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SYSTEMATIC REVIEW

COCHRANE REHABILITATION CORNER

Rehabilitation and COVID-19: systematic review by Cochrane Rehabilitation

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ABSTRACT

INTRODUCTION: Until the last update in February 2022, the Cochrane Rehabilitation COVID-19 Evidence-based Response (REH-COVER) action identified an increasing volume of evidence for the rehabilitation management of COVID-19. Therefore, our aim was to identify the best available evidence on the effectiveness of interventions for rehabilitation for COVID-19-related limitations of functioning of rehabilitation interest in adults with COVID-19 or post COVID-19 condition (PCC).

EVIDENCE ACQUISITION: We ran the searches on February 17th, 2023, in the following databases: PubMed, EMBASE, CENTRAL, CINHAL, and the Cochrane COVID-19 Study Register, applying a publication date restriction to retrieve only papers published in 2022. To retrieve papers published before 2022, we screened the reference lists of previous publications included in the REH-COVER action, covering papers from early 2020 to the end of 2022. This current review includes only randomised controlled trials and concludes the rapid living systematic reviews of the Cochrane Rehabilitation REH-COVER action. The risk of bias and certainty of evidence were evaluated in all studies using the Cochrane Risk of Bias tool and GRADE, respectively. We conducted a narrative synthesis of the evidence. PROSPERO registration number: CRD42022374244.

EVIDENCE SYNTHESIS: After duplicate removal, we identified 18,950 individual records and 53 RCTs met the inclusion criteria. Our findings suggest that the effect of breathing and strengthening exercise programs on dyspnea and physical exercise capacity compared to no treatment in non-severe COVID-19 patients is uncertain. Multicomponent telerehabilitation may slightly increase physical exercise capacity compared to educational intervention in adults with PCC. There is, however, uncertainty about its effect on lung function and physical exercise capacity when compared to no treatment. Finally, the effect of inspiratory muscle training on maximal inspiratory pressure compared to no treatment in adults with PCC is uncertain.

CONCLUSIONS: Interventions that are part of comprehensive pulmonary rehabilitation approaches may benefit dyspnea and exercise tolerance in adults with COVID-19 and PCC. The available evidence has several methodological limitations that limit the certainty of evidence and the clinical relevance of findings. Therefore, we cannot provide robust suggestions for practice. While high-quality RCTs are being conducted, clinicians should consider using high-quality evidence from other pulmonary conditions to rehabilitate patients with COVID-19 or PCC using context-specific interventions.

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KEY WORDS: Rehabilitation; COVID-19; Post-acute COVID-19 syndrome; Systematic review; International Classification of Functioning, Disability and Health.

Introduction

More than three years after the COVID-19 pandemic outbreak, the World Health Organization (WHO) reports more than 6.9 million deaths and 771 million confirmed cases.[1] Many patients now experience SARS-CoV-2 infection with mild-to-moderate or no symptoms.[2] However, it has been estimated that at least 65 million individuals worldwide are developing long-lasting symptoms that do not resolve for months.[3] This condition, often called Long COVID, was labelled by the WHO in 2021 as "Post COVID-19 Condition" (PCC).[4] According to a recent systematic review, the five most prevalent symptoms in PCC are the following, with corresponding estimated pooled symptom-specific prevalence: fatigue at 0.23 (95% CI: 0.17, 0.30), memory problems at 0.14 (95% CI: 0.10, 0.19), dyspnoea at 0.13 (95% CI: 0.11, 0.15), sleep problems at 0.11 (95% CI: 0.05, 0.23), and joint pain at 0.10 (95% CI: 0.04, 0.22).[5] A large cohort study on 3465 people with COVID-19 reported a crude estimated prevalence of PCC of 18.5%, and identified four symptom profiles: muscle pain, fatigue, cardiorespiratory, and ageusia/anosmia.[6] These symptoms can affect individuals' physical, cognitive, and mental functioning with different severity, resulting in reduced independence in activities of daily living (ADL) and worsened quality of life (QoL).[7]

From the outset of the pandemic, healthcare services have prioritized enhancing the survival of SARS-CoV-2 infected patients. This emphasis has centered on critical care, drug treatments, as well as vaccine development and distribution.[8, 9] However, considering the high impact of COVID-19 on motor and cognitive functions, effective rehabilitation management seems to be one of the most relevant needs for patients in the post-acute phase or with PCC.[10, 11] Even if the pandemic crisis seems to have passed,[12] a considerable number of individuals who have been or will be affected by COVID-19 could benefit from the best available evidence to inform rehabilitation management and services. In 2020, Cochrane Rehabilitation launched the REH-COVER (Rehabilitation – COVID-19 Evidence-based Response) action to address this need.[13] REH-COVER evolved in the subsequent years and focused on updating and synthesizing the growing evidence on the role of rehabilitation for the management of COVID-19 patients.[14, 15] In February 2022, REH-COVER action documented an increasing amount of evidence about the clinical rehabilitation of patients with COVID-19. Overall, the evidence was of low methodological quality.[16] It was concluded that good quality effectiveness studies of interventions were needed.

This systematic review aimed to update the previous reviews and identify the best available evidence from randomized controlled trials on the effectiveness of interventions for rehabilitation (alone or in addition to any other intervention) for COVID-19-related limitations of functioning of rehabilitation interest (LFRI) in adults with COVID-19 or PCC.

Evidence acquisition

We performed a systematic review and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The protocol was registered in PROSPERO (CRD42022374244). This study concludes the rapid living systematic reviews by the Cochrane Rehabilitation REH-COVER action,[18] summarizing all the evidence identified in the previous Reviews until the end of 2022, including only randomised controlled trials (RCTs).

Selection criteria

Type of study

Considering the emerging evidence on rehabilitation for people with COVID-19 or PCC, we included RCTs only.

Population

We considered studies involving adults with COVID-19 or PCC, either hospitalized or managed at home, with any degree of severity of COVID-19 (critical, severe, non-severe) according to the WHO Living guidance-COVID-19 clinical management.[19]

Interventions

We included any type of intervention for rehabilitation aiming at optimizing functioning according to the Rehabilitation definition for research purposes.[20] Specifically, we included oxygen therapy, non-invasive ventilation, and prone position only if they were integrated into a rehabilitation program that includes breathing exercises. We excluded studies providing any intervention that did not meet the aforementioned definition (e.g., stand-alone pharmacological or surgical interventions).

Comparator(s)

We considered studies comparing interventions for rehabilitation to any other type of intervention, usual care, sham/placebo, and no intervention. Considering that the definition of usual care is rarely consistent across trials and

based on the investigators' definition,[21] and that "no intervention" is hardly ever an true absence of interventions, we decided to report all components of usual care or no intervention following description provided in each trial (to increase transparency and applicability of the results).

Outcomes

We included all types of outcomes addressing functioning in COVID-19 or PCC patients, categorizing them, as much as possible, according to the International Classification of Functioning, Disability and Health (ICF).[22]

Primary outcomes:

1. body functions:
   - neuromusculoskeletal and movement-related functions (*e.g.*, Medical Research Council scale [MRC], Short Physical Performance Battery [SPPB])
   - functions of the respiratory systems (*e.g.*, forced expiratory volume in the first second [FEV_1], forced vital capacity [FVC], maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP], FEV_1/FVC%, 6-Minute Walking Test [6MWT], Borg Scale);
   - mental functions (*e.g.*, State Trait Anxiety Inventory [STAI]; Mini Mental State Examination [MMSE]; Sleep Quality Scale [SQS]);
2. activities and participation:
   - self-care and household tasks (*e.g.*, Barthel Index [BI], Functional Independence Measure [FIM]).
3. not classified with ICF:
   - quality of life (*e.g.*, Short Form 36 Health Questionnaire [SF36], Short Form 12 Health Questionnaire [SF12], EuroQol-5 [EQ-5D]).

The tools suggested are only examples and not an exhaustive list.

Secondary outcomes not classified with ICF: adverse events.

