Pulmonary rehabilitation for COVID-19: A living systematic review protocol

Rehabilitación pulmonar en COVID-19: protocolo de una revisión sistemática viva

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Abstract

Objective

This living systematic review aims to provide a timely, rigorous and continuously updated summary of the evidence available on the role of pulmonary rehabilitation in the treatment of patients with COVID-19.

Design

This is the protocol of a living systematic review.

Data sources

We will conduct searches in the L·OVE (Living OVerview of Evidence) platform for COVID-19, a system that maps PICO questions to a repository maintained through regular searches in electronic databases, preprint servers, trial registries and other resources relevant to COVID-19. No date or language restrictions will be applied.

Eligibility criteria for selecting studies and methods

We adapted an already published common protocol for multiple parallel systematic reviews to the specificities of this question. We will include randomized trials evaluating the effect of pulmonary rehabilitation as monotherapy or in combination with other interventions-versus sham or no treatment in patients with COVID-19. Two reviewers will independently screen each study for eligibility, extract data, and assess the risk of bias. We will pool the results using meta-analysis and will apply the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the certainty of the evidence for each outcome.

Ethics and dissemination

No ethics approval is considered necessary. The results of this review will be widely disseminated via peer-reviewed publications, social networks and traditional media.

Resumen

Objetivo

Proporcionar un resumen oportuno, riguroso y continuamente actualizado de la evidencia disponible sobre el papel de la rehabilitación pulmonar en el tratamiento de los pacientes con COVID-19.

Diseño

Es el protocolo de una revisión sistemática viva.

Fuente de datos

Realizaremos búsquedas en la plataforma L·OVE (Living OVerview of Evidence) para COVID-19, un sistema que mapea los componentes de las preguntas de investigación (PICO) en un repositorio mantenido a través de búsquedas regulares en bases de datos electrónicas, servidores de pre-impresión, registros de ensayos y otros recursos relevantes para COVID-19. No se aplicarán restricciones de fecha ni de idioma.

Criterios de elegibilidad para la selección de estudios y métodos

Se adaptó un protocolo común ya publicado para revisiones sistemáticas paralelas múltiples a las especificidades de la pregunta. Se incluirán ensayos aleatorios que evalúen el efecto de la rehabilitación pulmonar como monoterapia o en combinación con otras intervenciones frente a un tratamiento simulado o ningún tratamiento en pacientes con COVID-19. Dos revisores examinarán de forma independiente cada estudio para determinar su elegibilidad, extraerán los datos y evaluarán el riesgo de sesgo. Se agruparán los resultados mediante un metaanálisis y se aplicará el sistema Grading of Recommendations Assessment, Development and Evaluation (GRADE) para evaluar la certeza de las pruebas para cada resultado.

Ética y difusión

No se considera necesaria la aprobación ética. Los resultados de esta revisión se difundirán ampliamente a través de publicaciones revisadas por pares, redes sociales y medios de comunicación tradicionales

Main messages

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection patients are left with debilitating sequelae, with an overall decrease in quality of life.
- Pulmonary rehabilitation is a standard management approach in treating several cardiopulmonary diseases to increase quality of life and exercise capacity and decrease dyspnea and fatigue.
- Clarifying the role of pulmonary rehabilitation in the treatment of SARS-CoV-2 infection is essential, as it could improve disease management and respiratory function.

Introduction

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. It was first identified in Wuhan, China, on December 31, 2019[2]; thirteen months later, more than ninety million cases of contagion had been identified across 197 countries[3]. On March 11, 2020, World Health Organization (WHO) characterized the COVID-19 outbreak as a pandemic[4].

Although COVID-19 is typically conceptualized as an acute condition, many patients do not return to normality right after recovery from the condition[5-10]. For instance, 50% of patients report fatigue, and 40% report persistent dyspnea three months after the onset of symptoms[11,12] which can decrease physical and functional capacity, hindering their quality of life[13].

Pulmonary rehabilitation could be a useful tool to decrease the physical and functional impact of COVID-19, regardless of its degree of severity. Pulmonary rehabilitation is defined by the American Thoracic Society and the European Respiratory Society as "... *a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours*"[14] and has shown clear evidence of improvement in the physical and psychological condition of individuals with chronic and acute respiratory disease (for example, chronic obstructive pulmonary disease, cystic fibrosis, severe acute respiratory syndrome)[15-18].

In patients with mild COVID-19, defined as individuals who have any symptoms and signs of COVID-19 (cough, fever, muscle pain, for example) but without difficulty in breathing or altered chest image, and moderate COVID-19, characterized as a pulmonary disease with greater than or equal blood oxygen levels to 94% in room air[19], pulmonary rehabilitation may improve pulmonary ventilation by positioning, secretion removal techniques, respiratory exercises, low-intensity exercises and education about the disease and healthy lifestyles[20,21].

