experience of 8.1 ± 6.3 years, from 50 sports, mostly athletics (12%). All respondents were of various ethnicities who resided in one of 13 states or 3 Federal Territories in Malaysia (Table 1; Figure 1). During the lockdown, athletes were training at home (74%), with <2% having access to gym facilities. At their homes, para-athletes (43%) received more assistance with training equipment than World-Class (23%), Team (9%) and Endurance (4%) athletes.

Training practices of athletes are shown in Table 2. Athletes trained for general strength and health (88%), and muscular endurance (71%). More International- (62%) and National-level (56%) athletes than recreational athletes (36%) dedicated time to improving muscle balance. More females (42%) than males (29%) sourced training materials from social media (e.g., YouTube). More World-Class (64%) and International (55%) athletes received training programs from coaches, or from coaches combined with their own programs (65% in Internationals). More females (30%) than males (19%) trained with partners of equal capacity (fitness), and similarly for World-Class (42%) compared to State and Recreational athletes (16%). More State athletes were training alone (96%) compared to higher classification-level counterparts (≤86%). As part of lockdown training, more World-Class (48%) than lower classification-level athletes (≤34%) used innovative/modern training modalities (e.g., digital based, Avatars, Zwift racing) to maintain/improve fitness. A greater proportion of higher classification-level (especially World Class athletes, 48%) athletes performed weightlifting/strength training than State athletes (20%). More International (45%) and National (44%) athletes performed plyometric training than the other athlete classifications. Also, more International athletes performed plyometrics (43%) and sport-specific technical skills (46%) than others (Table 2).

Changes in training intensity (Figure 2), frequency, and duration are shown in Figure 3. Overall, the training intensity of sport-specific training during lockdown was approximately 66% of pre-lockdown levels, without a marked difference among the comparators (Figures 2, 3). There was a ~20% reduction in athletes who trained ≥5 sessions/week, during lockdown. World-Class athletes had similar training frequencies pre- and during-lockdown (84% vs. 85%). Training

FIGURE 1
Distribution of respondents based on athletes' residence in Malaysia.

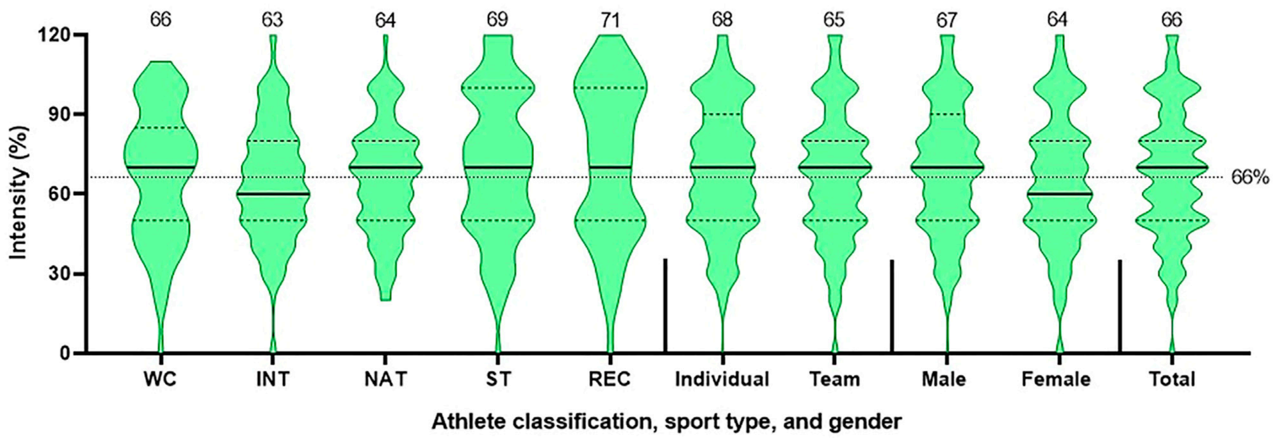

FIGURE 2
Training intensity depicted by athlete classification, sport-type, gender, and total cohort (*n* = 665). (Question: Do/did you maintain your pre-lockdown intensity for sports specific training (practicing your sport) during the lockdown? Can you estimate how much in percentage? (100% represents the same intensity as before the lockdown). Note: The violin plot includes a 5-point summary, which represents the number in dataset: minimum (lower extreme); 25% percentile (first dashed line/lower quartile); median (black thick line); 75% percentile (second dashed line/third quartile); and maximum (upper extreme). The thin dotted line across all charts/violins represents average intensity.

duration of all athletes was reduced (24%–59%), especially the National (50%), International (39%) and World-Class (40%) athletes. In terms of training space and equipment (Figure 4), athletes had less training space/access (69%), including equipment (69%), for cardiorespiratory training, which was more available for technical and strength training (Figure 4). More World-Class athletes (62%) had greater access to necessary equipment for strength training than the other classifications (<50%) (Figure 4).

Athletes' monitoring, recovery, and injury prevalence are shown in Table 3; Figure 5. During lockdown, contact with a coach/trainer at least once per day occurred more among World-Class (41%) and International (40%) than State (18%) and Recreational (19%) athletes. A large number of World-Class athletes monitored training load (77%) than other athletes. Training monitoring by fitness coaches occurred more commonly among World-Class athletes (45%), than State (19%) and Recreational (7%) athletes. World-Class athletes had their training loads monitored mostly *via* questionnaire (33%) and RPE (27%) scales/methods. One main mode of physical recovery, which was similar across all comparative variables, was stretching (68%). Overall, 38% of athletes included injury prevention exercises (e.g., stretching, stability, mobility, flexibility) and 18% reported experiencing mild injury. Of these, 18% (across all athletes) received a medical diagnosis, mostly among International athletes (31%). The reported injuries (*n* = 82) were mostly related to the knee (29%) and ankle (26%) (Figure 5).

Psychological and financial status of athletes are shown in Table 4; Figure 6. Lower classification athletes, especially State (44%) athletes agreed that the mandated lockdown increased feelings of mental vulnerability. More of these athletes (36%) also agreed feeling anxious during lockdown, compared to higher classification-level

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TABLE 2 Training practices during COVID-19 lockdown in Malaysia by athlete classification, sport-type, gender, and total cohort (percentage of respondents).

	Athlete classification					Sport-type		Gender		
	WC^{A}	INT^{B}	NAT^{C}	ST^{D}	REC^{E}	Ind	Team	Male	Female	Total
1. What are/were your general purpose(s) of training during the lockdown? *To maintain/develop:*										
. . .general fitness and health	83	91	84	91	84	87	89	89	86	88
. . .skills/technique	45	49	53	47	51	48	49	53	45	49
. . .strength and power	56	68	65	66	65	64	66	67	62	65
. . .muscular endurance	75	73	72	64	75	68	72	72	68	71
. . .abdominal strength	53	60	58	43	40	50	55	54	51	53
. . .aerobic fitness	52	62	61	63	56	64	57	61	60	61
. . .general flexibility	45	54	48	39	42	44	48	48	44	46
To improve muscle balance	52	62^{DE}	56^{E}	38	36	48	53	53	48	51
Weight management	55	65	59	55	56	61	57	59	59	59
Other	0	1	1	2	2	2	1	1	1	1
2. Who is prescribing/prescribed the training program during the lockdown?										
Own training program	27	27	38	51^{AB}	67^{AB}	41	41	39	40	40
Coach or trainer	47	65^{DE}	60^{E}	47	36	50	58	58*	50	55
Combination of above	64^{DE}	55^{DE}	48^{E}	37	20	45	47	45	48	46
External source: YouTube etc.	17	35	36^{A}	38^{A}	31	35	34	29	42*	34
Other	0	0	2	1	4	1	1	1	1	1
3. Do/did you train?										
Alone	77	86	85	96^{ABC}	93	85	90	90	86	88
With partners of equal capacity	42^{DE}	26	24	16	16	24	24	19	30^{A}	24
With other family/friends	23	24^{D}	15	11	15	19	15	16	18^{A}	17
Others	0	0	1	1	0	0	1	0	1	0
4. Do you/have you been using innovative/modern ways to maintain/improve your fitness levels to adapt to the lockdown conditions?										
Yes	48^{BCDE}	28	34	30	30	31	33	34	29	32
No	52	72	67	70	70	69	67	66	71	68
5. What are the type of exercises that you are doing/have been doing consistently (at least twice a week) during lockdown?										
Body-weight based exercises	59	66^{D}	57	46	52	56	55	53	59	56
Strength/weightlifting training	48^{DE}	35^{D}	38^{D}	20	18	25	35	30	33	32
Technical skills (sport specific)	41	50	44	39	30	40	44	40	45	43
Technical imitation	34	32	28	23	29	28	27	26	30	28
Cardio training (e.g., HIIT)	63	53	57	74^{BC}	66	62	65	64	60	62
Plyometrics	16	45^{ADE}	44^{ADE}	29	23	31	42	37	36	36
Others	0	1	0	2	7	2	1	2	1	1

(Continued on following page)

TABLE 2 (*Continued*) **Training practices during COVID-19 lockdown in Malaysia by athlete classification, sport-type, gender, and total cohort (percentage of respondents).**

	Athlete classification					Sport-type		Gender		
	WC[A]	INT[B]	NAT[C]	ST[D]	REC[E]	Ind	Team	Male	Female	Total
6. What are the types of specific training you are/were able to do with the same intensity during the lockdown (very similar to pre-lockdown)?										
Warm up and stretching	84	91	87	81	82	85	87	87	85	86
Strength/weightlifting training	35	30	37	28	22	28	33	29	33	31
Plyometrics	24	43[D]	38	28	24	33	37	36	33	34
Technical skills (sport-specific)	30	46[D]	36	30	27	40	31	35	36	36
Speed training	24	40	32	40	44	30	42	31	40*	36
Speed endurance	21	32	27	37	42	28	34	29	33	31
Long endurance	30	33	36	45	44	37	38	35	39	37
Interval training	41	48	45	57	47	48	51	51	48	49
Change of directions	10	16	15	13	7	9	18	10	16*	13
Others	0	1	0	1	0	0	1	1	0	0

Note: Unless otherwise specified, the number of participants for each question is at least 95% ($n = 650$) of the total cohort; WC, world-class; INT, international; NAT, national; ST, state; REC, recreational; Ind, individual sports; Team—team sports. *significantly higher ($p <$ .05) or significant contributor to the relationship (for sport-type and gender); and superscript letters. A/B/C/D/E (for athlete classification) indicates significance ($p < .05$), based on residuals of >1.96.

athletes (14%–21%). A greater proportion of higher classification-level athletes, especially International (62%) compared to State athletes (42%), developed their mental skills/performance by watching competitions or practising mental training. More Individual-sport (79%) than team-sport (63%) athletes experienced financial difficulty during lockdown, as well as World-Class athletes (86%) compared to National and State athletes (both 67%) (Figure 6).

Sleep pattern data during lockdown is shown in Table 5. Lower-classification athletes practised power naps during the daytime, both before (State 71%, Recreational 78%) and during lockdown (70% and 71%, respectively). More athletes indicated that their sleep quality was "normal" (49%) and improved (35%), than those who reporting "worsened" sleep (16%). Similarly, for sleep quantity, 49% of respondents indicated normal, 27% improved, and 14% worsened. State athletes typically had inferior sleep quality (27%) and quantity (24%) (Table 5).

Discussion

Key training variables of athletes from Malaysia were substantially altered during the mandated COVID-19 lockdown, especially for different classification athletes (World-Class, National, State, and Recreational). Despite the observed overall reduction in training frequency, the proportion of World-Class athletes training at least five times weekly during lockdown was preserved. This group, and other athletes, however, reduced their training duration per session, training intensity (during sport-specific training), and performed alternative training modes. Most athletes aimed to maintain or develop general strength and health, and muscular endurance, utilising body-weight-based exercises. Interestingly, most of higher classification-level athletes (World-Class, International) received their training programs from coaches, using innovative/modern methods (e.g., digital-based), with more opportunities to perform weightlifting/strength (proper equipment), plyometrics, and sport-specific technical skills than lower classification-level athletes. Higher classification-level athletes had regular contact with coaches/trainers, which facilitated their training monitoring. Even though some athletes practised injury prevention exercises, ~18% reported suffering from a mild injury (e.g., knees and ankles) during the lockdown. These findings indicate that athletes, coaches, and support staff need logistical support that facilitates training in a lockdown situation.

Athletes reported that lockdown situations made them mentally more vulnerable, along with increased anxiety feeling, especially the lower classification-level athletes, regardless of sport type (individual or team) or gender. Higher classification-level athletes (e.g., International) spent more time training mental skills/performance by watching competitions or undertaking mental training. Interestingly, sleep patterns were generally unaffected as more athletes indicated sleep quality and quantity to be "normal" or "improved" during lockdown compared to pre-lockdown. Conversely, "worsened" sleep was reported among lower classification-level (State) athletes. The majority of athletes reported financial difficulties, especially among individual sports, and World-Class athletes. During lockdown situations, decisive efforts to scale-up assistance (e.g., physical, mental and wellbeing related support) are necessary, e.g., put into place measures that facilitate the training (even if quarantine- or home-based) and protect the wellbeing (including mental and finance related support) of athletes.

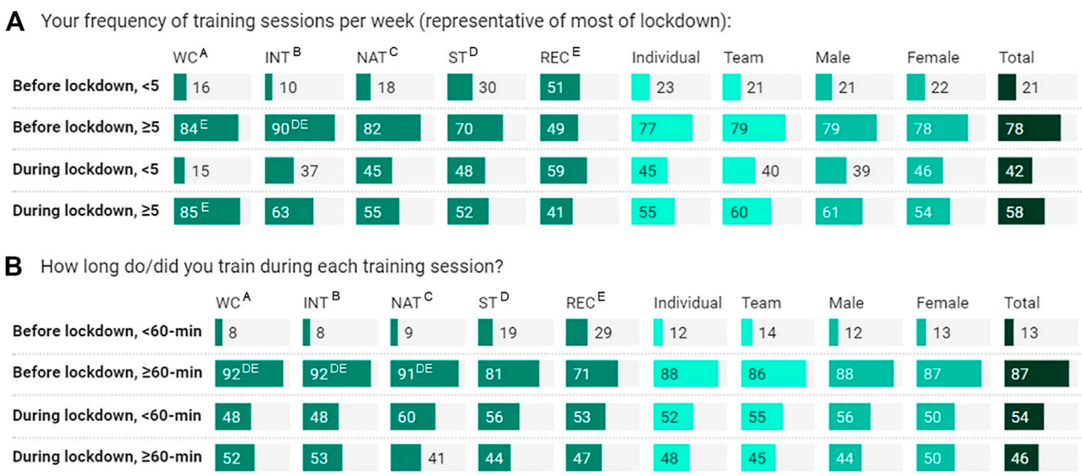

FIGURE 3
Training frequency (< or ≥ 5 sessions/week; **(A)**) and duration (< or ≥ 60 min/session **(B)**) based on athlete classification, sport-type, gender, and total cohort, before and during lockdown; data are column % of respondents (n = 661). Percentage, within athlete classification, sport-type, and gender represents "yes" answer, relative to "no" answer. WC, world-class; INT, international; NAT, national; ST, state; REC, recreational. *Significantly higher (or significant contributor to the relationship); superscript letter represents significantly higher than A/B/C/D/E; all at p < .05, based on residuals of >1.96.

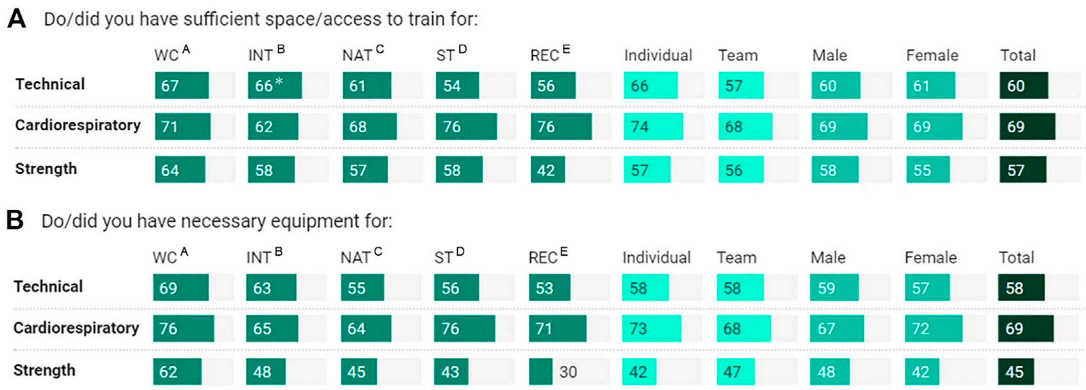

FIGURE 4
Training space/access **(A)** and equipment **(B)** for technical, cardiorespiratory, and strength by athlete classification, sport-type, gender, and total cohort (n = 660). Percentage, within athlete classification, sport-type, and gender, represents "yes" answer, relative to "no" answer. WC, world-class; INT, international; NAT, national; ST, state; REC, recreational. *Significantly higher (or significant contributor to the relationship); superscript letter represents significantly higher than A/B/C/D/E; all at p < .05, based on residuals of >1.96.

Home/modified training (in a lockdown context) appeared to compromise weekly training frequency, intensity of sport-specific training, and session duration. These negative impacts in training variables are likely associated with facility limitations, e.g., limited availability of training space and equipment, as reported among athletes in many other countries worldwide (Pillay et al., 2020; Washif et al., 2022b; Pagaduan et al., 2022). A similar proportion of World-Class athletes (~86%) maintained their pre- and during-lockdown training frequency of ≥5 times per week. When lockdowns were instigated, many World-Class athletes were already in their preparation for major competitions (e.g., Olympic Games, World cups, and international tours), and endeavoured to practice "everyday". Some of these athletes also received/bought new equipment, further enabling this training consistency/maintenance (Washif et al., 2022b; Meier et al., 2022). During lockdown, home-based or modified training (i.e., bodyweight-based) widely replaced the traditional resistance training, which is similar to the changes reported in our global study (Washif et al., 2022b). It is reasonable to surmise that these changes were responsible for the 35% reduction in training intensity in the current study. An important caveat is that training intensity is a key component required to preserve fitness (Mujika, 2010), including endurance and strength performance (Izquierdo et al., 2007; Mujika, 2010; McMaster et al., 2013; Spiering et al., 2021). It is important that a decrease in strength level may be observed after a 3-week cessation of resistance training, and exacerbated after ≥5 weeks (McMaster et al., 2013). It would seem that athletes in Malaysia preserved their weekly training frequency (especially the World-Class cohort) when other key training variables (e.g., duration, intensity) were compromised.

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TABLE 3 Monitoring, recovery, and injury by athlete classification, sport-type, gender, and total cohort, during COVID-19 lockdown in Malaysia (percentage of respondents).

	Athlete classification					Sport-type		Gender		
	WC^{A}	INT^{B}	NAT^{C}	ST^{D}	REC^{E}	Ind	Team	Male	Female	Total
1. If your coach or trainer is/was in contact with you, is/was this?										
At least once a day	41^{D}	40^{E}	29	18	19	30	29	30	30	30
At least once a week	37	38	42	35	25^{ABCD}	34	39	39	34	37
Two to three times a month	13	11	11	13	11	11	12	10	14	12
Once a month or less	3	5	7	7	2	4	7	6	6	6
They never contacted me	3	4	6	13^{A}	6	9	6	8	6	7
Other	3	2	5	14^{BC}	38^{BC}	12	7	8	11	9
2. Is/was there anybody monitoring your training load and/or wellness during your lockdown training?										
Yes	77^{DE}	60	62	44	44	57	56	56	57	57
No	23	40	38	56	56	43	44	44	43	43
3. If Yes, who does/did this?										
Sports scientist	16^{CE}	14^{CE}	6	7	2	10	8	9	8	9
Fitness coach	45^{DE}	27^{E}	27^{E}	19	7	20	27*	28*	21	25
Coach	50^{DE}	24	17	9	5	14	17	17	16	17
Other	8	4	5	4	12	7	4	3	9	5
4. If Yes, which tools are used/were used to monitor your training load?										
No tools are/were used	20	23	35^{D}	18	27	20	28	28*	21	25
Heart rate monitors	20	14	10	18	14	19	12	14	16	15
Rating of Perceived Exertion	27^{CD}	13	9	7	7	15	9	10	13	11
Daily diary	23	21	20	21	14	24	16	20	21	20
Questionnaire(s)	33^{BCDE}	16	13	11	4	14	14	13	16	14
GPS	6	10	5	8	13	11	6	9	6	8
Other	6	4	5	7	11	8	5	6	6	6
5. What are the modes of physical recovery that you are using/have been using consistently (at least once a week) during the lockdown?										
Not applicable/inconsistent	20	18	24	23	36^{B}	22	23	24	20	23
Ice bath	25	19	19	19	9	17	21	21	16	19
Massage	19	24	16	22	29	18	24	22	20	21
Acupuncture	0	1	2	0	0	2	0	1	1	1
Sauna	9^{C}	3	2	3	0	4	3	4	3	3
Stretching	61	69	71	68	57	69	67	65	72	68
Meditation/relaxation	22	18	16	18	20	17	20	17	19	18
Other	0	2	1	3	4	3*	1	1	3	2
6. During your training, do/did you include any injury prevention exercises at least once weekly?										
Yes (n = 126)	38	37	36	34	30	34	37	38	32	36
No (n = 560)	63	63	64	66	70	66	63	62	68	64

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TABLE 3 (*Continued*) Monitoring, recovery, and injury by athlete classification, sport-type, gender, and total cohort, during COVID-19 lockdown in Malaysia (percentage of respondents).

	Athlete classification					Sport-type		Gender		
	WC[A]	INT[B]	NAT[C]	ST[D]	REC[E]	Ind	Team	Male	Female	Total
7. Did you sustain any mild injury during the lockdown period?										
Yes (*n* = 23)	22	17	18	17	23	19	18	19	17	18
No (*n* = 103)	78	83	82	83	77	81	82	81	83	82
8. If Yes, did you receive a medical diagnosis from a health care professional?										
Yes (*n* = 23)	21	31[D]	16	12	0	16	19	21	12	18
No (*n* = 103)	79	69	84	88	100	85	81	79	88	82

Note: Unless otherwise specified, the number of participants for each question is at least 95% ($n = 650$) of the total cohort; WC, world-class; INT, international; NAT, national; ST, state; REC, recreational; Ind, individual sports; Team – team sports. *significantly higher ($p <$ .05) or significant contributor to the relationship (for sport-type and gender); and superscript letters. A/B/C/D/E (for athlete classification) indicates significance ($p <$ .05), based on residuals of >1.96.

Training duration (volume) is crucial among athletes requiring a high level of endurance. We observed that ~41% of athletes maintained a training duration of ≥60 min (per session), during the lockdown. A similar proportion of athletes training at shorter duration of 30 to ≤60 min (~43%) or at ≥60 min (46%) during lockdown, globally (Washif et al., 2022b). In this context, a weekly training volume of ~380 min (4–5 sessions/week) can improve aerobic fitness and maintain muscular power of soccer players (Rampinini et al., 2021a). Essentially, athletes who were in possession of a home treadmill or a bike would be the least affected by the lockdown situations. This group of athletes appeared to preserve the majority of specific training they performed daily (Washif et al., 2022b). In particular, a previous study reported that endurance runners (especially top-level athletes) predominantly undertake low-intensity, long-duration training, with the addition of highly intensive bouts (Seiler, 2010). Meanwhile, a review of 9 studies (in team sports players) described the typical home training comprising of an average ~5 ± 2 weekly training sessions, with a session duration of ~45–90 min (Paludo et al., 2022). The latter authors reported VO_2max changes from +6% to -9% (highly variable results), increased sprint times (.4%–36%) reflective of poorer sprint performance; and changes in countermovement jump height (−5% to +15%) after home/modified training that focused on muscular strength and endurance (Paludo et al., 2022). Furthermore, with similar training focuses, minor changes were reported in reactive agility performance of −12% (Pucsok et al., 2021), and one-repetition maximum strength of −3% (Pedersen et al., 2021). It appears there are highly variable between-athlete changes in physiological and performance changes due to the COVID-19 lockdowns (Paludo et al., 2022).

