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ASSESSMENT OF PULMONARY FUNCTION AND FUNCTIONAL CAPACITY OF RECOVERED COVID-19 PATIENTS AFTER PULMONARY REHABILITATION PROGRAM: CRITICAL SYSTEMATIC REVIEW

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ABSTRACT

The effects of pulmonary rehabilitation on lung function and functional capacity of individuals who recovered from COVID-19 were analyzed systematically. A randomized clinical trial and three case series that compared lung function and functional capacity of individuals who contracted COVID-19 before and after undergoing pulmonary rehabilitation programs were included in this review. The bias analysis of the randomized clinical trial was performed using the Rob tool from Cochrane, while the analysis of the case series was performed using the Checklist for case series – Critical Appraisal tools for use in JBI Systematic Reviews. Of the 6,868 abstracts selected, 45 full-text articles were reviewed and only four met the inclusion criteria. In conclusion, both lung function and functional capacity of individuals cured of COVID-19 after undergoing a pulmonary rehabilitation program showed significant improvement.
Keywords: covid-19, pulmonary telerehabilitation, functional capacity, respiratory function, telerehabilitation

AVALIAÇÃO DA FUNÇÃO PULMONAR E CAPACIDADE FUNCIONAL DE PACIENTES RECUPERADOS DE COVID-19 APÓS PROGRAMA DE REABILITAÇÃO PULMONAR: REVISÃO SISTEMÁTICA CRÍTICA

RESUMO

Os efeitos da reabilitação pulmonar na função pulmonar e na capacidade funcional de indivíduos recuperados da COVID-19 foram analisados sistematicamente. Foram incluídos, nesta revisão, um ensaio clínico randomizado e três séries de casos que compararam a função pulmonar e a capacidade funcional de indivíduos que contraíram a COVID-19 antes de e após serem submetidos a programas de reabilitação pulmonar. A análise de viés do ensaio clínico randomizado foi realizada pela ferramenta Rob da Cochrane, enquanto a análise da série de casos, através da ferramenta Checklist for case series – Critical Appraisal tools for use in JBI Systematic Reviews. Dos 6.868 resumos selecionados, 45 artigos de texto completo foram revisados e apenas quatro atenderam aos critérios de inclusão. Em suma, tanto a função pulmonar quanto a capacidade funcional de indivíduos curados da COVID-19 após realizarem um programa de reabilitação pulmonar apresentaram melhora significativa.
Palavras-chaves: covid-19; telereabilitação pulmonar; capacidade funcional; função respiratória; telereabilitação

INTRODUCTION

In December 2019, a new Coronavirus (2019-nCoV) emerged in Wuhan, China, which spread rapidly, giving rise to a Pandemic that persists to the present day.[1] The Coronavirus affects both humans and animals, causing respiratory and enteric compromise, which previously to the outbreak of severe acute respiratory syndrome (SARS-Cov) in 2002 and 2003 in China was a virus considered benign in humans.[2,3]

According to the World Health Organization (WHO), the modes of transmission can be divided and specified in: dispersed, clustered, and community-based. As reported by the WHO, about 80% of patients infected with COVID-19 are asymptomatic or do not have many symptoms. Hospital care corresponds to an average of 20% of cases due to respiratory compromise, of which 5% may need the use of some type of ventilatory support.[4] The most frequent symptoms are: fever, fatigue, cough, expectoration, muscle pain, chest tightness, dyspnea, nausea, vomiting, diarrhea, and headache. Patients who developed COVID-19-associated pneumonia had bilateral lung injury and respiratory failure or acute respiratory distress syndrome.[5]

It is common for patients hospitalized for COVID-19 to manifest hypoxemia due to respiratory failure, requiring the use of oxygen during treatment and, even if there is a reduction in the need for this, in some cases even after discharge, use must be continuous.[6,7]

In this scenario, patients who survived COVID-19 showed signs of muscle weakness, neurological impairment and/or nutritional disorder, and restrictive lung pattern, which may be linked to an increased risk of developing comorbidities. [8,9,10]

It is known that cured patients need comprehensive rehabilitation after the period of hospitalization, according to the experts.[11] Therefore, pulmonary rehabilitation is strongly indicated, in order to improve lung function, exercise tolerance, and resistance to fatigue.[12]

