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Enhancing exercise intervention for patients with post-acute COVID-19 syndrome using mobile health technology: The COVIDReApp randomised controlled trial protocol

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Abstract

Objectives: To analyse the effectiveness of a physical exercise programme guided by a mobile health technology system (COVIDReApp) for patients with post-acute COVID-19 syndrome. This syndrome is a multisystem disease that occurs in people with a history of COVID-19 between 1 and 3 months after the onset of the disease. This study will assess the impact of the intervention on fatigue, post-exertional dyspnoea, quality of life, pain severity, physical fitness, anxiety, depression and cognitive function. We also aim to analyse whether there are associations between the variables studied and the evolution of these associations during follow-up.

Design: A single-blind randomised controlled trial.

Methods: One hundred patients diagnosed with post-acute COVID-19 will be enrolled and randomly assigned to two groups. The experimental group will perform the intervention through a physical exercise programme guided by the COVIDReApp system, whereas the control group will perform the programme in paper format. Study outcomes will be collected at baseline and at 4, 12 and 24 weeks. Student's *t*-tests or Mann–Whitney *U*-tests will be used to analyse differences between groups, mixed ANOVA for differences over time and longitudinal structural equations for associations between variables at follow-up.

Discussion: This study is based on current evidence regarding exercise prescription recommendations for patients with post-acute COVID-19 syndrome. Our intervention is supported by a solid theoretical framework; however, challenges include tailoring the physical exercise programme to everyone's predominant symptoms and ensuring adherence to the programme.

Trial registration number: NCT05725538.

Keywords

Post-COVID-19 condition, post-acute COVID-19 syndrome, long COVID, exercise, mobile health, smartphone, mHealth, telerehabilitation, COVIDReApp

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Introduction

A second disease derived from SARS-CoV-2 has emerged known as post-acute COVID-19 syndrome (PACS) or long COVID.[1] It is a multi-systemic syndrome characterised by a range of symptoms involving biological, psychological and social factors.[2] This, together with the fact that the sequelae of this disease are long lasting and that it is still not well known in clinical care, means that people with PACS are often forgotten and misunderstood by the health system.[3] Therefore, it is imperative to study the symptomatic process, initiate the early diagnosis of symptoms, and establish treatment and rehabilitation protocols.[4]

Regarding rehabilitation programmes, research has mainly focused on the application of physical exercise programmes and respiratory exercises, showing beneficial physical effects with these therapies.[5] In this sense, the use of mobile wireless technologies for public health or mHealth,[6] to support the treatment of patients with various pathologies has already been observed as a useful tool, as well as conventional treatment,[7] allowing them to take a more active part in the management of their disease.

Background and rationale

Currently, the definition of PACS is controversial. Some authors[8] define it as an illness that appears in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19, with symptoms lasting at least 2 months that cannot be explained by an alternative diagnosis. Other authors[1] use this term to refer to symptoms that persist for over 4 or even 12 weeks after the onset of the disease or appear later in individuals with an asymptomatic infection. The incidence of PACS is estimated to range from 10% to 35% and may be as high as 85% in patients requiring hospitalisation.[9] Although over 200 symptoms have been described,[10] the most common symptoms are fatigue, dyspnoea, cognitive dysfunction, memory loss, pain, anxiety and depression.[11] These symptoms may recur after recovery from the initial acute episode or persist after the initial illness. Related to this, it should be noted that all these symptoms in PACS have been demonstrated to have a detrimental effect on health-related quality of life,[12] persisting even 1 year after the diagnosis of the disease. This relationship has also been documented in other pathologies, which indicates the need to address all physical and mental effects of PACS.[13]

Current literature[14] has shown that patients with COVID-19 can experience physical, functional and respiratory limitations in the months following the acute phase of the disease, such as gait impairments, decreased respiratory muscle strength, decreased exercise tolerance, increased fatigue, spirometry abnormalities, diffusing capacity and lung imaging abnormalities. The need to develop effective treatment and rehabilitation options is highlighted by these variable consequences.[15] Consequently, treatment should be delivered through a multimodal approach.[16]

Regarding rehabilitation programmes for patients with COVID-19, the current literature outlines the benefits of physical rehabilitation therapy through aerobic, endurance, and respiratory exercise training in terms of parameters such as functional capacity, lung function, quality of life and mental health status.[17] In this sense, current recommendations[18] state the need to tailor exercise prescription to the type of patient and the severity of their symptoms, especially for those with post-exertional malaise (PEM). PEM is the most characteristic symptom of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and is highly prevalent in at least 45.2% of patients with PACS.[19] Indeed, Fairbank[18] has drawn attention to the detrimental effects that physical exercise programmes can have on people with PACS with PEM, contraindicating their use. Moreover, it is recommended to include face-to-face supervision sessions on exercise technique and intensity throughout home exercise programmes.[16]