Search strategy and study selection

An author with experience in bibliographic searches (SGL) designed the search strategies and ran the searches on February 17th, 2023. The following electronic databases have been included: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane COVID-19 Study Register. No language restriction was applied to the search strategies. A publication date restriction was applied to retrieve only papers published in 2022. To retrieve papers published before 2022, the reference lists of the REH-COVER action previous publications, covering studies from early 2020 till the end of 2022, have been screened.[13, 14, 16, 23-34] Further, we hand-searched the reference lists of included studies. The search strategies are listed in Supplementary Digital Material 1 (Supplementary Table I).

Based on the selection criteria, study selection was performed by two couples of independent reviewers (CC, EP and EA, FN) using DistillerSR (https://www.distillersr.com/). A discussion with a third review author (CA) resolved any disagreement, obtaining a final consensus. We excluded no English studies due to a lack of funding for the translation process.

Assessment of risk of bias and critical appraisal in included studies

Two independent review authors (CC, SGL) assessed the risk of bias in the included studies using the Cochrane Risk of Bias tool (RoB1).[35] Disagreements were solved by consensus or consultation with a third review author (CA).

Data extraction

Two review authors (CC, EP) extracted data on study characteristics using pilot-tested data extraction forms in DistillerSR, including:

- paper characteristics (year, author, title, journal, DOI, country);
- participants characteristics (groups of interest, number of participants at randomization and at the end of the study in each group of interest, disease severity according to WHO "COVID-19 Clinical management: living guidance");[19]
- intervention characteristics (description of intervention, frequency, and duration);
- comparator characteristics (description of intervention, frequency, and duration);
- outcomes assessed and measures (type of outcomes and how outcomes were measured);
- numerical data for outcomes of interest (effect size between groups, statistical significance, mean and standard deviation for continuous outcomes, absolute number of events for dichotomous outcomes);

Disagreements were solved by consensus or consultation with a third review author (SGL).

Statistical analysis

We conducted narrative syntheses for each outcome of interest. Where PICO (population, intervention, comparison and outcome) characteristics of each study permitted, we undertook the following comparisons: interventions for

rehabilitation versus usual care, any other active interventions and no treatment. If studies could be grouped in these comparisons for synthesis, but the methodological quality was poor, we categorized them by comparisons without performing a meta-analysis and described them narratively.[36] In this case, we also calculated the effect estimation recording mean change from baseline or post-intervention mean values and standard deviation (SD) for continuous variables. Mean differences (MDs) for outcomes measured with the same metrics or standardized mean differences (SMDs) for outcomes measured with different metrics with 95% CIs were calculated, as well as risk ratios (RRs) with 95% CIs for dichotomous outcomes, such as adverse events. All the analyses have been performed using Review Manager (RevMan) 5.4.1 software. If the studies could not be grouped for PICO characteristics, we categorized them by outcomes of interest only and described them narratively. We did not account for methodological quality (risk of bias assessment) when synthesizing the evidence.

Summary of findings and assessment of the certainty of the evidence

Two independent authors (SGL, CA) assessed narratively the certainty of evidence for all the outcomes summarized in each comparison identified using the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[37] We could not judge the certainty of evidence for the studies not grouped within the same comparison.

We performed these assessments and presented the results in 'Summary of findings' (SOF) tables, including the reason(s) for downgrading, when applicable. SOF tables have been generated using GRADEpro GDT software.[38]

Evidence synthesis

Study selection

Starting from 28,762 individual records, 262 study reports have been assessed for eligibility, and 53 studies[39-91] have finally been included in the systematic review (Figure 1). The list of excluded studies is reported in Supplementary Digital Material 2 (Supplementary Table II).

Characteristics of studies

Description of included studies

We included 53 RCTs (3882 randomized participants). The sample size ranged from 10 to 298 participants (median 56 participants). Nearly half (45%) of the studies have been conducted in Asia, followed by Europe (32%), America (17%) and Africa (6%). Supplementary Digital Material 3 (Supplementary Table III)[39-91] shows the characteris-

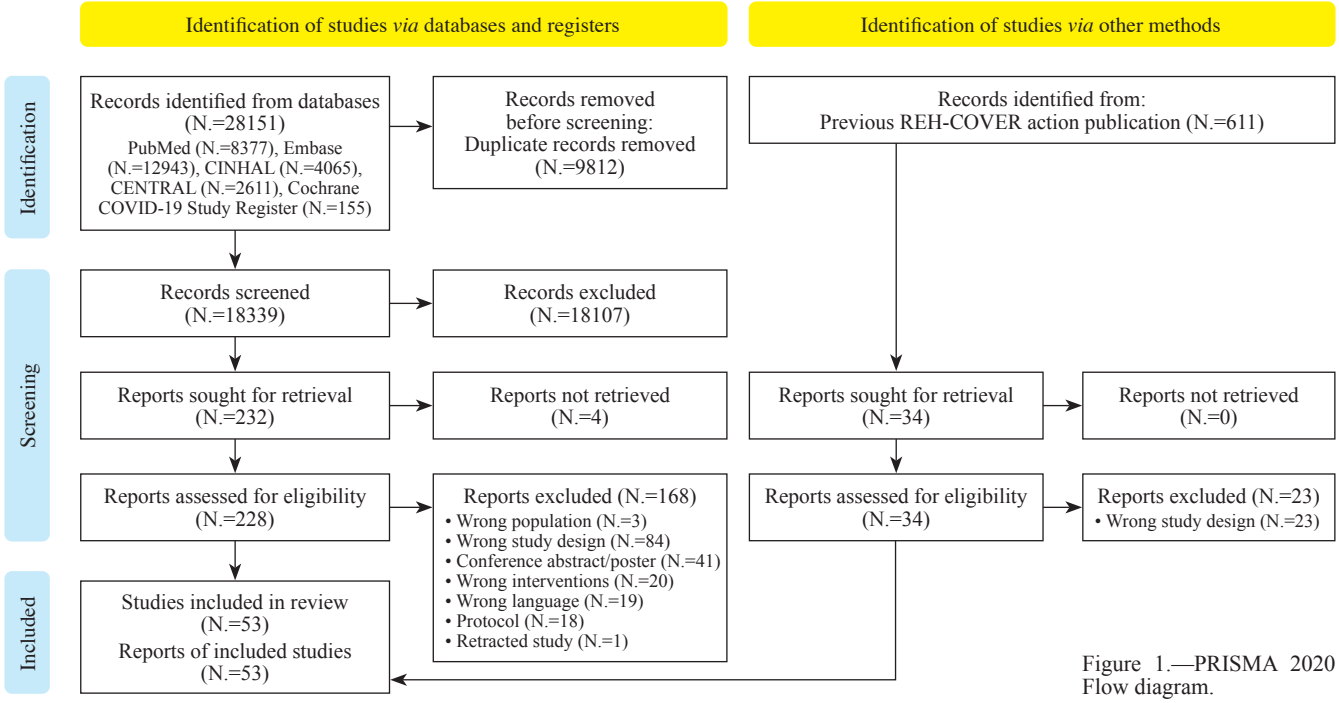

Figure 1.—PRISMA 2020 Flow diagram.

tics of the included studies. More than half of the studies (57%, N=30, 2075 participants) included adults with PCC,[42-46, 48-51, 53, 56, 57, 59-62, 64, 66, 67, 70-72, 74-76, 81, 83, 85, 88, 89] followed by adults with non-severe (34%, N.=18, 1489 participants), severe (6%, N.=3, 230 participants)[39, 63, 86] and critical COVID-19 (4%, N.=2, 88 participants).[41, 90]

Risk of bias of included studies

Information on the risk of bias is summarized in Figure 2 and 3.