By definition, pulmonary rehabilitation consists of a broad intervention, which is based on a comprehensive assessment of the patient, which later builds individualized therapies through physical training, health education, and behavioral change, designed to improve the physical conditioning of respiratory patients.[13]

Pulmonary rehabilitation in individuals cured of COVID-19 presents a decrease in symptoms of dyspnea, anxiety, and disabilities and maintains functional activities, in addition to improving the quality of life of these patients.[13,14]

Due to the emerging need for rehabilitation demand for these post-COVID-19 patients, randomized clinical trials have been conducted in order to analyze the effects of rehabilitation on this type of patient. Therefore, it becomes pertinent to develop a critical systematic review of the literature in order to summarize this evidence and assist in the clinical practice of professionals involved in the cardiopulmonary rehabilitation process, especially physical therapists. It is relevant to know the effects of rehabilitation on lung function and functional capacity of these individuals, as they are largely affected in the process of COVID-19. Therefore, it is necessary to analyze systematically the effects of pulmonary rehabilitation on lung function and functional capacity of individuals recovered from COVID-19.

METHODS

This systematic review was approved by the ethics and research committee (CPDI protocol number: 6662), registered with PROSPERO (ID: CRD42021272296), and conducted in accordance with the Cochrane handbook guideline for systematic reviews of interventions.[15]

SEARCH STRATEGY AND SELECTION CRITERIA

Two evaluators (LR, ETS) performed an electronic search in the following databases, originally on July 20 and 26, 2021 and updated on September 23, 2021: Pubmed, Lilacs, Scielo, PeDro, and MedLine.

There was a date restriction from 2019 to July 2021 because there are already other studies in the literature that include SARS-CoV, and a filter of clinical trials only performed in humans was also applied. Reference lists of identified articles were examined for additional relevant articles. According to the selection criteria defined a priori, randomized controlled trials, case series, and case reports with clearly defined inclusion criteria were included if they reported the effects of pulmonary rehabilitation on pulmonary function and functional capacity of individuals diagnosed with COVID-19. Studies that addressed rehabilitation outside the pulmonary context, such as rehabilitation in neurological or orthopedic patients, were excluded.

Manual searches were performed with the following terms for the condition:

COVID – 19	PULMONARY REHABILITATION	OUTCOMES
Coronavirus	Rehabilitation	Functional Residual Capacity
Coronavirus Infections Spike Glycoprotein, Coronavirus	Hospitals, Rehabilitation Cardiac Rehabilitation	Total Lung Capacity Respiratory Function Tests
COVID-19	Telerehabilitation	
SARS-CoV-2	Exercise Therapy	
SARS-CoV-2 variants	Physical Therapy Modalities	
spike protein, SARS-CoV-2	Physical Therapy Specialty	
COVID-19 serotherapy	Physical Therapy Department, Hospital	
COVID-19 stress syndrome	Resistance Training	
	Exercise	
	Breathing Exercises	
	Cardiorespiratory Fitness	
	Respiratory Therapy	
	Respiratory Therapy Department, Hospital	

We impose a period restriction of 2.5 years of publication.

The selected terms were combined using Boolean operators (OR and AND). In addition, a manual search was performed in the aforementioned databases. All references were analyzed using the EndNote Web software.

STUDY SELECTION AND DATA EXTRACTION

Two reviewers (LR, ETS) independently analyzed all titles and abstracts using EndNote Web. Pre-screened full-text reviews were performed separately using inclusion and exclusion criteria. Any discrepancies between authors were discussed with a third author (GSOMP) scoring the main criteria to include or exclude studies from the project.

Data extraction and relevant data capture were performed by two independent authors (GSOMP, EGS), including bibliographic data (authors and year of publication), participant characteristics (e.g. age, sex, body mass index), sample size, hemodynamic parameters (blood pressure, heart rate), dyspnea, perceived exertion, scores on quality of life questionnaires (functional independence measure - FIM, Barthel rating scale), in addition to function parameters (forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, diffusing capacity for carbon monoxide (DLCO), oxygen saturation (SaO2), partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2) and functional capacity by the following tools: 6-minute walk test (6MWT) and Short Physical Performance Battery (SPPB).