The development of mobile technology has led to the rise of 'mHealth', which means utilising mobile technology to support medical and public health for various purposes, including collecting clinical data, delivering health services, communicating with patients and promoting adherence to treatment and monitoring medication. This field is essential for current economic growth. In fact, the value of the global mHealth market is expected to grow at a compound annual growth rate of approximately 10.8% from 2023 to 2030, based on a 2022 estimate of USD 56.8 billion.[6] In addition, research has shown an increasing tendency to use new technologies to develop remote rehabilitation programmes for patients with COVID-19.[20] The latest research stated that telerehabilitation is a useful and safe intervention to improve dyspnoea, lower limb muscle strength, ambulation ability and depression in patients with COVID-19.[21] In this line, the use of telerehabilitation through combined aerobic, strength and breathing exercise programmes has shown beneficial effects on physical performance, respiratory capacity, quality of life and psychological symptomatology in people with PACS.[22] Currently, there is no exercise-based mHealth tool available for patients with PACS; however, there is a randomised clinical trial of mHealth rehabilitation called ReCOVery APP, whose primary results have not demonstrated benefits in improving the quality of life of these patients. This study also reported low levels of adherence to the app by participants.[23] Therefore, further research is needed to ensure the level of evidence and to measure the effectiveness in relation to other symptoms of PACS, such as anxiety and depression, pain, dyspnoea, fatigue and cognitive dysfunction.

Based on the above, we expect that participants in the COVIDReApp intervention group will perform better

than those in the control group on all the variables studied. In addition, there will be a relationship between physical and psychological variables during follow-up, which will impact quality of life.

Objectives

The main aim of this research protocol is to evaluate the effectiveness of a physical exercise programme based on an mHealth technology intervention, COVIDReApp, for patients with PACS. This intervention focuses on providing physical exercise guidance, and its effectiveness will be measured by analysing several outcomes such as fatigue, post-exertional dyspnoea, quality of life, pain severity, physical fitness, anxiety, depression, and cognitive function. We also aim to analyse the relationship between fatigue, post-exertional dyspnoea, quality of life, pain severity, physical fitness, anxiety, depression and cognitive function in patients with PACS during follow-up. We also intend to assess user satisfaction with the COVIDReApp application.

Trial design

A 24-week, single-blind, parallel-group, randomised controlled trial (RCT) in patients with PACS will be planned. The protocol for this study will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013 Statements).[24]

Methods

Participants and the study setting

This study will include patients who experienced COVID-19 during the pandemic and were diagnosed with PACS by their physicians. These individuals will be chosen from among patients under follow-up by the Internal Medicine Service of the Hospital Universitario Puerta del Mar in Cadiz, Spain. Physicians in charge of potential participants with PACS will propose inclusion in the study by applying the inclusion and exclusion criteria. The participants will also be reassessed by the physiotherapist during the first study debriefing. Patients will receive the general information and consent form from their doctors at a future appointment and will be contacted within 2 days to assess their interest in participating in the trial.

Inclusion criteria

The criteria used to select potential study participants are as follows: (a) male and female patients with PACS aged over 18 years, (b) without physical or cognitive problems that would prevent them from engaging in physical activity, (c) who had a smartphone with Internet access and (d) who could understand and write Spanish.

Exclusion criteria

The following criteria were used to exclude patients: (a) comorbidities limiting physical activity, (b) contraindications to physical activity determined by their physician and (c) performance of moderate-to-high-intensity physical activity at the start of the study for at least 30 minutes, three times per week.

Interventions

Physical exercise programme. Both study groups will perform a 6-month physical exercise programme of 40 to 60 minutes, three times per week, in line with the recommendations for the management of ME/CFS from the National Institute for Health and Care Excellence (NICE).[25] In addition, users will be advised to personalise the exercise programme, intensity, and duration according to their physical self-perception and symptoms, as proposed in the Covid Rapid Guidelines19[26] and recommendations for physical exercise prescription for people with ME/CFS.[25] Each daily session consists of a warm-up, aerobic exercise, strengthening exercises and cool-down (Table 1).

In addition, to progressively increase the intensity and duration of the main part of the physical exercise programme, three phases of the programme will be carried out during the 6 months of the intervention (Table 2).