During the Malaysian lockdown, athletes modified their training aims, and mostly trained for general strength and health, and muscular endurance. It is important that the prevalence of athletes training for muscular endurance was relatively higher (71% vs. 55%) than that reported in a global study (Washif et al., 2022b). These changes were associated with restrictions during the lockdown, further reducing training specificity (e.g., different training modes/types). It is important that, unlike the “transition phase,” “altered training” during lockdown is usually designed to limit detraining effects i.e., to maintain or even improve performance (Washif et al., 2022c). This approach can be facilitated by regular contact with coaches/trainers, i.e., training monitoring (e.g., loading regulation) and prescriptions (e.g., training programs); for athletes to perform an appropriate training program that permits adaptation while reducing the risk of “overreaching” and injury. In the current study, such provisions were seen more often among higher classification-level athletes (i.e., World-Class, International). According to a recent study, World-Class athletes were the least to adopt a self-designed training routine, since they received the greatest support from their coaching team (Pagaduan et al., 2022). Indeed, a structured home-based training program during the COVID-19 lockdown preserved lower limb explosive strength (Font et al., 2021). Additionally, a 3-month period of home-based and group-based interventions (mainly for strength, jump, and sprints) during lockdown was effective for maintaining strength, jumping, and sprinting ability among high-level female football players (Pedersen et al., 2021). In the case of facing limited resources (lockdown situation), a tailor-made home-based exercise program (typically bodyweight-based; Yousfi et al., 2020) not only ensures regular and consistent training, but helps promote health-related

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TABLE 4 Athletes' psychological responses by athlete classification, sport-type, gender, and total cohort, during a COVID-19 lockdown in Malaysia (percentage of respondents).

	Athlete classification					Sport-type		Gender		
	WC^{A}	INT^{B}	NAT^{C}	ST^{D}	REC^{E}	Ind	Team	Male	Female	Total
1. Lockdown can make me mentally vulnerable (mental)										
Strongly agree	6	6	7	11	11	9	8	8	8	8
Agree	25	24	25	44^{BC}	40	29	33	30	33	31
Neutral	36^{D}	29^{D}	34^{D}	15	22	24	30	28	26	27
Disagree	17	36	27	23	20	29	25	29	25	27
Strongly disagree	16^{B}	4	6	8	6	9*	4	6	8	7
Don't know	0	1	1	0	2	0	1	0	1	1
2. During lockdown I feel/felt anxious (anxiety)										
Strongly agree	8	4	7	7	4	5	6	5	6	6
Agree	14	21	18	36^{ABC}	22	20	26	24	23	23
Neutral	39	27	32	24	33	30	29	28	30	29
Disagree	20	41^{AD}	33	24	29	31	30	32	30	31
Strongly disagree	17	6	10	8	9	12*	7	9	9	9
Don't know	2	2	2	2	4	2	2	2	2	2
3. During the lockdown I am/was constantly scared to get infected by the COVID-19 virus										
Strongly agree	10	14	12	12	18	10	16*	14	11	13
Agree	27	36	31	29	27	28	34	31	31	31
Neutral	35	27	30	24	16	28	26	29	23	27
Disagree	21	14	16	22	20	21*	14	13	24*	18
Strongly disagree	6	7	10	12	16	11	9	10	10	10
Don't know	2	2	2	1	2	2	1	2	1	2
4. Do you/have you been watch(ing) competitions from your sport or practiced mental training in order to work on (improve) your mental skills/performance?										
Yes	58	62^{D}	53	42	53	55	50	56	49	53
No	42	38	47	58	47	45	50	44	51	47

Note: Unless otherwise specified, the number of participants for each question is at least 95% ($n = 650$) of the total cohort; WC, world-class; INT, international; NAT, national; ST, state; REC, recreational; Ind, individual sports; Team—team sports. *significantly higher ($p < .05$) or significant contributor to the relationship (for sport-type and gender); and superscript letters. $^{A/B/C/D/E}$ (for athlete classification) indicates significance ($p < .05$), based on residuals of >1.96.

TABLE 5 Sleep pattern during lockdown in Malaysia based on athlete classification, sport-type, gender, and total cohort (percentage of respondents).

	Athlete classification					Sport-type		Gender		
	WC^{A}	INT^{B}	NAT^{C}	ST^{D}	REC^{E}	Ind	Team	M	F	Total
1. Usually, pre-lockdown I used to have naps during the day time.										
Yes	59	52	55	71^{BC}	78^{BC}	69*	55	57	65*	61
No	41	48	46	29	22	31	45	43	35	40
2. Usually, during lockdown I used to have naps during the day time.										
Yes	57	51	53	70^{BC}	71	66*	54	57	62	59
No	44	49	47	30	29	34	46	43	38	41
3. Compared to pre-lockdown, during lockdown my average sleep quality is/has been:										
Very much improved	3	9	11	6	2	9	7	7	8	8
Improved	30	25	26	19	38^{D}	21	28	26	24	25
Normal	52	52	46	47	49	52	47	51	46	49
Worsened	13	12	13	27^{BCE}	7	16	16	14	19	16
Very much worsened	3	2	4	1	4	2	3	2	4	2
4. Compared to pre-lockdown, during lockdown my average sleep quantity is/has been:										
Very much improved	3	9	9	7	9	10	6	8	8	8
Improved	30	27	30	21	33	23	30	27	27	27
Normal	50	54	47	47	47	52	47	51	46	49
Worsened	13	10	12	24^{BC}	7	14	15	13	16	14
Very much worsened	5	2	3	0	4	2	3	1	3	2

Note: Unless otherwise specified, the number of participants for each question is at least 95% ($n = 650$) of the total cohort; WC, world class; INT, international; NAT, national; ST, state; REC, recreational; Ind, individual sports; Team—team sports. *significantly higher ($p < .05$) or significant contributor to the relationship (for sport-type and gender); and superscript letters. $^{A/B/C/D/E}$ (for athlete classification) indicates significance ($p < .05$), based on residuals of >1.96.

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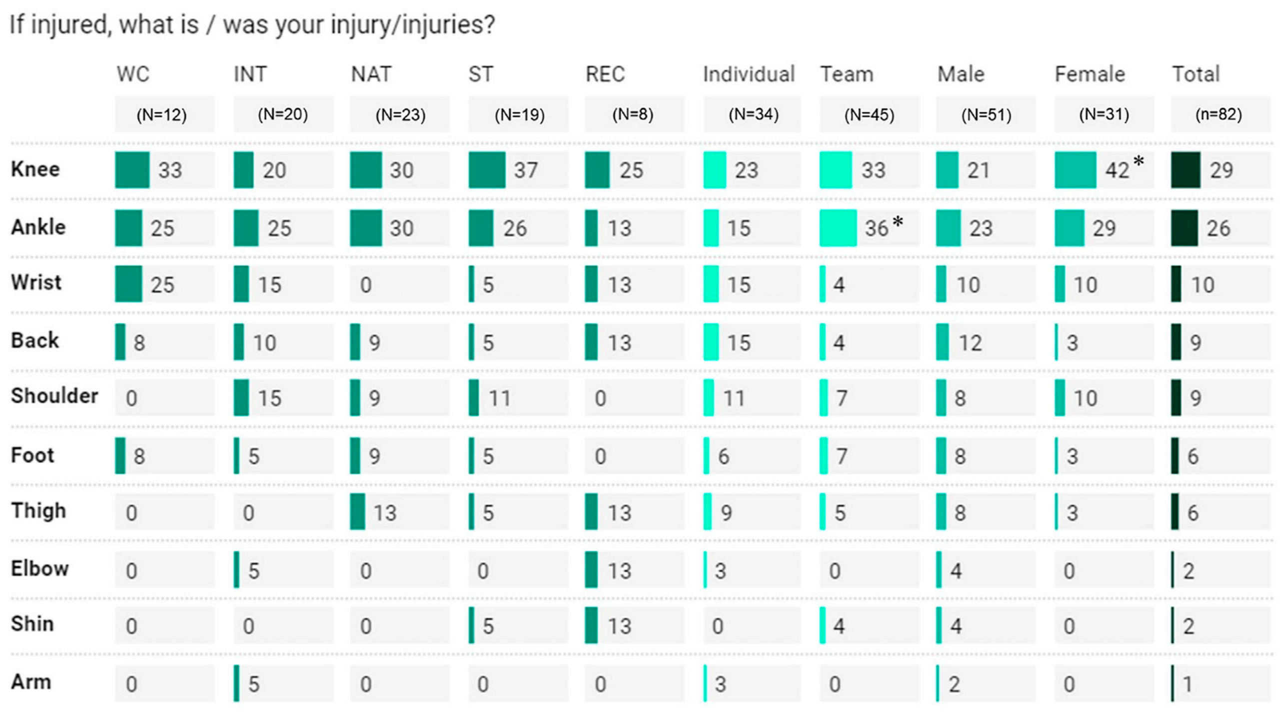

FIGURE 5
Injury prevalence as shown by muscle areas Percentage, within athlete classification, sport-type, and gender, represents "yes" answer, relative to "no" answer. WC, world-class; INT, international; NAT, national; ST, state; REC, recreational. *Significantly higher at $p < .05$ (within the specific comparative variable).

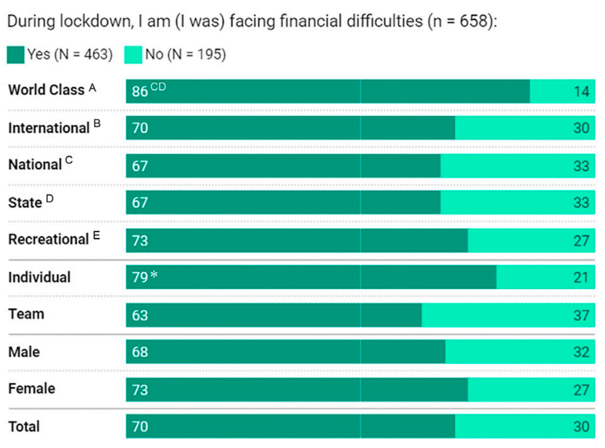

FIGURE 6
Financial challenges during lockdown based on athlete classification, sport-type, gender, and total cohort; data are presented in percentage. [CD]Significantly higher than National and State, *significantly higher at $p < .05$ (within the specific comparative variable).

benefits (mental, emotional, and physical). Further, athletes may take advantage of the hot and humid conditions (e.g., Malaysia), and use clothing/garments that restrict heat loss while training at home as a means to 'heat up' the body temperature and heart rate to boost metabolic responses (Willmott et al., 2018). Even though beneficial for fitness maintenance (or improvement), the safety ramifications of home-based and modified training have not been assured (Washif et al., 2022b). In the current study, ~18% of athletes reported a mild injury, mostly knee and ankle injuries, irrespective of sports, gender, and level of athletes, despite ~36% of the athletes implementing injury prevention exercises as part of their training at home. These phenomena could be as a result of the abrupt resumption of high-intensity training to be ready for the competitions after lockdown (Bazett-Jones et al., 2020; DeJong et al., 2021).

Remote conditioning training aims at maintaining some level of training and preserving some social connections. Collaterally, decreases in training were linked with higher depression, anxiety, and stress symptoms during the COVID-19 lockdown (Facer-Childs, et al., 2021). Some elite athletes reported psychological distress due to training cessation during lockdown (di Cagno et al., 2020; Jia et al., 2022; Venturelli et al., 2022), changes in sleep (Facer-Childs et al., 2021; Romdhani et al., 2022b), financial problems, among others. In the current study, the majority of athletes reported financial difficulties, especially among individual-sport, and World-Class athletes; an extra stressor that potentially impacted the athletes' mental health (Busch et al., 2022). Individual and team-based sports obtained mixed results with both categories indicating increased risks for poor mental and emotional health (Jia et al., 2022). In professional football, the prevalence of anxiety (8%–18% in females) and depression (6%–13% in males) increased during the COVID-19 lockdown (Gouttebarge et al., 2022). Athletes in the present study, especially the lower classification-levels, reported that they felt mentally vulnerable, and similarly, had increased anxiety levels. Such observations may relate to reduced or missing interactions with teammates, including "online team training" that was also limited among lower classification-level athletes, as shown in the current study. In contrast, higher classification-level athletes might have adequate (more) social support and/or connections (e.g., during "online training" sessions), with some athletes practising their mental skills to improve their mental status. Concomitantly, mental health was associated with lockdown-induced sleep pattern changes (i.e., increased total sleep time and sleep latency) (Facer-Childs et al., 2021). In the current study, sleep patterns were generally unaffected as more athletes indicated that their sleep quality and quantity were "normal", and for some sleep was "improved" during the lockdown. However, relatively poorer sleep patterns were reported among lower classification-level (State) athletes. We are unable to directly identify what caused the worsening of sleep in the lower classification-level athletes, but it can likely be attributed to several factors, including financial difficulties and/or reduced social connections during training.

To our knowledge, only a few country-specific studies have investigated training practices, recovery, sleep, mental, and injury prevalence of athletes for different classification athletes (recreational to World-Class levels), different sports, and gender. Here we report the results of athletes from 50 sports (individual and team). However, this study is not without limitations. Subjective questionnaires were used to obtain responses from participants retrospectively and therefore subject to recall bias. Here we considered a convenience sampling approach that limits the generalisability of our findings. Furthermore, a qualitative analysis through interviews might address more detailed (or specific) issues of athletes from a different perspective of performance; whereas questionnaires we used were specific to our objectives, albeit checked and verified by a large number of researchers and scientists including experts (e.g., in sports performance, periodisation, detraining, recovery, sleep, psychology, injury, among others). Ramadan fasting occurred in the early the lockdown, and might have impacted on the results (Romdhani et al., 2022a), which we addressed elsewhere (Washif et al., 2022d). Moreover, data concerning injury prevalence is only specific to athletes with acute mild (light) injury as we did not consider the participation (survey) of athletes having moderate or severe injuries, which further limits the conclusions regarding injury prevalence during the lockdown.

Conclusion

The early mandated COVID-19 lockdown in Malaysia (2020) induced more severe effects on the training-related practices of lower classification-level athletes. World-Class athletes experienced the fewest effects on training-related issues (e.g., training programs, sport-specific training, monitoring, and equipment). Overall, the key training variables of frequency, intensity, duration, and modes were compromised. During the lockdown, athletes focused more on preserving (or possibly enhancing) general strength and health, with an emphasis on muscular endurance given high accessibility to bodyweight-based related exercises. Some other exercises (e.g., plyometrics) were emphasised and their use was mediated by athlete classification level. Training at home (including modified training) was associated with safety considerations, as a substantial proportion of athletes reported having had mild "injuries" during the lockdown. Recognising the associated challenges, a one-size-fits-all program may not be ideal during lockdowns. Thus, we recommend objective-driven country-specific support to athletes; possibly implemented as home-based support e.g., fitness training, psychology, financial, and lifestyle. It might be necessary to consider an arrangement that permits "bubble training/competition" to reduce lockdown-associated challenges, and facilitate regular training during the lockdown, not only for high classification-level athletes, but also State- and/or National-level athletes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by National Sports Institute of Malaysia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The study was designed by all authors. All authors involved in the survey development. JW, L-YK, and CJ involved in data collection. JW and AF performed the statistical analysis. JW prepared the first draft. The manuscript was critically revised by all authors. All authors approved the manuscript's final version.

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Conflict of interest

Author CJ is employed by Hong Kong Sports Institute Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The causal effect of physical activity intensity on COVID-19 susceptibility, hospitalization, and severity: Evidence from a mendelian randomization study

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The protection of physical activity (PA) against COVID-19 is a rising research interest. However, the role of physical activity intensity on this topic is yet unclear. To bridge the gap, we performed a Mendelian randomization (MR) study to verify the causal influence of light and moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity. The Genome-Wide Association Study (GWAS) dataset of PA (n = 88,411) was obtained from the UK biobank and the datasets of COVID-19 susceptibility (n = 1,683,768), hospitalization (n = 1,887,658), and severity (n = 1,161,073) were extracted from the COVID-19 Host Genetics Initiative. A random-effect inverse variance weighted (IVW) model was carried out to estimate the potential causal effects. A Bonferroni correction was used for counteracting. The problem of multiple comparisons. MR-Egger test, MR-PRESSO test, Cochran's Q statistic, and Leave-One-Out (LOO) were used as sensitive analysis tools. Eventually, we found that light PA significantly reduced the risk of COVID-19 infection (OR = 0.644, 95% CI: 0.480–0.864, p = 0.003). Suggestive evidence indicated that light PA reduced the risks of COVID-19 hospitalization (OR = 0.446, 95% CI: 0.227 to 0.879, p = 0.020) and severe complications (OR = 0.406, 95% CI: 0.167–0.446, p = 0.046). By comparison, the effects of moderate-to-vigorous PA on the three COVID-19 outcomes were all non-significant. Generally, our findings may offer evidence for prescribing personalized prevention and treatment programs. Limited by the available datasets and the quality of evidence, further research is warranted to re-examine the effects of light PA on COVID-19 when new GWAS datasets emerge.

KEYWORDS
COVID-19, public health, sports science, exercise, individual treatment

1 Introduction

Coronavirus disease 19 (COVID-19) is an infectious disease first detected in December 2019, which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus (Yuki et al., 2020; Chen Y. et al., 2022). This virus is primarily transmitted *via* airborne routes, making it highly infectious and thereby a global pandemic (Greenhalgh et al., 2021). According to the Center for Systems Science and Engineering at Johns Hopkins University, the pandemic has caused over 623.9 million confirmed cases and over 6.5 million confirmed deaths by 14 October 2022 (Weber et al., 2016). Vaccine injection is currently the most effective strategy against the pandemic (Chen Y. et al., 2022). However, the vaccine's effectiveness appears to be unsatisfactory owing to the SARS-CoV-2 mutation, such as the Omicron variant (Abdool Karim and de Oliveira, 2021; Zhang M. et al., 2022; Singanayagam et al., 2022). Given that, identifying behaviorally protective factors in mitigating COVID-19 is necessary for prescribing personalized treatment programs and reasonably allocating public health resources (Chen X. et al., 2022).

Physical activity (PA) is one of the most popular strategies for public health promotion (Zhang et al., 2022a; Zhang et al., 2022b). In the past decades, PA has been widely implemented to cope with various health problems, such as cardiovascular disease (Wannamethee and Shaper, 2001), Alzheimer's disease (Scarmeas et al., 2009), and most importantly, upper-respiratory tract disease (Matthews et al., 2002). These underscore the potential of PA in the prevention and treatment of COVID-19. For instance, observational studies have implied that PA is associated with a lowered risk of COVID-19 hospitalization, severity, and mortality (Hamer et al., 2020; Steenkamp et al., 2022). However, due to the inherent defects of traditional observational studies that the possibility of reverse causality and confounding factors cannot be entirely excluded (Sekula et al., 2016), the efficacy of PA in preventing COVID-19 remains unclear.

Mendelian randomization (MR), by contrast, is an ideal approach to cope with the defects described above. MR can effectively preclude confounding factors and uncover causal relationships by using genetic variants randomly allocated conception to proxy exposure (Davey Smith and Hemani, 2014; Davies et al., 2018). So far, several MR studies have been performed to check the effect of PA on COVID-19 outcomes. Zhang et al. (2020) found that some PA variables (except for moderate-to-vigorous PA) lowered the COVID-19 infection and outpatient, and similar findings were reported elsewhere (Chen X. et al., 2022). These studies collectively indicate that the effect of PA on COVID-19 outcomes may vary with intensity. Nevertheless, the other ranges of PA intensity, such as light PA, are understudied. Accordingly, the current MR study aimed to examine the causal effects of light and moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity.

2 Materials and methods

2.1 Study design

In the current study, a two-sample Mendelian randomization design was selected to estimate the potential causal influence of light and moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity. Single nucleotide polymorphisms (SNPs) were used as instrumental variables to exclude confounding factors and infer causality. To control population stratification bias, we kept mainly individuals of European ancestry for the current analyses (Lin et al., 2022). Our study design is as follows:

(1) SNPs associated with exposure (light and moderate-to-vigorous PA) were identified at the genome-wide significance threshold;
(2) SNPs are independent of potential confounders;
(3) SNPs affect COVID-19 only *via* exposure.

2.2 Data sources and single-nucleotide polymorphisms selection

2.2.1 Physical activity

Genome-wide association study (GWAS) data for accelerometer-measured PA was obtained from the UK Biobank (http://www.nealelab.is/uk-biobank) (Qi et al., 2022). The GWAS data involve 88,411 European ancestry participants (Qi et al., 2022). The GWAS data were adjusted for age, sex, and the first 20 genetic principal components (Qi et al., 2022). Two PA phenotypes were included in the current MR analysis as exposures, including light and moderate-to-vigorous intensity. Light PA was defined as the duration during which the acceleration was at least 30 mg (Milli-gravity) but lower than 100 mg. On the other hand, moderate-to-vigorous PA was defined as the duration during which the acceleration was at least 100 mg. The SNPs were selected by the following criteria: 1) SNPs associated with accelerometer-measured PA were identified at the genome-wide significance threshold ($p < 5 \times 10^{-7}$) (Kanai et al., 2016); 2) SNPs without linkage disequilibrium ($r^2 < 0.01$ and clump window <10 MB) (Yuan et al., 2022); 3) SNPs without potential pleiotropic effects (Bahls et al., 2021); and 4) SNPs having F-statistic >10 was considered evidence of valid instrumental variables and were excluded from MR analysis (Papadimitriou et al., 2021; Ren et al., 2022).

Finally, seven SNPs were used as instrumental variables (IVs) for light PA (Supplementary Table S1), and five SNPs were used for moderate-to-vigorous PA (Supplementary Table S2).

2.2.2 COVID-19 outcomes

The GWAS datasets for COVID-19 outcomes were obtained from the COVID-19 Host Genetics Initiative, which is an international genetics collaboration aiming to discover the genetic determinants of COVID-19 and its consequences (COVID19-HGI, 2021; Leong et al., 2021). The GWAS datasets were adjusted for age, age^2, sex, age × sex, principal components, and study-specific covariates by the original GWAS investigators (Yeung et al., 2022). Three COVID-19 phenotypes were included in the current study as outcomes, including susceptibility, hospitalization, and severity. The GWAS dataset of COVID-19 susceptibility compares COVID-19 cases (n = 38,984) with population controls (n = 1,644,784). In the dataset, COVID-19 cases are defined as laboratory-confirmed SARS-CoV-2 positive from electronic health records or doctor diagnoses or self-reported (Chen X. et al., 2022). Population controls are defined as any individuals without a history of COVID-19 (Chen X. et al., 2022). The GWAS dataset of COVID-19 hospitalization compares hospitalized COVID-19 cases (n = 9,986) with population controls (n = 1,877,672). In the dataset, hospitalized COVID-19 cases are defined as hospitalized patients with COVID-19 (Chen X. et al., 2022). Population controls are defined as any individuals without hospitalization experience for COVID-19 (including individuals without COVID-19) (Chen X. et al., 2022). The GWAS dataset of COVID-19 severity compares severe COVID-19 cases (n = 5,870) with population controls (n = 1,155,203). In the dataset, severe COVID-19 cases are defined as hospitalized individuals with COVID-19 who required respiratory support (such as intubation, continuous positive airway pressure, bilevel positive airway pressure, etc.,) (Cui and Tian, 2021). Population controls are defined as any individuals without several COVID-19 (including individuals without COVID-19) (Cui and Tian, 2021).

TABLE 1 Results of the IVW model and statistic power.