METHODOLOGICAL QUALITY ASSESSMENT

Two reviewers (GSOMP, EGS) independently assessed the risk of bias for each included study, and a third reviewer was consulted to resolve any discrepancies. We classified the randomized clinical trial as having high, low, or uncertain risk of bias for each criterion, using the RoB tool provided by Cochrane.[16.] To assess the risk of case series bias, the Checklist for case series – Critical Appraisal tools for use in the JBI Systematic Reviews tool was used.[17]

In addition, the PEDro scale was also included which is based on the Delphi list, which was developed by Verhagen and colleagues in the Department of Epidemiology, Maastricht University (Verhagen AP et al. (1988)). The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41). This list is based on expert consensus rather than empirical data. Its objective is to help users of the PEDro database to identify which are randomized or quasi-randomized controlled studies and which may provide significant statistical information so that their data can be interpreted.[18]

RESULTS

Search outcomes

From the 6,868 abstracts that were selected, 45 full-text articles were reviewed. Only 4 articles met the inclusion criteria (figure 1). There were no duplicates. Articles that did not analyze the desired outcomes or had different populations were excluded. The description of the included studies is presented in table 1.

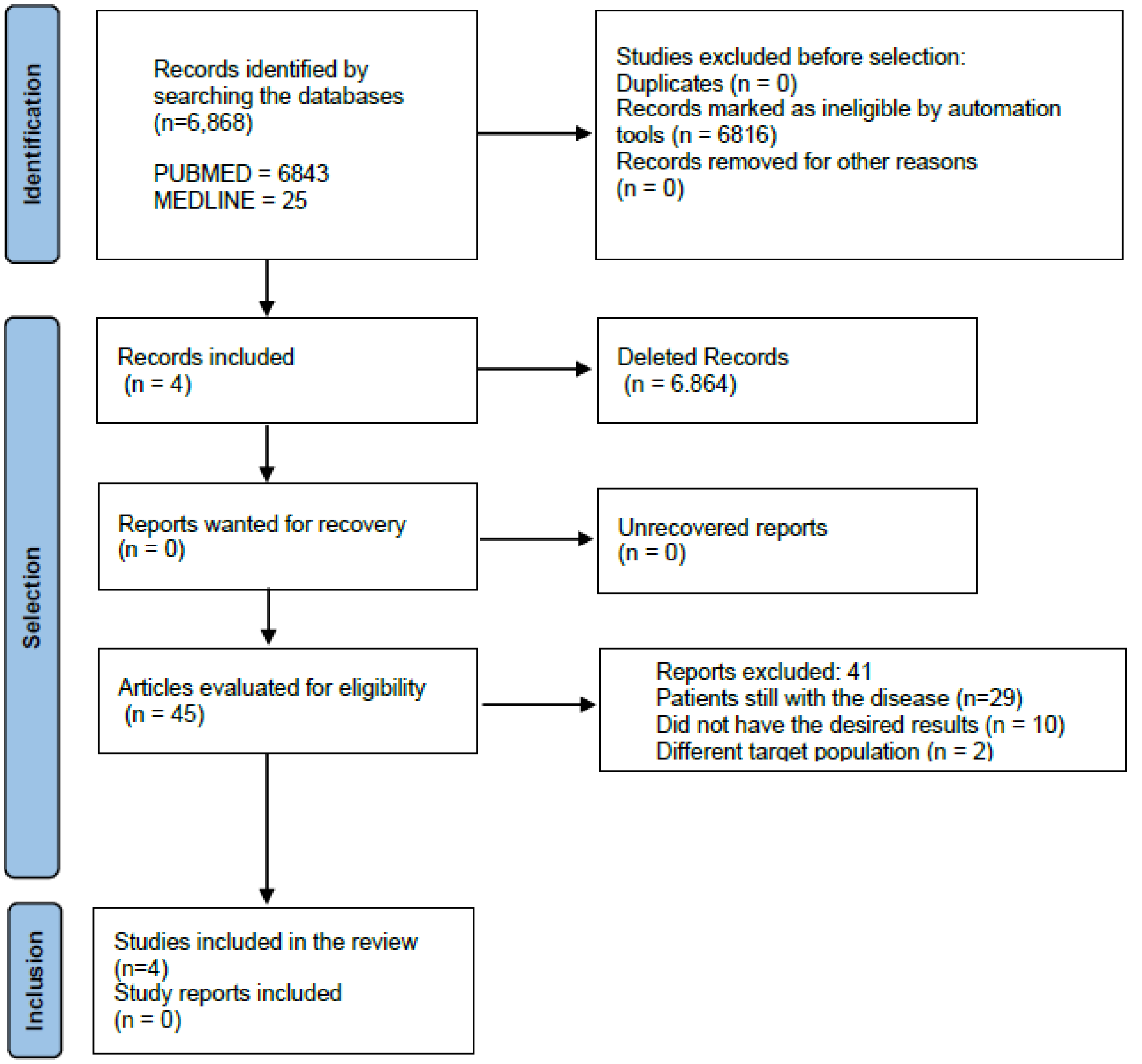

Figure 1. PRISMA Flow Diagram.

Table 1. Description of studies. [19]

Authors	Population	Authors' conclusion	PEDro
Kai Liu, et al. [20]	Elderly (65 years and over) with COVID-19, 49 men and 23 women. Half of the sample (n=36) were part of the intervention group.	There was an improvement in respiratory function, quality of life, and anxiety, but no improvement in depressive state and ADLs.	6/10
Elisabetta Zampogna, et al. [21]	Patients recovering from COVID-19 with a negative RT-PCR test and admitted to the hospital for pulmonary rehabilitation.	Pulmonary rehabilitation is possible and effective in patients recovering from COVID-19.	-
Mauro Maniscalco, et al. [22]	Patients with and without comorbidities recovering from COVID-19 post-hospitalization	Unable to formulate a solid conclusion.	-
Vasileios T. Stavrou, et al.[23]	Previously hospitalized COVID-19 survivors.	Unsupervised pulmonary rehabilitation may be an effective and beneficial practice to promote exercise and symptom recovery after COVID-19.	-

Risk of bias in included studies

Details of the 'risk of bias' assessment across all included trials and for each item in the included trials are shown in Figure 2 and Table 2.

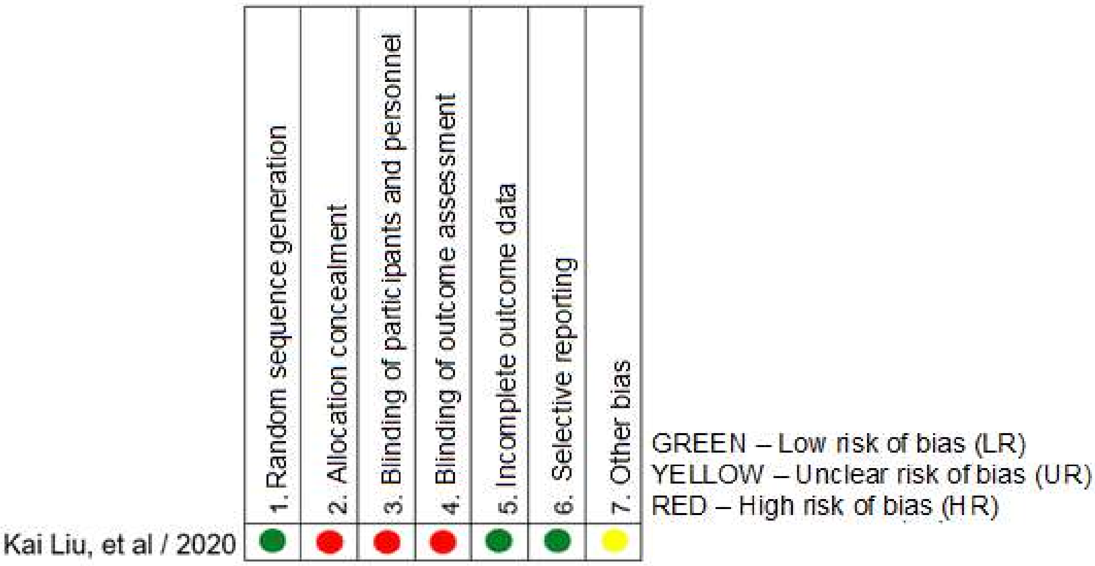

Figure 2. Risk of bias in a randomized clinical trial.

