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REVIEW ARTICLE

Therapeutic management of post-COVID-19 syndrome: a scope review

Manejo terapêutico da síndrome pós-COVID-19: uma revisão de escopo

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ABSTRACT

Introduction: Post-COVID-19 syndrome is characterized by a set of signs and symptoms that appear or persist after the acute phase of infection by the new coronavirus. It is estimated that among people diagnosed with COVID-19, approximately 10% to 20% will develop the syndrome. Objective: Thus, considering the following guiding question "What options have been investigated and used for the therapeutic management of post-COVID-19 syndrome?", this research was carried out to describe the therapeutic management of post-COVID-19 syndrome, through the analysis of studies aimed at this purpose. **Method:** This is a scoping review guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), registered with protocol DOI 10.17605/OSF.IO/TJK6E. The search strategy was used in the Pubmed, Lilacs, Medline and CAPES Periodicals databases. **Results:** After applying the inclusion criteria, of the 2,136 studies initially found, 11 were selected to compose the review. Among these, the use of inspiratory muscle training aimed at strengthening muscles and improving cardiopulmonary function stood out, as well as the use of corticosteroid therapy to prevent respiratory dysfunctions. **Conclusion:** There was a significant advance in therapies and techniques for improving the physical symptoms of long COVID, especially those related to physiotherapy. On the other hand, more interventions aimed at managing mental and cognitive disorders are still possible, given that the studies found in the present work are incipient for this purpose.

Keywords: Acute post-COVID-19 Syndrome; Therapy; COVID-19.

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RESUMO

Introdução: A Síndrome pós-COVID-19 caracteriza-se como um conjunto de sinais e sintomas que aparecem ou persistem após a fase aguda da infecção pelo novo coronavírus. Estima-se que entre as pessoas diagnosticadas com COVID-19, cerca de 10% a 20% desenvolverão a síndrome. Objetivo: Assim, tendo em vista a seguinte pergunta norteadora "Quais opções têm sido investigadas e empregadas para o manejo terapêutico da síndrome pós-COVID-19?", esta pesquisa foi realizada com o intuito de descrever o manejo terapêutico da síndrome pós-COVID-19, por intermédio da análise dos estudos voltados a essa finalidade. **Método:** Trata-se de uma revisão de escopo guiada pelo Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR), cadastrada com protocolo DOI 10.17605/OSF. IO/TJK6E. A estratégia de busca foi empregada nas bases de dados PubMed, Lilacs, Medline e Periódicos CAPES. **Resultados:** Após a aplicação dos critérios de inclusão, dos 2.136 estudos encontrados inicialmente, 11 foram selecionados para compor a revisão. Dentre esses, destacou-se a utilização do treinamento muscular inspiratório voltado ao fortalecimento muscular e melhora da função cardiopulmonar, bem como o uso de corticoterapia para a prevenção de disfunções respiratórias. **Conclusão:** Observou-se o avanço significativo de terapias e técnicas para a melhoria dos sintomas físicos da COVID longa, sobretudo relacionadas à fisioterapia. Por outro lado, ainda são permitidas mais intervenções voltadas ao manejo das afecções mentais e cognitivas, tendo em vista que os estudos encontrados no presente trabalho são incipientes para esse fim.

Palavras-chave: Síndrome pós-COVID-19 aguda; Terapêutica; COVID-19.

Introduction

In December 2019, a new respiratory disease was discovered in China that mainly affects immunocompromised individuals and has the SARS-CoV-2 virus as its causative agent. However, it was only in March 2020 that the World Health Organization declared a public emergency, and with more than 100,000 confirmed cases, the COVID-19 pandemic was declared[1].

In Brazil, the first confirmed case was in the state of São Paulo in February 2020, and after that, there was a sharp increase in the detection rate of the virus. As the pandemic progressed, it was found that a significant portion of the primary infected individuals presented new symptoms, and persistence or recurrence of existing ones. This condition was called post-COVID-19 syndrome, or long COVID, and refers to a set of clinical manifestations that remain or appear after the acute phase of SARS-CoV-2 infection[2].

The literature indicates that the first signs and symptoms of COVID-19 usually appear between the second and fifth day after infection, with the acute phase resolving within 21 days. In post-COVID-19 syndrome, symptoms persist or emerge three months after the initial infection[3]. While most patients have mild manifestations, approximately 5% require hospitalization in intensive care units, which can further prolong the symptomatic course and aggravate long-term sequelae[4].