Outcome	Intensity	OR (95% CI)	*p*	F-statistical
Susceptibility	Light PA	0.644 (0.480–0.864)	$p = 0.003$**	3,840
	M-V PA	1.243 (0.530–2.916)	$p = 0.617$	2,533
Hospitalization	Light PA	0.446 (0.227–0.879)	$p = 0.020$*	4,305
	M-V PA	1.987 (0.320–12.332)	$p = 0.461$	2,840
Severity	Light PA	0.406 (0.167–0.446)	$p = 0.046$*	2,648
	M-V PA	1.966 (0.334–11.559)	$p = 0.455$	1767

Note: PA; physical activity, M-V; moderate to vigorous, *; suggestive evidence ($0.008 < p < 0.05$), **; statistically significant ($p < 0.008$).

TABLE 2 Results of sensitively tests.

		Q statistic	MR-egger	Leave-one-out
Susceptibility	Light PA	$p = 0.367$	$p = 0.165$	No outliers
	M-V PA	$p = 0.002$*	$p = 0.505$	No outliers
Hospitalization	Light PA	$p = 0.198$	$p = 0.878$	Outliers
	M-V PA	$p = 0.001$*	$p = 0.638$	No outliers
Severity	Light PA	$p = 0.401$	$p = 0.592$	Outliers
	M-V PA	$p = 0.046$*	$p = 0.283$	No outliers

Note: PA; physical activity, M-V; moderate to vigorous, *; statistically significant ($p < 0.05$).

2.3 Statistical analysis

In the current MR study, a random-effect inverse variance weighted (IVW) model was carried out to verify the causal influence of PA intensity (light and moderate-to-vigorous intensity) on COVID-19 susceptibility, hospitalization, and severity (Burgess et al., 2017). The IVW model can offer a pooled causal estimate by combining the Wald ratio of each SNP on the outcome (Chen X. et al., 2022). The results of the IVW model were presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). The statistical power of SNPs was calculated by an online tool available at http://cnsgenomics.com/shiny/mRnd/ (Brion et al., 2013). Considering multiple testing, Bonferroni-correction was used for setting significance level (Larsson et al., 2020). A *p*-value <0.008 (0.05/2 exposures/3 outcomes) was considered statistically significant, and a *p*-value between 0.008 and 0.05 was considered suggestive evidence for a causal association (Larsson et al., 2020). Finally, four sensitivity tests were performed as follows: 1) The MR-Egger intercept test was used to assess the directional horizontal pleiotropy, a major threat to the IVW estimator (Bowden et al., 2015). This intercept test can assess the average horizontal pleiotropy of all IVs under the "InSIDE" assumption. An intercept not significantly different from 0 is the evidence of no directional horizontal pleiotropy, otherwise, there can be a directional horizontal pleiotropy or the "InSIDE" assumption is violated (or both) (Burgess and Thompson, 2017); 2) Funnel plots were also used for assessing directional horizontal pleiotropy, and a symmetrical distribution is evidence of no directional pleiotropy; 3) The MR-PRESSO test was also used for assessing horizontal pleiotropy, which evaluates the overall horizontal pleiotropy amongst all IVs in a single MR test by comparing the observed distance of all the variants to the regression line (residual sum of squares) to the expected distance under the null hypothesis of no horizontal pleiotropy (Verbanck et al., 2018). The MR-PRESSO can also re-evaluate the association based on IVW after removing pleiotropic SNPs; 4) Cochran's Q statistic was used to assess the degree of heterogeneity across the individual effect estimates derived from every genetic variant (Liu et al., 2021) and a non-significant Q value may also to a certain extent imply the absence of horizontal pleiotropy issue (Hemani et al., 2018); 5) The Leave-One-Out (LOO) was used to examine if the pooled estimate is disproportionately influenced by each genetic variant (Liu et al., 2021). In the current study, all analyses were conducted using the TwoSampleMR package (version 0.5.6) in R software (version 4.2.1).

3 Results

3.1 MR analysis

3.1.1 Light physical activity

Seven SNPs (rs10166518, rs11179465, rs12021614, rs1268539, rs647347, rs74800845, and rs9878906) were used as instrumental variables for light PA, and no bias of weak instrument was observed in the statistic power test (F-statistic >10). Table 1 shows the causal influence of genetically proxied light PA on COVID-19 susceptibility, hospitalization, and severity. According to the result of the IVW model (Table 1), light PA significantly reduced the risk of COVID-19 infection (OR = 0.644, 95% CI: 0.480–0.864, $p = 0.003$). However, only suggestive evidence indicated that light PA significantly reduced the risk of COVID-19 hospitalization (OR = 0.446, 95% CI: 0.227–0.879, $p = 0.020$) and severe complications (OR = 0.406, 95% CI: 0.167–0.446, $p = 0.046$).

3.1.2 Moderate-to-vigorous physical activity

Five SNPs (rs10067451, rs10880697, rs12041071, rs55938136, and rs6002268) were used as instrumental variables for moderate-to-vigorous PA, and no bias of weak instrumental was observed in the statistic power test (F-statistical >10). Table 1 shows the causal

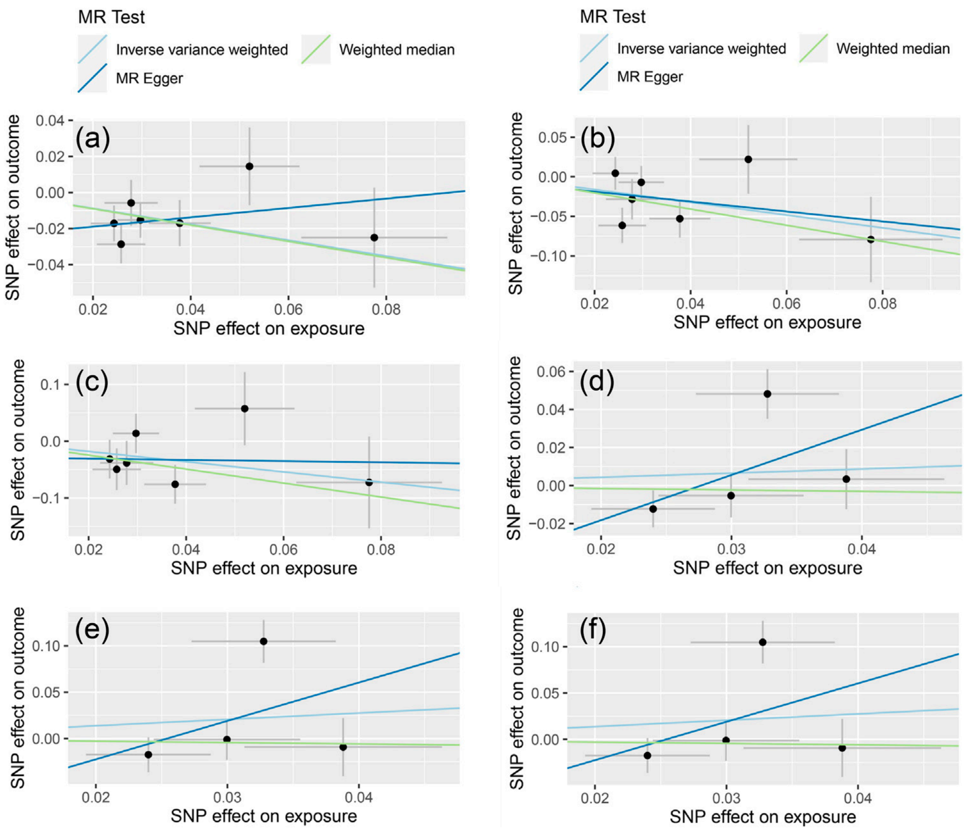

FIGURE 1
The results of MR-Egger regression [The **(A–C)** represent the causal influence of light PA on COVID-19 susceptibility, hospitalization, and severity respectively, the **(D–F)** represent the causal influence of moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity respectively].

influence of genetically proxied moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity. According to the results of the IVW model (Table 1), no statistically significant association was observed regarding the three COVID-19 outcomes.

3.2 Sensitively analysis

In the current MR analysis, we used four sensitive analyses to estimate the robustness of results as following.

3.2.1 Horizontal pleiotropy

The MR-Egger test was performed to assess the directional horizontal pleiotropy, and the results were demonstrated in Table 2; Figure 1. No significant directional horizontal pleiotropy was observed in all results ($p > 0.05$ and the intercept approximated zero). The funnel plots also showed low risks of directional horizontal pleiotropy regarding our IVW estimations (Figure 2). The MR-PRESSO detected no horizontal pleiotropy for the associations of light PA with COVID-19 infection, hospitalization, and severe complications. Some pleiotropic SNPs were found for other non-significant associations, but the re-analyses without those pleiotropic SNPs did not substantially change the results.

3.2.2 Heterogeneity

The Cochran's Q statistic was performed to assess the degree of heterogeneity, and the results were demonstrated in Table 2. No significant heterogeneity was observed regarding light PA results ($p > 0.05$). By contrast, significant heterogeneities were observed in the effects of moderate-to-vigorous PA on susceptibility ($p = 0.002$), hospitalization ($p = 0.001$), and severity ($p = 0.046$).

3.2.3 Leave-one-out (LOO)

The LOO results were demonstrated in Table 2; Supplementary Figure S1. The causal influence of light PA on COVID-19 susceptibility was not substantially altered by any individual SNP. By comparison, the effects of light PA on the risk of COVID-19 hospitalization and severe complications were affected by a single SNP.

4 Discussion

As far as we know, this is the first study using large-sample GWAS data to investigate the causal influence of different PA intensities on COVID-19 susceptibility, hospitalization, and severity. Our finding indicates that genetically-proxied light PA may reduce COVID-19 susceptibility. Regarding COVID-19 hospitalization and severity, we found that genetically-predicted light PA, to a certain extent, reduced

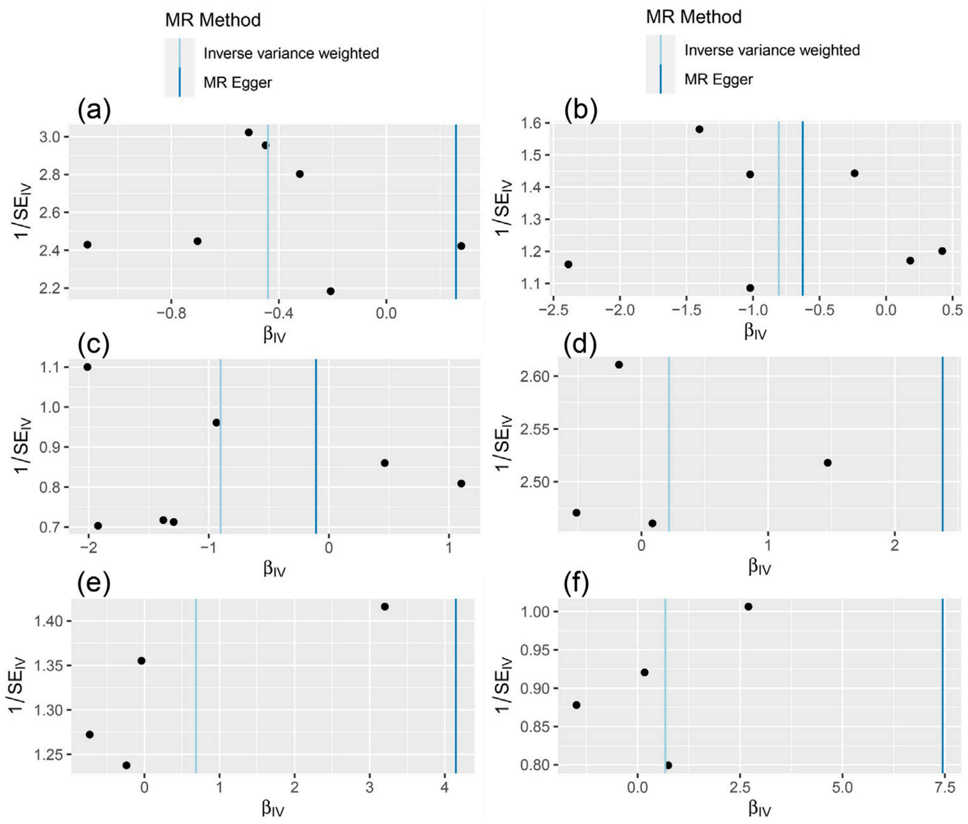

FIGURE 2
The results of funnel plot [The **(A–C)** represent the causal influence of light PA on COVID-19 susceptibility, hospitalization, and severity respectively, the **(D–F)** represent the causal influence of moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity respectively].

the risk of hospitalization and severity. These results, however, need to be interpreted with caution given their relaxed/uncorrected significance level. Furthermore, the sensitivity analysis (LOO) indicated that the effects of light PA on COVID-19 hospitalization and severity could be altered by a specific SNP. Considering these limitations, more studies are still necessary to clarify the role of light PA in affecting COVID-19 hospitalization and severity.

Regarding moderate-to-vigorous PA, our finding indicates that no causal influence of it on COVID-19 susceptibility, hospitalization, and severity. These findings were consistent with previous MR studies. Chen X. et al. (2022) performed an MR study to investigate the impact of self-reported moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity, and observed similar results. Another MR study by Zhang et al. (2020) found a non-significant effect of moderate-to-vigorous PA on COVID-19 outpatient and deaths (Zhang et al., 2020). These findings collectively indicate that moderate-to-vigorous PA may not be a protective factor against COVID-19 events.

In general, our findings concerning the two PA intensities indicate that light PA may decrease the risk of COVID-19 infection, but the effect may disappear with increasing intensity. These findings partially support the J-theory that increasing PA intensity is associated with a higher risk of upper respiratory tract infections (Nieman, 1994; Matthews et al., 2002). However, it is notable that the J-theory highlights the effectiveness of moderate PA value, but not light PA (Matthews et al., 2002). The limited GWAS datasets we have may be a reason for this difference. Our dataset rudely divided PA intensity into two categories (light and moderate-to-vigorous intensity), which forbids us to specify the effect of moderate intensity. To offer more persuasive evidence, we recommend focusing on the dose-response relationship between the full range of PA intensity and COVID-19 outcomes.

From the epidemiological perspective, immune modulation is the fulcrum of most diseases, and COVID-19 is no exception (Cui and Tian, 2021). Currently, two major mechanisms have been proposed to explain the protective effect of PA against COVID-19 infection (Nigro et al., 2020), which may help explain our findings. First, PA can improve the function and action of tissue macrophages and promote the activation and recirculation of key immune system factors, and then strengthen the immune system (Nigro et al., 2020). These effects contribute to limiting viruses' entry, translation, replication, and assembly (Jee, 2020; Diamond and Kanneganti, 2022). Second, PA can raise the level of salivary lactoferrin (one of the main antimicrobial proteins in saliva) (Woods et al., 2020). The lactoferrin secretion contributes to preventing DNA and RNA viruses from infecting cells, thereby reducing the risk of upper respiratory tract infections (Woods et al., 2020).

Although some distinctive causal associations were observed in this study, some limitations should be noted when interpreting our findings. First, our MR analysis only included European ancestry participants. Thus, our findings cannot be generalized to other populations. Second, only a few SNPs (n = 5 and 7) were used as instrumental variables, which might limit the power of the analyses. Furthermore, owing to the limited available GWAS data, the PA intensity was rudely divided into two categories (light and moderate to vigorous intensity), which may mask the true relationships between different PA intensities and COVID-19 outcomes. Thus, future study needs to consider extra or continuous intensity ranges when new GWAS data emerge.

5 Conclusion

The current MR study utilizes large sample GWAS datasets to examine the causal influence of light and moderate-to-vigorous PA on COVID-19 susceptibility, hospitalization, and severity. Despite some limitations, we provide genetic evidence that light PA may lower the risk of COVID-19 infection. To provide more scientific and quantitative evidence, we call for future research to focus on the full range of PA intensity when new GWAS datasets emerge.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

Conceptualization, HL; data curation, XZ; formal analysis, XZ; investigation, XZ and HL; project administration, SF and HL; supervision, SF and HL; writing—original draft, XZ and HL; writing—review and editing, XZ, XY, and HL. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2023.1089637/full#supplementary-material

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Blood flow restriction as a potential therapy to restore physical function following COVID-19 infection

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Accumulating evidence indicates that some COVID-19 survivors display reduced muscle mass, muscle strength, and aerobic capacity, which contribute to impairments in physical function that can persist for months after the acute phase of illness. Accordingly, strategies to restore muscle mass, muscle strength, and aerobic capacity following infection are critical to mitigate the long-term consequences of COVID-19. Blood flow restriction (BFR), which involves the application of mechanical compression to the limbs, presents a promising therapy that could be utilized throughout different phases of COVID-19 illness. Specifically, we hypothesize that: 1) use of passive BFR modalities can mitigate losses of muscle mass and muscle strength that occur during acute infection and 2) exercise with BFR can serve as an effective alternative to high-intensity exercise without BFR for regaining muscle mass, muscle strength, and aerobic capacity during convalescence. The various applications of BFR may also serve as a targeted therapy to address the underlying pathophysiology of COVID-19 and provide benefits to the musculoskeletal system as well as other organ systems affected by the disease. Consequently, we present a theoretical framework with which BFR could be implemented throughout the progression from acute illness to outpatient rehabilitation with the goal of improving short- and long-term outcomes in COVID-19 survivors. We envision that this paper will encourage discussion and consideration among researchers and clinicians of the potential therapeutic benefits of BFR to treat not only COVID-19 but similar pathologies and cases of acute critical illness.

KEYWORDS

post-acute sequelae of SARS-CoV-2, occlusion training, muscle strength, aerobic capacity, pandemic, pathophysiology

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Abbreviations: ACE2, Angiotensin-Converting Enzyme 2; BFR, Blood Flow Restriction; BFR-RE, Resistance Exercise with Blood Flow Restriction; BFR-AE, Aerobic Exercise with Blood Flow Restriction; BFR-P, Passive Blood Flow Restriction; BFR-NMES, Neuromuscular Electrical Stimulation with Blood Flow Restriction; COVID-19, Coronavirus Disease 2019; ICU, Intensive Care Unit; VO2, Oxygen Consumption; 1RM, One-repetition Maximum; ME/CFS, Myalgic Encephalomyelitis or Chronic Fatigue Syndrome; PAI-1, plasminogen activator inhibitor-1; RAS, Renin Angiotensin System; tPA, Tissue Plasminogen Activator.

Introduction

To date, there have been over 759 million reported cases of coronavirus disease 2019 (COVID-19) and over 6.8 million deaths worldwide (World health Organization, 2023). In addition to the acute complications associated with COVID-19 infection, accumulating evidence (Groff et al., 2021; Huang et al., 2021; Lopez-Leon et al., 2021; Nasserie et al., 2021; Salamanna et al., 2021) indicates that a variety of symptoms can persist for weeks and/or months following the acute phase of illness (i.e., long COVID, post-acute sequelae of COVID-19, post-COVID-19 syndrome). Among the most prevalent symptoms are fatigue, dyspnea, cognitive dysfunction, muscle and joint pain, and weakness. Moreover, physical function, which is the ability to move around and perform daily activities, can be impaired for up to 6 months following acute illness (de Oliveira Almeida et al., 2022). While these outcomes have been reported across acute illness severities, individuals with more severe illness requiring hospitalization appear to be most affected.

Physical function is influenced by the integration of multiple organ systems, particularly the musculoskeletal and cardiorespiratory systems. Accordingly, skeletal muscle mass and muscular strength (Wang et al., 2020), as well as aerobic capacity (Misic et al., 2007) (i.e., peak oxygen consumption), are important determinants of physical function. Individuals who become critically ill with COVID-19 experience rapid muscle wasting (de Andrade-Junior et al., 2021), loss of muscle strength (de Andrade-Junior et al., 2021; Paneroni et al., 2021), and reduced aerobic capacity (Baratto et al., 2021) during hospitalization. Furthermore, these losses are not recovered months following acute infection. Ramirez-Velez and colleagues (Ramírez-Vélez et al., 2022) reported low muscle mass and strength in COVID-19 survivors at 3 months following acute illness. Aparisi and colleagues (Aparisi et al., 2022) also reported lower aerobic capacity in survivors with some evidence indicating that impairments may persist up to 12 months after initial infection. Together, these data suggest that diminished skeletal muscle mass, muscle strength, and aerobic capacity are likely contributors to long-term impairments in physical function. The mechanisms responsible for these effects are not well understood (Ferreira and Oliveira, 2021; Seixas et al., 2022; Serviente et al., 2022) and may be multifactorial including factors associated with general critical illness (i.e., extended periods of inactivity, pharmacological therapies, malnutrition) and/or mechanisms specific to COVID-19 pathophysiology (i.e., direct viral infiltration, renin angiotensin system dysregulation, systemic inflammation, and oxidative stress).

Collectively, the chronic manifestations of COVID-19 infection may be comprising long-term health and setting those individuals who become infected on a path toward frailty and disease. Persistent physical function impairments following COVID-19 occur in both middle aged and older adults and are associated with lower physical activity levels (Delbressine et al., 2021; Ramírez-Vélez et al., 2022), increased risk of sarcopenia (Xu et al., 2022), and may increase chronic conditions such as obesity, cardiovascular disease, and diabetes. Furthermore, long-term physical functional impairments may drastically impact the workforce. A recent report (Ladlow et al., 2023) indicated that half of British Armed Forces were medically non-deployable at 12 months after COVID-19 infection. As COVID-19 continues to impact the world, the health and economic consequences of long-term symptoms could be astronomical.

Currently, evidence-based strategies for restoring physical function in those individuals suffering from short-to long-term complications following COVID-19 are limited. Developing safe, feasible, and cost-effective interventions to mitigate the loss of muscle mass, muscle strength, and aerobic capacity are of paramount importance and align with COVID-19 initiatives (US Department of Health and Human Services, 2022). Based on the unique symptoms, pathophysiology, and challenges associated with COVID-19, innovative rehabilitation strategies are required. Recently, Udina and colleagues (Udina et al., 2021) demonstrated that a multicomponent exercise intervention consisting of aerobic, resistance, and balance exercise (30 min/day, 7 days/wk) resulted in improved physical function in COVID-19 patients. Some individuals with COVID-19, however, may not be able to perform or tolerate such an aggressive exercise regimen that includes movements performed at moderate- and high-intensity. Alternatively, blood flow restriction (BFR), a modality for increasing muscle mass, muscle strength, and aerobic capacity while training at relatively low-intensity, may have application following COVID-19. Indeed, some authors have suggested the use of BFR as an intervention to counteract muscle and strength loss during the COVID-19 pandemic (de Oliveira et al., 2022) and as a treatment strategy for COVID-19 patients (Roman-Belmonte et al., 2020). Accordingly, the present paper aims to discuss the potential use of blood flow restriction (BFR) as a rehabilitation modality during and following COVID-19 infection to improve physical function.

Hypothesis

Our working hypothesis is that implementation of BFR can facilitate recovery of physical function following COVID-19 infection. Specifically, we hypothesize that BFR can be applied during: 1) acute infection in those individuals with critical illness to mitigate the loss of muscle mass and muscle strength and 2) convalescence in those individuals recovering from critical illness to regain muscle mass, muscle strength, and aerobic capacity. To support these hypotheses, we first describe how BFR has been used with a broad range of populations and subsequently provide a rationale for how BFR offers a targeted therapy that specifically addresses the underlying pathophysiology of COVID-19. We also present a theoretical framework for using BFR throughout the progression from acute illness to outpatient rehabilitation.