Table 2. Risk of case series bias.

JBI checklist questions	Elisabetta Zampogna et al. 2021 [21]	Mauro Maniscalco et al. 2020 [22]	Vasileios T. Stavrou et al. 2021 [23]
Were there clear criteria for inclusion in the case series?	No	No	Yes
Was the condition measured in a standard and reliable way for all participants included in the case series?	Yes	No	Yes
Were valid methods used to identify the condition of all participants included in the case series?	Yes	Yes	Yes
Did the case series include consecutive participants?	Yes	Yes	Yes
Was the case series fully inclusive of participants?	Yes	Unclear	No
Was there a clear account of the study participants' demographics?	Yes	Yes	Yes
Was there a clear report of the participants' clinical information?	Yes	Yes	Yes
Were the results or follow-up of cases clearly reported?	Yes	Yes	Yes
Were there clear reports of demographic information from the clinical presentation site?	Yes	Yes	Yes
Was the statistical analysis appropriate?	Yes	Yes	Yes

Outcomes

The study by Kai Liu, et al. started with 92 patients, 9 of whom did not agree to participate, 3 had FEV1 ≤ 70%, 4 had severe heart disease and the remainder (76 patients) were randomized into two groups of 38 each. In the control group (CG), there were 2 patients unable to proceed with rehabilitation. In the intervention group (IG), 2 patients dropped out of the study before completing the 12 rehabilitation sessions. The allocation order was computer-generated where odd numbers were allocated to the intervention group and even numbers to the control group. [20]

The interventions performed were: respiratory muscle training (they used the Threshold PEP manual resistance device; Philips Co., and performed three sets of 10 breaths; the parameters were set at 60% of maximal expiratory pressure with a rest period of 1 minute between sets), coughing exercise (three sets of 10 active coughs), diaphragmatic training (30 maximal voluntary diaphragmatic contractions in the supine position, placing an average weight 1–3 kg on the anterior abdominal wall to resist diaphragmatic descent), stretching (respiratory muscles were stretched under the guidance of a physical therapist, in dorsal or lateral decubitus with knees flexed to correct lumbar lordosis, patients were instructed to move the upper limbs in flexion, extension, abduction and external rotation) and home exercises (pursed-lip breathing and cough training, and they were asked to perform 30 sets per day).[20]

The intervention group, when compared to the control group, showed a statistically significant improvement in lung function between FEV1 (CG 1.26 ± 0.32; IG 1.44 ± 0.25; $p<0.05$), FVC (CG 2, 08 ± 0.37; IG 2.36 ± 0.49; $p<0.05$) and FEV1/FVC (CG 61.23 ± 6.43; IG 68.19 ± 6.05; $p<0.05$) after 6 weeks of pulmonary rehabilitation.[20]

As for functional capacity, there was a significant improvement in the intervention group (mean: 212.3; standard deviation: 82.5; $p<0.05$) in relation to the beginning of rehabilitation and when compared to the control group (mean: 157 .2; standard deviation: 71.7; $p<0.05$) after 6 weeks of pulmonary rehabilitation.[20]

The study by Elisabetta Zampogna, et al. started with 140 patients who were evaluated using the Short Physical Performance Battery (SPPB) before and after the hospital rehabilitation program. Based on the score of this assessment, patients were divided into level A (SPPB < 6), which addressed training based on mobilization, active exercises, and free walking, peripheral limb muscle activities, or level B (SPPB ≥ 6), which addressed training based on calisthenics, strengthening, balance, walking and breathing exercises when necessary.[21]

Level A patients could perform or be limited to performing one or more of the following exercises: mobilization, active exercises, free walking, peripheral limb muscle activities, shoulder, and full arm rotation. Level B patients could perform or be limited to performing one or more of the following exercises: calisthenics, strengthening, balance exercises, and paced walking. The exercises could be performed without devices or using instruments such as balls, gait aids, balance boards, or lightweight resistance bands. In addition, respiratory physiotherapy was performed with bronchial hygiene techniques, using disposable devices and lung re-expansion maneuvers when necessary. As for intensity, time, and modality of intervention, they were individually adapted for the patient based on age, clinical severity, immobilization time, and comorbidities, starting with a daily session of at least 20 to 30 minutes. For level B patients with greater physical autonomy who performed low-intensity exercise on a cycle ergometer <3.0 METs, the modified BORG scale was used to quantify the subjective perception of effort.[21]