The overall rating for all RCTs was high risk of bias. In particular, thirty-seven (70%) and 16 (30%) studies were judged as having a low risk of bias on the sequence generation process and allocation concealment, respectively. In comparison, two (4%) and one (2%) were judged as having a high risk of bias. Seven (13%) studies were considered low risk of performance bias, while 44 (83%) were judged as high risk. Considering the detection bias, 26 (49%) and nine (17%) studies for objective outcomes, while six (11%) and 37 (70%) for subjective outcomes were judged as low risk and as high risk of bias, respectively. Eight studies (15%) did not measure objective or subjective outcomes. Thirty-four studies (64%) were judged as low risk, while 16 (30%) were at high risk of attrition bias. Twenty-seven studies (51%) did not provide information on trial registration, while the remaining (49%) were judged as low risk of reporting bias. None of the studies were judged as high risk of reporting bias.

Effects of interventions

Only 11 RCTs[46, 55, 61, 62, 64, 66, 67, 74, 79, 80, 85] were similar enough to be grouped within the same comparisons, but the risk of bias across these studies was high and unclear in most of the bias domains. Consequently, we did not pool the data in a meta-analysis but synthesized the evidence narratively. Four of these studies[46, 61, 74, 85] reported that no adverse events occurred during the study period, while the others did not report any information on adverse events. The remaining 42 studies did not have similar PICO characteristics, and consequently, we categorized them by outcomes and synthesized them narratively.[22] Four studies[39, 40, 51, 84] did not report any outcome of interest.

Studies synthesized within the same comparisons

Breathing exercises compared to no treatment in non-severe COVID-19 patients

Dyspnea (b460 Sensations associated with cardiovascular and respiratory functions)

Two studies[55, 80] assessed dyspnea, showing an effect in favor of breathing exercises when compared to no treatment

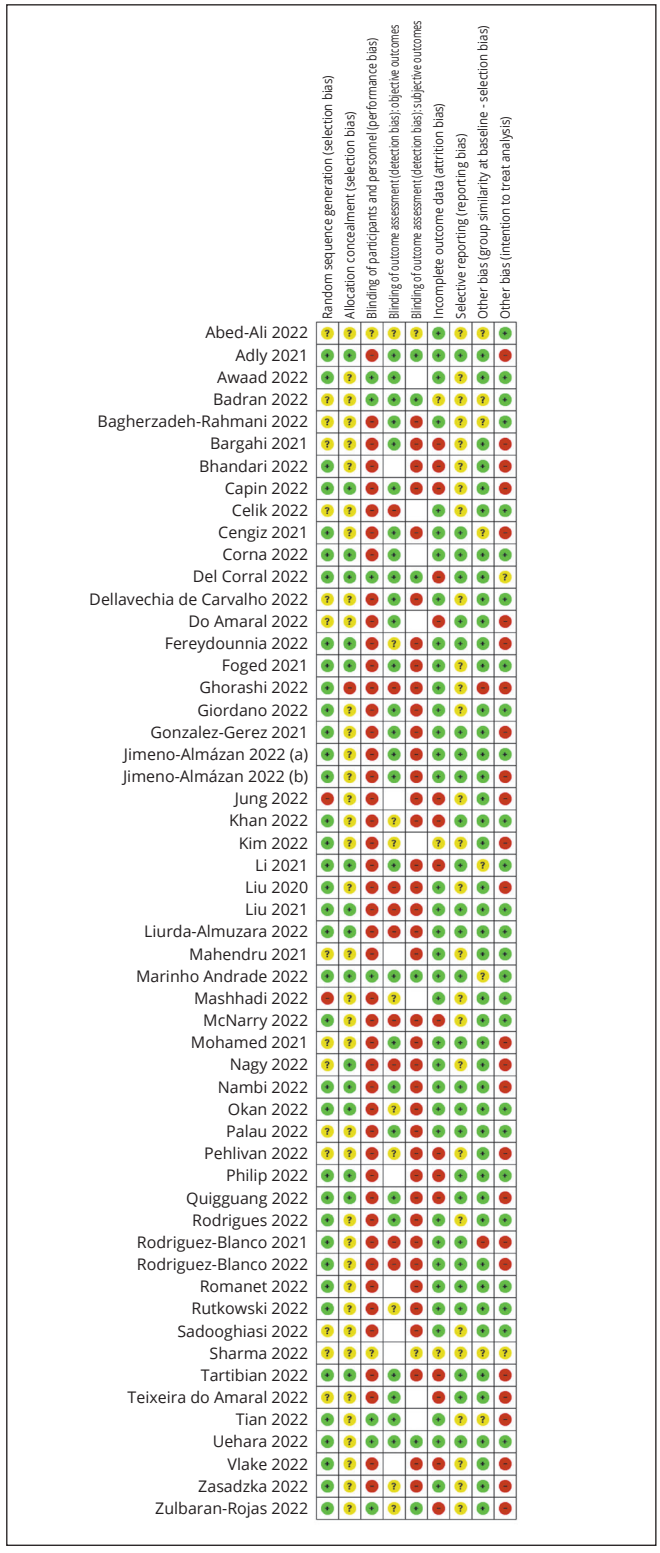

Figure 2.—Risk of bias summary.

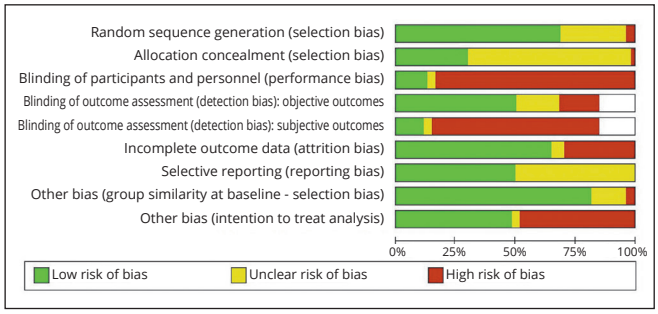

Figure 3.—Risk of bias graph.

in non-severe COVID-19 patients (Figure 4, 5) (very low certainty of evidence).

PHYSICAL EXERCISE CAPACITY (B455 EXERCISE TOLERANCE FUNCTIONS)

Two studies[55, 80] assessed physical exercise capacity, showing an effect in favour of breathing exercises when compared to no treatment in non-severe COVID-19 patients (Figure 6, 7) (very low certainty of evidence).

Muscle strengthening exercise program compared to no treatment in non-severe COVID-19 patients

DYSPNEA (B460 SENSATIONS ASSOCIATED WITH CARDIOVASCULAR AND RESPIRATORY FUNCTIONS)

Two studies[79, 80] assessed dyspnea, showing an effect in favor of a muscle strengthening exercise program when compared to no treatment in non-severe COVID-19 patients (Figure 8) (very low certainty of evidence).

PHYSICAL EXERCISE CAPACITY (B455 EXERCISE TOLERANCE FUNCTIONS)

Two studies[79, 80] assessed physical exercise capacity, showing an effect in favor of a muscle strengthening exercise program when compared to no treatment in non-severe COVID-19 patients (Figure 9, 10) (very low certainty of evidence).

Multicomponent telerehabilitation compared to educational intervention in PCC

PHYSICAL EXERCISE CAPACITY (B455 EXERCISE TOLERANCE FUNCTIONS)

Three studies[46, 61, 64] assessed physical exercise capacity, showing an effect in favor of multicomponent telerehabilitation compared to educational intervention in adults with PCC (Figure 11) (low certainty of evidence).