Blood flow restriction

To date, there are more than 50 reviews published in applied physiology, exercise and sport science, and rehabilitation journals that discuss the application, effectiveness, and safety of BFR with populations ranging from adults living with chronic disease to elite athletes. Briefly, this modality (Figure 1) involves applying mechanical compression to the proximal portion of a limb, typically with a pneumatic cuff, which serves to partially reduce

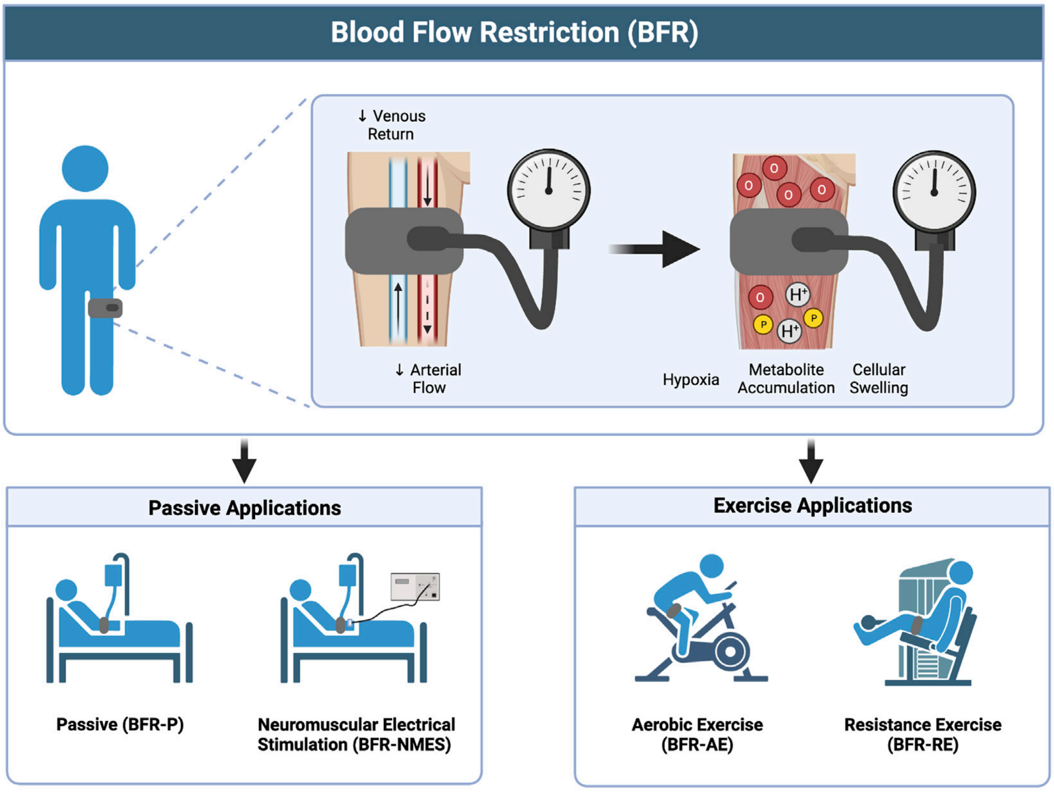

FIGURE 1
Overview of BFR and the different methods of application. Image created with BioRender and published with permission.

arterial blood flow to the limb while limiting most of the venous return (Kilgas et al., 2019). The reduced blood flow causes localized tissue hypoxia (Ilett et al., 2019), metabolite accumulation, and cellular swelling (Loenneke et al., 2012a) which may help to augment changes in muscle size, muscle strength, and/or aerobic capacity. Blood flow restriction is endorsed by the American Physical Therapy Association and is used in rehabilitation. It has been implemented with a variety of clinical populations including individuals with advanced age (Bennett and Slattery, 2019; Centner et al., 2019; Gronlund et al., 2020), orthopedic limitations (Hughes et al., 2017), critical illness (Barbalho et al., 2019), cardiovascular disease (Nakajima et al., 2010; Madarame et al., 2013; Kambič et al., 2019; Ogawa et al., 2021), hypertension (Wong et al., 2018), diabetes (Fini et al., 2021; Malekyian Fini et al., 2021), renal dysfunction (Corrêa et al., 2021a; Corrêa et al., 2021b), and neurological conditions (Gorgey et al., 2016; Yasuda et al., 2021; Douris et al., 2022). Notably, some of these conditions share similar pathophysiological presentations to COVID-19, characterized by increased levels of inflammation, oxidative stress, autonomic, and endothelial dysfunction.

Most commonly, BFR has been applied in combination with the performance of voluntary exercise, including both resistance exercise (BFR-RE) (Loenneke et al., 2012b; Slysz et al., 2016; Grønfeldt et al., 2020) and aerobic exercise (BFR-AE) (Bennett and Slattery, 2019; Formiga et al., 2020). Additionally, it has been implemented passively in the absence of muscle contraction (BFR-P) (Barbalho et al., 2019; Cerqueira et al., 2020) and in combination with involuntary muscle contraction elicited via neuromuscular electrical stimulation (BFR-NMES) (Natsume et al., 2015; Gorgey et al., 2016; Slysz and Burr, 2018). These applications of BFR may have use during the different phases of acute infection and post-acute recovery from COVID-19. Specifically, we propose that passive applications of BFR (BFR-P and BFR-NMES) can help to mitigate losses in muscle mass and muscle strength during acute COVID-19 illness and that the combination of BFR with exercise (BFR-AE and BFR-RE) can provide a viable way to restore muscle mass, muscle strength, and aerobic capacity to adequate levels during convalescence.

Hypothesis 1—mitigate muscle and strength loss during acute infection

Muscle and strength loss are common during admittance to the intensive care unit (ICU) (Schefold et al., 2020) and correlate with hospital length of stay (Gruther et al., 2008) and physical function after discharge (Mayer et al., 2020). de Andrade-Junior and colleagues (de Andrade-Junior et al., 2021) reported that after 10 days in the ICU, COVID-19 patients displayed a 30% reduction in rectus femoris muscle cross-sectional area and a 19% reduction in the thickness of the anterior compartment of the quadriceps muscles. These rates of muscle loss are greater than those reported in other critically ill patients during ICU admission (Puthucheary et al., 2013). At hospital discharge, Paneroni and colleagues (Paneroni et al., 2021) reported that 80% of COVID-

19 patients presented with muscle weakness and displayed quadriceps and biceps brachii muscle strength that were 54% and 69% of predicted values. Furthermore, accumulating evidence (Piotrowicz et al., 2021) indicates that COVID-19 survivors are at an increased risk of developing acute sarcopenia. Efforts to reduce rates of muscle and strength loss during severe acute COVID-19 infection may improve patient outcomes and reduce the time needed to recover physical function to adequate levels following discharge. However, viable therapies to mitigate the effects of critical illness on skeletal muscle are limited as hospitalized patients typically experience prolonged immobility and have a reduced ability to perform voluntary muscle contractions. As described below, the application of BFR-P and BFR-NMES may help to slow the rate of muscle and strength loss in those individuals hospitalized with severe COVID-19 illness.

BFR-P

Emerging evidence (Barbalho et al., 2019; Cerqueira et al., 2020) indicates that the intermittent application of BFR passively in the absence of muscle contraction mitigates losses in muscle and strength that occur during immobilization. Barbalho and colleagues (Barbalho et al., 2019) demonstrated that the addition of BFR to passive mobilization reduced rates of muscle wasting in older adults admitted to the ICU with coma. Compared to a control limb receiving passive mobilization alone, the addition of a tourniquet cuff to the proximal thigh during once daily passive mobilization decreased the rate of quadriceps muscle loss by 6% over an 11 day period. Other reports, which have been previously reviewed (Cerqueira et al., 2020), indicate that a BFR-P protocol consisting of 5 sets of 5 min restriction and 3 min reperfusion performed twice daily diminished disuse of the knee extensors by 11% following anterior crucial ligament reconstruction (Takarada et al., 2000) and prevented strength losses during 2 weeks of simulated cast immobilization in healthy adults (Kubota et al., 2008; Kubota et al., 2011). Although the mechanisms underlying these effects are largely unknown, it has been hypothesized (Loenneke et al., 2012a) that cellular swelling as a result of venous pooling may enhance muscle retention by inhibiting protein breakdown and/or increasing protein synthesis.

BFR-NMES

Neuromuscular electrical stimulation (NMES) is a technique that consists of generating involuntary muscle contractions using low level electrical currents delivered through electrodes applied to the skin. The addition of NMES to standard care (Liu et al., 2020) in critically ill patients reduces the rate of muscle loss, improves muscle strength, shortens length of stay in the hospital, and improves ability to perform activities of daily living. Some evidence (Natsume et al., 2015; Gorgey et al., 2016; Slysz and Burr, 2018) indicates that low-intensity NMES combined with BFR promotes more robust effects on muscle size and strength than low-intensity NMES or BFR-P performed alone. For example, Gorgey and colleagues (Gorgey et al., 2021) reported that 6 weeks of BFR-NMES in individuals living with spinal cord injury increased wrist extensor muscle cross-sectional area and improved electronically evoked wrist extensor torque. Changes in wrist extensor cross-sectional area were 17% greater in the treatment limb receiving BFR-NMES compared to a control limb receiving NMES alone. In another report (Natsume et al., 2015), BFR-NMES performed twice daily (5 days/week) in the lower-body increased quadriceps muscle thickness and maximal knee extension strength after 2 weeks of training in young males. No changes were observed in a control limb performing NMES alone which is consistent with related reports (Slysz and Burr, 2018).

Pathophysiology of COVID-19

Endothelial dysfunction has been suggested to be a major pathogenic mechanism of COVID-19 (Del Turco et al., 2020; Bonaventura et al., 2021) and persists for months beyond acute infection (Serviente et al., 2022). Endothelial dysfunction is associated with numerous chronic diseases (Hadi et al., 2005) as well as risk of future cardiovascular events (Green et al., 2011) and likely contributes to long-term symptoms in COVID-19 survivors (Charfeddine et al., 2021). In a systematic review and meta-analysis including 292 participants, Gu and colleagues (Gu et al., 2021) reported that BFR-P protocols, referred to as ischemic preconditioning, augment endothelial function via increased flow mediated dilation. Several authors (Jeffries et al., 2018; Rytter et al., 2020) have also reported enhanced microvascular function when implementing similar protocols. Like BFR-P protocols discussed previously, ischemic preconditioning involves the cyclical application of blood flow restriction and reperfusion, however, tourniquets are applied at higher pressures that result in complete arterial occlusion. A large body of evidence (Stokfisz et al., 2017) demonstrates that ischemic preconditioning protects tissues from subsequent ischemia and reperfusion injury and that these effects also occur in remote tissues (i.e., remote ischemic conditioning) that are not directly subject to the localized ischemic preconditioning stimulus. Indeed, lung and cardiovascular injury (Guzik et al., 2020) are common with severe COVID-19 illness and ischemic preconditioning may confer a systemic protective effect. The use of ischemic preconditioning in COVID-19 patients has been previously suggested (Incognito et al., 2021; Cahalin et al., 2023). Additionally, COVID-19 patients display impaired hemostasis (Hanff et al., 2020) which is characterized by overactivation in the coagulation system with reduced fibrinolytic activity. Accordingly, thrombotic complications are common in COVID-19. Longstanding evidence indicates that vascular compression stimulates the fibrinolytic system without elevating the coagulation cascade (Holemans, 1963; Robertson et al., 1972; Stegnar and Pentek, 1993; Kohro et al., 2005). Accordingly, when applied in COVID-19 patients, various BFR-P approaches could potentially help to reduce risk for thrombotic complications. While there is extensive literature supporting the application of BFR-P and its effects on numerous organ systems, reports implementing BFR-NMES are limited. To the best of our knowledge, only one report has investigated the effects of BFR-NMES on vascular function in which the authors (Gorgey et al., 2016) demonstrated acute increases in brachial artery flow mediated dilation following BFR-NMES when compared BFR alone. These preliminary data suggest vascular benefits with the addition of NMES, however, more work is needed to characterize the effects of BFR-NMES.

Low aerobic capacity in COVID-19 survivors, as assessed through an incremental exercise test for determination of VO_{2peak}, has been attributed to both central and peripheral factors (Aparisi et al., 2022). Thus, impairments throughout the oxygen transport pathway are likely present. In addition to potentially enhancing oxygen delivery via improved peripheral vascular function, BFR-P could attenuate reductions in aerobic capacity during critical COVID-19 illness by reducing cardiac deconditioning and improving oxygen kinetics in skeletal muscle.

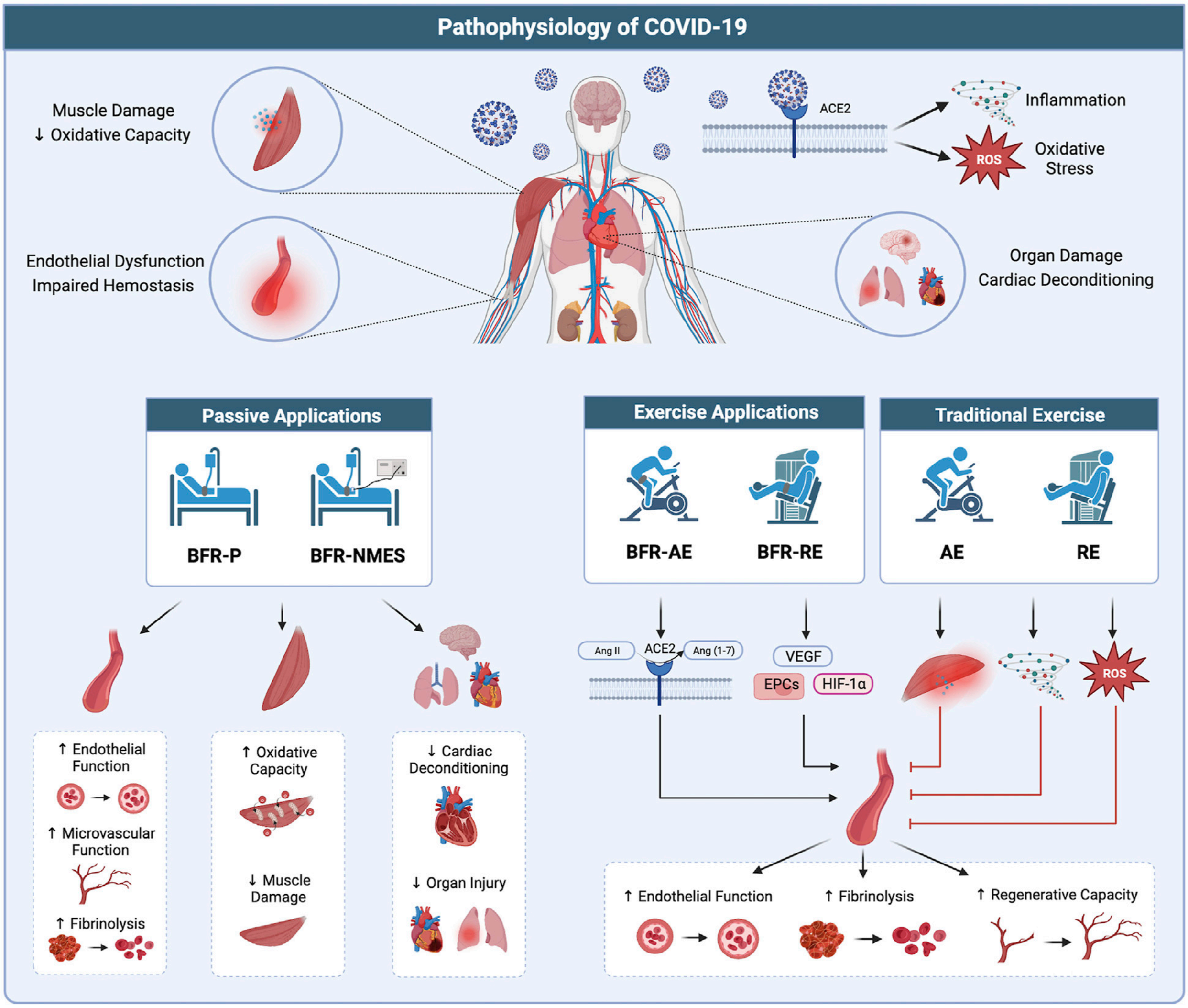

FIGURE 2
Potential therapeutic benefits of BFR in treating the pathophysiology of COVID-19. (Top) Infection with COVID-19 results in widespread organ dysfunction which may be the result of systemic viral infiltration, hyper-inflammation, and oxidative stress. (Bottom left) Passive applications of BFR (BFR-P and BFR-NMES) promote positive effects in the vasculature, skeletal muscle, and vital organs which may serve to combat multiple organ dysfunction occurring with COVID-19. (Bottom right) Exercise applications of BFR (BFR-AE and BFR-RE) promote benefits to the vascular system through increased ACE2 activity, stimulating the release of hematopoietic stem cells, and promoting the expression of factors related to vascular growth and regeneration. Additionally, compared to high-intensity exercise without BFR, low-intensity exercise with BFR results in lower levels of muscle damage, inflammation, and oxidative stress, which could exacerbate the pathophysiological mechanisms of COVD-19 and worsen symptoms. Image created with BioRender and published with permission.

Nakajima and colleagues (Nakajima et al., 2008) reported similar hemodynamic responses to that of upright standing when BFR-P was applied to the proximal thighs of participants placed in a 6-degrees head-down tilt position. These data let us speculate that BFR-P could approximate the cardiac demands of standing and attenuate cardiac deconditioning and orthostatic intolerance occurring during prolonged bedrest. Additionally, some authors (Saito et al., 2004; Patterson et al., 2015) have reported that repeated ischemic preconditioning exposure improves local skeletal muscle oxygen dynamics during exercise. Data from Jeffries and colleagues (Jeffries et al., 2018) demonstrated that 7 consecutive days of lower-body ischemic preconditioning increased local skeletal muscle oxidative capacity. Together, BFR-P protocols could help to preserve skeletal muscle mass and strength during critical illness and offer a systemic strategy that can provide benefits to the musculoskeletal system and possibly other organ systems, some of which are affected during COVID-19 infection (Figure 2; bottom left).

Hypothesis 2—increase muscle mass, muscle strength, and aerobic capacity during convalescence

Exercise training is a promising therapy in the rehabilitation of COVID-19 as it: 1) promotes healthy function in multiple organ systems, 2) effectively treats a variety of diseases that share similar pathophysiological presentations to COVID-19, 3) increases muscle mass, muscle strength, and aerobic capacity, and 4) improves physical function. A recent systematic review (Ahmadi Hekmatikar et al., 2022) including 233 COVID-19 survivors found that a combination of aerobic and resistance exercise training following hospital discharge increased muscle strength, physical function, and quality of life. It is important to note that several concerns have been raised about exercise after COVID-19 including the risk of cardiac injury, thromboembolic complications, and post-exertional symptom exacerbation (Salman et al., 2021; World Physiotherapy, 2021). Given these concerns, along with frequently reported symptoms of fatigue, joint and muscle pain, and weakness, exercise prescription in COVID-19 survivors requires careful consideration. Indeed, higher exercise intensities needed to promote increases in muscle size, strength, and aerobic capacity may be challenging or contraindicated. Alternatively, exercise training with BFR could offer a unique approach for COVID-19 survivors to attain the benefits of high-intensity exercise. The main advantages of exercise with BFR compared to traditional exercise are: 1) increases in muscle size, strength, and aerobic capacity can be achieved with lower exercise intensities (Loenneke et al., 2012b; Bennett and Slattery, 2019; Clarkson et al., 2019), 2) adaptations from BFR occur faster, and 3) muscle size and strength can be increased with both aerobic and resistance exercise (Slysz et al., 2016). Although the exact mechanisms responsible for these adaptations are unknown, evidence (Jessee et al., 2018) suggests that increases in muscle size and strength are likely driven by cellular swelling and increased muscle activation occurring due to metabolite induced fatigue. Currently, increases in aerobic capacity are thought to occur via enhanced conduit artery blood flow, muscle capillary density, and muscle oxidative capacity in response to both the hypoxic stimulus during exercise and increased vascular shear stress upon cuff release (Formiga et al., 2020). A more comprehensive discussion surrounding the mechanisms responsible for adaptions to exercise with BFR are reviewed by Jessee and colleagues (Jessee et al., 2018) and Pignanelli and colleagues (Pignanelli et al., 2021). The following sections briefly discuss the effects of BFR-AE and BFR-RE on muscle size, muscle strength, and aerobic capacity and highlight unique advantages of these exercise modalities over that of high-intensity exercise without BFR in potentially managing the pathophysiology of COVID-19.

BFR-AE

The combination of aerobic exercise, such as walking or cycling, with BFR increases muscle size and strength in younger (Slysz et al., 2016) and older adults (Centner et al., 2019). Importantly, these adaptations are achieved at low exercise intensities (e.g., 45% heart rate reserve or 40% VO_{2peak}) and occur as early as 3 weeks, sooner than that observed with high-intensity resistance training without BFR. In addition to increases in muscle size and strength, BFR-AE also facilitates increases in aerobic capacity in young adults (Bennett and Slattery, 2019; Formiga et al., 2020). Thus, BFR-AE provides an efficient exercise mode that improves both muscle size and strength as well as aerobic capacity simultaneously. Importantly, a systematic review by Clarkson and colleagues (Clarkson et al., 2019) indicated that adaptations to BFR-AE translate to improvements in objective measures of physical function, including the 30-s sit-to-stand, timed up and go, and 6-min walk test. This modality has been safely applied in individuals living with a variety of diseases including hypertension (Barili et al., 2018), end-stage kidney disease (Clarkson et al., 2020), chronic heart failure (Tanaka and Takarada, 2018), and obesity (Karabulut and Garcia, 2017).

BFR-RE

Increases in muscle size and strength with the performance of resistance exercise in combination with BFR have been reported in reviews of healthy young (Loenneke et al., 2012b; Slysz et al., 2016; Grønfeldt et al., 2020) and older populations (Centner et al., 2019; Grønfeldt et al., 2020), as well as those individuals with orthopedic limitations (Hughes et al., 2017). Adaptations from BFR-RE are achieved with lower exercise intensities (20%–40% 1RM) and are greater than those attained with low-intensity resistance exercise performed without BFR. Relative to BFR-AE, the magnitude of muscle size and strength improvements with BFR-RE are greater (Slysz et al., 2016) and also translate to improvements in objective measures of physical function (Clarkson et al., 2019; Baker et al., 2020). Few studies have investigated the effects of BFR-RE on aerobic capacity, however, one report (Nakajima et al., 2010) noted increases in aerobic capacity when BFR-RE was performed for 3 months in individuals living with ischemic heart disease. Thus, BFR-RE may have the potential to promote cardiovascular adaptations in diseased and less trained populations. This modality has been applied in individuals living with hypertension (Wong et al., 2018), diabetes (Fini et al., 2021; Malekyian Fini et al., 2021), chronic kidney disease (Corrêa et al., 2021a; Corrêa et al., 2021b), and cardiovascular disease (Nakajima et al., 2010; Fukuda et al., 2013; Madarame et al., 2013; Ishizaka et al., 2019; Kambič et al., 2019; Ogawa et al., 2021).

Pathophysiology of COVID-19

Elevated levels of inflammation and oxidative stress have been suggested (Del Turco et al., 2020) to play important roles contributing to organ dysfunction with COVID-19. Furthermore, evidence indicates that oxidative stress (Ratchford et al., 2021) and inflammation (Montefusco et al., 2021) remain elevated beyond acute infection and likely contribute to long-term symptoms. Accordingly, it is important that interventions aimed at restoring muscle mass, muscle strength, and aerobic capacity in COVID-19 survivors do not exacerbate the underlying pathological mechanisms of the disease. Traditional high-intensity exercise without BFR can result in acute elevations in oxidative stress, muscle damage, and inflammation (Cerqueira et al., 2019). These responses are greatest in individuals that are deconditioned and unaccustomed to exercise. Given the combination of prolonged immobilization, deconditioning, and pre-existing inflammatory and oxidant-antioxidant imbalances, the acute physiological perturbations associated with high-intensity exercise could be deleterious in those recovering from severe COVID-19. Additionally, meta-analyses (Li et al., 2020; Wu et al., 2020; Bansal et al., 2021) have reported elevated makers of skeletal muscle damage (i.e., creatine kinase, lactate dehydrogenase, myoglobin) associated with COVID-19 infection and case studies (Husain et al., 2020; Jin and Tong, 2020; Mukherjee et al., 2020) have documented rhabdomyolysis in patients. Exercise resulting in muscle damage and a subsequent inflammatory response could further deteriorate physical function, suppress the immune system, and worsen symptoms.