The most representative symptoms of post-COVID-19 syndrome include dyspnea, persistent fatigue, cognitive difficulties (such as "brain fog"), muscle and joint pain, and sensory changes such as anosmia, ageusia, and hypogeusia. In addition, gastrointestinal problems such as diarrhea are also frequent, as are emotional and psychological disorders such as anxiety, depression, and insomnia, which have a significant impact on the quality of life of affected patients[2,5].

Recent data indicate that, among people diagnosed with COVID-19, approximately 10% to 20% will develop post-COVID-19 syndrome[6]. In another study, this number rose to 50% of the people analyzed developing long COVID after primary infection with the SARS-CoV-2 virus[7]. This

scenario reinforces the urgency of strategies that expand knowledge about the management of this condition, aiming to mitigate its impacts on the quality of life and functionality of those affected.

Thus, considering the gap in the literature regarding the grouping of evidence that discusses the new possibilities for the clinical, physical and biopsychosocial treatment of post-COVID-19 syndrome, a scoping review was carried out with the aim of describing the therapeutic management of post-COVID-19 syndrome, through the analysis of studies aimed at this purpose.

Methods

This is a scoping review, a methodology that aims to synthesize evidence and assess the scope of the literature on a given research topic, as well as identify possible gaps. The article was guided by the *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR) protocol and consists of: title, structured abstract, rationale, objectives, protocol and registration, eligibility criteria, information sources, research, selection of evidence sources, data extraction model, data items, summary of results, limitations and conclusions[8].

The protocol for this study was registered in the *Open Science Framework* with DOI identification: https://doi.org/10.17605/OSF.IO/TJK6E. Next, to develop the research question, the Population, Concept, and Context (PCC) strategy was used, whose application was: people with post-COVID-19 syndrome, therapeutic perspectives of care and post-COVID-19, respectively. Based on this, the following guiding question was obtained: **What options have been investigated and used for the therapeutic management of post-COVID-19 syndrome?**

A highly rigorous methodological search was carried out to select studies in June 2024, based on the *Medical Subject Headings* (MeSH) and Health Sciences Descriptors (DeCS): "Acute Post-COVID-19 Syndrome", "Therapeutics", "Program", "Rehabilitation" and "COVID-19", combined with the Boolean operators *AND* (between descriptors) and *OR* (between synonyms). The strategy was used in the following databases: United States National Library of Medicine (Pubmed), Latin American and Caribbean Literature in Health Sciences (Lilacs), Online System for Retrieval and Analysis of Medical Literature (Medline) and Journals of the Coordination for the Improvement of Higher Education Personnel (CAPES).

Rayyan® reference manager was used for exporting and initial screening of studies. This step was conducted by two independent and blinded evaluators (LSC and LASS), who resolved disagreements by consensus. The following inclusion criteria were applied: publications on therapeutic perspectives for care for people with post-COVID-19 syndrome, between 2020 and 2023, in English, Spanish or Portuguese. Primary, quantitative and qualitative research of any design or methodology was included. Letters to the editor, reviews, abstracts in conference proceedings, incomplete articles, non-free articles, studies in the design phase or with no results yet were excluded.

Data were extracted by two reviewers (ISR and LASS) and organized into structured forms in the *software Microsoft Excel*®. To ensure greater accuracy for this phase, a third reviewer (LSC) analyzed the information, and disagreements were resolved by consensus. This stage was guided by the *Joanna Briggs Institute* (JBI) instrument, which recommends the extraction of data related to authorship, reference, country, year of publication, objective, study design, sample number and main results[8].

The process of interpretation and synthesis of the results was guided by Bardin's Content Analysis technique, which is composed of three main pillars (pre-analysis, exploration of the material and treatment of the results)[9] . In view of this, the sensitivity of the stages took into consideration the following points: exhaustiveness, representativeness, homogeneity and relevance; with categorization and grouping of the identified contents[9]. Finally, the information was synthesized and inserted in Table 1.

Results

The steps of identification, selection, eligibility and inclusion of studies were described in Figure 1.

This review consisted of 11 studies, of which 4 were observational, 6 were experimental and 1 was quasi-experimental. The total sample consisted of 1,592 participants, mostly women. The geographic distribution of the analysis included people living in Spain **(n=2)**, France (n=2), Italy (n=2), the United Kingdom (n=2), Brazil (n=1), Malawi (n=1) and the United States (n=1). Table 1 presents a summary of the results found in the studies.