Multicomponent telerehabilitation compared to no treatment in PCC

RESPIRATORY FUNCTION (B440 RESPIRATORY FUNCTION)

Three studies[62, 66, 85] assessed respiratory function (FEV1, FVC), showing an effect in favor of multicomponent telerehabilitation compared to no treatment in adults with PCC on FEV_1 (Figure 12), but no evidence of an effect on

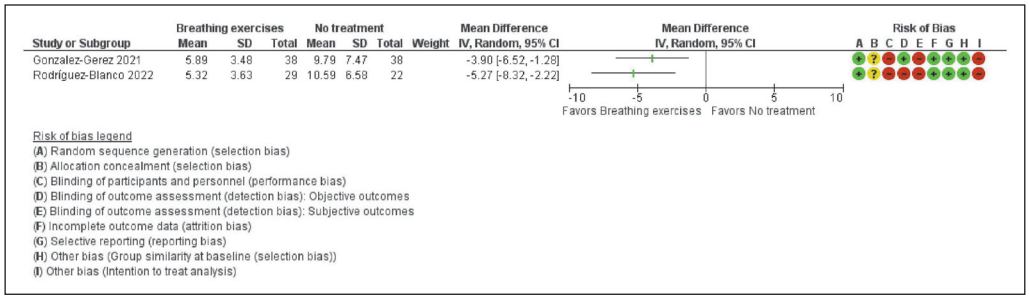

Figure 4.—Forest plot of comparison: dyspnea (MD12) - breathing exercises *versus* no treatment in non-severe COVID-19 patients.

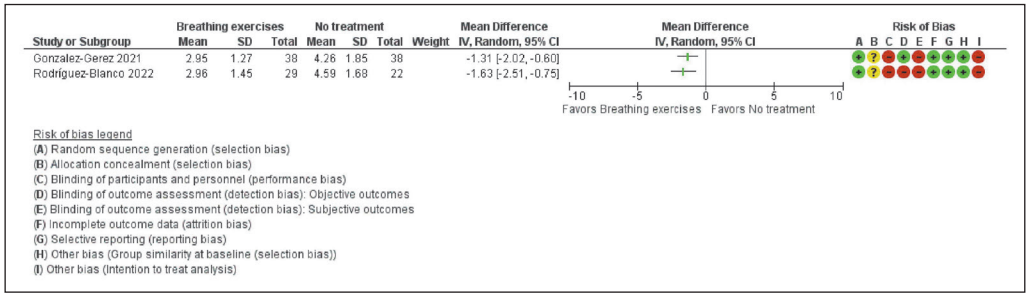

Figure 5.—Forest plot of comparison: dyspnea (Borg Scale) - breathing exercises compared to no treatment in non-severe COVID-19 patients.

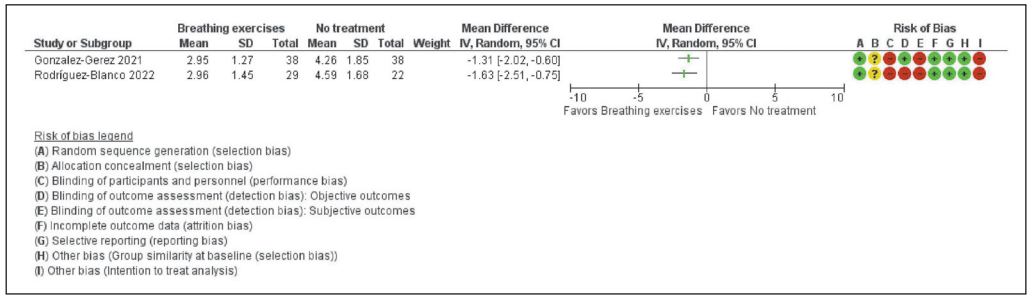

Figure 6.—Forest plot of comparison: functional exercise capacity (6MWT) [Steps] - breathing exercises compared to no treatment in non-severe COVID-19 patients.

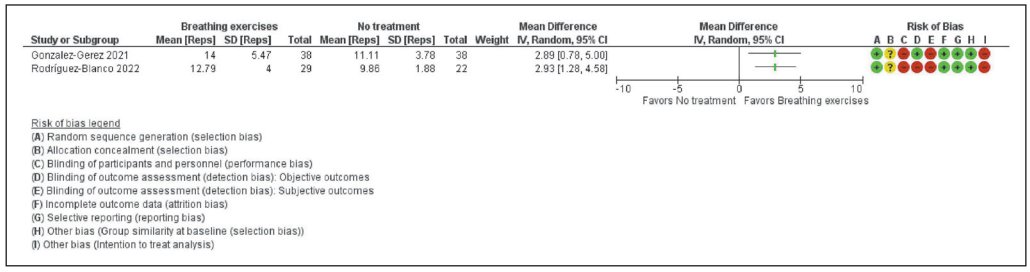

Figure 7.—Forest plot of comparison: functional exercise capacity (30STST) [Reps] - breathing exercises compared to no treatment in non-severe COVID-19 patients.

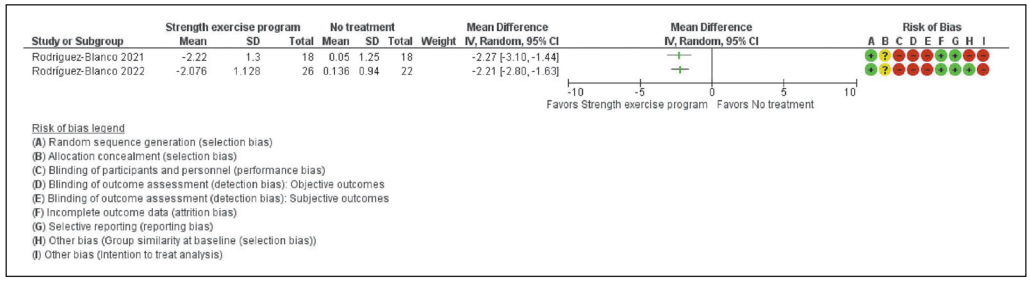

Figure 8.—Forest plot of comparison: dyspnea (Borg Scale) - strength exercise program compared to no treatment in non-severe COVID-19 patients.

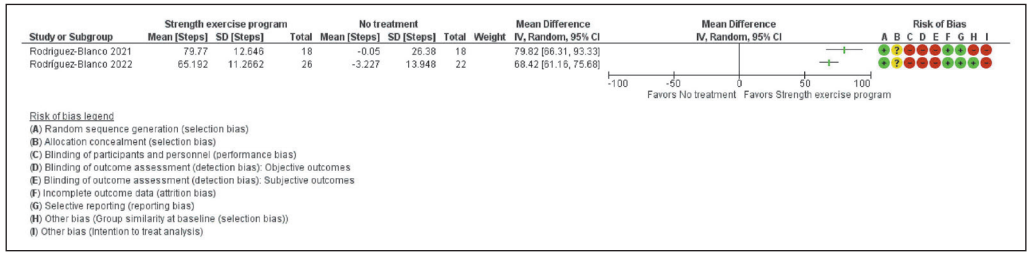

Figure 9.—Forest plot of comparison: functional exercise capacity (6MWT) [Steps] - strength exercise program compared to no treatment in non-severe COVID-19 patients.

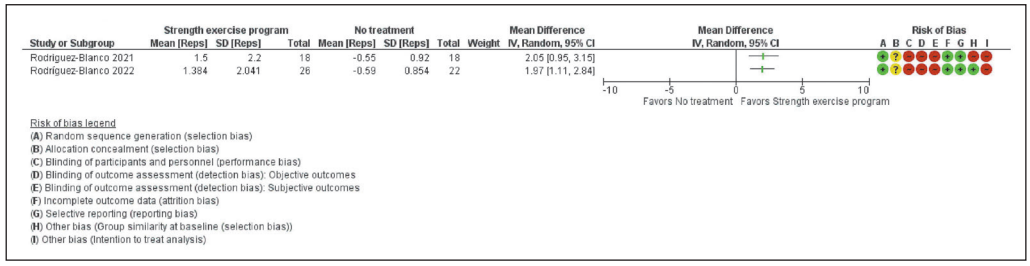

Figure 10.—Forest plot of comparison: functional exercise capacity (30STST) [Reps] - strength exercise program compared to no treatment in non-severe COVID-19 patients.