Patients will receive their first face-to-face session at the Hospital Universitario Puerta del Mar (Cádiz, Spain), where we will explain the physical exercise programme and, in the experimental group, how to use the smartphone application. Their physicians decide beforehand whether patients can engage in regular activities. An elastic band will be used to practice strengthening exercises, which will be provided to each patient. In the first session, a physical therapist will explain how to control the length of the elastic band to change the level of resistance. Generally, an exercise intensity of 70% to 80% of the patient's 1 repetition maximum (1RM) will be recommended, allowing for 8 to 10 repetitions.[27]

Moreover, to monitor participants' progress with the exercise programme, follow-up group sessions will be organised in person at 4, 12 and 24 weeks. In addition, personalised telephone follow-up will be provided, and participants will be encouraged to contact the responsible physiotherapist in case of doubt or clinical worsening with the exercise programme.

Experimental group. The physical exercise programme of the experimental group will be monitored and guided using a mobile health technology system called COVIDReApp. The COVIDReApp group should use the mobile application three times a week, with at least 24 hours between workouts, for 24 weeks.

Table 1. Exercises used in each category.

Category	Description
Warm-up	Five respiratory exercises: (a) diaphragmatic breaths, (b) thoracic breaths, (c) opening arm raises, (d) lateral thoracic breaths, (e) prolonged exhalations, and 3 joint mobility exercises: (f) mobility of ankles, (g) mobility of trunk and hips and (h) mobility of the neck.
Aerobic training	Walking for 10 to 20 minutes. so that the patient can maintain a conversation but having to stop to breathe from time to time.
Strengthening	It will focus on six exercises: (a) squats, (b) flies, (c) inverted flies, (d) lateral pull-ups, (e) core exercise (abdominal stability with elastic band) and (f) monopodial balance.
Cool down	It will comprise stretching exercises: (a) chest, (b) quadriceps, (c) hamstrings and (d) back.

Table 2. Physical exercise programme phases.

Phases	Aerobic training	Strengthening
1 (0^{th}–1^{st} month)	10 minutes	Exercises (a) to (d): 2 sets of 10 repetitions. Exercises (e) and (f): 2 sets of 1 repetition of 20 seconds.
2 (1^{st}–3^{rd} month)	15 minutes	Exercises (a) to (d): 3 sets of 10 repetitions. Exercises (e) and (f): 2 sets of 1 repetition of 25 seconds.
3 (3^{rd}–6^{th} month)	20 minutes	Exercises (a) to (d): 3 sets of 15 repetitions. Exercises (e) and (f): 2 sets of 1 repetition of 30 seconds.

The web platform and smartphone applications are two components of this system. The web platform allows healthcare professionals to add and visualise patients, training sessions and programmes. A mobile application (Figure 1(a)) allows users to interact with their personal devices. The software displays the programme structure as warm-up, aerobic training, strengthening and cool-down. Only one training session per day is allowed. The patient must complete one category before moving on to the next (Figure 1(b)). In addition, the patient must wait until the next day to perform the exercises if the exercise programme is cancelled by the patient (details of the reason must be provided and documented). The COVIDReApp software provides videos and detailed explanations for each exercise (Figure 1(c)). During each exercise, the user can track the duration and replay the exercise description (Figure 1(d)). Users can also access their exercise log history to confirm that they have completed the daily programme (Figure 1(e)). The COVIDReApp will track adherence to interventions through the collected data.

The control group. Patients randomly assigned to the control group will receive the same intervention (Table 1) for 24 weeks but traditionally (on paper) without using the mobile health system. Participants will receive a leaflet with pictures and details of the exercises that they must perform. Adherence to the intervention will not be recorded in this group.

Outcomes

To analyse the effectiveness of the physical exercise programme, fatigue, post-exertional dyspnoea, quality of life, pain severity, physical fitness, presence of depression and/or anxiety, and cognitive function will be assessed. The primary outcomes of the study will be fatigue, post-exertional dyspnoea and quality of life, whereas the secondary outcomes will include pain severity, physical fitness, anxiety, depression and cognitive function. All study variables will be collected at baseline and at 4-, 12- and 24-week reviews.