The assessment of pulmonary rehabilitation through physical and digital physiotherapy was present in 45.4% and 27.2% of the articles, respectively[10-12,14-17,20]. Among the results obtained with the application of the two modalities, most patients obtained improvement in persistent dyspnea and fatigue. However, a Brazilian study also demonstrated the reduction of these symptoms when applying a cardiovascular rehabilitation program in 4 patients classified with different levels of severity[12].

Furthermore, clinical developments associated with improvements in respiratory muscle strength, exercise capacity and physical fitness were observed with the application of inspiratory muscle training[15,16]. In line with this, a new program that used singing techniques for respiratory retraining showed considerable benefits for respiratory function, well-being and quality of life related to mental health[17].

Furthermore, a study used digital tools to implement a pulmonary telerehabilitation program[10]. Among these, the use of *smartphones to access online* physiotherapy sessions stood out. The practice consisted of a series of guided exercises, which were easily applicable, via *WhatsApp* text messages, video and audio calls, with the intensity adjusted according to the patient's progress throughout the program. This intervention was 100%

effective and, after discharge, the participant returned to their usual daily activities without complaints[10].

Regarding pharmacotherapy, the efficacy of Palmitoylethanolamide (PEA) and Luteolin was evaluated for individuals with persistent smell or taste disorders, and after 90 days, a significant improvement in olfactory dysfunction was observed[9]. In addition, the effectiveness of drug treatment for the prevention of such disorders was also analyzed[13,15].

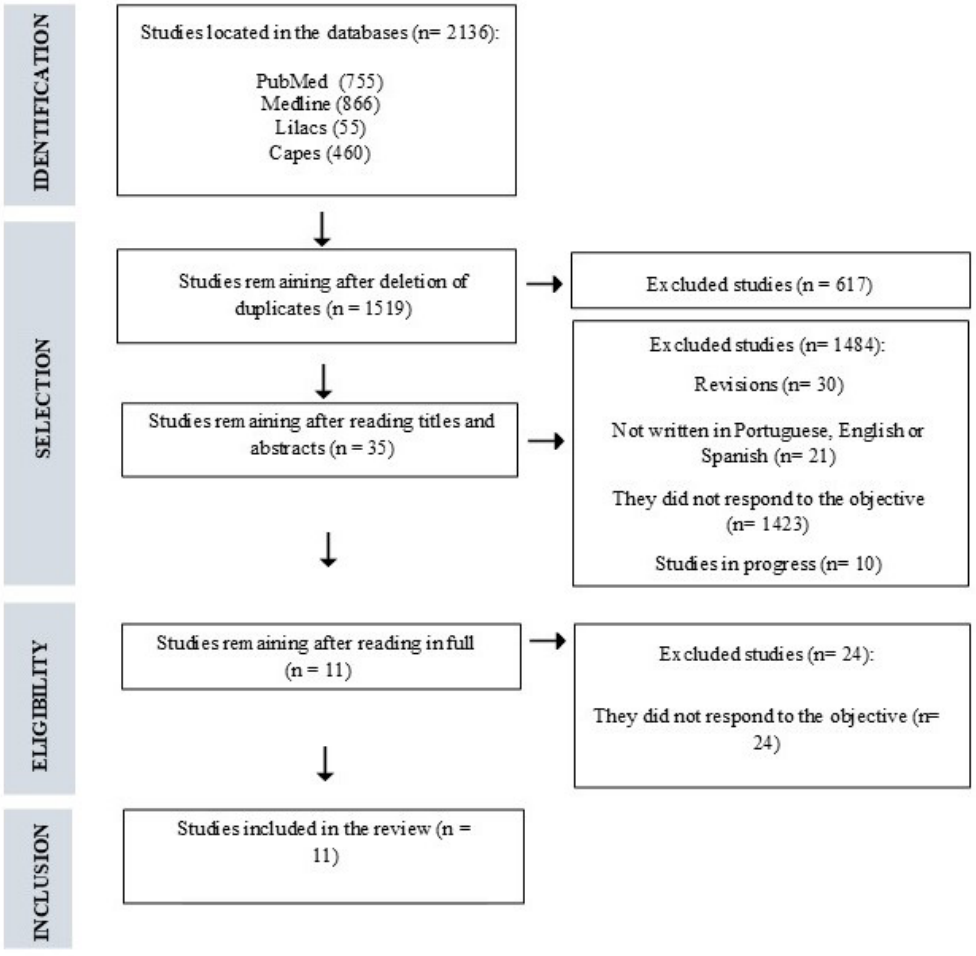

Figure 1. Article selection flowchart.