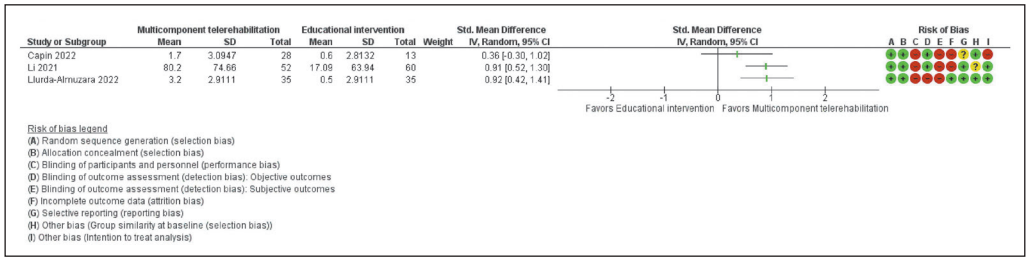

Figure 11.—Forest plot of comparison: functional exercise capacity - multicomponent telerehabilitation compared to educational intervention in PCC.

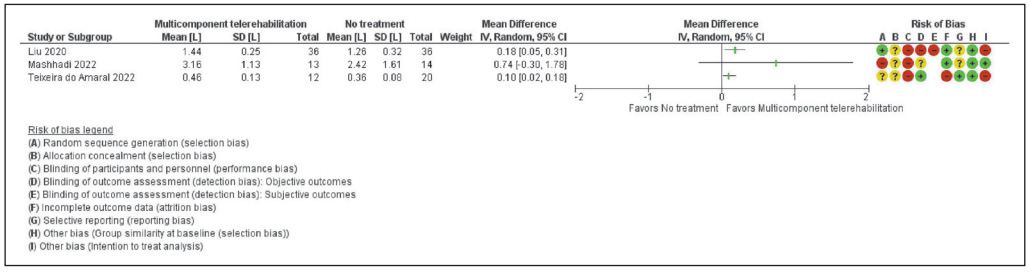

Figure 12.—Forest plot of comparison: respiratory outcome (FEV_1) [L] - multicomponent telerehabilitation compared to no treatment in PCC.

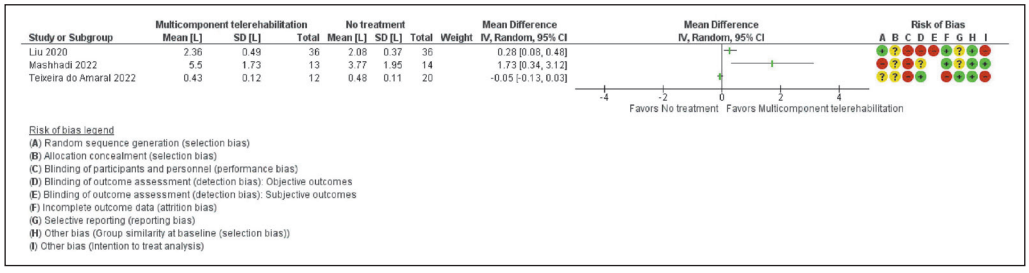

Figure 13.—Forest plot of comparison: respiratory outcome (FVC) [L] - multicomponent telerehabilitation compared to no treatment in PCC.

FVC between multicomponent telerehabilitation and no treatment in adults with PCC (Figure 13) (very low certainty of evidence). Two of these studies[62, 66] also assessed respiratory function in terms of FEV1/FVC%, showing no evidence of an effect between multicomponent telerehabilitation and no treatment in adults with PCC (Figure 14) (very low certainty of evidence).

PHYSICAL EXERCISE CAPACITY (B455 EXERCISE TOLERANCE FUNCTIONS)

Three studies[62, 66, 85] assessed physical exercise capacity, showing an effect in favor of multicomponent telerehabilitation compared to no treatment in adults with PCC (Figure 15) (very low certainty of evidence).

Inspiratory muscle training compared to no treatment in PCC

RESPIRATORY FUNCTION (B440 RESPIRATORY FUNCTION)

Two studies[67, 74] assessed respiratory function (MIP), showing no evidence of an effect between inspiratory muscle training and no treatment in adults with PCC (Figure 16) (very low certainty of evidence).

Certainty of evidence

The certainty of evidence, evaluated with GRADE, was low to very low for all outcomes. We downgraded the evidence for risk of bias, inconsistency, and imprecision (less than 400 or 200 participants) (Supplementary Digital Material 4: Supplementary Table IV, V, VI, VII, VIII).

Studies synthesized for outcomes of interest

See Supplementary Digital Material 5 (Supplementary Table IX) for full details.

Dyspnea (b460 Sensations associated with cardiovascular and respiratory functions)

NON-SEVERE COVID-19 PATIENTS

One study[77] reported a significant difference in dyspnea, assessed with modified Borg Dyspnea Scale, when Liu-

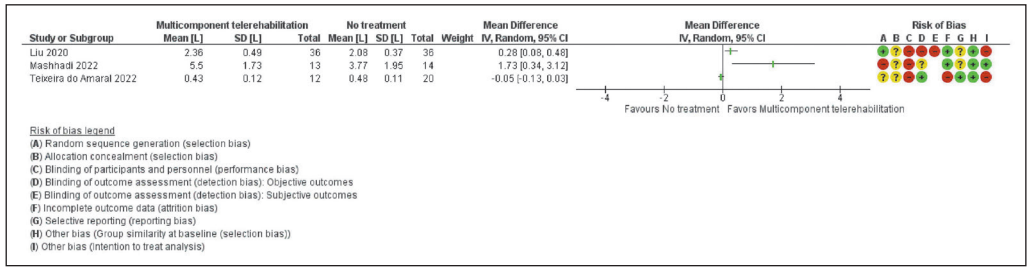

Figure 14.—Forest plot of comparison: respiratory outcome (FEV1/FVC%) [%] - multicomponent telerehabilitation compared to no treatment in PCC.

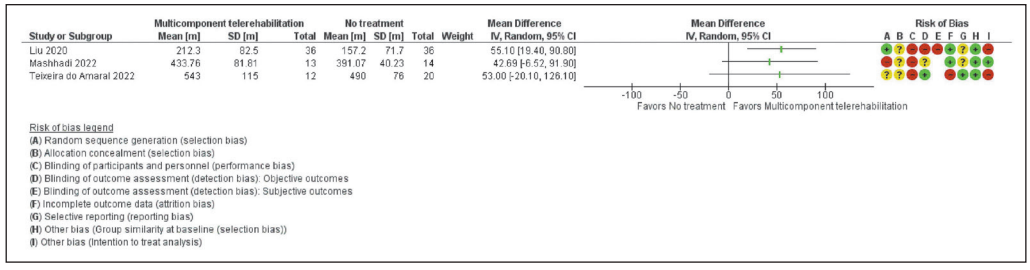

Figure 15.—Forest plot of comparison: functional exercise capacity (6MWT) [m] - multicomponent telerehabilitation compared to no treatment in PCC.

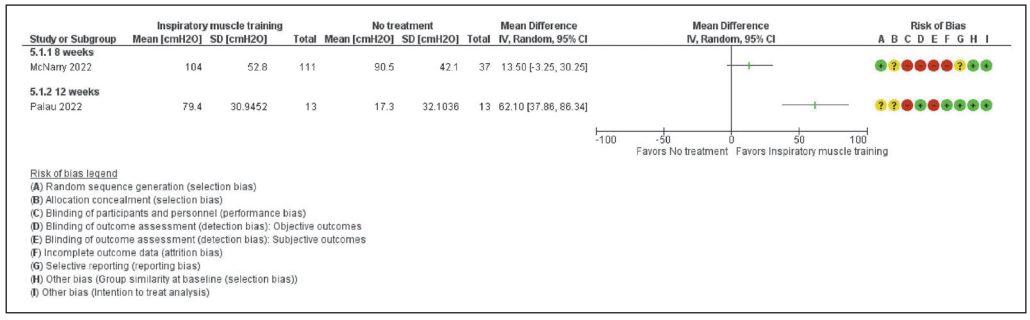

Figure 16.—Forest plot of comparison: respiratory function (MIP) [cmH_2O] - inspiratory muscle training compared to no treatment in PCC.