For the collection of sociodemographic and clinical data, a structured questionnaire will be used that will include the following variables: sociodemographic characteristics and anthropometric measures (height, weight and body mass index (BMI)), date of diagnosis of COVID-19, whether hospitalisation was required, and if so, clinical situation on admission established in the hospital protocol, including the need for oxygen supply: by nasal goggles, high flow, non-invasive mechanical ventilation or orotracheal intubation and the place of admission: conventional ward, pneumo-COVID ward or ICU admission; patient

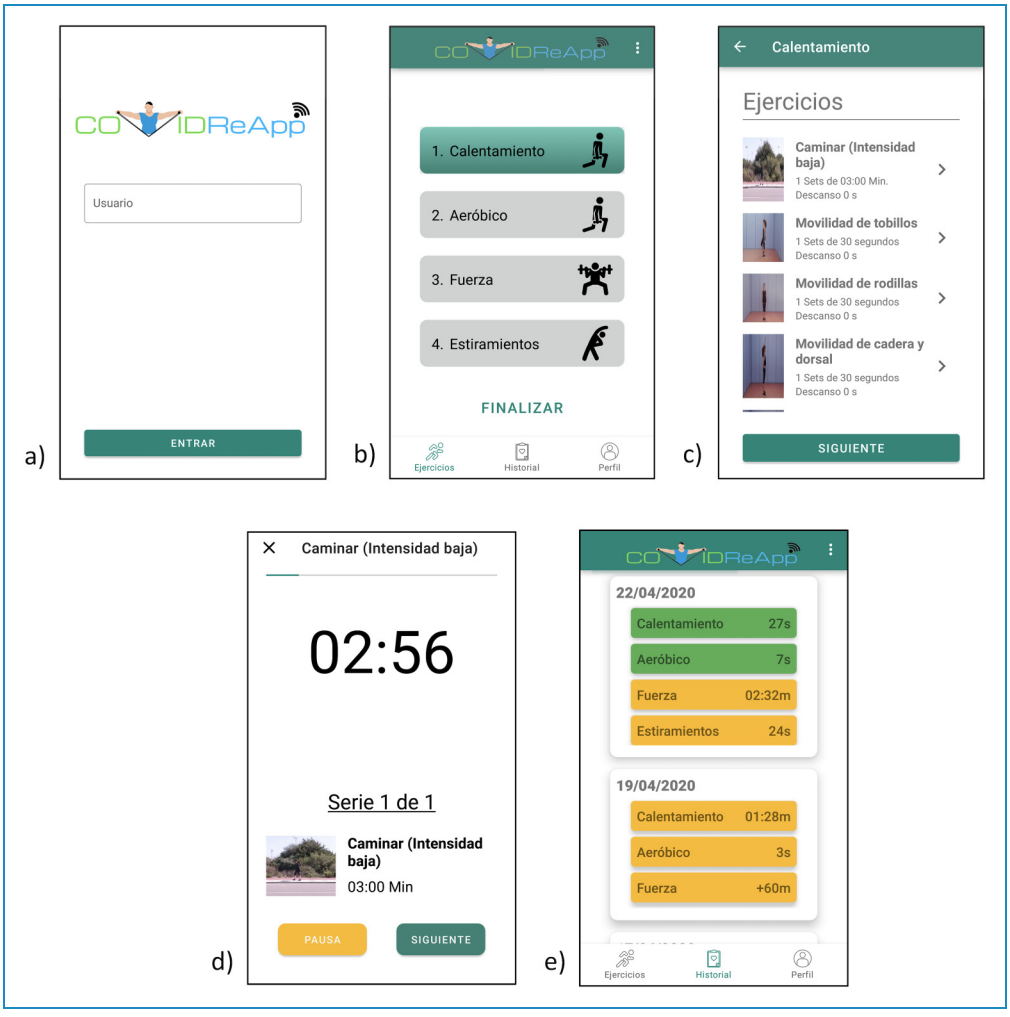

Figure 1. COVIDReApp screenshots: (a) user login screen, (b) physical exercise programme structure (warm-up, aerobic training, strengthening, and cool down), (c) list and description of exercises by category, (d) exercise guidance screen and (e) historical daily training records.

experience: self-perceived health status, self-perceived worsening health and self-perceived disability; duration of PACS symptoms, COVID-19 derived symptoms leading to associated disability: fatigue or asthenia, general malaise, fever, dyspnoea, coughing, retrosternal chest pain, chest tightness, heart palpitations, diarrhoea, neck pain, back pain, muscle pain, joint pain, tingling, loss of smell (anosmia), loss of taste (ageusia), headache, dizziness, low mood, anxiety, attention deficit or lack of concentration, memory lapses, insomnia; treatment for derived symptoms; physiotherapy; presence of comorbidities by the Charlson comorbidity index (CCI)[28] (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic respiratory disease, gastroduodenal ulcer, liver disease, diabetes, renal disease, oncological disease, autoimmune disease, acquired immune deficiency syndrome (AIDS)); presence of pain, type of pain (musculoskeletal pain, visceral pain, neuropathic pain, undefined pain), localisation of pain (headache pain, cervical pain, mid-back pain, low-back pain, limb pain, thoracic pain, abdominal pain, widespread pain); number of pain locations, duration of pain; analgesic treatment for pain; and the use of alternative therapies the week before the start of the study (mindfulness, yoga, pilates and/or others) and during follow-up.