After rehabilitation, SPPB items improved significantly across all scopes in 7 (mean: 6.9; standard deviation: 3.8) and 89 patients reached the Minimum Clinically Important Difference (MCID). An evaluation was also performed using the Barthel Index (BI), in which there was an improvement in the score from 55 to 95 after the rehabilitation program ($p=0.00$). In terms of functional capacity, 81 patients walked 285 meters in the 6MWT (mean: 298.2; standard deviation: 116.7 m). Of these 81, only 42 patients were able to complete the test at the beginning and end of the rehabilitation program, showing an improvement (mean: 327.9; standard deviation: 97.8).[21]

In the study by Mauro Maniscalco, et al., 95 patients were recruited from the Pulmonary Rehabilitation Unit of the Istituti Clinici Scientifici Maugeri Spa SB, IRCCS of Telese Terme, Benevento, Italy, after being discharged from the COVID-19 acute care ward and after recovery of COVID-19. All included patients underwent a 5-week pulmonary rehabilitation program with daily sessions totaling 30 sessions, including physical exercise, dietary counseling, and psychosocial counseling. Exercises to strengthen upper and lower extremity muscle groups, treadmill walking and stationary bicycle exercise were performed at moderate to high intensity, which was increased during the rehabilitation period based on dyspnea and fatigue symptoms scores. All patients underwent flexibility exercises, general physical exercises for the lower and upper limbs, and daily supervised 30-minute outdoor walks.[22]

As an outcome, in the group of patients without underlying cardiorespiratory comorbidities, in which it was also possible to perform spirometry on admission, there was a significant improvement in pulmonary function measurements, with an increase in FEV1 of 267.1 mL (95% CI: 161.3- 372.9; p<0.0001) and a mean increase in FVC of 415.0 mL (95% CI: 278.1-551.9; p<0.0001) and 6MWT increased by 149.2 m (95% CI: 128.3-170.2; p<0.0001). In the group of patients with underlying cardiorespiratory diseases, FEV1 and FVC improved by 205.5 mL (95% CI: 106.3-304.9; p=0.0003) and 310.4 mL (95% CI: 176.0 -444.8; p<0.0001) respectively. For these patients, the rehabilitation program significantly increased (p<0.0001) the distance walked as assessed by the 6MWT (151.5m, 95% CI: 121.9-181.1).[22]

The study by Vasileios T. Stavrou, et al. included 26 patients, who participated in an eight-week pulmonary rehabilitation program, while each patient participated in 3 training sessions per week. The duration of each training session was approximately 100 minutes, which included a 5-minute warm-up at the beginning and a 5-minute recovery period with flexibility and mobility exercises at the end. It also included aerobic exercises with a 50-minute walk, yoga exercises for breathing and/or proprioception for 20 minutes, and multi-joint strength exercises for 20 minutes. In the set of aerobic exercises, the patients walked on a flat and rigid surface and their heart rate and oxygen saturation were checked every five minutes, and then the total distance traveled was recorded.[23]

In the 6-minute walk test, distance showed statistically significant associations before and after the eight weeks of unsupervised pulmonary rehabilitation (uns-PR) (433.8 ± 102.2 vs 519.2 ± 95.4 m, t(19)= −5.587,p< 0.001) and with a percentage of predicted values (baseline: 83.6 ± 17.3 vs. post-uns-PR: 99.1 ± 11.4% of predicted, t(19)= −5.971, p< 0.001). In terms of lung function, there was no significant difference in FEV1 before and after the rehabilitation program (mean: 84.1; standard deviation: 18.0 vs. mean: 88.2; standard deviation: 17.4; p=0.235). The same occurred with FVC (mean: 84.8; standard deviation: 15.7 vs. mean: 88.6; standard deviation: 14.7 p=0.214).[23]

DISCUSSION

Most of the four studies analyzed showed an improvement in FEV1, FVC, and the FEV1/FVC ratio after undergoing a pulmonary rehabilitation program. The same occurred with functional capacity, which in all analyzed studies showed a significant increase after the application of rehabilitation protocols.