Source: Prepared by the authors (2024).

Table 1. Systematization of the results found in the studies.

Author and year	Type of study and country	Intervention and instruments used	Outcomes
Bickton et al. (2021)[10]	Case report Malawi	3-week pulmonary telerehabilitation program in a 46-year-old patient. mMRC CIS- *Fatigue* CAT	Nine exercise sessions were performed, resulting in a decrease in all respiratory severity scores. The patient reported no new or ongoing complaints and returned to work after discharge.
D'Ascanio et al. (2021)[11]	Blinded randomized clinical trial Italy	Rehabilitation with olfactory training and supplementation with Palmitoylethanolamide and Luteolin in 12 patients. SSTB	Patients who took supplements with Palmitoylethanolamide and Luteolin had significant improvement in olfactory dysfunction.

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Author and year	Type of study and country	Intervention and instruments used	Outcomes
Tozato et al. (2021)[12]	Case report series Brazil	Application of 6-minute walk test, peripheral muscle strength and double product at rest for three months and frequency of 300 minutes per week in 4 patients. 6MWT	There was an increase of between 16% and 94% in the distance covered during the walking test. Peripheral muscle strength improved by 20% over baseline values. The resting double product was reduced by 8% to 42%.
Vaira et al. (2021)[13]	Prospective randomized multicenter study Italy	Use of systemic prednisone and nasal irrigation with betamethasone, ambroxol and rinazine for 15 days in 18 people. CCCRC *Test*	The use of corticosteroids demonstrated significant improvement in the olfactory performance of patients in the treatment group after 20 days and 40 days of therapy.
Estebanez-Pérez et al. (2022)[14]	Quasi-experimental clinical trial Spain	4-week digital physiotherapy program applied to 32 participants. SPPB STS	A significant improvement was observed in the functions evaluated (balance, walking speed and strength).
McNarry et al. (2022)[15]	Randomized clinical trial United Kingdom	8-week inspiratory muscle training program with 281 patients. K-BILD TDI *Chester Step Test*	There was improvement in the domains of dyspnea, thoracic symptoms, respiratory muscle strength and estimated aerobic fitness.
Palau et al. (2022)[16]	Randomized clinical trial Spain	12-week inspiratory muscle training program with 26 patients. EQ-5D-3L	Improvements in peak oxygen volume were observed. In patients with previous hospitalization for pneumonia, the intervention was associated with improvements in exercise capacity and quality of life.
Philip et al. (2022)[17]	Randomized clinical trial United Kingdom	*English National Opera* 's *Breathe* breathing program with 50 patients. MHC PHC EVE	There was an improvement in the score related to mental health, but not in the score associated with physical health. Analysis of the participants' experience identified that the particular use of singing and music were considered good additional tools to the standard treatment.
Bramante et al. (2023)[18]	Quadruple-blind randomized clinical trial United States	Metformin, fluvoxamine and ivermectin were administered for 9 months in 1,074 patients. *Log-rank Test* *Kaplan-Meier*	The use of metformin has consistently shown a reduction in the risk of long COVID, especially if started 4 days after the onset of symptoms. Ivermectin and fluvoxamine did not show significant effects.

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Author and year	Type of study and country	Intervention and instruments used	Outcomes
Hausswirth et al. (2023)[19]	Randomized clinical trial. France	Program of ten 30-minute Rebalance® sessions over five weeks with 49 participants. CFS PSS PMS HADS EVE	The Rebalance® program improved all subjective reports as well as cognitive performance, especially on reaction time-based tasks.
Romanet et al. (2023)[20]	Multicenter, controlled study France	Application of physical training rehabilitation for 90 days in 60 patients. MDP mMRC *Short-Form Survey Scores*	People who still suffered from shortness of breath had significantly improved dyspnea scores. The mean multidimensional dyspnea profile after the intervention was 42% lower.