A recent systematic review and meta-analysis (Ferlito et al., 2023) indicates that low-intensity exercise with BFR results in lower acute elevations in biomarkers of oxidative stress when compared to high-intensity exercise without BFR. Additionally, Petrick and colleagues (Petrick et al., 2019) demonstrated that skeletal muscle mitochondrial reactive oxygen species emission rates were acutely decreased 2 h following low-intensity BFR-RE but not after the same exercise protocol performed without BFR. Evidence (Loenneke et al., 2014; Nielsen et al., 2017) also suggests that low-intensity BFR-RE results in minimal muscle damage based on direct (integrity of muscle fibers) and indirect (alterations in muscle strength, range of motion, blood markers) assessments. Accordingly, exercise with BFR provides a novel method to increase muscle size, muscle strength, and aerobic capacity which elicits relatively smaller acute elevations in oxidative stress and muscle damage compared to high-intensity exercise without BFR. Thus, this modality provides an alternative way to restore physical function that may be less likely to exacerbate pathophysiological mechanisms of COVID-19.

A potential mechanism by which COVID-19 promotes systemic pathology, particularly endothelial dysfunction, is interaction of SARS-CoV-2 with the renin angiotensin system (RAS). The principal target of SARS-CoV-2 binding is angiotensin-converting enzyme 2 (ACE2), a membrane bound protein found in numerous tissues throughout the body. The active form of ACE2 opposes the action of the RAS. Specifically, ACE2 degrades Angiotensin I (Ang I) and converts Angiotensin II (Ang II) into Ang (1,7), which exerts vasodilatory and anti-inflammatory effects. With COVID-19 infection, the consumption and downregulation of ACE2 via SARS-CoV-2 binding leaves RAS unopposed, increasing the ratio of ANG II to ANG (1,7) and drives excessive vasoconstriction, inflammation, and oxidative stress. Joshi and colleagues (Joshi et al., 2020) reported that BFR-RE performed in the lower-body substantially increased ACE2 activity and enhanced the ACE2-to-ACE ratio following exercise. Additionally, these authors reported increases in circulating hematopoietic stem/progenitor cells which were associated with three-fold increases in vascular endothelial growth factor receptors. Further, a recent meta-analysis (Li et al., 2022) demonstrated that exercise with BFR facilitates greater expression of angiogenesis related factors than exercise performed without BFR. Collectively, this evidence suggests that exercise with BFR may combat RAS dysregulation in COVID-19 and enhance the adaptive and regenerative capacity of the vascular system. Other data have reported direct benefits of exercise with BFR throughout the vascular tree. In a recent meta-analysis, Pereira-Neto and colleagues (Pereira-Neto et al., 2021) reported that 4 or more weeks of BFR-RE improves endothelial function (i.e., flow mediated dilation, reactive hyperemia blood flow, and reactive hyperemia index) and some data (Evans et al., 2010; Hunt et al., 2013) report enhanced capillary growth.

Among the benefits of exercise is its positive impact on hemostasis. High-intensity resistance training without BFR acutely enhances fibrinolytic activity (deJong et al., 2006), increasing tissue plasminogen activator (tPA) and decreasing plasminogen activator inhibitor-1 (PAI-1), without elevating activity in the coagulation system. Evidence indicates similar responses in the fibrinolytic system with the performance of low-intensity exercise with BFR. Nakajima and colleagues (Nakajima et al., 2007) reported significant increases in tPA antigen and unchanged PAI-1 activity during low-intensity BFR-RE (30% 1RM) performed after 24 h of bedrest. Similarly, Clark and colleagues (Clark et al., 2021) reported a 33% increase in tPA antigen immediately following acute bouts of BFR-RE with no alterations in markers of coagulation. Responses were similar to those observed with high-intensity resistance exercise without BFR. Furthermore, studies (Shimizu et al., 2016; Rapanut et al., 2019) implementing the chronic performance of BFR-RE have demonstrated decreases in von Willebrand factor (vWF) after 4 weeks. Taken together, these data demonstrate that exercise with BFR provides similar fibrinolytic effects as high-intensity exercise without BFR, albeit at lower exercise intensities, and could protect against short and long-term thrombotic complications associated with COVID-19. Exercise with BFR appears to promote a variety of positive adaptations in the vascular system and may confer several unique benefits to COVID-19 survivors that are not achieved with traditional higher intensity exercise (Figure 2; bottom right).

Theoretical framework

An evidence-based model of BFR progression from bed rest to outpatient rehabilitation for clinical populations was originally proposed by Loenneke et al. (2012c) and colleagues. The novelty of this approach is that BFR-assisted rehabilitation has the potential to reduce the time needed to reach the stage where patients can tolerate higher loads and intensities and thus accelerate recovery of physical function (Bielitzki et al., 2021). Here, we apply this model to COVID-19 and construct a theoretical framework for which BFR could be used with COVID-19 patients throughout the transition from acute illness to outpatient rehabilitation. As illustrated in Figure 3, our framework includes three phases of BFR application. ***Phase I*** consists of applying passive BFR applications (BFR-P and BFR-NMES) during severe acute COVID-19 illness to reduce muscle and strength loss while patients are immobilized. Importantly, these modalities can be implemented early in acute care and do not require active cooperation from the patient. Once capable of mobilization, patients can progress to ***Phase II***, which consists of performing BFR-AE to regain muscle mass, muscle strength, and aerobic capacity. Before patients are capable of ambulating, BFR-AE could be performed during early active mobilization activities such as bed mobility, transfers (e.g., supine-to-sit, sit-to-stand), arm ergometry, or supine leg ergometry. Once physically capable, patients can progress to more traditional BFR-AE exercise modes including walking and cycling. As patients' mobility and tolerance to exercise increases, they can progress to ***Phase III***, which includes the addition of BFR-RE to provide a more robust method for increasing muscle mass and strength. Based on patient progress and physical ability, BFR-RE could be initiated in the post-acute rehabilitation setting or during outpatient rehabilitation. Given the substantial and prolonged decrements in aerobic capacity of COVID-19 survivors, it would be advised to continue BFR-AE during this phase and/or begin integrating high-intensity aerobic exercise without BFR based on patient tolerance. While initial resistance exercise training protocols can focus on BFR-RE exclusively, high-intensity resistance exercise without BFR should be slowly incorporated into the rehabilitation program as tolerated to stimulate additional improvements in muscle strength. Collectively, progression through each phase of

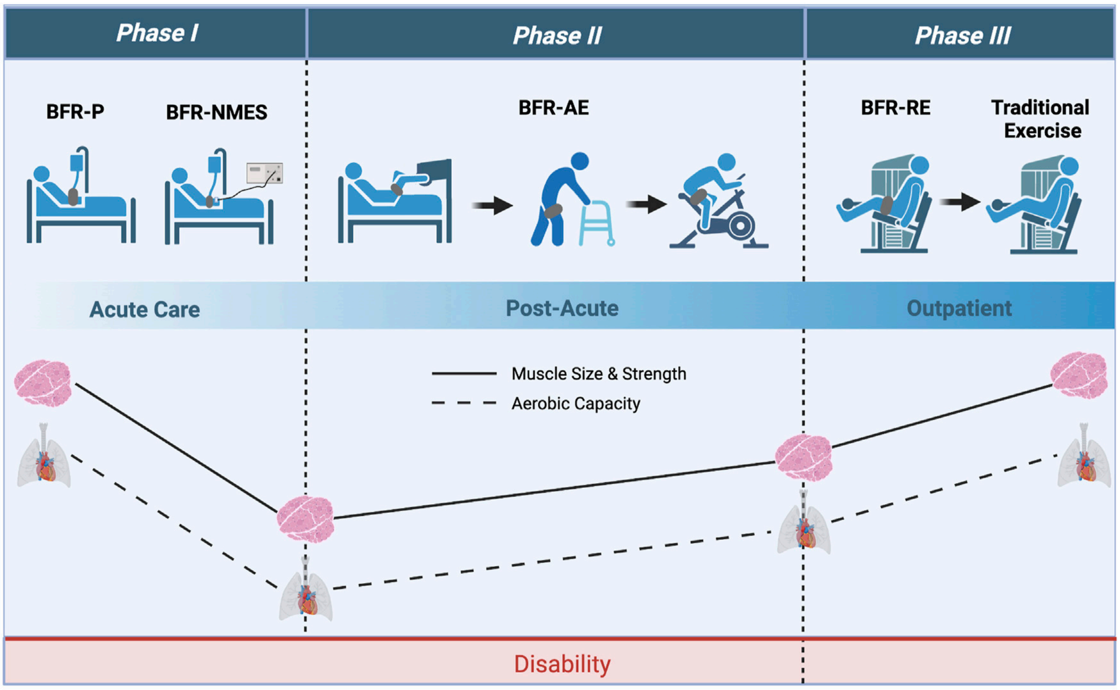

FIGURE 3
Theoretical framework with which BFR could be applied to COVID-19 survivors throughout acute care and outpatient rehabilitation. *Phase I* consists of using passive applications of BFR (BFR-P and BFR-NMES) to prevent losses in muscle mass and strength during acute care. *Phase II* consists of using various modes of BFR-AE to improve muscle mass, muscle strength, and aerobic capacity during post-acute care. Lastly, *Phase III* consists of using BFR-RE to provide further increases in muscle mass and strength while transitioning COVID-19 survivors to high-intensity exercise without BFR. Image created with BioRender and published with permission.

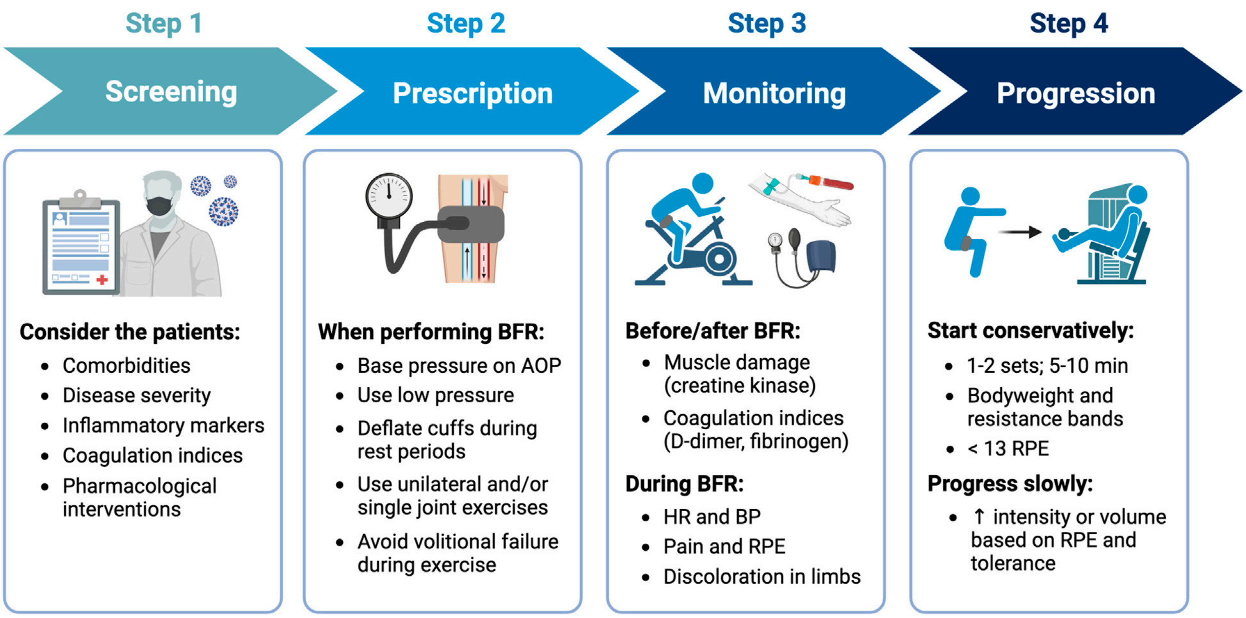

FIGURE 4
General recommendations for implementing BFR with COVID-19 survivors. Step 1 - screen patients for risk factors and/or contraindications, Step 2 - utilize prescriptions that minimize cardiovascular and perceptual demands, Step 3 - monitor patients before, during, and after performing BFR for adverse responses, and Step 4 - progress exercise slowly based on RPE and tolerance. Image created with BioRender and published with permission.

BFR application can help to restore physical function and reduce the long-term consequences of severe COVID-19 infection. Notably, our framework is also consistent with other reports (de Oliveira et al., 2022) suggesting progressive application of BFR as a counteracting home-based intervention to maintain physical function during the COVID-19 pandemic.

When implementing BFR with COVID-19 patients, there are several important factors to consider (Figure 4). First, robust screening for potential risk factors and/or contraindications is critical. Nascimento and colleagues (Nascimento et al., 2022) suggested that the decision to implement exercise with BFR in COVID-19 patients should consider each patient's unique profile, including any pre-existing comorbidities, their disease severity, inflammatory markers, coagulation indices, and pharmacological interventions. Second, it is important to standardize the degree of blood flow restriction by basing cuff pressures on individual arterial occlusion pressure (McEwen et al., 2019), which is the minimum pressure required to occlude arterial blood flow to a limb. Moreover, acute cardiovascular and perceptual responses to exercise with BFR are reduced when utilizing lower cuff pressures (Mattocks et al., 2017), implementing intermittent *versus* continuous cuff pressure protocols (Brandner et al., 2015), selecting exercises that involve smaller amounts of muscle mass (Kilgas et al., 2019), and not performing exercise to volitional failure (Sieljacks et al., 2019). Third, initial BFR prescriptions for those individuals with or recovering from COVID-19 should be conservative and follow similar approaches to those used in other clinical populations. For example, when implementing BFR-RE in patients following cardiovascular surgery, Ogawa and colleagues (Ogawa et al., 2021) began with relatively low exercise intensities (e.g., 10%–20% 1RM) and volumes (1-2 exercises: 1 set x 20 repetitions). Fourth, hemodynamic (blood pressure, heart rate) and perceptual (perceived exertion, pain) responses should be carefully monitored during BFR and specific criteria (Nascimento et al., 2022) for stopping the modality should be followed. Additionally, markers of muscle damage (creatine kinase) and coagulation indices (D-dimer, fibrinogen) should also be monitored before and after exercise. Finally, once tolerance to BFR is established, intensity and volume can be slowly progressed based on the individual's rate of perceived exertion during exercise. Guidelines for exercise progression in COVID-19 survivors based on perceived exertion have previously been recommended (Sari and Wijaya, 2023). It is important to note that some data (Clarkson et al., 2017) indicate that perceived exertion during exercise with BFR is highest during initial sessions but decreases with repeated exposure.

Limitations and considerations

While BFR theoretically appears to be a viable solution for restoring physical function following COVID-19 infection, there are three notable limitations to our hypothesis. First is the safety of implementing BFR (Nascimento et al., 2022). Specifically, some authors (Spranger et al., 2015; Cristina-Oliveira et al., 2020) have appropriately raised concern for potential adverse cardiovascular responses to exercise with BFR in populations with cardiovascular disease (i.e., hypertension, heart failure, peripheral artery disease) who possess altered exercise pressor reflex function. The pathophysiology of COVID-19 resembles that of cardiovascular and inflammatory disease and those individuals developing severe COVID-19 illness are commonly older in age and have multiple pre-existing comorbidities. Furthermore, some evidence (Stute et al., 2022) indicates an augmented exercise pressor response in COVID-19 survivors. Therefore, concerns surrounding acute cardiovascular responses to exercise with BFR should be extended to those individuals infected with or recovering from COVID-19. Perhaps the biggest concern in this population is that of thrombotic complications given the high prevalence of hemostatic abnormalities. As stated above, robust screening for potential risk factors and/or contraindications is critical. Second, is the extent to which individuals could tolerate BFR. For example, low-intensity exercise with BFR generally leads to equal or only slightly lower ratings of perceived exertion and discomfort when compared to high-intensity exercise without BFR (De Queiros et al., 2022). Although exercise with BFR seems to be well tolerated in older adults and a variety of clinical populations, adoption and adherence may be challenging among those with and recovering from COVID-19 who display exercise intolerance. As discussed, modifications to various BFR prescriptions (i.e., cuff pressure, intermittent pressure application, exercise selection, and proximality to failure) may help to enhance exercise tolerance and adherence. Importantly, many COVID-19 survivors experience myalgic encephalomyelitits or chronic fatigue syndrome (ME/CFS) (Jason and Dorri, 2022) and may experience post-exertional malaise even with the performance of light exercise. Therefore, the utilization of any exercise type in COVID-19 survivors should exclude those individuals displaying symptoms consistent with ME/CFS. Lastly, is the capacity of medical professionals to implement BFR safely and effectively in clinical settings. Adequate training of BFR methodology and awareness of potential side effects and adverse outcomes is essential for making an informed decision about whether BFR is appropriate. Furthermore, access to proper technologies (i.e., cuffs and equipment for determining appropriate pressures) and knowledge of BFR exercise prescription plays a critical role in minimizing patient risk (Patterson et al., 2019). A comprehensive overview of BFR methodology, prescription, and safety is provided by Patterson and colleagues (Patterson et al., 2019).

Summary

We hypothesize that the use of BFR could be an effective strategy to rehabilitate physical function in COVID-19 survivors. The application of BFR-P and BFR-NMES during acute infection has the potential to mitigate muscle and strength loss occurring with severe COVID-19 illness requiring hospitalization. During post-acute and outpatient rehabilitation, the combination of BFR with voluntary exercise (BFR-AE and BFR-RE) presents an alternative to high-intensity exercise without BFR to restore muscle mass, muscle strength, and aerobic capacity. Additionally, the various applications of BFR may offer a systemic therapy to combat organ dysfunction. A progressive model of BFR application throughout the phases of acute infection and rehabilitation offers a theoretical approach to address the long-term consequences of COVID-19. We hope that this paper encourages discussion and consideration among researchers and clinicians about the therapeutic potential of BFR to improve outcomes not only in COVID-19 survivors but in similar pathologies and cases of acute critical illness.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

IW, JD, JM, and SE all contributed significantly to the included content and preparation of the manuscript. IW, JD, JM, and SE were responsible for the first draft of the manuscript. IW was responsible for the creation of figures. IW, JD, JM, and SE edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of a multi-professional intervention on body composition, physical fitness and biochemical markers in overweight COVID-19 survivors: a clinical trial

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Introduction: The sequelae post-COVID can affect different systems. In this sense, considering the multi-factorial etiology of COVID-19, multi-professional interventions could be a relevant strategy for recovery health indicators.

Objective: This study aimed to investigate the effects of multi-professional intervention on body composition, physical fitness, and biomarkers in overweight COVID-19 survivors with different symptomatology.

Methodology: A non-randomized parallel group intervention included 69 volunteers (BMI ≥25 kg/m^2), divided into three groups according to SARS CoV-2 symptomatology, but only 35 finished the longitudinal protocol [control group (n = 11); moderate group (n = 17) and severe group (n = 7)]. The groups were submitted to a multi-professional program (nutritional intervention, psychoeducation, and physical exercise intervention) for 8 weeks, and the volunteers underwent body composition assessments (primary outcome) and physical and biochemical tests (secondary outcome) in pre- and post-intervention. This study was registered on the Clinical Trials Registration Platform number: RBR-4mxg57b and with the local research ethics committee protocol under number: 4,546,726/2021.

Results: After the 8-week multi-professional intervention, the following results were observed for the moderate COVID-19 group: improved dynamic strength of lower- and (p = 0.003), upper-limbs (p = 0.008), maximal isometric lumbar-traction strength (p = 0.04), flexibility (p = 0.0006), and albumin (p = 0.0005), as well as a reduction in the C reactive protein (CRP) ($p = 0.003$) and fasting glucose ($p = 0.001$); for the severe COVID-19 group: an improvement in dynamic lower-body strength ($p = 0.001$), higher values of albumin ($p = 0.005$) and HDL-c ($p = 0.002$), and lower values of CRP ($p = 0.05$), and for the control group: an improvement in sit-up repetitions ($p = 0.008$), and a reduction of CRP ($p = 0.01$), fasting glucose ($p = 0.001$) and total cholesterol ($p = 0.04$) were identified. All experimental groups reduced triglycerides after intervention ($p < 0.05$).

Conclusion: Finally, 8 weeks of multiprofessional intervention can be an efficient tool for reversing the inflammatory process and promoting improvements in daily activities and quality of life, although it is believed that the severe COVID-19 group needs longer interventions to improve different health indicators.

Clinical Trial Registration: https://ensaiosclinicos.gov.br/, identifier: RBR-4mxg57b.

KEYWORDS

coronavirus, health promotion, multi-professional intervention, physical exercise, chronical disease

1 Introduction

Long COVID-19, associated with several health problems due to sequelae of SARS-CoV-2 (Davis et al., 2023), is characterized by persistent post-COVID symptoms of 12 weeks or more (Astin et al., 2023). The sequelae can affect different systems, such as cardiopulmonary, immunological, neurological, skeletal muscle, circulatory, and mental health (Davis et al., 2023). To clarify the nature and frequency of persistent symptoms, *Van-Kessel et al.* (Van Kessel et al., 2022) concluded that fatigue, dyspnea, chest pain, and headache are long-COVID-19 affecting work and daily functioning. Thus, rehabilitation strategies for COVID-19 survivors are indispensable to combat a condition with different sequelae with significant impacts on the population, the health of individuals, and the economy (Astin et al., 2023). It is well established that obesity, comorbidities, and low physical activity levels may worsen the clinical outcome of COVID-19 survivors (Lemos et al., 2022). The World Health Organization (WHO) has published the *"Clinical Management of COVID-19: living guidance"* (World Health Organization, 2021a), establishing four classifications of COVID-19 symptoms, such as mild, moderate, severe, and critical, according to the progression and worsening of the symptoms of COVID-19. Symptom progression commonly depends on the primary health condition of the individual and the immune response provoked by the infection (Shi et al., 2020).

In this sense, answering questions regarding cardiorespiratory and neuromuscular treatment strategies can provide patients with a return to activities of daily living and consequent patient health improvement for those with long COVID (Lemos et al., 2022). Psychological sequelae have also been described in a previous study as factors that justify early multi-professional actions to recover the physical and mental health of COVID-19 survivors (Ryal et al., 2023). Although strategies to treat acute sequelae are under assessment, little attention has been given to the treatment of sequelae affecting the long-term quality of life. Therefore, interventions aimed at the patient's recovery from actions that provide physical activity practice, healthy nutrition, and psychoeducation can reduce the sequelae of the disease and the complications resulting from the post-COVID syndrome in overweight individuals (Lemos et al., 2022).

Previous findings have investigated the role of physical exercise as a potential strategy to counteract the deleterious effects of COVID-19 but have yet to consider the other multi-professional aspects that involve public health promotion policies and the severity of COVID-19 (Dalbosco-Salas et al., 2021; Jimeno-Almazán et al., 2023). To the best of these authors' knowledge, the effects of physical exercise, nutritional education, and psychoeducation, i.e., multi-professional interventions considering the specific symptoms (moderate and severe/critical) and including a control group (without diagnoses of COVID-19), were not investigated in the scientific literature. Considering the symptoms among the groups could be relevant to promote assertive interventions and recovery prognoses.

Therefore, the present study aimed to analyze the effects of multi-professional intervention on body composition, physical fitness, and biomarkers in overweight COVID-19 survivors. Based on previous studies (Dalbosco-Salas et al., 2021; Jimeno-Almazán et al., 2023), as a primary outcome, the authors of this research propose that the 8 weeks of multi-professional intervention model can improve body composition and physical fitness and, as a secondary outcome, metabolic parameters, regardless of the symptomatology of the disease.

2 Methods

2.1 Experimental approach to the problem

This study adopted an experimental design of repeated measures and parallel groups non-randomized for 8 weeks, following *Consolidated Standards of Reporting Trials* (CONSORT) (Schulz et al., 2010) from October to December 2021. The experimental groups (severe COVID-19, moderate COVID-19 group, and non-COVID-19 group/control group) were submitted to a multi-professional program of theoretical (nutritional intervention and psychoeducation) and physical exercise (concurrent training).

Participants were assessed at baseline (pre-intervention) and after 8 weeks (post-intervention).