Zi-Jue exercise was compared with no treatment. Three studies[52, 69, 73] reported no significant changes in dyspnea, assessed with modified Borg Dyspnea Scale[52, 69] and Dyspnea-12 Questionnaire[73] when comparing respiratory muscle training[69, 73] to no treatment[69] or usual care (UC),[73] and when comparing respiratory physiotherapy and myofascial release therapy[52] to respiratory physiotherapy alone.

Severe COVID-19 patients

One study[63] reported a significant difference (P=0.018) in dyspnoea, assessed with the modified Medical Research Council (mMRC) scale when qigong exercise and acupressure rehabilitation program (QARP) was compared with UC.

Post COVID-19 Condition patients

Six studies[48, 67, 70, 75, 76, 83] reported significant improvement following interventions for rehabilitation for dyspnea measured with mMRC, Multidimensional Dyspnea Profile, Baseline Dyspnea Index, Transition Dyspnea Index visual analogue scale (VAS) and chronic obstructive pulmonary disease (COPD) assessment test score, modified Borg Dyspnea Scale. In particular, respiratory muscle training in addition to manual therapy compared with respiratory muscle training,[70] supervised pulmonary rehabilitation (PR) compared with unsupervised PR,[75] endurance rehabilitation compared with UC,[48] respiratory muscle training through telerehabilitation compared with UC,[67] 6-week online breathing associated with wellbeing program compared with no treatment[76] and PR delivered in telerehabilitation compared with UC.[83]

Two other studies[56, 57] reported no effect of respiratory muscle and resistance training alone or combined and multimodal exercise training on dyspnea measured with mMRC compared to UC.

Other respiratory symptoms

Non-severe COVID-19 patients

Two studies[68, 77] reported a significant improvement following aerobic training associated with UC[68] and breathing exercise alone[77] in the severity of respiratory symptoms, such as cough, fever, expectoration, chest tightness assessed with Wisconsin Scale or with a score from 0 (absence) to 10 (severe) when compared with UC and no treatment, respectively. One study[52] reported that respiratory physiotherapy and myofascial release therapy, compared with respiratory physiotherapy alone, show no significant changes in ease of breathing but significant improvement in chest expansion.

Oxygenation (Respiratory structures [s430] and related functions [Respiration b440-455])

Non-severe COVID-19 patients

One study[47] reported that respiratory muscle training compared with no treatment show significant changes in oxygenation, measured with oxygen saturation (SpO_2) and a checklist that evaluated the need for high-flow oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation, and mortality. Two studies reported that respiratory muscle training[73] and single session receptive music therapy[54] show significant changes in oxygenation, assessed through SpO_2, when compared with UC.

Three studies[52, 77, 78] reported non-significant difference in oxygenation, assessed as SpO_2 and vital signs (heart rate and blood pressure). Two studies[52, 77] compared breathing exercises alone[77] or in addition to manual therapy[52] with no treatment and breathing exercises only, respectively. The third study[78] considered virtual rehabilitation (VR) compared with non-specific VR.

Severe COVID-19 patients

One study[63] reported no significant difference in oxygen saturation when QARP were compared with UC.

Critical COVID-19 patients

One study[41] reported that active High-Definition transcranial Direct Current Stimulation (HD-tDCS) associated with respiratory rehabilitation shows a significant difference in the number of days free from mechanical ventilation for at least 48 consecutive hours when compared with sham HD-tDCS associated with respiratory rehabilitation.

Respiratory function (Respiratory functions b440-455)

Non-severe COVID-19 patients

One study[47] reported that high-frequency chest wall oscillation treatment, in addition to standard medical treatment, shows a significant improvement in FEV1, FVC, FEV_1/FVC, and peak expiratory flow (PEF) compared with standard medical therapy alone.

Post COVID-19 Condition patients

Two studies reported that Pilates or aqua Pilates training compared with no treatment[44] show a significant improvement in FVC, FEV_1, FEV_1/FVC, and Maitland thoracic mobilization associated with lumbar stabilization exercises compared with breathing exercises[60] show a significant improvement on FVC, FEV_1, FEV1/FVC, and PEF. Two studies reported that multimodal exercise training compared with UC[57] and multicomponent telerehabilitation program compared with educational instructions[61] show no effect in FEV1, FVC, FEV_1/FVC, FEV25-75%, and PEF. Still, it seems to show a significant improvement in maximal voluntary ventilation. One study[70] reported that respiratory muscle training, in addition to manual therapy compared with respiratory muscle training alone, shows significant improvement in inspiratory muscle strength, assessed with maximum static inspiratory pressure.

Physical exercise capacity (b455 Exercise tolerance functions)

Non-severe COVID-19 patients

Three studies[58, 82, 83] reported that breathing and muscle strengthening exercises alone or combined show significant improvement in the perceived effort, assessed with the Borg scale compared to no treatment. One study[78] reported that VR, compared with non-specific VR, shows no effect on the perceived effort. One study[52] reported that respiratory physiotherapy associated with myofascial release therapy compared with respiratory physiotherapy alone shows no effect in exercise tolerance, evaluated with 6MWT, but a significant improvement in fatigue perception during 6MWT, assessed with the Borg scale.

Severe COVID-19 patients

One study[63] reported that QARP compared with UC shows a significant difference in perceived effort, assessed with modified Borg Dyspnea Scale.

Post COVID-19 Condition patients

Three studies[70, 72, 81] reported a significant improvement in exercise tolerance, evaluated with 6MWT. The first study[70] compared respiratory muscle training in addition to manual therapy with respiratory muscle training alone. The second one[72] compared breathing exercises, administered by telerehabilitation, with breathing exercises without supervision. The last study[81] compared multicomponent VR with UC. One study[75] reported that supervised PR compared with unsupervised PR shows no effect on functional exercise capacity, evaluated with short physical performance battery (SPPB) and 30-seconds sit to stand (30sSTS) test. Three studies[46, 49, 85] reported non-significant changes in physical function, assessed with time up and go (TUG) test, when comparing multicomponent telerehabilitation to educational instructions[46] or no treatment[85] and when comparing aerobic training with UC.[49] One study[50] reported that respiratory muscle training at home using a threshold pressure device compared with sham respiratory muscle training (device without resistance) shows no effect on exercise tolerance assessed with the Ruffier Test. Another study[53] reported that three supervised high-intensity interval training (HIIT) protocols compared among them show no effect on exercise tolerance assessed with a 10-point Likert scale and on achieved intensity, assessed with Rate of perceived exertion (RPE).

Muscle strength (b730 Muscle power functions)

Non-severe COVID-19 patients

One study[55] reported that breathing exercises administered through telerehabilitation compared to no treatment show a significant improvement in lower limb muscle strength, assessed with 30s STS test.

Critical COVID-19 patients

One study[90] reported that functional electrical stimulation (E-stim) application compared with non-functional E-stim application shows no significant difference in ankle muscle strength and gastrocnemius muscles endurance.

Post-COVID-19 Condition patients

Six studies[46, 49, 50, 64, 71, 85] assessed lower limb muscle strength with chair raise test,[46, 64] STS test,[49, 50, 85] Quadriceps and mid-calf muscle mass (using MRI).[71] However, only two studies[50, 64] reported a significant improvement in lower limb muscle strength when comparing respiratory muscle training to sham treatment[50] and multicomponent telerehabilitation program to educational instructions.[64] One study[56] reported that resistance training and respiratory muscle training alone or combined show significant improvement in lower limb muscle strength and no effect in upper limb muscle strength when compared with UC. Another study[57] reported that multimodal exercise training compared with UC shows significant improvement in the upper limb muscle strength measured with bench press and lower limb muscle strength. Five studies[49, 64, 71, 85, 89] evaluated upper limb muscle strength with the handgrip force test. However, only two studies[64, 71] reported that multicomponent telerehabilitation[64] and low-intensity multimodal training[71] show a significant improvement in upper limb muscle strength when compared to educational instructions and high-intensity multimodal training, respectively.