Fatigue will be assessed using the Fatigue Severity Scale (FSS). The FSS includes nine phrases about how fatigue interferes with particular activities and assigns each of the nine questions a severity rating ranging from one to seven, where a score of 1 indicates 'strongly disagree' and 7 indicates 'strongly agree'. Therefore, the scale scores range from 9 to 63 points. Lower scores correspond to better fatigue results and higher scores to worse fatigue results.[29]

The Dyspnoea-12 test evaluates post-exertional dyspnoea and is a short questionnaire that captures elements

that may contribute to dyspnoea, including both emotional and sensory elements. Six of the topics addressed the emotional aspects of dyspnoea, whereas the other six addressed sensory aspects. Each question in the questionnaire is graded from 0 (moderate symptoms) to 3 (severe symptoms). The total rating is the combination of the scores for all questions and ranges from 0 to 36, with 36 representing the maximum severity and 0 representing the minimum severity as possible.[30]

The 12-item Short-Form Health Survey version 2 (SF-12v2) will be used to evaluate the quality of life. This tool includes 12 elements that constitute its eight-dimensional profile: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. Higher scores indicate better conditions, with global scores ranging from 0 to 100. It also includes two global ratings: PCS-12 for physical health, and MCS-12 for mental health. The scores for these two global dimensions are studentised with median = 50.[31]

The Numeric Rating Scale for Pain (NRS Pain) measures pain intensity. It is a subjective pain measure in which the patient chooses a number between 0 and 10 (11-point numeric scale), showing the intensity of pain that they believe they are experiencing. A score of 0 corresponds to no pain at all, and a score of 10 corresponds to the worst pain imaginable.[32]

Three physical performance exercises will be performed to assess physical fitness. The 30-s arm curl test (30 ACT) will evaluate upper body muscular strength. The aim of this test is to complete as many push-ups as possible in 30 seconds with a hand weight of 2.3 kg for women and 3.6 kg for men.[33] For lower body muscular strength, the 30-second chair stand test (30 CST) will be applied, calculating the maximum number of times a person can stand up and sit down from a chair in 30 seconds.[33] Finally, the 2-minute walk test (2MWT) assesses walking ability, functional endurance, and functional capacity.[34] It entails gauging the patient's walking distance for 2 minutes as quickly as possible, safely, and without help.

The Hospital Anxiety and Depression Scale (HADS), which has 14 questions and is divided into two subscales for anxiety (HADS-A) and depression (HADS-D), will be used to evaluate depression and anxiety. Responses to each question are on a Likert-type scale with scores ranging from 0 to 3. Therefore, the scores for each subscale range from 0 to 21 points. Minimum scores between 0 and 7 indicate the absence of depression and/or anxiety, intermediate scores between 8 and 10 indicate a clinically significant disorder, and maximum scores between 11 and 21 denote moderate to severe depression and/or anxiety.[35]

Cognitive function will be assessed using the Test Your Memory Screening Test (TYM). This instrument comprises ten tasks, each with a score between 0 and 50. The score was derived using the following 10 cognitive dimensions: anterograde memory, retrograde memory, executive function, naming, visuospatial ability, similarities, calculation, verbal fluency, orientation and copying. The threshold is 42/50 (≤41 points show cognitive impairment), and a superior value suggests an improved cognitive function.[36]

Finally, participants who use the COVIDReApp system will log their daily activity. This enables us to learn about participant adherence, exercise difficulty and execution time for each exercise. Furthermore, a rating system will gauge user satisfaction with the COVIDReApp application, where the patient chooses a score from 0 to 10, in which a value of 0 indicates no satisfaction and a score of 10 indicates a high level of satisfaction.

Sample size

The sample size was estimated to identify differences between the groups in the measurement scales to be administered. The calculations were performed using the statistical software Epidat 3.1 (Conselleria de Sanidade de la Xunta de Galicia, Santiago de Compostela, Spain), with a confidence level of 95% and a power of 80%. Table 3 shows the results for all scales.