In this scenario, since the study by Elisabetta Zampogna, et al.[20]; Mauro Maniscalco, et al.[21]; and Vasileios T. Stavrou, et al.[19] is a case series, we cannot say that the results obtained after the pulmonary rehabilitation protocols were in fact efficient because in this type of study there is no control group. Therefore, there is room for error, for example: the patients' improvement may have been caused by other factors that are not related to pulmonary rehabilitation, which are the natural progression of the disease and the association with pharmacological therapy. This does not mean that the rehabilitation has not, in fact, shown good results in terms of lung function and functional capacity, but we cannot say with certainty that these are statistically significant due to the design of the studies, since by the time the research was developed, that is, a pandemic scenario where the population had to adopt many precautionary measures, such as social distancing and mask use, it became more difficult to carry out scientific research.

On the other hand, when we analyze the study by Kai Liu, et al., which is a randomized clinical trial, we can say from the study design that the improvement in lung function and functional capacity is statistically significant.[20]

Still about pulmonary rehabilitation, in a study that aimed to investigate the correlation between changes in exercise capacity and other functional markers after pulmonary rehabilitation in Chronic Obstructive Pulmonary Disease (COPD), in which a rehabilitation program was carried out for 4 weeks that was based on chest wall stretching, controlled breathing techniques, and personalized programming of cycling and treadmill exercises, improvement in functional capacity was found by increasing the distance covered by the 6MWT (mean: 360, CI 95%: 178–543 m) vs (mean: 420, 95% CI: 238–601 m, p<0.05) and functional parameters.[24] In a randomized, controlled clinical trial that aimed to investigate the appropriate intensity of exercise training in pulmonary rehabilitation for patients with moderate to severe COPD, through a 20-week supervised hospital stay, where patients underwent conventional bicycle physical training for 20 minutes, with 10 minutes of warm-up (walking and strength exercises) before training, as well as 10 minutes of relaxation exercises (stretching and walking) after training, totaling 40 minutes of session, significant differences were found that show improvement in distance from 6MWT and significant improvement in FEV1 of the high-intensity pulmonary rehabilitation group when compared to the low- and moderate-intensity groups.[25] Thus, we can observe that pulmonary rehabilitation had already shown improvement in lung function and functional capacity in other respiratory diseases.

Regarding the risk of bias analysis of the study by Kai Liu, et al., items related to the randomization of groups regarding outcomes were considered low risk of bias, as there was no loss of data, and selective outcome reporting, as the study included all desired outcomes. As for the items related to blinding, all of them have a high risk of bias, because there was no blinding of the participants, professionals, and evaluators.[20]

In the analysis of the risk of bias in the case series, we found that there is no high variability of data, and most of the criteria were met by the three studies evaluated. As for the inclusion criteria, these were not clearly defined in the studies by Elisabetta Zampogna, et al and Mauro Maniscalco, et al.[21,22] Furthermore, in the study by Mauro Maniscalco, et al. the assessment instruments were also not performed in a standard and reliable way for all the participants and the author did not explain whether the participants were fully included.[22] Still about the total inclusion of participants, Vasileios T. Stavrou, et al. did not include the participants in their entirety.[23]

Given the above, it can be concluded that both lung function and functional capacity of individuals cured of COVID-19 after undergoing a pulmonary rehabilitation program showed significant improvement in lung function and functional capacity.

However, it must be taken into account that COVID-19 is a disease whose discovery is recent and highly dispersed, which explains the limited number of studies and treatment protocols, which directly interferes with the results of the analyzed studies, having given that little was known about the proper management of pulmonary and functional sequelae in this population. Therefore, it is suggested that future research be carried out in the context of pulmonary rehabilitation in patients who recovered from COVID-19, in order to summarize with this study, further enriching clinical practice.

As a limitation, this project presented a reduced number of studies due to the scenario in which it was developed, due to the high rate of spread of the virus, the high number of deaths, and the physical contact restriction measures.

Conflict of interest

The authors declare that there is no potential conflict of interest that could interfere with the impartiality of this scientific work.

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