2.2 Participants

Participants were recruited via the Municipal Secretary of Health of Maringa, the Municipal Hospital of Maringa, and through TV, radio, and social media dissemination. The control group (non-COVID-19 group) was recruited through TV, radio, and social media dissemination. Interested parties contacted the Interdisciplinary Laboratory for Intervention in Health Promotion (LIIPS) multi-professional team at Cesumar University. Eighty-nine volunteers of both sexes were invited to participate in the study according to the following inclusion criteria: i) male and female participants between 19 and 65 years of age; ii) body mass index (BMI) > 25.0 kg/m^2; iii) positive diagnosis confirmed via RT–PCR (reverse transcriptase-polymerase chain reaction) for COVID-19 (only for moderate and severe COVID-19 groups); iv) received medical clearance to participate in the present study; v) received the first dose of COVID-19 vaccine; vi) available to participate in multi-professional interventions 2x/week for 8 weeks and vii) having contracted COVID-19 between January 03rd/2021 and July 01st/2021 (only for moderate and severe COVID-19 groups). An equivalent control group was recruited without COVID-19 diagnostics. Exclusion criteria included the following: i) debilitating neurological diseases (i.e., Alzheimer's or Parkinson's); ii) contraindications for physical exercise, and iii) pregnancy. Data collection and intervention occurred at the LIIPS in Maringa, Paraná, Brazil.

The *a priori* sample size calculation was based on weight loss (4.4 ± 4.0 kg) in 8 weeks of aerobic and resistance training program under dietary control in overweight men (Perissiou et al., 2020). Nine participants per group were necessary to achieve a statistical power of 80% with an alpha error of 5%. Since a large number (55.4%) of COVID-19 survivors have been reported to abandon exercise programs (Dalbosco-Salas et al., 2021), a minimum of 14 patients should be recruited for each study group. The present study was approved by the Local Research Ethics Committee (protocol n° 4,546,726) and followed the Declaration of Helsinki. The study was registered in the Brazilian Clinical Trials Registry Platform (REBEC) under RBR-4mxg57b. All subjects were informed about the purposes of the study and signed an informed consent form.

2.3 Procedures

Seventy-one volunteers were accepted to participate in the program and were allocated according to COVID-19 symptomatology (moderate or severe/critical symptoms) (World Health Organization, 2021b) and the control group (without the diagnosis of COVID-19), following the groups: severe COVID-19 (n = 16), moderate COVID-19 (n = 23), and control (n = 30). The baseline measures were conducted over 2 days. First, the subjects underwent a clinical assessment by a pulmonologist and an ICU physician, consisting of patient history (history of surgeries, preexisting non-communicable chronic diseases, continuous use of medications, main signs and symptoms presenting possible sequelae of COVID-19, and type and length of stay at the hospital (ward/room or intensive care unit)), anthropometric and body composition assessment and blood collection for biochemical analyses.

On the second day, the following data were collected: i) blood pressure (BP) after 5 min of rest, according to the VIII Guideline on Arterial Hypertension (Barroso et al., 2020); ii) measurement of heart rate (HR) and peripherical oxygen saturation (%SpO$_2$), both at rest; iii) posterior chain flexibility test on the Wells bench (sit and reach test); iv) maximum isometric handgrip strength (MIHS) and maximum isometric lumbar traction (MILT) with specific dynamometers; v) sit-up test; vi) 30-s chair-stand-test; vii) push-up and (viii) cardiorespiratory fitness test [6-min walk test (6MWT)]. After the 6MWT, the following variables were collected: BP, HR, and %SpO$_2$. All tests are described in the sections below. After the clinical assessment, the self-reported signs and symptoms were considered for the non-randomized allocation of participants in the experimental COVID-19 groups according to the *"Clinical Management of COVID-19: living guidance"* (World Health Organization, 2021a).

Over the 8 weeks, 25 participants dropped out of the project for different reasons. Figure 1 presents the flowchart of the present study's participants based on the CONSORT Guidelines (Schulz et al., 2010) and Figure 2 illustrates the methodology used for the 8-week intervention.

2.4 Body composition

Participants' height was measured using a stadiometer (Welmy R-110®, Santa Bárbara D′ Oeste, São Paulo, Brazil) coupled to a scale with 2.2 m capacity and 0.1 cm accuracy. Participants' body composition was measured using tetrapolar bioimpedance (*InBody* 570®, *Biospace* Co. Ltd., Seoul, Korea), with a capacity of 250 kg and accuracy of 100 g, according to the manufacturer's instructions and following the recommendations to improve the validity and reliability (Heyward, 2001). All participants were previously instructed about the recommendations. The following parameters were measured: BMI (kg/m^2), lean mass (kg), fat mass (kg), body fat percentage (%), and skeletal muscle mass (kg).

2.5 Health-related physical fitness tests

The chosen physical tests to evaluate the outcomes of the COVID-19 survivors follow the order: i) sit and reach test; ii) maximum isometric handgrip strength (MIHS), maximum isometric lumbar traction (MILT); iii) sit-up test for abdominal strength-resistance; iv) 30-s chair-stand-test for lower limbs; v) push-up test for upper limbs and (viii) cardiorespiratory fitness test [6-min walk test (6MWT)]. The participants were instructed about the procedures for all physical tests, and the researchers respected a rest between the tests. Furthermore, the choice of physical tests was based on promoting the assessment of physical fitness test parameters in places with low resources and clinics, public hospitals, gyms, and others.

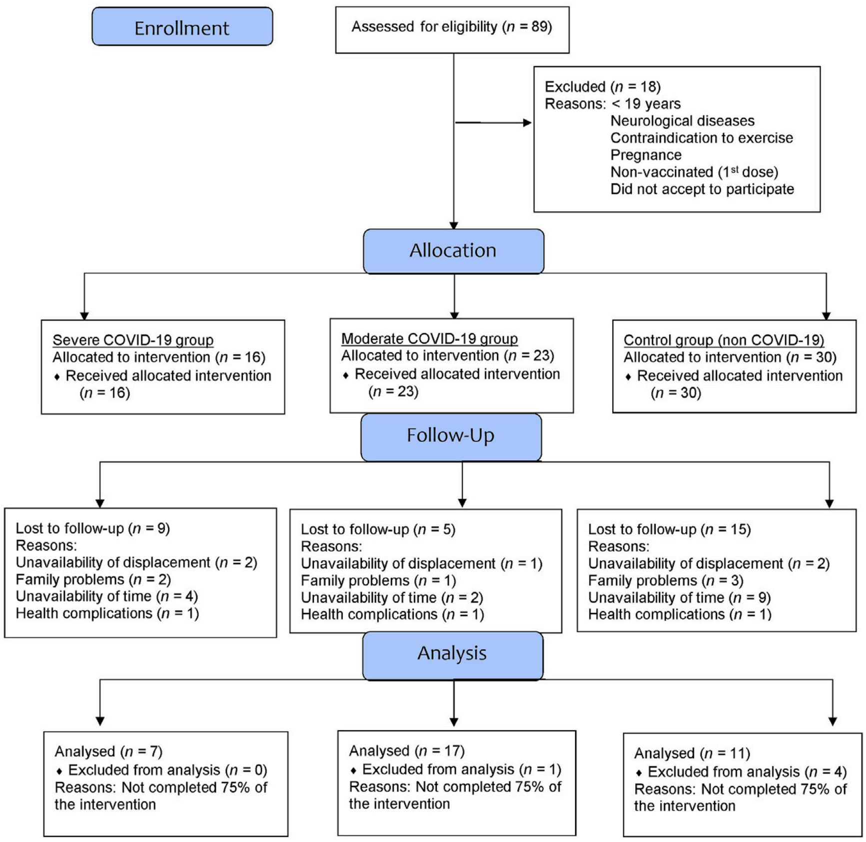

FIGURE 1
Flowchart diagram of the participants of the present study.

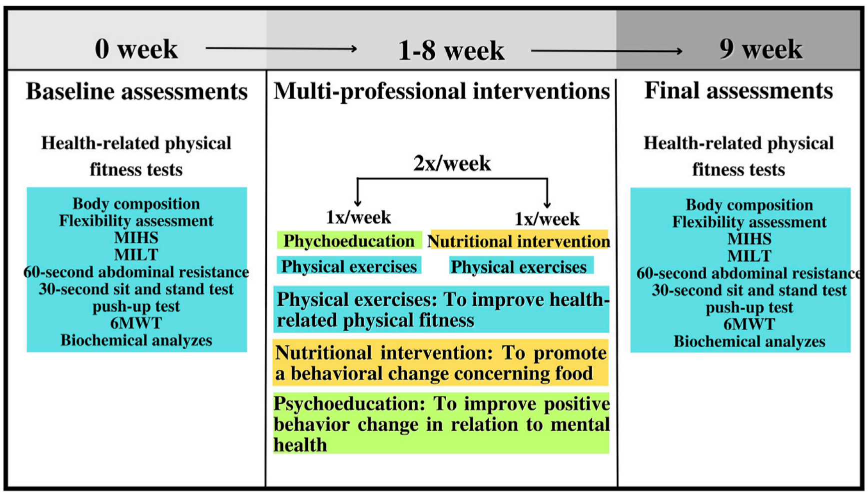

FIGURE 2
Methodological design of the present study. Note: MIHS = maximal isometric handgrip strength; MILT = maximal isometric lumbar-traction strength; 6MWT = 6-min walk test.

2.6 Flexibility assessment

The sit and reach test was employed to evaluate the flexibility of the posterior chain using the Wells Bench. Participants were instructed according to previously described procedures (Wells and Dillon, 1952). The test was repeated three times, with a 60-s interval between attempts. The highest value obtained was recorded and expressed in cm.

2.7 Maximal isometric strength tests

To assess MIHS, a TKK 5101 dynamometer (Takei Physical Fitness Test®, Tokyo, Japan) with a capacity of 100 kg was used. MILT was evaluated using a Takei dynamometer (Takei Physical Fitness Test®, Back Strength Dynamometer, type 2, Japan) with a capacity of 300 kg. According to previous recommendations, three trials were performed for both tests, lasting 3–5 s with a 1-min rest between trials (Branco et al., 2018). The highest value was recorded in kg.

2.8 Dynamic muscle strength-endurance assessment

To assess dynamic muscle, sit-up, 30-s chair-stand, and push-up tests were performed according to the procedures described in previous studies (Jones et al., 1999; Cuenca-Garcia et al., 2022). For the sit-up and push-up tests, the maximum number of repetitions achieved in 60 s was recorded, and for the 30-s chair-stand test, the muscular endurance of the lower limbs was evaluated from the maximum number of repetitions performed in 30 s.

2.9 Cardiorespiratory fitness test

The 6MWT was applied to verify the cardiorespiratory fitness of the present study participants. The 6MWT test was performed per American Thoracic Society guidelines (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Volunteers were instructed to walk as fast as possible to achieve the greatest distance at the end of 6 min (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). The peak oxygen consumption (VO_2peak) was calculated using a previous study (Cahalin et al., 1996).

2.10 Biochemical analyses

The blood collection procedures followed the guidelines of the Clinical and Laboratory Standards Institute (Williamson and Synder, 2013). Participants were previously instructed on how to prepare for the collections that took place at the Clinical Analysis Laboratory of the University facilities, and after collection, participants were instructed to press on the puncture site to avoid bruising. The collected blood samples were distributed in the following tubes: Vacuplast® collection tubes, tubes with the anticoagulant ethylene diamine tetra acetic acid (EDTA) K2, and tubes with anticoagulant fluoride/EDTA. Subsequently, to obtain serum and plasma, the samples containing the fluoride/EDTA activator were centrifuged in a CENTRILAB® analog centrifuge at 3,500 rpm (relative centrifugal force) for 15 min at room temperature. The following laboratory tests were analyzed: glycemic control, lipid profile (total cholesterol, HDL-c: high-density lipoprotein, LDL-c: low-density lipoprotein, and TGL: triglycerides), liver enzymes (ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GAMMA-GT: gamma-glutamyl transferase and albumin), C-reactive protein (CRP) and glycated hemoglobin (HbA1C). The analyses were performed using Gold Analisa Diagnostic Kits (Belo Horizonte, Minas Gerais, Brazil) in the semiautomatic biochemical and turbidimetric analyzer device URIT 8021® from MHLab. All analyses were performed in triplicate. The Finecare ® FIA Meter Plus analyzer from WONDFO was used for HbA1C.

TABLE 1 The training program for the severe COVID-19, moderate COVID-19, and control groups.

Order	Training program a	Training program B
1	Warm-up	Warm-up
2	Plank torso strength	Plank torso strength
3	Rectus abdominis	Rectus abdominis
4	Aerobic exercises (5′)	Hip bridge
5	Squat	Leg press
6	Leg extension	Aerobic exercises (5′)
7	Bench press	Leg curl
8	Aerobic exercises (5′)	Push up
9	Cable pulldown	Cable straight back seated row
10	Dumbbell shoulder press	Front raise
11	Triceps pulley	Biceps curl
12	Aerobic exercises (5′)	Aerobic exercises (5′)

2.11 Physical exercise intervention

The physical exercise intervention sessions lasted approximately 60 min and were held in the university facilities. Physical exercises focused on improving cardiorespiratory and neuromuscular fitness (concurrent training) to increase muscle strength and, if necessary, motor coordination and balance. The concurrent training plan consisted of performing 2 weeks of anatomical adaptation with low volume and intensity, that is, 3 sets of 15 repetitions and 5 min of aerobic exercise at the end of the session, and the other weeks of physical exercise (plus 6, in total) had volume progression and gradual intensity (via classic linear model); that is, the loads used were readjusted over the weeks, as well as the number of sets and repetitions. In weeks 3 and 4, 3 sets of 12 repetitions were performed; in weeks 5 and 6, the training sessions consisted of 3 sets of 20 repetitions; and finally, in weeks 7 and 8, 4 sets of 12 repetitions were performed. Concerning aerobic exercise, 2 sets of 5 min were performed in weeks 3 and 4; 1 set of 5 and 1 set of 10 min was performed in weeks 5 and 6; and finally, in weeks 7 and 8, 2 sets of 10 min were performed. The concurrent training was performed twice weekly, with resistance exercises focused on large muscle groups and cardiorespiratory fitness performed on a treadmill, vertical/horizontal bicycle, or rowing ergometer, according to the preference and physical condition of the volunteers. For a third day, the participants were requested to improve their physical activity (especially walking, 1 hour a week–if possible, following their physical training). Table 1 presents the training program performed by the experimental groups during the 8 weeks of multi-professional intervention.

2.12 Training monitoring

The concurrent training sessions were monitored via perceptual scales (rating of perceived recovery and exertion). Before each training session, the perceived recovery status (RPR) scale proposed by *Laurent et al.* (Laurent et al., 2011), which identifies the recovery status, was used. After the end of the training session, the rating of perceived exertion (RPE) to quantify the intensity of the training session, proposed by *Foster et al.* (Foster et al., 2001), was measured. All volunteers were instructed about the scales in a meeting before starting the physical exercises. SpO_2 and blood pressure (systolic: SBP and diastolic: DBP) were measured before (initial) and after (final) each exercise session. In addition, the volunteers self-reported the slightest sign of chest discomfort, extreme tiredness, sweating, and shortness of breath; SpO_2 was measured to verify hypoxemia, and if a patient had $SpO_2 < 88\%$, the physical exercise was immediately terminated (Yang and Yang, 2020).

2.13 Nutritional intervention

The nutritional intervention was focused on the Food Guide for the Brazilian population (Brasil Ministério da Saude, 2014) to instruct participants about healthy eating, quality of life, and the importance of reducing risks associated with chronic non-communicable diseases (NCDs). Nutritional interventions were performed once a week in groups.

2.14 Psychoeducation

Psychoeducation was based on therapeutic interventions to provide knowledge and the possibility of change in the face of the psychological consequences of the COVID-19 pandemic based on a model of treatment and prevention of psychiatric illnesses (Authier, 1977). In this sense, they were asked about the importance of physical exercise, anxiety, factors associated with obesity, the role of food, stress, insomnia, fear, and binge eating (Ryal et al., 2023). Therapeutic interventions were performed once a week in groups.

2.15 Statistical analysis

All statistical analyses were performed using GraphPad Prism 8.1.0 software. Previously, the normality of the data was tested using the Shapiro–Wilk test. Similarly, the homogeneity of the data was tested by Levene's test. After confirming normality and homogeneity, the numerical data were expressed as the mean and standard deviation (±SD), and the categorical data were expressed as absolute and relative frequency (%). Mauchly's test of sphericity was used to test the Greenhouse–Geisser correction, if necessary. To analyze the clinical characteristics, a one-way analysis of variance (ANOVA) was used to compare numerical data, and the chi-square non-parametric statistical test was used to compare categorical data. Two-way mixed-measures analysis of variance (ANOVA) was used to compare the groups and time (pre- and post-intervention). The Bonferroni *post hoc* test was used when a significant difference was found. A paired t-test (pre-*vs.* post-intervention) was applied when a time difference was detected to identify possible statistical significance in intra-groups conditions (Franchini et al., 2016), and the confidence interval (CI) was also calculated. The effect size was calculated using Cohen's *d* (Cohen, 2013) as follows: 0.2 (*small effect*), 0.5 (*moderate effect*), and 0.8 (*large effect*). The effect size for eta-square (η^2) was also calculated conforming proposed by Richardson (Richardson, 2011): 0.0099 (*small effect*), 0.0588 (*moderate effect*), 0.1379 (*large effect*). The significance level established was $p \leq 0.05$.

3 Results

Table 2 presents the clinical characteristics of the present study participants stratified by the symptoms of COVID-19: severe ($n = 7$), moderate ($n = 17$), and the control group, without the diagnosis of COVID-19 ($n = 11$). No differences were observed for age ($p = 0.09$), BMI ($p = 0.83$), resting heart rate ($p = 0.10$), SBP ($p = 0.32$), DPB ($p = 0.37$), and SpO_2 ($p = 0.29$). Regarding persistent symptoms self-reported by the COVID-19 participants (moderate and severe COVID-19 groups), fatigue (severe: 85.7%; moderate: 64.7%), memory deficit (severe: 85.7%; moderate: 45.1%) and difficult concentration (severe: 71.4%; moderate: 41.1%) were more prevalent. However, no significant difference between groups was observed for fatigue ($p = 0.30$), memory deficit ($p = 0.08$), and difficulty concentration ($p = 0.18$). In addition, differences were not detected for the other clinical characteristics (medical history, medication in use, self-reported post-COVID-19 symptoms, smoking, and physical activity: $p > 0.05$).

3.1 Body composition

Figure 3 shows the pre- and post-intervention body composition assessments.

For BMI, no group ($F_{2,28} = 0.46$; $p = 0.63$; $\eta^2 = 0.03$; *small effect*), no time ($F_{1,28} = 0.18$; $p = 0.66$; $\eta^2 = 0.006$; *small effect*) and no interaction effects ($F_{2,28} = 2.85$; $p = 0.07$; $\eta^2 = 0.16$; *large effect*) were observed.

For lean mass, a group difference was detected ($F_{2,29} = 8.02$; $p = 0.001$; $\eta^2 = 0.35$; *large effect*), with the Bonferroni *post hoc* test showing higher values for the control group when compared to the moderate group ($p = 0.001$). However, no time ($F_{1,29} = 2.86$; $p = 0.10$; $\eta^2 = 0.08$; *medium effect*) and no interaction effects ($F_{2,29} = 0.52$; $p = 0.59$; $\eta^2 = 0.30$; *large effect*) were detected.

For fat mass, no group ($F_{2,28} = 0.50$; $p = 0.61$; $\eta^2 = 0.03$; *small effect*), no time ($F_{1,28} = 2.28$; $p = 0.14$; $\eta^2 = 0.07$; *medium effect*), and no interaction effects ($F_{2.28} = 2.33$; $p = 0.11$; $\eta^2 = 0.14$; *large effect*) were observed.

For body fat percentage, a group difference was detected ($F_{2,28} = 3.89$; $p = 0.03$; $\eta^2 = 0.21$; *large effect*), with the Bonferroni *post hoc* test indicating lower values for the control group than the moderate

TABLE 2 Clinical characteristics of participants of the severe COVID-19, moderate COVID-19, and control groups.

Variables	Severe	Moderate	Control	*p*-value
Age (years old)	45 ± 10.0	51 ± 13.9	42 ± 9.1	p = 0.09
Gender				p = 0.30
Male	6 (85.7%)	11 (64.7%)	10 (90.9%)	
Female	1 (14.3%)	6 (35.3%)	1 (9.1%)	
BMI (kg/m^2)	29.7 ± 2.3	32.5 ± 8.4	30.8 ± 7.9	p = 0.83
Medical history				
Hypertension	1 (14.3%)	3 (17.6%)	1 (9.1%)	p = 0.82
Diabetes	1 (14.3%)	1 (5.9%)	0 (0%)	p = 0.12
Dyslipidemia	0 (0%)	2 (11.8%)	0 (0%)	p = 0.34
COPD	0 (0%)	0 (0%)	0 (0%)	-
Asthma	0 (0%)	0 0%)	0 (0%)	-
CAD/revascularization	3 (42.8%)	2 (11.8%)	0 (0%)	p = 0.09
Others	1 (14.3%)	5 (29.4%)	0 (0%)	p = 0.13
Smoking				p = 0.30
No	2 (28.5%)	7 (41.1%)	7 (63.6%)	
Past or today	5 (71.4%)	10 (58.8%)	4 (36.3%)	
Medications in use				
Antihypertensive	3 (42.8%)	4 (23.5%)	1 (9.1%)	p = 0.22
Antidiabetic	0 (0%)	1 (5.9%)	0 (0%)	p = 0.58
Statin	0 (0%)	1 (5.9%)	0 (%)	p = 0.58
Platelet antiaggregant	0 (0%)	0 (0%)	0 (0%)	-
Anticoagulant	0 (0%)	1 (5.9%)	0 (0%)	p = 0.64
Others	0 (0%)	1 (5.9%)	1 (9.1%)	p = 0.14
Post-COVID-19 symptoms self-reported				
Fatigue	6 (85.7%)	11 (64.7%)	-	p = 0.30
Dyspnoea	3 (42.8%)	6 (35.3%)	-	p = 0.73
Muscle pain	4 (57.1%)	5 (29.4%)	-	p = 0.20
Joint pain	4 (57.1%)	5 (29.4%)	-	p = 0.20
Headache	1 (14.3%)	4 (23.5%)	-	p = 0.61
Dizziness	2 (28.5%)	4 (23.5%)	-	p = 0.80
Memory deficit	6 (85.7%)	8 (45.1%)	-	p = 0.08
Difficulty concentrating	5 (71.4%%)	7 (41.1%)	-	p = 0.18
Feeling of hearing loss	1 (14.3%)	3 (17.6%)	-	p = 0.84
Hair loss	4 (57.1%)	6 (35.3%)	-	p = 0.32
Loss of smell	1 (14.3%)	4 (23.5%)	-	p = 0.73
Physical activity ≥ 150 min/week	3 (42.8%)	6 (35.3%)	5 (45.4%)	p = 0.85
Baseline vital signs				
HR (bpm)	90 ± 15.8	82 ± 10.1	91 ± 10.3	p = 0.10

(Continued on following page)

TABLE 2 (*Continued*) Clinical characteristics of participants of the severe COVID-19, moderate COVID-19, and control groups.

Variables	Severe	Moderate	Control	*p*-value
SBP (mmHg)	120 ± 10	120 ± 9.3	125 ± 7.5	p = 0.32
DBP (mmHg)	80 ± 8.1	80 ± 8.1	80 ± 4.9	p = 0.37
% SpO_2	95 ± 0.9	96 ± 1.8	96 ± 0.9	p = 0.29

Note: numerical data are expressed as mean ± standard deviation, and categorical data are expressed as absolute and relative frequency (%); BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; $\%SpO_2$: oxygen saturation; significance level $p< 0.05$.