Anxiety and depression (b152 Emotional functions)

Non-severe COVID-19 patients

Two studies[54, 58] reported that single session receptive music therapy[54] and psychological rehabilitation[58] show a significant effect on anxiety when compared with UC. Another one[91] reported that yoga-based breathing techniques in association with meditation daily significantly affect anxiety when compared with no treatment. Two studies[65, 73] reported that respiratory muscle training[73] and breathing exercises[65] show no effect on anxiety when compared with UC. One study[78] reported that VR, compared to non-specific VR, shows no effect on anxiety. Another one[87] reported that transcutaneous auricular vagus nerve stimulation (taVNS) shows no difference in anxiety compared to sham taVNS. Two studies[58, 65] reported that psychological rehabilitation[58] and breathing exercises[65] show significant effect on depression when compared to UC. One study[77] reported that Liu-Zi-Jue exercise shows no significant change in depression compared to no treatment.

Severe COVID-19 patients

One study[63] reported that QARP show no effect on depression when compared with UC.

Post COVID-19 Condition patients

Five studies[45, 56, 57, 62, 76] assessed anxiety with General Anxiety Disorder scale (GAD-7),[56, 57, 76] Hamilton Anxiety Rating Scale (HAMA)[45] and self-rating anxiety scale (SAS).[62] Only two studies[45, 62] reported that yoga and Ayurveda alone or combined[45] and multi component telerehabilitation[62] show a significant improvement in anxiety

when compared to no treatment. Six studies[45, 46, 56, 57, 62, 75] considered depression assessed with Beck's Depression Inventory (BDI),[45, 75] Patient-Health Questionnaire (PHQ-8 or PHQ-9),[46, 56, 57] self-rating depression scale (SDS).[62] Only two studies[45, 56] reported that yoga and Ayurveda alone or combined among them compared to no treatment[45] and resistance and respiratory muscle training alone or combined among them when compared to UC[56] show a significant effect on anxiety. Two studies[50, 81] assessed anxiety and depression with Hospital Anxiety and Depression scale (HADS), however, only the second study[81] reported that multicomponent VR shows a significant improvement compared to UC. One study[46] reported that multicomponent telerehabilitation shows no effect on loneliness, assessed with Three-Item Loneliness Scale, when compared to educational instructions.

Delirium (b160 Thought functions)

Critical COVID-19 patients

One study[41] reported that active HD-tDCS associated with respiratory rehabilitation show no significant difference in delirium when compared with sham HD-tDCS plus respiratory rehabilitation.

Activities of daily living (Any Activity limitation and participation restriction [d])

Post COVID-19 Condition patients

Three studies[49, 62, 89] assessed activities of daily living (ADL) with functional independence measure (FIM) and Barthel Index (BI), however, only one study[49] reported that aerobic training in addition to UC shows a significant improvement when comparing to UC. Two studies[56, 57] considered functional limitations, assessed with post-COVID-19 functional status (PCFS) scale, when comparing resistance training and respiratory muscle training alone or combined[56] and multimodal exercise training[57] to UC. However, only the second study[57] reported a significant difference.

Balance (b755 Involuntary movement reaction functions)

Post COVID-19 Condition patients

Two studies[46, 64] assessed balance with four-stage balance test[46] and SPPB,[64] however, only the second study[64] reported that a multicomponent telerehabilitation program shows a significant improvement in balance when compared to educational instructions.

Cardiorespiratory fitness (b440 Respiratory function; b455 Exercise tolerance function)

Post COVID-19 Condition patients

Two studies[56, 57] considered maximal oxygen consumption (VO_2 max) as an index of cardiorespiratory fitness when comparing resistance training and respiratory muscle training alone or combined[56] and multimodal exercise training[57] to UC. However, only the second study[57] reported a significant difference.

Clinical improvement and Patient Reported Outcomes Measurement and Information System (any other body structure and function-generic)

Non-severe COVID-19 patients

Two studies[78, 91] reported that yoga associated with meditation[91] and VR[78] showed a significant effect on symptoms' severity change, evaluated with demographic and disease symptoms' checklist[91] and Edmonton Symptom Rating Scale[78] when compared to no treatment and non-specific VR, respectively.

Severe COVID-19 patients

One study[86] reported that short-wave diathermy (SWD) treatment compared with placebo SWD showed a significant effect both on clinical and radiological improvements.

Post COVID-19 Condition patients

Two studies[43, 57] reported that vagus nerve stimulation (VNS) compared to sham VNS[43] and multimodal exercise training compared to UC[57] show no significant effect on symptoms' improvement.

One study[46] reported that multicomponent telerehabilitation shows no effect on Patient Reported Outcomes Measurement and Information System (PROMIS) that have a major impact on quality of life, assessed with PROMIS-Short Form, compared to educational instructions.

Cognitive function (b117 Intellectual functions)

Post COVID-19 Condition patients

Two studies[46, 50] reported that multicomponent telerehabilitation compared to educational instructions[46] and respiratory muscle training at home using a threshold pressure device compared with sham respiratory muscle training (device without resistance)[50] show no difference in cognitive function, assessed with Montreal Cognitive Assessment (MoCA) test.

Fatigue (b4552 Fatiguability)

Non-severe COVID-19 patients

Two studies[77, 79] reported that breathing exercises[77] and strength exercises[79] show a significant improvement in fatigue, assessed with Fatigue Scale-14 and VAS-Fatigue.

Severe COVID-19 patients

One study[63] reported that QARP, compared to UC, did not show any effect on fatigue.

Post COVID-19 Condition patients

Four studies[56, 57, 70, 83] reported statistical significance in fatigue assessed with Fatigue Severity Scale (FSS),[56, 57, 70] and Chalder Fatigue Scale (CFQ-11)[56, 57] and VAS.[83] The first study[56] compared respiratory muscle and resistance training alone or combined with UC. The second one[57] compared multimodal training exercises to UC. The third study[70] compared respiratory muscle training in addition to manual therapy with respiratory muscle training alone. The last study[83] considered PR and UC. Two studies[75, 89] reported that supervised PR compared to unsupervised PR[75] and neurological rehabilitation associated with electromyography rehabilitation robot compared to neurological rehabilitation only[89] show no effect on fatigue, evaluated with VAS,[75] Fatigue Assessment Scale and muscle fatigue assessment model using the LUNA Rehabilitation Robot.[89] One study[57] reported that multimodal exercise training shows no difference in myalgic encephalomyelitis/chronic fatigue syndrome symptoms, assessed with DePaul Symptom Questionnaire (DSQ-14) short form, compared to UC.

Frailty (no ICF classification)

Post COVID-19 Condition patients

One study[42] reported that VNS in addition to physiotherapy program compared to sham VNS in addition to physiotherapy program shows a significant difference in disability, assessed with Human Development Index (HDI). One study[64] reported that multicomponent telerehabilitation shows a significant difference in frailty, assessed with FRAIL scale, compared to educational instructions.

Mobility (d455 Moving around)

Post COVID-19 Condition patients

Two studies[46, 49] assessed mobility with FitBit activity monitors and Cumulated Ambulation Score — Italian Version (CAS-I), respectively, however, only the second one[49] reported that aerobic training in addition to UC shows a significant improvement in mobility when comparing to UC only. One study[67] reported that respiratory muscle telerehabilitation shows a significant effect on changes in daily mobility, evaluated with actigraph measures, such as physical activity, sedentary time and sleep analyses, compared to UC.

Memory and attention (b144 Memory, b140 Attention functions)

Non-severe COVID-19 patients

One study[87] reported that taVNS shows a significant improvement in memory and attention, assessed with Clinical Global Impression-Improvement, when comparing to sham VNS.

Quality of life (no ICF classification)

Non-severe COVID-19 patients

One study[73] reported that expiratory muscle training compared to UC shows a significant effect on quality of life, assessed with World Health Organization Quality of Life Brief Version (WHOQOL-Bref).