In view of these calculations, a sample size of 45 subjects (90), was established to meet all objectives. However, to account for potential dropouts, the total sample size was increased by 10% to 99 patients, resulting in the final inclusion of 50 patients from each group.

Assignment of interventions

Each patient will be randomly allocated to a group using Epidat 3.1 software (Conselleria de Sanidade de la Xunta de Galicia, Santiago de Compostela, Spain). Two lists of 50 random numbers between 1 and 100 will be generated by allocating subjects to the treatment module, with groups of equal size. This tool will make it possible to decide in advance which group each patient will belong to, depending on the time of enrolment. The randomisation process will continue to use the 'balanced group' strategy if the initially estimated sample size exceeds. As a result, both groups will increase by chance in an equal distribution, because the likelihood of inclusion in each group will be inversely proportional to the number of individuals currently in that group.

Blinding

There will be a single blinding in this study. The data analyst will be the only blinded person.

Data collection

Participant data and variables were gathered, as depicted in Figure 2. Post-intervention evaluations will be performed by a researcher who is blinded to participant allocation.

Table 3. Calculation of required sample size.

Scale	Differences	Standard deviations	Sample in each group	Total sample	Reference
SF-12v2	5	8	45	90	Jayadevappa et al. (2017)
FSS	1.20	1.6	28	56	Pouchot et al. (2008)
30 ACT	2.53	2.3	13	26	Bhattacharya et al. (2016)
30 CST	1.16	1.75	36	72	Bhattacharya et al. (2016)
2MWT	42.50	32.8	10	20	Bohannon et al. (2015)
D-12	2.83	4.88	40	80	Ekström et al. (2020)
NRS Pain (0–10)	0.90	0.9	16	32	Kelly (1998)
HADS	1.50	2.34	39	78	Puhan et al. (2008)
TYM	11.60	4.4	6	12	Brown et al. (2019)

SF-12v2: 12-item Short-Form Health Survey version 2; FSS: Fatigue Severity Scale; 30 ACT: 30 seconds arm curl test; 30 CST: 30 second chair stand test; 2MWT: 2-Minute Walk Test; D-12: dyspnoea-12 questionnaire; NRS pain: Numeric Rating Scale for pain; HADS: Hospital Anxiety and Depression Scale; TYM: Test Your Memory Screening Test.

Statistical methods

The data will be subjected to descriptive analysis, with the distribution of the data represented by absolute frequencies (n) and relative frequencies (%) for qualitative variables. Measures of central tendency (mean) and dispersion (standard deviation) will be used as the quantitative variables. The normality of the distributions of the latter will be examined using the Kolmogorov–Smirnov test. Student's t-tests, in the event of normality, or Mann–Whitney U-tests otherwise, and Chi-squared tests will be used to analyse differences between groups (intervention vs. control). Mixed ANOVA will be used to analyse differences over time between and within groups (with adjustments such as Pillai's Trace, Roy's Largest Root, Greenhouse-Geiser, or Lower Limit if some assumptions such as normality or equality of variances fail), in which the time variable will be the intra-group factor and the intervention group will be the inter-group variable. The confidence level will always be fixed at 95%.

To analyse the relationships between fatigue, post-exertional dyspnoea, quality of life, pain, physical fitness, anxiety, depression and cognitive function, multivariate structural equation models with latent variables will be performed, both at baseline and during follow-up, using the aforementioned models in their version for repeated measures.[37] Latent variables, also known as factors, are variables that cannot be directly quantified but are instead inferred from observable variables that are expressions of the same latent variable. The technique combines factor analysis with the linear regression method and allows testing of the degree of fit of observed data to a hypothetical model expressed as a path diagram.[38] The final analysis contrasts each relationship and shows the degree to which the actual data fit a theoretical model, in this case, of the relationships between the abovementioned variables. These are powerful models that are increasingly used in practice and health. These models are one of the most commonly used methods for analysing longitudinal data. In these cases, in addition to examining the relationships of certain constructs, the effect of the relationships over time is analysed. Thus, it is possible to jointly study the directional effects of some variables on others and the evolution of the variables themselves.[37] Statistical software IBM SPSS v.29 and AMOS will be used to conduct the analysis.