Legend: mMRC = modified Medical Research Council dyspnea scale; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; SSTB = Sniffin Sticks Test; CIS-Fatigue = Checklist Individual Strength fatigue subscale; 6MWT = 6-Minute Wpsalk Test; CCCRC Test = Connecticut Chemosensory Clinical Research Center olfactory test; SPPB = Short Physical Performance Balance; STS = 1-min sit-to-stand test; K-BILD = King's Brief Interstitial Lung Disease; TDI = Transition Dyspnea Index; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version questionnaire; MHC = RAND 36-item short form survey instrument mental health composite; PHC = Physical Health Composite; VAS = visual analogue scale; CFS = Chalder fatigue scale; PSS = Perceived stress scale; PMS = Profiles of mood states; HADS = Hospital anxiety and depression scale; MDP = Multidimensional Dyspnoea Profile.
Source: Prepared by the authors (2024).

In this context, the use of systemic prednisone, nasal betamethasone, ambroxol, and rinazine demonstrated an increase in the olfactory performance of patients[13]. In another study, metformin, ivermectin, and fluvoxamine were administered for this purpose; however, only metformin demonstrated a consistent reduction in this risk, especially if started 4 days after the onset of the acute condition[15].

Discussion

Studies have demonstrated the use of different protocols and treatments aimed at the signs and symptoms of long COVID. In this scenario, the vast majority highlighted the use of new techniques related to physical therapy, such as inspiratory muscle training, for muscle strengthening and improving cardiopulmonary function, as well as the use of corticosteroid therapy to prevent respiratory dysfunctions[10,13]. On the other hand, based on the application of singing techniques, only one study produced results aimed at managing the cognitive and emotional changes resulting from the syndrome[17].

The incorporation of digital physiotherapy, through personalized exercises and home monitoring, highlights the benefit of using technologies to monitor the effectiveness and application of interventions[21]. In this sense, the study carried out in Malawi demonstrated the success of pulmonary telerehabilitation, even in contexts where resources are limited[10]. This achievement emerges as an innovative option for areas with difficult access and poor health infrastructure, as it expands the reach of health care to communities that would otherwise face significant barriers[21].

Furthermore, the studies highlighted the multiple pathological manifestations that may be included in the clinical picture of post-COVID-19 syndrome, as well as the role of different professionals within this scenario[10-12,14-17,20]. This justifies the specificity of the interventions tested, while also relating to the expanded conception of health, which advocates the participation of multidisciplinary teams for more comprehensive care for the person in need[22].

Regarding the drug treatment for anosmia, the use of PEA and Luteolin stood out as an efficient approach to this disorder[11]. This outcome is supported by the results presented by a Belgian study that used the *Sniffin Sticks test* to evaluate the efficacy of an oral supplement containing PEA 700 mg and Luteolin 70 mg in 72 patients[23]. In this study, a significant improvement in the scores evaluated was observed, confirming the efficacy of this pharmacological approach in the management of this symptom[24].

It is worth noting that, as this is a secondary study, the limitations of the included articles may be reflected in the results of this study. Thus, the small number of participants in the studies implies an analysis with low statistical power, which may not represent the general population affected by post-COVID-19 syndrome. Furthermore, considering that

this is a recent condition with no consolidated guidelines for management, the short period in which the studies were conducted may have limited the assessment of the effectiveness of the interventions tested, since aspects such as risk of relapse and long-term effectiveness were not addressed in detail. Additionally, the use of non-systematic methodologies may have interfered with the accuracy of the interventions performed, as well as their evaluation. Finally, the inclusion criteria related to languages may have restricted the scope of the search.

Conclusion

Analysis of the studies revealed important advances in the therapeutic management of post-COVID-19 syndrome, highlighting the effectiveness of physiotherapy in relieving physical symptoms, such as dyspnea and fatigue, and in strengthening respiratory and muscular function. In the pharmacological field, approaches such as the use of corticosteroids and palmitoylethanolamide and luteolin supplements have shown promise in the treatment of sensory dysfunctions.

Although important advances have been achieved, there remains a need to explore strategies aimed at cognitive and emotional changes, which are still little investigated. However, with the increasing scientific evidence, new treatment possibilities can be envisioned.

Authors' contribution:

The authors' contributions are structured according to the taxonomy (CRediT) described below:

Coelho LSC proposed the topic, carried out the bibliographic survey and participated in the writing and preparation of the final version of the article. Santos LAS took part in the literature survey, synthesizing the results and writing the article. Ramos IS took part in the process of summarizing the results and writing the article. Paulo VS took part in the theoretical discussion and writing of the final version of the article. Barreto JC took part in the theoretical discussion and drafting of the final version of the article. Jesus FAM took part in writing the final version of the article. Borges GF guided the study and revised the article. All the authors discussed, read and approved the final version of the article.

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