For critical patients with COVID-19, defined as individuals who have oxygen level below 94% in room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) less than 300 millimetres of mercury, respiratory frequency higher than 30 breaths/minute, or lung infiltrates in more than 50% of the lungs, patients with severe COVID-19 are characterized for respiratory failure, septic shock, and/or multiple organ

dysfunction[19]. It is important to consider the functional consequences to which those admitted to critical units are exposed, since 75% of them are estimated to be subject to mechanical ventilation, and 39% of these patients would require neuromuscular blockade and use of corticoids[22]. These conditions increase the risk of developing Intensive Care Unit-acquired weakness, characterized by global deconditioning, loss of strength and muscle mass, myopathy and neuropathy[19,22]. In this context, pulmonary rehabilitation may decrease the duration of mechanical ventilation and delirium, improving patients' future functional status[23-27]. The intervention should be delivered as soon as possible to increase its benefits, and might include techniques such as positioning, early mobilization and specific respiratory management (for example, lung recruitment maneuver, secretion management)[20,28,29].

Finally, upon discharge from hospital, a specific pulmonary rehabilitation programme is suggested for each patient, seeking to gradually increase their activity level and allow them to return to society, regardless of the severity of their clinical picture[20]. The recommended interventions include patient and family education, mainly oriented towards understanding the disease and adherence to treatment and the execution of low/moderate intensity aerobic exercises, strength, and balance training. Moreover, support in activities of daily living is also recommended[20,21,26].

Considering the large number of patients who have survived COVID-19 and their persistent symptoms, it is important to consider pulmonary rehabilitation as a tool to increase respiratory function, which facilitates the execution of life activities and thus achieves the reincorporation of patients into society as soon as possible, improving their quality of life[30]. There is little evidence to support the use of this treatment in COVID-19. However, clinical practice guidelines and recommendation manuals available worldwide include different modalities of pulmonary rehabilitation, guided by the patient's condition[30-32]. Therefore, it is important to assess the effectiveness and safety of pulmonary rehabilitation in patients with COVID-19.

Using innovative and agile processes, taking advantage of technological tools, and resorting to the collective effort of several research groups, this living systematic review aims to provide a timely, rigorous and continuously updated summary of the evidence available on pulmonary rehabilitation in patients with COVID-19.

Methods

This manuscript complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses[33].

A protocol stating the shared objectives and methodology of multiple evidence syntheses (systematic reviews and overviews of systematic reviews) to be conducted in parallel for different questions relevant to COVID-19 was published elsewhere[34]. This protocol was adapted to the specificities of the question assessed in this review and submitted to PROSPERO (CRD42020185394).

Search strategies

Electronic searches

Our literature search was devised by the team maintaining the L·OVE (Living OVerview of Evidence) platform, using the following approach:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology[35] to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms.
4. Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.

We systematically searched in L·OVE platform for COVID-19, a system that maps PICO questions to a repository developed by Epistemonikos Foundation. This repository is continuously updated through searches in more than 40 sources, including electronic databases, preprint servers, trial registries and other resources relevant to COVID-19 [36].

At the time of submitting this protocol, this repository includes more than 190,536 articles relevant to COVID-19, coming from the following databases, trial registries and preprint servers: Epistemonikos database, Pubmed/medline, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Latin American & Caribbean Health Sciences Literature (LILACS), Wanfang Database, Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), VIP Chinese Scientific Journal Database (CSJD-VIP), WHO-Institutional Repository for Information Sharing (WHO IRIS), Pan American Health Organization-Institutional Repository for Information Sharing (IRIS PAHO), Índice Bibliográfico Español en Ciencias de la Salud (IBECS), Microsoft Academic, International Clinical Trials Registry Platform (ICTRP Search Portal), Clinicaltrials.gov, International Standard Randomised Controlled Trial Number Register (ISRCTN registry), Chinese Clinical Trial Registry, Iranian Registry of Clinical Trials (IRCT), European Union Clinical Trials Register: Clinical trials for COVID-19, National Institute of Public Health Clinical Trials Search (Japan), Japan Primary Registries Network (JPRN), Japan Medical Association Center for Clinical Trials (JMACCT), University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), Japan Registry of Clinical Trials (JRCT), Japanese Pharmaceutical Information Center Clinical Trials Information (JAPIC CTI), Clinical Research Information Service (CRiS), Republic of Korea, Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), Clinical Trials Registry-India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), German Clinical Trials Register (DRKS), Lebanese Clinical Trials Registry (LBCTR), Thai Clinical Trials Registry (TCTR), The Netherlands National Trial Register (NTR), Pan African Clinical Trial Registry (PACTR), Peruvian Clinical Trial Registry (REPEC), Sri Lanka Clinical Trials Registry (SLCTR), medRxiv, bioRxiv, Social Science Research Network (SSRN) Preprints, ChinaXiv, SciELO Preprints, Research Square.