Ethics

The current clinical trial has been approved by the Ethical Committee of the Province of Cádiz (Cádiz, Spain) and has been recorded in the database delivered by the U.S National Library of Medicine, ClinicalTrials.gov, with identifier code NCT05725538. In this sense, potential participants will be required to complete a written informed consent form, indicating their willingness to voluntarily participate in the study. The Consolidated Standards of Reporting Trials (CONSORT)[39] declaration will be followed to publish the study's findings in international peer-reviewed journals and present the findings at conferences throughout the world. Additionally, as part of our knowledge translation strategy, we will disseminate the findings on institutional websites and social media, contact news organisations, and identify partner institutions that are interested in the findings.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT**	t_{-1}	0	t_0	t_1	t_2	t_3
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Experimental group COVIDReApp system			◆—	—	—	—◆
Control group Conventional treatment: paper format			X	X	X	X
ASSESSMENTS:						
Baseline socio-demographic variables			X			
Alternative therapies (mindfulness, yoga, Pilates, etc.)			X	X	X	X
Height, weight, and body mass index			X	X	X	X
Clinical symptomatology related to Post-Acute COVID-19 and self-perceived health			X	X	X	X
Fatigue (FSS)			X	X	X	X
Post-exertional dyspnoea (Dyspnoea-12)			X	X	X	X
Quality of life (SF-12v2)			X	X	X	X
Pain severity (NRS Pain)			X	X	X	X
Pain killer's consumption			X	X	X	X
Physical fitness (2MWT)			X	X	X	X
Upper limb strength (30s arm curl test)			X	X	X	X
Lower limb strength (30s chair stand test)			X	X	X	X
Depression and anxiety (HADs)			X	X	X	X
Cognitive function (TYM)			X	X	X	X
COVIDReApp adherence*			◆—	—	—	—◆
Exercise difficulty*			◆—	—	—	—◆
Time of exercise execution*			◆—	—	—	—◆

t_{-1}, completed in clinical setting; 0, completed before first session; t_0, initial baseline assessment and first face-to-face session; t_1, 4 weeks; t_2, 12 weeks; t_3, 24 weeks.
* This outcome was only assessed in the experimental group (COVIDReApp system).

Figure 2. COVIDReApp timetable for enrolment, interventions, and assessments. Solid lines indicate periods of continuous or daily collection or evaluation, while 'X' indicates collection on specific days.

Confidentiality

To guarantee accuracy in data gathering and analysis, certain steps will be followed. Neither the paper log nor the COVIDReApp log will have any characteristics in the participant data that may identify the patient. All information will be kept electronically or on paper at the Research Unit of the Pain Observatory at the University of Cadiz, either on a password-protected computer or in a locked cabinet. Documentation of the project should be maintained for at least 10 years. Data-collection

forms will be destroyed after this point, and any electronic records will be deleted.

An encrypted code safeguards any data sent from a smartphone application to the server. Each participant will be given a special code (such as NLeuG4kz) to begin the programme as recommended by a medical professional. The information will not be stored in a cloud storage system at any point during its transmission. A dedicated server will be installed at the facilities of the University of Cadiz.

Discussion

This study aims to assess the impact of a physical exercise programme guided by a mobile health technology system on fatigue, post-exertional dyspnoea, quality of life, pain intensity, physical fitness, anxiety, depression and cognitive function in patients with PACS. It is expected that providing patients with access to COVIDReApp will improve adherence to exercise interventions and highlight the well-documented benefits of physical activity for this specific patient population.

These results are expected, based on previous studies. First, regarding the benefits of exercise in PACS, current evidence based on aerobic and resistance exercises in people with chronic diseases showed that exercise can be beneficial for functional capacity, quality of life, and psychological consequences, such as stress, anxiety, and depression.[40] In this context, in agreement with the previous authors, a disease management guideline supports the idea that appropriate and personalised exercise is a promising and effective therapy to alleviate the symptoms of PACS and help people recover faster and increase their autonomy, functionality and quality of life.[41] In this line, another literature review on rehabilitation in patients with PACS argues for the need to base exercise therapy as an indispensable tool for disease management and that it has beneficial repercussions on the control of fatigue, exercise intolerance, dyspnoea, mental health and sleep-related problems and musculoskeletal pain.[42] Second, respiratory exercises are commonly included in exercise-based rehabilitation programmes. They have been a useful tool for improving physical fitness and may have beneficial effects on lung function, dyspnoea, and quality of life.[5] In fact, most published rehabilitation programmes for the management of this disease focus on training the respiratory muscles.[5] In that sense, a systematic review stated that the combination of respiratory muscle exercises and strength training is effective in improving functional capacity and quality of life and reducing fatigue and dyspnoea.[43] This finding was also reported by recent studies showing that exercise programmes that combine endurance and resistance training plus respiratory muscle training had better results in terms of fatigue, dyspnoea, quality of life, lung function, health status, functional capacity, lower limb muscle strength, hand grip strength, respiratory muscle strength and depression than those that only include respiratory exercises.[44–46]