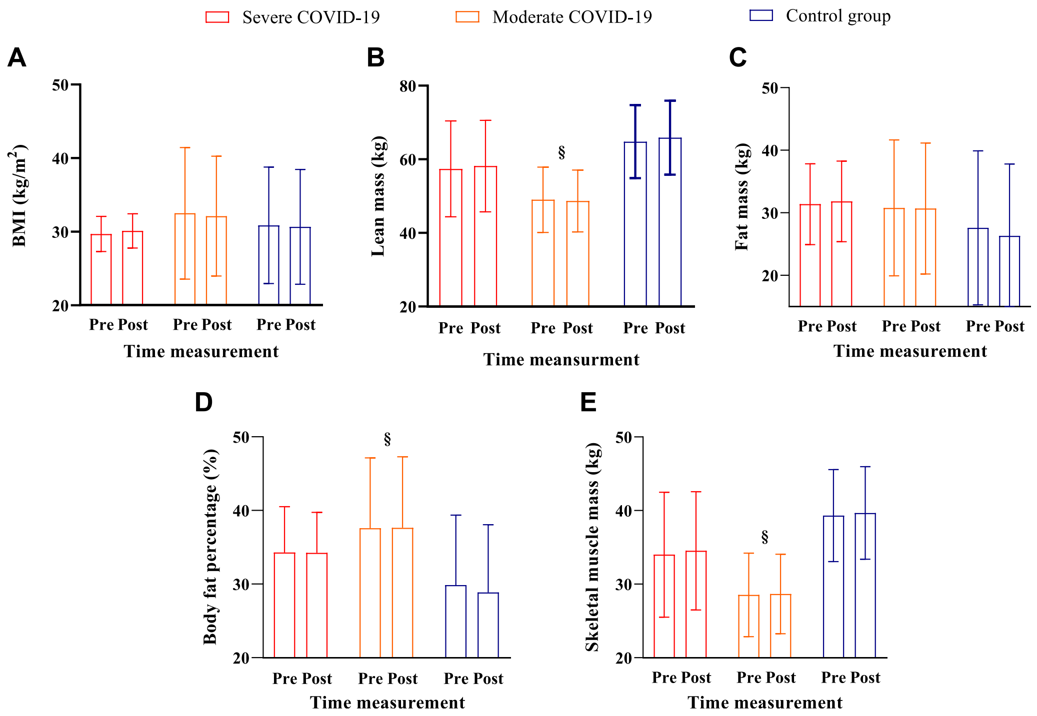

FIGURE 3
Body composition in the pre- and post-assessment interventions for the severe COVID-19, moderate COVID-19, and control groups. Note: Data are expressed as the mean ± standard deviation; § = a group difference with lower values for the moderate group compared to the control group; significance level established $p < 0.05$. **(A)** body mass; **(B)** lean mass; **(C)** fat mass; **(D)** body fat percentage (%), and **(E)** skeletal muscle mass.

group ($p = 0.03$). However, no time ($F_{1,28} = 4.05$; $p = 0.05$; $\eta^2 = 0.12$; *large effect*) and no interaction effects ($F_{2,28} = 0.95$; $p = 0.39$; η^2 = 0.06; *medium effect*) were found.

For skeletal muscle mass, a group difference ($F_{2,29} = 8.52$; p = 0.001; $\eta^2 = 0.37$; *large effect*) was observed, with the Bonferroni *post hoc* test indicating higher values for the control when compared to the moderate COVID-19 group ($p = 0.0008$). However, no time ($F_{1,29} = 3.76$; $p = 0.06$; $\eta^2 = 0.11$; *medium effect*) and no interaction effects ($F_{2,29} = 0.04$; $p = 0.95$; $\eta^2 = 0.003$; *small effect*) were detected.

3.2 Health-related physical fitness tests

Figure 4 shows the physical fitness tests of the COVID-19 groups and a control group before and after 8 weeks of intervention.

For sit and reach test, no group ($F_{2,31} = 0.66$; $p = 0.52$; $\eta^2 = 0.04$; *small effect*) and no interaction effects were observed ($F_{2,31} = 0.01$; $p = 0.98$; $\eta^2 = 0.001$; *small effect*). However, a time difference was detected ($F_{1,31} = 32.32$; $p = 0.000003$; $\eta^2 = 0.51$; *large effect*), with the Bonferroni *post hoc* test indicating a significant increase after 8 weeks of intervention ($p = 0.000001$). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 group ($t_7 = 2.034$; $p = 0.08$; CI: −0.8695 to 9.441; *d = 0.40; moderate effect*). However, isolated t-test revealed higher values in post than pre-intervention in moderate COVID-19 ($t_{16} = 4.308$; $p = 0.0006$; CI: 2.163 to 6.399; *d =0.04; small effect*) and control groups ($t_{11} = 4.125$; $p = 0.0021$; CI: 2.098 to 7.029; *d = 0.05; small effect*).

For MIHS, no group ($F_{2,32} = 2.87$; $p = 0.07$; $\eta^2 = 0.15$; *large effect*), no time ($F_{2,32} = 3.75$; $p = 0.06$; $\eta^2 = 0.10$; *large effect*) and no interaction effects ($F_{2,32} = 0.41$; $p = 0.66$; $\eta^2 = 0.02$; *small effect*) were observed.

For MILT, no group ($F_{2,32} = 1.12$; $p = 0.33$; $\eta^2 = 0.06$; *medium effect*) and no interaction effects were detected ($F_{2,32} = 0.64$; p = 0.52; $\eta^2 = 0.03$; *large effect*). However, a time effect was found

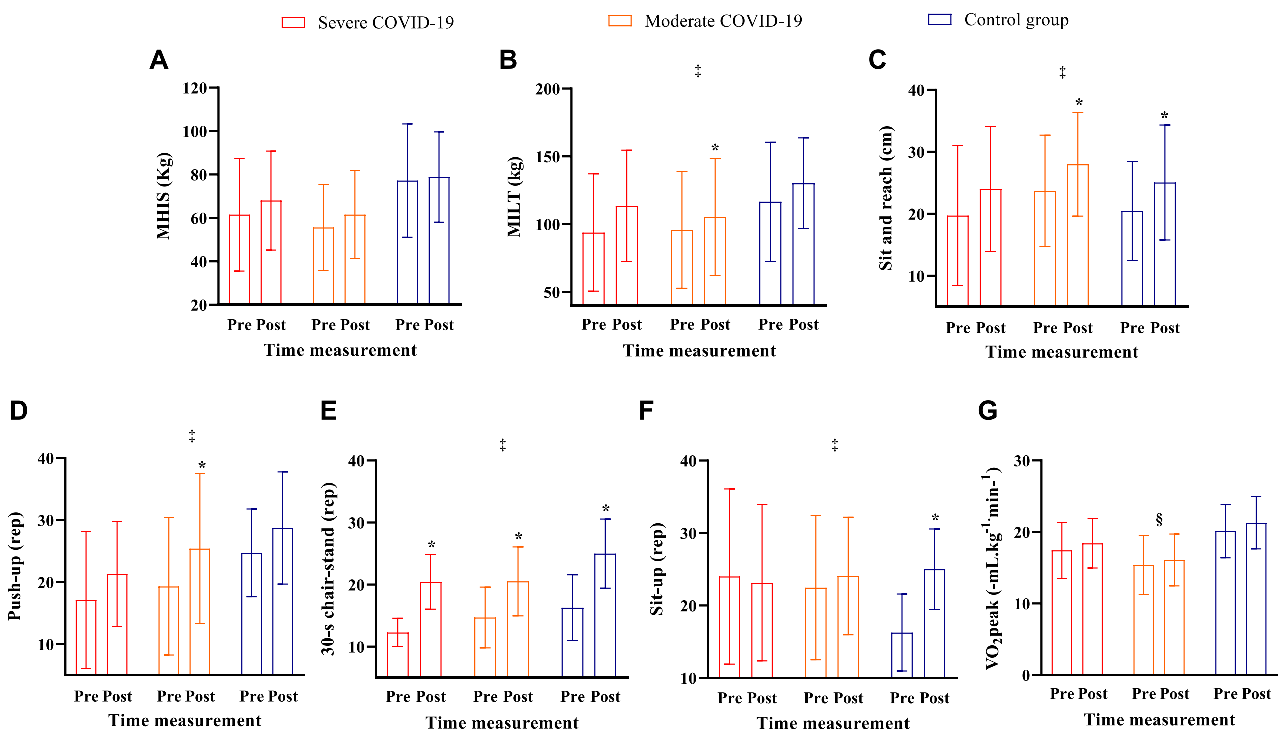

FIGURE 4
Physical tests in the pre- and post-assessment interventions for the severe COVID-19, moderate COVID-19, and control groups. Note: Data are expressed as the mean ± standard deviation; ʆ = a group difference with lower values for the moderate group when compared to the control group; ‡ = time difference from post-intervention; * = significant difference between pre- and post-intervention for the same group intervention; significance level established $p < 0.05$. **(A)** MIHS; **(B)** MILT; **(C)** sit and reach; **(D)** push-up; **(E)** 30-s chair-stand; **(F)** sit-up and **(G)** VO_2peak.

($F_{1,32}$ = 15.35; p = 0.0004; η^2 = 0.32; *large effect*), with the Bonferroni *post hoc* test indicating a significant increase after 8 weeks of intervention (p = 0.0006). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_7 = 1.566; p = 0.168; CI: −3.658 to 16.6; d =*0.26; small effect*) and control groups (t_{11} = 0.3145; p = 0.75; CI: −10.07 to 13.38; d =*0.07; small effect*). However, the isolated t-test revealed higher values in post than pre-intervention in the moderate COVID-19 group (t_{17} = 2.178; p = 0.04; CI: 0.1601 to 11.79; d = *0.29; small effect*).

For push-up test, no group ($F_{2,30}$ = 1.37; p = 0.26; η^2 = 0.08; *medium effect*) and no interaction effects were detected ($F_{2,30}$ = 0.12; p = 0.88; η^2 = 0.008; *small effect*). However, a time effect was observed ($F_{1,30}$ = 12.23; p = 0.001; η^2 = 0.28; *large effect*), with the Bonferroni *post hoc* test indicating a significant increase in push-up test after 8 weeks of intervention (p = 0.0006). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_7 = 1.442; p = 0.19; CI: −2.889 to 11.17; d = *0.06; small effect*) and control groups (t_{11} = 1.888; p = 0.08; CI: −0.7218 to 8.722; d =*0.04; small effect*). Nonetheless, the isolated t-test indicated higher values in post than pre-intervention in the moderate COVID-19 group (t_{15} = 3.048; p = 0.008; CI: 1.561 to 8.972; d = *0.52; moderate effect*).

For the 30-s chair-stand test, no group ($F_{2,32}$ = 3.03; p = 0.05; η^2 = 0.16; *large effect*) and no interaction effects were observed ($F_{2,32}$ = 0.80; p = 0.45; η^2 = 0.04; *small effect*). A time effect was observed ($F_{1,32}$ = 43.95; p = 0.0000000; η^2 = 0.57; *large effect*) with a significant increase in repetitions confirmed by Bonferroni *post hoc* test (p = 0.000000). The isolated t-test for each group indicated an increase in the repetitions performed in the severe COVID-19 (t_7 = 5.362; p = 0.001; CI: 4.427 to 11.86; d =*0.23; small effect*), moderate COVID-19 (t_{17} = 3.460; p = 0.003; CI: 2.256 to 9.391; d = *0.11; small effect*) and control groups (t_{11} = 4.498; p = 0.001; CI: 4.404 to 13.05; d = *0.16; small effect*).

For the sit-up test, no group ($F_{2,26}$ = 0.62; p = 0.54; η^2 = 0.04; *small effect*) and no interaction effects were observed ($F_{2,26}$ = 3.24; p = 0.05; η^2 = 0.19; *large effect*). However, a time difference was verified ($F_{1,26}$ = 5.46; p = 0.02; η^2 = 0.17; *large effect*), with the Bonferroni *post hoc* test indicating higher values after 8 weeks of intervention (p = 0.004). Isolated t-test did not confirm this effect for the severe COVID-19 (t_5 = 0.1721; p = 0.87; CI: −10.28 to 9.082; d = *0.07; small effect*) and moderate COVID-19 groups (t_{13} = 1.130; p = 0.28; CI: −2.426 to 7.656; d = *0.01; small effect*). However, the isolated t-test indicated increased repetitions performed in the control group (t_{11} = 4.498; p = 0.0011; CI: 4.404 to 13.05; d = *0.16; small effect*).

For VO_2 peak, a group difference was found ($F_{2,31}$ = 5.96; p = 0.006; η^2 = 0.27; *large effect*), with the Bonferroni *post hoc* test indicating higher values for the control group when compared to moderate COVID-19 group (p = 0.004). However, no time ($F_{1,31}$ = 3.96; p = 0.05; η^2 = 0.11; *medium effect*) and no interaction effects ($F_{2,31}$ = 0.29; p = 0.74; η^2 = 0.01; *small effect*) were observed for cardiorespiratory fitness.

TABLE 3 Training monitoring of the severe COVID-19, moderate COVID-19, and control groups in pre- and post-assessment intervention.

Variables	Severe		Moderate		Control	
	Pre	Post	Pre	Post	Pre	Post
% SpO_2 initial[a]	96 ± 1	97 ± 2	96 ± 2	97 ± 2	97 ± 2	97 ± 1
% SpO_2 final	93 ± 3	93 ± 5	95 ± 3	96 ± 1	96 ± 3	95 ± 2
SBP initial (mmHg)	120 ± 7	120 ± 7	120 ± 15	120 ± 8	120 ± 10	130 ± 9
SBP final (mmHg)[b]	130 ± 13	120 ± 10[c]	130 ± 13	120 ± 13	130 ± 13	130 ± 13
DBP initial (mmHg)	80 ± 8	70 ± 12	80 ± 8	70 ± 9	80 ± 9	70 ± 12
DBP final (mmHg)[b]	80 ± 9	70 ± 10	80 ± 7	70 ± 8[c]	80 ± 7	70 ± 9
RPE (*u.a*) [b]	5 ± 1	7 ± 1	6 ± 1	6 ± 2	5 ± 1	7 ± 1[c]
RPR (*u.a*)[b]	7 ± 2	9 ± 1	7 ± 2	8 ± 1	8 ± 1	8 ± 1
Tonnage (kg) [b]	3,507 ± 2,615	11,156 ± 5545[c]	3,967 ± 2,123	8,713 ± 4346[c]	6,005 ± 1855	11,602 ± 8,690

Note: data expressed as mean and ±standard deviation; $\%SpO_2$ = peripherical oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating perceived exertion; RPR, rating perceived recovery.
[a]a group difference with lower values for the severe and moderate group when compared to the control group.
[b]time difference from post-intervention.
[c]significant difference between pre- and post-intervention for the same group intervention; significance level established $p< 0.05$.

3.3 Training monitoring

Table 3 presents the training monitoring results of the three experimental groups (moderate and severe COVID-19 and a control group) before and after 8 weeks of intervention.

For initial SpO_2, a group difference ($F_{2,31}$ = 5.3; p = 0.01; η^2 = 0.25; *large effect*) was detected with higher values for the control group when compared to moderate COVID-19 (p = 0.04) and severe COVID-19 groups (p = 0.01). A time difference was detected ($F_{1,31}$ = 5.0; p = 0.03; η^2 = 0.13; *large effect*), but the Bonferroni *post hoc* did not confirm these findings (p > 0.05). Besides that, no interaction effect was observed ($F_{2,31}$ = 0.8; p = 0.46; η^2 = 0.04; *small effect*).

About the final SpO_2, a group difference was observed ($F_{2,32}$ = 3.32; p = 0.04; η^2 = 0.17; *large effect*), but the Bonferroni *post hoc* did not confirm these differences (p > 0.05). Besides that, no time ($F_{1,32}$ = 0.85; p = 0.36; η^2 = 0.02; *small effect*), and no interaction effects ($F_{2,32}$ = 1.02; p = 0.37; η^2 = 0.05; *small effect*) were found.

For initial SBP, no group ($F_{2,31}$ = 0.04; p = 0.95; η^2 = 0.002; *small effect*), no time ($F_{1,31}$ = 0.02; p = 0.88; η^2 = 0.00007; *small effect*) and no interaction effects ($F_{2,31}$ = 1.22; p = 0.30; η^2 = 0.07; *medium effect*) were detected.

For the final SBP, no group ($F_{2,30}$ = 0.01; p = 0.98; η^2 = 0.0008; *small effect*) and no interaction effects were detected ($F_{2,30}$ = 0.29; p = 0.74; η^2 = 0.01; *small effect*). A time effect was observed ($F_{1,30}$ = 10.61; p = 0.002; η^2 = 0.26; *large effect*), with the Bonferroni *post hoc* test indicating lower values after 8 weeks of intervention (p = 0.003). An isolated t-test revealed lower values in post than pre-intervention in the severe COVID-19 group (t_7 = 2.500; p = 0.04; CI: −28.273 to 0.3034; d = *0.12; large effect*). However, when each group was analyzed and isolated by the t-test, this difference was not confirmed for the moderate COVID-19 (t_{15} = 1.702; p = 0.11; CI: −19.13 to 2.200; d = *0.05; small effect*) and control groups (t_{11} = 1.742; p = 0.11; CI: −19.68 to 2.412; d = *0.05; small effect*).

For initial DBP, no group ($F_{2,31}$ = 0.22; p = 0.80; η^2 = 0.01; *small effect*), no time ($F_{1,31}$ = 3.46; p = 0.07; η^2 = 0.10; *large effect*) and no interaction effects ($F_{2,31}$ = 0.16; p = 0.84; η^2 = 0.01; *small effect*) were observed.

For the final DBP, no group ($F_{2,30}$ = 2.41; p = 0.10; η^2 = 0.13; *large effect*) and no interaction effects were observed ($F_{2,30}$ = 0.29; p = 0.74; η^2 = 0.01; *small effect*). A time difference was detected ($F_{1,30}$ = 13.32; p = 0.0009; η^2 = 0.30; *large effect*) with the Bonferroni *post hoc* test indicating lower values after 8 weeks of intervention (p = 0.0004). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_7 = 1.698; p = 0.14; CI: −17.43 to 3.148; d = *0.10; small effect*) and control groups (t_{11} = 1.604; p = 0.13; CI: −13.03 to 2.124; d = *0.06; small effect*). However, the isolated t-test revealed lower values in post than pre-intervention in moderate COVID-19 group (t_{15} = 3.389; p = 0.004; CI: −14.15 to −3.182; d = *0.11; small effect*).

For the RPE, no group ($F_{2,23}$ = 0.22; p = 0.79; η^2 = 0.01; *small effect*) and no interaction effects were detected ($F_{2,23}$ = 2.67; p = 0.09; η^2 = 0.18; *large effect*). A time difference was found ($F_{1,23}$ = 12.57; p = 0.001; η^2 = 0.35; *large effect*), with the Bonferroni *post hoc* test indicating higher values after 8 weeks of intervention (p = 0.0038). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_5 = 1.800; p = 0.10; CI: −0.5884 to 4.188; d =*1.48; large effect*) and moderate COVID-19 groups (t_{12} = 0.5567; p = 0.58; CI: −0.8614 to 1.445; d = *0.17; small effect*). However, the isolated t-test revealed higher values in post than pre-intervention in the control group (t_9 = 1.778; p = 0.01; CI: 0.4588 to 3.097; d = *0.24; small effect*).

For the RPR, no group ($F_{2,23}$ = 0.63; p = 0.53; η^2 = 0.05; *small effect*) and no interaction effects were observed ($F_{2,23}$ = 1.26; p = 0.30; η^2 = 0.09; *medium effect*). Nonetheless, a time difference was observed for the RPR ($F_{1,23}$ = 9.59; p = 0.005; η^2 = 0.29; *large effect*), and the Bonferroni *post hoc* test indicating higher values after 8 weeks of intervention (p = 0.01). When each group was analyzed isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_5 = 1.871; p = 0.13; CI: −1.017 to 5.217; d = *0.26; small*

TABLE 4 Biochemical parameters of the severe COVID-19, moderate COVID-19, and control group in pre- and post-assessment intervention.

Variables	Severe			Moderate			Control		
	Pre	Post	Δ%	Pre	Post	Δ%	Pre	Post	Δ%
Fasting glucose (mg/dL)[a]	101.4 ± 15.8	96.1 ± 11.7	−4.5	95.9 ± 9.4	92.0 ± 13.3[b]	−6.2	96.9 ± 8.0	88.9 ± 8.6[b]	−8.3
HbA1C (%)	6.5 ± 0.6	6.1 ± 0.3	−5.9	6.1 ± 0.5	6.1 ± 0.8	−3.6	6.5 ± 0.7	6.1 ± 0.7	−6.3
Total cholesterol (mg/dL)[a]	175.5 ± 22.4	166.0 ± 23.1	−5.5	177.7 ± 33.2	157.9 ± 33.9	1.1	200.1 ± 44.9	177.1 ± 16.3[b]	−8.9
HDL-c (mg/dL)[a]	47.2 ± 6.8	52.1 ± 5.9[b]	11.2	54.6 ± 15.1	57.3 ± 12.9	6.2	52.7 ± 14.8	54.0 ± 12.2	3.1
LDL-c (mg/dL)	97.3 ± 23.6	91.3 ± 26.0	−7.2	93.1 ± 25.2	91.1 ± 27.1	−0.8	103.7 ± 26.5	99.1 ± 32.1	0.7
TGL (mg/dL)[a]	155.1 ± 59.3	112.2 ± 51.8[b]	−28.2	149.5 ± 79.6	91.0 ± 35.1[b]	−15.6	179.6 ± 101.6	147.7 ± 74.0[b]	−31.0
ALT (U/L)	35.8 ± 12.8	28.0 ± 7.6	−19.5	29.0 ± 16.0	29.8 ± 14.2	12.0	37.9 ± 18.9	40.3 ± 19.1	38.5
AST (U/L)	30.7 ± 8.9	27.4 ± 7.2	−6.7	33.0 ± 15.6	29.8 ± 5.8	−4.3	33.6 ± 12.1	38.1 ± 17.7	22.8
ALP (U/L)	63.0 ± 16.7	60.4 ± 20.3	−2.9	67.5 ± 15.1	72.1 ± 16.9	5.6	66.3 ± 12.6	67.4 ± 13.2	4.0
GAMMA-GT (U/L)	44.5 ± 12.6	39.7 ± 9.5	−9.8	38.2 ± 18.3	38.5 ± 17.3	11.7	38.2 ± 16.4	55.1 ± 27.2	45.1
Albumin (g/dL)[a]	4.1 ± 0.2	4.6 ± 0.2[b]	11.9	4.0 ± 0.3[b]	4.5 ± 0.1	12.2	4.3 ± 0.3	4.5 ± 0.1	6.1
CRP (mg/L)[a]	10.1 ± 8.9	2.5 ± 1.7	−56.6	8.9 ± 6.2	3.1 ± 3.2[b]	−68.4	11.7 ± 4.8	4.0 ± 4.5[b]	−25.1

Note: data expressed as mean and ±standard deviation; Δ% = relative delta; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; TGL, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GAMMA-GT, Gamma-glutamyl transferase; CRP = C-reactive protein; Δ = relative delta.
[a]time difference from post-intervention.
[b]significant difference between pre– and post-intervention for the same group intervention; significance level established $p<0.05$.

effect), moderate COVID-19 (t_{12} = 1.689; p = 0.11; CI: −0.3160 to 2.399; *d =0.63; moderate effect*) and control groups (t_9 = 1.189; p = 0.26; CI: −0.5220 to 1.633; *d = 0.36; small effect*).

3.4 Tonnage

Table 3 presents the tonnage results before and after 8 weeks of intervention.