The last version of the methods, the total number of sources screened, and a living flow diagram and report of the project is updated regularly on our website[36].

The searches will cover from the inception date of each database until the day before submission. No study design, publication status or language restriction will be applied.

The following strategy is used to identify in the repository the articles potentially relevant for COVID-19 affecting humans:

(coronavir* OR coronovirus* OR betacoronavir* OR "beta-coronavirus" OR "beta-coronaviruses" OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR covid* OR "2019-ncov" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR (wuhan* AND (virus OR viruses OR viral)) OR "2019-ncov-related" OR "cv-19-related" OR "n-cov-related" OR sars* OR sari OR "severe acute respiratory syndrome" OR antisars* OR "anti-sars-cov-2" OR "anti-sars-cov2" OR "anti-sarscov-2" OR "anti-sarscov-2" OR "post-COVID-19" OR "Not-of-COVID-19" OR "corona patients") AND (((chest* OR respiratory* OR breath* OR lung*) AND ((physical* AND (therap* OR modalit*)) OR physiotherap* OR kinesiotherap* OR (musc* AND train*))) OR ((("one way" OR "one-way" OR unidirection*) AND (speak* OR valve*)) OR passy*) OR (((airway* OR secretion* OR sputum* OR bronchi*) AND (clearance* OR removal* OR hygiene* OR expectoration*)) OR mucoactive*) OR (singing*) OR ((activ* AND cycle* AND breath*) OR ACBT) OR (((expirat* AND pressure*) AND (mask* OR device* OR physiotherapy*)) OR PEP OR hPEP OR "pep-mask" OR Therapep*) OR (oscillat* OR OPEP OR AOD OR IPV OR HFCC OR acapell* OR (flutter* AND (respirat* OR breath*)) OR cornet* OR "rc-cornet" OR (intrapulmonar* AND percuss*)) OR (autogenic* AND drain*) OR (breath* AND (technique* OR exercise* OR training* OR therap*)))

Eligibility criteria

Types of studies

This living review will only include randomized trials.

We will exclude studies evaluating the effects on animal models or in vitro conditions.

Types of participants

We will include trials that evaluate participants diagnosed with COVID-19 in any category of severity, inpatient or outpatient, independently the time of the onset of the symptoms.

Type of interventions

The intervention of interest is pulmonary rehabilitation, which includes, but is not limited to, the indication of physical exercise, such as endurance training, interval training, resistance/strength training, upper limb training, flexibility training, neuromuscular electrical stimulation, inspiratory/expiratory muscle training, and breathing and walking exercises. These techniques can be applied in combination or individually. We will not limit our criteria to any time interval, load or frequency of training. Educational interventions focused on behavioural change will also be included if combined with physical exercise modalities.

The comparison of interest will be a sham procedure (pulmonary rehabilitation plus optimal treatment versus sham intervention-in example, the intervention was not administered with sufficient specificity to achieve a therapeutic effect-plus optimal treatment) or no intervention (pulmonary rehabilitation plus optimal treatment versus optimal treatment).

Trials assessing pulmonary rehabilitation and other interventions will be eligible if the co-interventions are identical in both intervention and comparison groups.

Types of outcomes

We will not use the outcomes as an inclusion criterion during the selection process. Any article meeting all the criteria except for the outcome criterion will be preliminarily included and assessed in full text.

The outcomes will be categorized in relation to the severity of the disease and will be defined for clinical experts opinions and literature review:

Primary outcomes

- All-cause mortality
- Health-related quality of life

Secondary outcomes

- Activities of daily living
- Length of hospital stay
- Rehospitalization
- Dyspnea
- Exercise capacity

Selection of studies

The literature search results in the repository will be automatically incorporated into the L·OVE platform (automated retrieval), where at least two reviewers will independently screen the titles and abstracts against the inclusion criteria. We will obtain the full reports for all records that appear to meet the inclusion criteria or require further analysis to decide about their inclusion.

We will record the reasons for excluding trials in any stage of the search and outline the study selection process in a PRISMA flow diagram adapted for this project.

Extraction and management of data

Using standardized forms, two reviewers will independently extract data from each included study. We will collect the following information: study design, setting, participant characteristics (including disease severity and age) and study eligibility criteria; details about the administered intervention and comparison, including type and therapeutic scheme, duration, frequency and timing (in example, time after diagnosis); the outcomes assessed and the time they were measured; the source of funding of the study and the conflicts of interest disclosed by the investigators; the risk of bias assessment for each individual study. We will resolve disagreements by discussion, and one arbiter will adjudicate unresolved disagreements.