Moreover, knowledge about mHealth in people with PACS is still scarce, and no systematic reviews or meta-analyses are available specifically on this topic. However, there are scientific publications that have analysed this issue in patients with COVID-19. In this line, a meta-analysis analysing people with COVID-19 showed that telerehabilitation tools are effective in improving dyspnoea, lower limb strength, walking functionality and depression, but no improvements were found in anxiety and quality of life.[21] In this context, a scoping review focusing on digital interventions for people with PACS also found benefits in terms of dyspnoea, fatigue and functionality.[22] To complement this perspective, another qualitative study found positive effects on fatigue management in patients with PACS using a mobile application.[47] In view of these results, there are numerous inconsistencies between the studies conducted in this population, and further research is needed to understand the benefits of exercise-based mHealth interventions specifically in patients with PACS. Therefore, our mobile application COVIDReApp will provide new knowledge on the use of mHealth tools in people with PACS.

Furthermore, the use of mHealth and telemedicine in the prevention and rehabilitation of patients with PACS could be an effective tool to improve patient adherence.[48] However, current mHealth studies in this population show very low adherence rates of approximately 25%.[23] In our study, we aim to improve adherence by regular face-to-face follow-ups and telephone calls. This will lead to the development of a habit of physical activity that will help them better manage their disease. In addition, COVIDReApp will allow for better monitoring of physical development through a history of exercise sessions.

Besides, it is also necessary to assess the associations between the main variables affecting patients with PACS collected throughout the study. In this regard, it has already been shown that PACS has direct effects on fatigue, dyspnoea, quality of life, physical functioning, muscle strength, anxiety and/or depression, and that these effects also lead to a deterioration in the overall quality of life of people with PACS.[12,40,41,43,44,46,49] Therefore, we hypothesised that there will be associations between all variables, both primary and secondary, and that the consequences will also have a direct relationship with quality of life. It will also be found that these associations will be present before the intervention and will remain stable throughout the follow-up.

Finally, this study will provide evidence supporting the use of mHealth in patients with PACS. Current scientific evidence has shown that they do not obtain better results on quality of life outcomes than other conventional therapies, although they achieved improvements in mental health,

physical and cognitive status, and social support in the community.[23] In this sense, it seems that the reasons could be poor adherence to treatment and exercise-related worsening of those people with PACS who suffer from PEM.[18,23] In addition, it is important to note that many of the currently available RCTs of exercise-based interventions in people with PACS, included patients recovering from the acute phase of COVID-19 rather than those with persistent symptoms 1–3 months after disease onset.[5,43,45,46] This study will also contribute to understanding the biopsychosocial context of people with PACS and how it influences to their health and adherence to exercise-based mHealth interventions.

Strengths and limitations of this study

The ease with which the patient's daily routine can incorporate a physical exercise programme is a notable strength of this study. Patients can readily adhere to a home-based programme because the materials are inexpensive and minimal space is required for these activities. This aspect has proven to be a valuable addition to multimodal therapy, effectively augmenting exercise recommendations. Nevertheless, it is essential to acknowledge the limitations of this study. First, we will only be able to determine the actual adherence of the experimental group using data obtained from the COVIDReApp. However, the control group shall not report these data. Second, we cannot determine the patient exercise intensity. Our research team hopes to solve this problem by introducing new wearable technology that might offer this information in the future. However, patients will be given instructions to self-control the intensity during the first face-to-face session, and it is likely that the impact of the intensity will be examined by performance tests 30 ACT, 30 CTS and 2MWT.[33,34]

Another limiting factor to be considered in the results of the study is the heterogeneity of the patients. The characteristics of this disease are diverse. In addition, some symptoms can be very limiting for the disease, such as pain, PEM, post-exertional fatigue, anxiety and depression, which makes it difficult for some participants to follow the exercise programme closely or even drop out.

Conclusion

The proposed physical fitness intervention is supported by a robust theoretical framework. This aligns with the current scientific evidence regarding recommendations for exercise prescription in patients with PACS. The exercises are easily administered, affording patients autonomy over their performance, rendering this RCT a low-risk intervention. Consequently, if the intervention proves efficacious, it can lay the groundwork for integrating COVIDReApp into the routine therapeutic support. Furthermore, there is considerable scope for its integration into existing health systems.

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