For tonnage, no group ($F_{2,26}$ = 1.15; p = 0.33; η^2 = 0.08; *medium effect*) and no interaction effects were observed ($F_{2,26}$ = 0.53; p = 0.59; η^2 = 0.03; *small effect*). A time effect was detected for tonnage after intervention ($F_{1,26}$ = 22.03; p = 0.00007; η^2 = 0.45; *large effect*), with the Bonferroni *post hoc* showing higher values after intervention (p = 0.00008). When each group was analyzed isolated by the t-test, this difference was confirmed for the severe COVID-19 (t_6 = 3.576; p = 0.01; CI: 2,151 to 13,148; *d = 1.76; large effect;* Δ = 218.1%) and moderate COVID-19 groups (t_{14} = 4.827; p = 0.0003; CI: 2,705 to 7,089; *d =1.38; large effect;* Δ = 119.3%), but this effect was not confirmed for the control group (t_9 = 1.687; p = 0.13; CI: −2,122 to 13,680; *d = 0.89; large effect;* Δ = 93.1%). However, 8 weeks of intervention increased the tonnage of the experimental groups (severe: 218.1%; moderate: 119.3%; control: 93.1%) compared to the pre-intervention time.

3.5 Biochemical parameters

The analyses of the biomarkers, i.e., fasting glucose, HbA1C, lipid profile, liver enzymes, CRP, and delta percentage values, are presented in Table 4.

For CRP, no group ($F_{2,28}$ = 0.56; p = 0.57; η^2 = 0.03; *small effect*) and no interaction effects were observed ($F_{2,28}$ = 0.15; p = 0.86; η^2 = 0.01; *small effect*). However, a time difference was detected ($F_{1,28}$ = 26.53; p = 0.000018; η^2 = 0.48; *large effect*), with the Bonferroni *post hoc* test indicating a significant reduction in CRP after 8 weeks of intervention (p = 0.0001). The isolated t-test confirm this difference for the severe COVID-19 (t_7 = 2.346; p = 0.05; CI: −15.52 to 0.3268; *d = 0.23; small effect*), moderate COVID-19 (t_{13} = 3.582; p = 0.003; CI: −9.858 to −2.402; *d =1.17; large effect*), and control groups (t_{11} = 3.148; p = 0.01; CI: −13.02 to −2.227; *d = 0.61; moderate effect*).

For albumin, no group ($F_{2,28}$ = 2.07; p = 0.14; η^2 = 0.12; *large effect*) and no interaction effects were verified ($F_{2,28}$ = 3.03; p = 0.06; η^2 = 0.17; *large effect*). However, a time effect was detected ($F_{1,28}$ = 39.0; p = 0.000001; η^2 = 0.58; *large effect*), with the Bonferroni *post hoc* test showing higher values in post-intervention (p = 0.000001). The isolated t-test for each group indicated an increase in the values for the severe COVID-19 (t_7 = 5.160; p = 0.002; CI: 0.2584 to 0.7244; *d =0.23; small effect*) and moderate COVID-19 groups (t_{13} = 4.730; p = 0.0005; CI: 0.2381 to 0.6449; *d = 0.17; small effect*). However, *the* isolated t-test did not confirm this difference for the control group (t_{11} = 1.712; p = 0.11; CI: −0.05070 to 0.3871; *d = 0.06; small effect*).

For fasting glucose, no group ($F_{2,27}$ = 1.08; p = 0.35; η^2 = 0.07; *medium effect*) and no interaction effects were observed ($F_{2,27}$ = 0.34; p = 0.71; η^2 = 0.02; *small effect*). A time effect was detected ($F_{1,27}$ = 26.58; p = 0.00002; η^2 = 0.49; *large effect*), with the Bonferroni *post hoc* test indicating a significant reduction after 8 weeks of intervention (p = 0.000009). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 group (t_7 = 1.409; p = 0.20; CI: −14.47 to 3.896; *d = 6.15; large effect*). However, isolated t-test revealed lower values in post than pre-intervention in moderate COVID-19 (t_{12} = 4.084; p = 0.001; CI: −10.13 to −3.036; *d = 0.05; small effect*) and control groups (t_{11} = 4.619; p = 0.001; CI: −11.86 to −4.141; *d =0.09; small effect*).

For HbA1C, no group ($F_{2,27}$ = 1.65; p = 0.20; η^2 = 0.10; *medium effect*), no time ($F_{1,27}$ = 3.73; p = 0.06; η^2 = 0.12; *medium effect*), and no interaction ($F_{2,27}$ = 0.29; p = 0.75; η^2 = 0.21; *large effect*) were found.

For total cholesterol, no group ($F_{2,26}$ = 0.51; p = 0.60; η^2 = 0.03; *small effect*) and no interaction effects were observed ($F_{2,26}$ = 1.04; p = 0.36; η^2 = 0.07; *medium effect*). A time difference was detected ($F_{1,26}$ = 10.35; p = 0.003; η^2 = 0.28; *large effect*), with the Bonferroni *post hoc* test indicating a significant reduction after 8 weeks of intervention (p = 0.0002). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the severe COVID-19 (t_7 = 2.359; p = 0.06; CI: −19.50 to 0.3587; d = *0.04; small effect*) and moderate COVID-19 groups (t_{12} = 1.580; p = 0.14; CI: −21.74 to 3.573; d =*0.05; small effect*). However, the isolated t-test revealed lower values in post than pre-intervention in the control group (t_{10} = 2.379; p = 0.04; CI: −42.14 to −1.059; d =*0.08; small effect*).

For HDL-c, no group ($F_{2,27}$ = 0.93; p = 0.40; η^2 = 0.06; *medium effect*) and no interaction effects were detected ($F_{2,27}$ = 0.95; p = 0.39; η^2 = 0.06; *medium effect*). A time effect was verified ($F_{1,27}$ = 8.21; p = 0.007; η^2 = 0.23; *large effect*), with the Bonferroni *post hoc* test indicating higher values after intervention (p = 0.01). When each group was analyzed and isolated by the t-test, this difference was not confirmed for the moderate COVID-19 (t_{13} = 1.718; p = 0.11; CI: −0.6721 to 5.688; d = *0.19; small effect*) and control groups (t_{10} = 0.6141; p = 0.55; CI: −3.462 to 6.042; d = *0.09; small effect*). However, isolated t-test revealed higher values in post than pre-intervention in the severe COVID-19 group (t_7 = 4.186; p = 0.005; CI: 2.060 to 7.857; d = *0.07; small effect*).

For LDL-c, no group ($F_{2,28}$ = 0.22; p = 0.79; η^2 = 0.01; *small effect*), no time ($F_{1,28}$ = 1.58; p = 0.21; η^2 = 0.05; *small effect*) and no interaction effects ($F_{2,28}$ = 0.29; p = 0.74; η^2 = 0.02; *small effect*) were observed.

For TGL, no group difference ($F_{2,27}$ = 1.30; p = 0.28; η^2 = 0.08; *medium effect*) and no interaction effects were observed ($F_{2,27}$ = 0.02; p = 0.97; η^2 = 0.001; *small effect*). Nonetheless, a time difference was found ($F_{1,27}$ = 19.49; p = 0.0001; η^2 = 0.41; *large effect*), with the Bonferroni *post hoc* test indicating a significant decrease after intervention (p = 0.00008). Isolated t-test revealed lower values in post than pre-intervention in severe COVID-19 (t_7 = 4.597; p = 0.003; CI: −65.67 to −20.04; d = *0.07; small effect*), moderate COVID-19 (t_{13} = 2.789; p = 0.01; CI: −86.87 to −10.67; d = *1.23; large effect*) and control groups (t_{10} = 2.491; p = 0.03; CI: −87.96 to −4.236; d = *0.06; small effect*).

For ALT, no group ($F_{2,27}$ = 1.05; p = 0.36; η^2 = 0.07; *medium effect*), no time ($F_{1,27}$ = 0.68; p = 0.41; η^2 = 0.02; *small effect*) and no interaction effects ($F_{2,27}$ = 2.54; p = 0.09; η^2 = 0.15; *large effect*) were detected. For AST, no group ($F_{2,28}$ = 1.12; p = 0.34; η^2 = 0.07; *medium effect*), no time ($F_{1,28}$ = 0.03; p = 0.84; η^2 = 0.001; *small effect*) and no interaction effects ($F_{2,28}$ = 0.85; p = 0.43; η^2 = 0.05; *medium effect*) were observed. For ALP, no group ($F_{2,28}$ = 1.11; p = 0.34; η^2 = 0.07; *medium effect*) no time ($F_{1,28}$ = 0.46; p = 0.49; η^2 = 0.16; *large effect*), and no interaction effects ($F_{2,28}$ = 1.18; p = 0.32; η^2 = 0.07; *medium effect*) were detected. Finally, for GAMMA-GT, no group ($F_{2,27}$ = 0.96; p = 0.39; η^2 = 0.06; *medium effect*), no time ($F_{1,27}$ = 1.89; p = 0.18; η^2 = 0.06; *medium effect*), and no interaction effects ($F_{2,27}$ = 2.77; p = 0.07; η^2 = 0.17; *large effect*) were detected.

4 Discussion

The present study aimed to investigate the effects of multiprofessional intervention on body composition, physical fitness, and biomakers in overweight COVID-19 survivors. In summary, the main findings observed after 8 weeks of intervention were as follows: i) 8 weeks of multi-professional intervention did not produce significant improvements in body composition in the severe, moderate, and control COVID-19 groups; ii) no differences were observed for MIHS and VO_2peak for all intervention groups; iii) the moderate COVID-19 group showed improvement in MILT, sit and reach, and push-up tests and the control group showed improvement in sit-up test; all intervention groups showed improvement in 30-s chair-stand test; iv) final SBP showed a significant reduction for the severe COVID-19 group, and DBP showed a significant reduction for moderate COVID-19 group; v) tonnage was higher in the last training session for moderate and severe COVID-19 groups; vi) CRP presented a significant reduction in moderate and control groups vii) albumin showed a significant improvement in moderate and severe COVID-19 groups; (viii) fasting glucose showed a significant reduction in moderate and control groups ix) total cholesterol showed a significant reduction in control group; x) HDL-c showed a significant improvement in severe COVID-19 group and ***xi)*** TG was reduced in all intervention groups. Consequently, the study's hypothesis was not confirmed.

Despite not reducing the risk of infection by COVID-19, reducing body weight seems to be a protective measure against the worsening of COVID-19 disease, as it reduces the inflammatory processes caused by obesity (Queiroz et al., 2022). A previous study reported that hospitalized patients with COVID-19 showed higher values of fat mass and body fat percentage when compared to individuals who manifested the mild form with the same BMI (Lemos et al., 2022). Given this and supporting this perspective, regular physical exercise and healthy nutrition can help control these parameters and favor a better immune response against COVID-19 infection (Queiroz et al., 2022), regardless of disease symptomatology. Nonetheless, no significant BMI reductions or body composition improvements were observed at the end of the 8 weeks. The effects of the physical exercise program on body composition are directly related to the exercise dose (duration, intensity, and frequency), generating a negative energy balance and decreasing body fat (Gleeson et al., 2011). However, the lack of weight-loss success with physical exercise can be explained by compensatory responses that neutralize energy balance to maintain homeostasis (Flack et al., 2020). According to *Flack et al.* (Flack et al., 2020), individuals compensate for approximately 50% of the calories spent with physical exercise regardless of the exercise dose. In our study, we did not collect dietary records before and after the multi-professional interventions. Thus, we cannot establish a relationship between the participant's body composition and dietary intake.

In addition, given the qualitative analyses carried out by our multi-professional team, there was a significant limitation of COVID-19 survivors who had moderate or severe disease cases regarding motor coordination to perform strength exercises. The moderate COVID-19 group improved MILT, sit and reach, push-ups, and 30-s chair-stand test, and the severe COVID-19 group just showed an improvement in the 30-s chair-stand test. These responses suggest that 8 weeks of multi-professional intervention could not be enough to promote progress in physical fitness in the severe COVID-19 group. Even though there is no previous evidence regarding the optimal tonnage for patients post-COVID-19 disease (Goldbaum et al., 2021), there was an improvement for moderate and severe COVID-19 groups. The severe COVID-19 group had an increase of 218.1%, and the moderate COVID-19 group increased by 119.3%, despite the physical limitations of the hospitalized patients.

When the present study was developed, there was no scientific basis for physical exercise prescription for individuals affected by COVID-19, specifically regarding the dosage (duration, intensity, and frequency of exercise) since the clinical condition of patients can be very heterogeneous. In the present study, the exercise sessions lasted approximately 60 min twice a week and were periodized to achieve a moderate intensity score via the RPE scale. Thus, our results indicated moderate classification by the experimental groups. We consider moderate-intensity exercise to be more appropriate due to the suppressive response of the immune system to high-intensity exercise. It is well documented that high-intensity physical exercise can decrease the immune system's defense mechanisms, making the body sensitive to infection and viral reactivation for 3–72 h after the exercise session (Arazi et al., 2021). Therefore, prioritizing patient safety, the recommendations were followed to avoid strenuous and long-duration sessions in individuals more susceptible to viral infections. However, it is worth mentioning that the WHO later released guidelines for post-COVID-19 rehabilitation recommending 20–30 min of conditioning exercise five times a week and 3 sets of 10 repetitions of muscle-strengthening exercises three times a week but without specific specifications for control/reduction of body weight and positive changes in body composition (World Health Organization et al., 2021b).

Regarding health-related physical fitness tests, significant improvements were observed in the 30-s chair-stand test for the severe and moderate COVID-19 groups and control group after 8 weeks of intervention, independent of changes in anthropometric and body composition differences, corroborating the findings of *Li et al.* (Li et al., 2021) and *Dalbosco-Salas et al.* (Dalbosco-Salas et al., 2021) after 6 and 9 weeks of tele-exercises, respectively, posthospital discharge for COVID-19. The lack of significant differences in anthropometric and body composition was explained by a lockdown, in which people could not move freely and, consequently, spent low energy (Silva et al., 2022). It is worth mentioning that the participants needed sufficient intra- and inter-coordination to perform the exercises correctly and overcome inflammation (measured via CRP). No significant improvements were detected in sit and reach, push-up, sit-up, MILT, and MIHS for severe COVID-19. These findings do not corroborate those of *Everaerts et al.* (Everaerts et al., 2021), who found improved handgrip strength after 12 weeks of intervention in post-discharge patients.

Cardiorespiratory fitness was assessed using the VO_2peak to verify physical capacity, effort tolerance, and possible cardiopulmonary abnormalities (Cahalin et al., 1996; ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). The VO_2peak of the control group was higher than that of the moderate and severe COVID-19 groups. Furthermore, no significant difference was detected in VO_2peak for all groups after the intervention, indicating possible lower stimulus to improve aerobic capacity. Contrary to the results of the present study, a previous study has shown improvements in VO_2peak (Rinaldo et al., 2021) in response to concurrent training in patients after hospital discharge for COVID-19, which can be explained by differences in manipulations of training variables (duration, intensity, and frequency). The exercise dose can explain the absence of significant effects on cardiorespiratory fitness. According to *Bull et al.* (Bull et al., 2020), 150–300 min per week of moderate-intensity or 75–150 min of vigorous-intensity physical activity is the minimum necessary to maintain health status in eutrophic individuals, which did not occur in the present study due to the inability of the participants to visit the intervention location at a high enough frequency to achieve 120 min a week.

All physical exercises aimed at rehabilitation must be performed safely. Thus, SpO_2 was monitored. The present study showed higher SpO_2 values for the control group compared to both COVID-19 groups, but these responses could be expected according to the impacts of this disease (Lemos et al., 2022).

The final SBP was significative reduced in the final intervention for the severe COVID-19 group. This response was highly positive, considering that *Zheng et al.* (Zheng et al., 2020) pointed out that SARS-CoV-2 infection can lead to persistent autonomic dysfunction. Autonomic dysfunction is closely related to blood pressure control and, when altered, can result in unwanted increases in blood pressure levels. *Libby et al.* (Libby and Lüscher, 2021) found evidence of significant endothelial damage in patients with COVID-19, even in mild to moderate disease cases. The vascular endothelium plays a crucial role in regulating blood pressure, and any dysfunction in this layer of cells can lead to an imbalance in vascular homeostasis and ultimately contribute to the development of high blood pressure following COVID-19 infection (Libby and Lüscher, 2021). This finding suggests that ongoing assessment of cardiovascular health in patients recovered from COVID-19 is crucial, even in mild cases of the disease. Regular physical exercise has a proven and consistent acute and chronic hypotensive effect in normotensive and hypertensive individuals (Pescatello et al., 2004; Vona et al., 2009; Cornelissen and Smart, 2013). Several mechanisms are involved in this effect, including peripheral vasodilation, modulation of the autonomic nervous system, the release of nitric oxide, and reduction of oxidative stress and inflammation (Pescatello et al., 2004; Vona et al., 2009; Cornelissen and Smart, 2013). *Lemos et al.* (Lemos et al., 2022) identified higher DBP responses after 15 min of the Bruce test in hospitalized post-COVID-19 patients, a factor that suggests a sequel that involves endothelial damage and inflammatory responses, but the significant reduction observed in the moderate COVID-19 group takes the positive effects of physical exercise to promote non-medicamental treatment.

Another point that deserves attention is the self-reported symptoms with higher prevalence by the volunteers: fatigue (severe: 85.7%; moderate: 64.7%), muscle and joint pain (severe: 57.1%; moderate: 29.4%), and dyspnea (severe: 42.8%; moderate: 35.3%). Given this, independently of the COVID-19 severity disease, the sequels' monitoring should be indispensable to reduce possible health impacts on the survivors.

Some biochemical analyses showed no significant changes after intervention: HbA1C, LDL-c, ALT, AST, ALP, and GAMMA-GT.

However, the patient's biochemical analyses were among the normative values in the pre-intervention time (Williamson and Synder, 2013). Significant changes were verified after intervention for CRP, albumin, fasting glucose, total cholesterol, HDL-c, and TGL.

CRP is one of the biomarkers associated with the severity of COVID-19 (although it is a nonspecific inflammation biomarker), and elevated levels are observed in hospitalized COVID-19 patients, especially those with severe disease (Guan et al., 2020), generating a systemic inflammatory response and increasing the release of pro-inflammatory cytokines. In pre-intervention, a high concentration of CRP was observed in the experimental groups compared with reference values (Aguiar et al., 2013), corroborating a previous study that revealed a high concentration of CRP in patients after recovery from COVID-19 (Ali et al., 2021). After the intervention, the CRP concentration was significantly reduced in the severe and moderate COVID-19 groups and the control group in response to multi-professional intervention, a factor that reinforces the effectiveness of physical exercise in reversing the inflammatory process (Improta-Caria et al., 2021).

The albumin levels at the beginning of the intervention within the values considered as reference (3.5–4.8 d/dL) (Williamson and Synder, 2013); these findings are significant because, according to *Ali et al.* (Ali et al., 2021), hypoalbuminemia is seen in hospitalized COVID-19 patients, and this condition may persist after recovery and hospital discharge.

Following American Diabetes Association (Colberg et al., 2016), physical exercise is essential to control blood glucose in pre-diabetes and diabetes mellitus. The average values of the severe COVID-19 group in pre-intervention were classified in pre-diabetes, i.e., >100 mg/dL (Colberg et al., 2016) (pre: 101.4 ± 15.8 mg/dL and post: 96.1 ± 11.7; $\Delta = -4.5\%$). Despite no significant differences being observed for fasting glucose in the severe group, the relative delta reduction is positive since *Chourasia et al.* (Chourasia et al., 2023) pointed out aspects concatenated with diabetes post-COVID-19, linked with i) undiagnosed diabetes mellitus ii) SARS-CoV-2 virus affecting the pancreas and iii) hyperglycemia due to stress from acute COVID-19 infection that are associated with the disease severity. However, the moderate COVID-19 and control groups significantly reduced after the intervention. This response could be related to low-volume training (400 kcals/week) that increases insulin sensitivity in sedentary individuals (Dube et al., 2012).

The total cholesterol was significantly reduced for the control group after the intervention. Similar responses were identified after 8 weeks of concurrent training in untrained men (Ghahramanloo et al., 2009). The absence of differences between the moderate and severe COVID-19 groups could be explained because patients with COVID-19 may experience dysregulation of lipid profiles after COVID-19 (Zhao et al., 2022). Another point related to hospitalized COVID-19 patients is linked with low values of HDL-c during hospitalization and after discharge (Sampedro-Nuñez et al., 2021). Given this, considering the reduction of inflammation, healthy nutrition stimulus, and physical training intervention, the increased HDL-c in the severe COVID-19 group could be justified by the environmental, pathological, and physiological changes. Finally, the reduction of serum TGL is related to concurrent exercise stimulus at low to moderate intensity that promotes a considerable oxidation of this energetic substrate (Melzer, 2011).

A limitation of our study is the short-intervention period, which needed more to generate metabolic and physiological stress to produce significant changes in body composition and improvements in physical fitness, mainly in the severe COVID-19 group. Another limitation is lost follow-up among groups because the participants did not return for the final evaluations to perform a possible intent-to-treat analysis. Finally, consider the third limitation of the high drop-out rate among participants in our study, which promoted a β value lower than 80% for several analyses. Considering these responses, the findings observed in this article should be analyzed with caution and not be extrapolated for other spheres but could drive future multi-professional interventions. The high drop-out rate in longitudinal interventions is typical in Brazil since the study participants did not have financial support from the researchers. Many people needed to return to work after the governmental resources were finished. Thus, the patients returned to work, even with sequelae post-COVID-19.

To the best of these authors' knowledge, this is the first study to consider the effect of multi-professional interventions according to symptomatology with an additional control group. Furthermore, this is the first study to enroll volunteers in a complete assessment of body composition and health-related physical fitness tests, including specific muscle strength tests, cardiorespiratory fitness tests, and biochemical markers. It is noteworthy that despite the absence of effects on body composition, the present maintenance of the measured variables is of great value given the vicious cycle of physical inactivity and the deleterious effects of lack of muscle contraction. The strengths of this study are physical exercise (concurrent training) combined with a multi-professional program, which can help patients return to their families, society, and work. In addition, the present study highlights the importance of a multi-professional team for recovering the overall health conditions of those who contracted COVID-19.

4.1 Final considerations

In short, the study's design (clinical trial) with patients with different COVID-19 symptoms gives greater validity and a broader perspective of the effects of a physical exercise program enriched with nutritional education and psychoeducation in people with overweight and obesity. This study emphasizes the importance of developing strategies to recover health conditions through physical exercise, nutrition, and psychoeducation in COVID-19 survivors. Two months of concurrent training performed at a moderate intensity (according to the RPE scale) promoted significant improvements in lower limb muscle strength, increased albumin concentration, and significantly reduced inflammation in patients after hospital discharge for COVID-19. However, caution is needed since the hospitalized patients did not improve body composition and cardiorespiratory fitness, which suggests that long-term interventions are needed for COVID-19 survivors, especially for severe cases. Notably, COVID-19 responses were heterogeneous, and the biological individuality of each subject must be respected. Therefore, this study provides a concurrent training model that can be safely used in individuals affected by COVID-19 who wish to start a physical exercise program regardless of symptomatology and reinforces the importance of a multi-professional team with other health professionals, thereby seeking the individual's integral care and support.

The severity of COVID-19 is a factor that limits the progression of the physical exercise program. Another point to consider is the various sequelae observed in individuals affected by COVID-19, which implies the need for individualized training based on the most sensitive observed difficulties during the initial physical evaluation. Thus, when considering concurrent training as part of a multi-professional program, professionals who provide exercise prescriptions should complete physical fitness assessments, that is, body composition and physical tests, and if possible, check the individual's most recent blood test results. Concurrent training, proposed in this research, is a complete training model that stimulates cardiorespiratory and musculoskeletal fitness, thereby promoting improvements in physical fitness.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by 4,546,726/2021 of Cesumar University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Conceived and designed the experiments: AS, ML, DM, JR, MP, MM, MA, and BM. Performed the experiments: AS, ML, DM, JR, MP, MM, MA, and BM. Analyzed the data: AS, ML, BFS, SD, SF, PV-B, JM, and BM. Contributed reagents/materials/analysis tools: AS, SD, SF, PV-B, ML, and BM. Wrote the paper: AS, ML, JM, SD, SF, PV-B, and BM.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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