Risk of bias assessment

The risk of bias for each randomized trial will be assessed using the 'risk of bias' tool (RoB 2.0: a revised tool to assess risk of bias in randomized trials)[37]. We will consider the effect of assignment to the intervention for this review. Two reviewers will independently assess five domains of bias for each outcome result of all reported outcomes and time points. These five domains are: bias due to (1) the randomization process, (2) deviations from intended interventions (effects of assignment to interventions at baseline), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of reported results. Answers to signalling questions and collectively supporting information will lead to a domain-level judgement in the form of 'Low risk of bias', 'Some concerns', or 'High risk of bias'.

These domain-level judgements will inform an overall 'risk of bias' judgement for each result.

Discrepancies between review authors will be resolved by discussion to reach consensus. If necessary, a third review author will be consulted to achieve a decision.

Measures of treatment effect

For dichotomous outcomes, we will express the estimate of treatment effect of an intervention as risk ratios or odds ratios along with 95% confidence intervals[38].

We will use mean difference and standard deviation for continuous outcomes to summarise the data using a 95% confidence interval. Whenever continuous outcomes are measured using different scales, the treatment effect will be expressed as a standardized mean difference with 95% confidence interval. When possible, we will multiply the standardized mean difference by a standard deviation representative from the pooled studies, for example, the standard deviation from a well-known scale used by several of the studies included in the analysis on which the result is based. In cases where the minimally important difference is known, we will also present continuous outcomes as minimally important difference units or inform the results as the difference in the proportion of patients achieving a minimal important effect between intervention and control[39]. Then, these results will be displayed on the 'Summary of Findings Table' as to mean difference[39].

Strategy for data synthesis

If we include more than one trial, we will conduct a meta-analysis for studies clinically homogeneous using RevMan 5[40], using the inverse variance method with a random-effects model. A narrative synthesis will be presented for any outcomes where data were insufficient to calculate an effect estimate. This strategy for data synthesis also applies for non-randomized studies, if eligible.

Subgroup and sensitivity analysis

Whenever we find substantial clinical heterogeneity on how the condition was defined, we will explore it using a sensitivity analysis.

We will perform subgroup analysis according to the phase or severity of COVID-19 infection (for example, critical or severe vs moderate vs mild symptoms). If we identify significant differences between subgroups (test for interaction < 0.05), we will report the results of individual subgroups separately.

We will perform subgroup analysis to assess different techniques or modalities for pulmonary rehabilitation (in combination or individually) delivered in each study (for example, respiratory muscle training vs endurance training vs breathing exercises).

We will perform sensitivity analysis excluding the high risk of bias studies. In cases where the primary analysis effect estimates and the sensitivity analysis effect estimates significantly differ, we will either present the low risk of bias-adjusted sensitivity analysis estimates or present the primary analysis estimates but downgrading the certainty of the evidence because of risk of bias.

Assessment of certainty of evidence

The certainty of the evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE Working Group)[41], across the domains of risk of bias, consistency, directness, precision and reporting bias. Certainty will be adjudicated as high, moderate, low or very low. For the main populations, comparisons and outcomes, we will prepare Summary of Findings tables[40,41] and also interactive Summary of Findings tables. A Summary of Findings table with all the comparisons and outcomes will be presented as an appendix.

Living evidence synthesis

An artificial intelligence algorithm deployed in the COVID-19 topic of the L·OVE platform will provide instant notification of articles with a high likelihood to be eligible. The authors will review them, will decide upon inclusion, and will update the living web version of the review accordingly. We will consider resubmission to a journal if there is a change in the direction of the effect on the critical outcomes or a substantial modification to the certainty of the evidence. This review is part of a larger project set up to produce multiple parallel systematic reviews relevant to COVID-19[34].

Notes

Contributor roles

GR conceived the common protocol for all the reviews being conducted by the COVID-19 L·OVE Working Group. SA and GR drafted the manuscript, and all other authors contributed to it. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

Epistemonikos created the COVID-19 L·OVE Working Group and a number of expert teams to provide decision-makers with the best evidence related to COVID-19. Up-to-date information about the group and its member organizations is available here: epistemonikos.cl/working-group

Competing interests

All authors declare no financial relationships with any organization that might have a real or perceived interest in this work. There are no other relationships or activities that might have influenced the submitted work.

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This project was not commissioned by any organization and did not receive external funding.

Epistemonikos Foundation provides training, support, and tools at no cost for all the COVID-19 L·OVE Working Group members.

Ethics

As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

Data sharing

All data relating to the project will be made available. Epistemonikos Foundation will grant access to data.

PROSPERO

PROSPERO Registration number: CRD42020185394.

Language of submission

English.

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