Post COVID-19 Condition patients

Sixteen studies[44, 45, 48, 50, 56, 57, 61, 62, 67, 71, 72, 74-76, 81, 88] assessed quality of life with WHOQOL-Bref, EuroQol-5 questionnaire, short-form 12 health questionnaire (SF-12), short-form 36 health questionnaire (SF-36), 15-item King's Brief Interstitial Lung Disease (K-BILD) questionnaire, Sarcopenia and Quality of Life questionnaire, St George's Respiratory Questionnaire; eleven of which reported a significant improvement. Two studies[61, 62] reported that multicomponent telerehabilitation compared to educational instructions[61] or no treatment[62] shows a significant improvement in quality of life. One study[44] reported that Pilates or aqua Pilates show significant effect on quality of life when comparing to no treatment. One study[50] reported that respiratory muscle training at home using a threshold pressure device compared with sham respiratory muscle training (device without resistance) shows a significant improvement on quality of life. Another study[74] reported that respiratory muscle training significantly improves in quality of life when compared to UC. Two studies[57, 71] reported that multimodal training compared to UC[57] and low-intensity multimodal training compared to high-intensity multimodal training[71] show a significant

improvement in quality of life. One study[72] reported that breathing exercises administered through telerehabilitation show a significant effect when compared to unsupervised breathing exercises. Another study[75] reported that supervised PR, compared to unsupervised PR, significantly improved quality of life. Two studies[48, 76] reported that educational intervention compared to no treatment[76] and endurance rehabilitation compared to UC[48] show a significant effect on quality of life.

Pain and kinesiophobia (b280 Sensation of pain)

Post COVID-19 patients

One study[42] reported that VNS, in addition to a physiotherapy program, shows a statistically significant pain improvement, assessed with VAS, when comparing to placebo. One study[75] reported that unsupervised PR shows no effect on pain, assessed with VAS, compared to unsupervised PR. One study[71] reported that low-intensity multimodal training compared to high-intensity multimodal training shows no effect on kinesiophobia, assessed with Tampa Scale of kinesiophobia.

Sense of smell (b1562 Olfactory perception)

Post COVID-19 Condition patients

One study[59] reported that comparing bimodal or unimodal training with patient-preferred scents, or bimodal or unimodal training with physician-assigned scents to watchful waiting shows no clinically meaningful difference in the smell identification test (UPSIT score).

Psychological component and stress level (b152 Emotional functions)

Non-severe COVID-19 patients

One study[65] reported that breathing exercises compared with UC show a significant improvement in stress level, assessed with 21-Likert type questions (DASS21). One study[82] reported that meditation shows a significant effect on psychological well-being, assessed with Ryff's Psychological Well-being Scale, when compared to UC.

Post COVID-19 patients

Two studies[45, 50] assessed post-traumatic stress disorder (PTSD) with Davidson Trauma Scale (DTS) or PTSD checklist (PCL-C self- rating questionnaire), however, only the first study[45] reported that yoga alone or in addition to Ayurveda show a significant difference on PTSD when compared to no treatment. The second study[50] considered respiratory muscle training, which was compared to sham treatment. One study[88] reported that VR shows no effect on psychological recovery, assessed with Impact of Event Scale-Revised and HADS, when compared to no treatment.

Organ dysfunction (Any other body function-generic [b])

Critical COVID-19 patients

One study[41] reported that active High-Definition transcranial Direct Current Stimulation (HD-tDCS) associated with respiratory rehabilitation shows no significant difference in organ dysfunction when compared with sham HD-tDCS associated with respiratory rehabilitation.

Quality of sleep (b1343 Quality of sleep)

Non-severe COVID-19 patients

Two studies[58, 65] reported that psychological rehabilitation[58] and breathing exercises[65] show a significant effect on quality of sleep, assessed with Korean Version of the Insomnia severity Index and DASS-21, when compared to UC.

Adverse events (no ICF classification)

Non-severe COVID-19 patients

Two studies[77, 87] reported that, when breathing exercise was compared to no treatment[77] and taVNS was compared to sham VNS,[87] there were no adverse events. One study[40] reported some side effects of BiPAP, such as facial skin and eye irritation, mild oropharyngeal dryness, mild abdominal gaseous distention, and stomach pain.

Fifteen studies[47, 52, 54, 55, 58, 65, 68, 69, 73, 78-80, 82, 84, 91] did not address adverse events.

Severe COVID-19 patients

Two studies[63, 86] reported adverse events. One study[86] reported that the most frequent events were headache and dizziness, however, it reported that SWD shows no significant effect on adverse events when compared to placebo SWD. One study[39] did not address adverse events.

Critical COVID-19 patients

One study[90] reported that when functional E-stim was compared with non-functional E-stim application, no adverse events occurred. One study[41] reported five and three mild adverse events (*i.e.*, transient skin redness) in the active HD-tDCS and sham groups, respectively.

Post COVID-19 patients

Fourteen studies[43, 46, 49, 53, 56, 57, 61, 72, 74, 76, 83, 85, 88, 89] reported that no adverse events occurred. One study[50] reported that only one person in the sham group presented symptom exacerbation when comparing respiratory muscle training administered through telerehabilitation to sham treatment. One study[59] reported adverse effects during the olfactory training, including two (0.8%) reports of headaches and one (0.4%) report of worsening parosmia associated with the intervention. Fourteen studies[42, 44, 45, 48, 51, 60, 62, 64, 66, 67, 70, 71, 75, 81] did not address adverse events.

Discussion

We aimed to evaluate the effectiveness of interventions for rehabilitation on functioning outcomes in adults with COVID-19 or post COVID-19 condition. We included 53 RCTs, and most of them included adults with PCC. Due to the heterogeneity of interventions and outcomes, only 11 RCTs were similar enough to be grouped within the same comparisons, but the risk of bias across these studies did not allow us to pool them in a meta-analysis. Consequently, we synthesized them narratively. Our findings show that the evidence is very uncertain about the effect of breathing exercises and muscle-strengthening exercise programs on dyspnea and physical exercise capacity compared to no treatment in non-severe COVID-19 patients. Multicomponent telerehabilitation may result in a slight increase in physical exercise capacity compared to educational intervention in adults with PCC, not clinically relevant. Still, there is uncertainty about its effect on lung function and physical exercise capacity when it is compared with no treatment and the effect of inspiratory muscle training on MIP compared to no treatment in adults with PCC.

The inclusion of breathing exercises and strength training as potentially effective strategies for non-severe COVID-19 patients is not unexpected, considering that, among people with stable respiratory diseases, these kinds of interventions proved to have beneficial effects in improving pulmonary function, exercise endurance, dyspnea, quality of life, and respiratory muscle strength.[92, 93] Similar findings were also reported by two studies.[94, 95] The findings of the first study[94] suggest that rehabilitation interventions are linked to enhancements in functional exercise capacity, dyspnea, and quality of life. There is a high likelihood of improvement compared to the current standard care, with moderate certainty of evidence for functional exercise capacity and quality of life, and low certainty for other outcomes. Furthermore, the other study[95] reports that there is highly uncertain evidence regarding the impact of pulmonary rehabilitation on exercise capacity and respiratory function in patients with mild COVID-19 and PCC.

Results in PCC patients are in line with treatment hypotheses previously provided by Cochrane Rehabilitation, looking at other health conditions, showing that multicomponent interventions and telerehabilitation can be associated with beneficial effects on dyspnea and exercise tolerance or fatigue.[96, 97] Also, the WHO[19] supports to use of a combination of education and skills training on self-management strategies; physical exercise training; psychological support to address contributing factors such as anxiety; and cognitive exercises to address the cognitive dysfunctions as they apply to daily functioning in patients with PCC. The narrative synthesis reports a great heterogeneity in terms of interventions and outcome measures across the studies, making it challenging to synthesize any effect of each intervention for rehabilitation on COVID-19-related outcomes in any population. To address this relevant limitation and provide more consistent data for both clinical care and research on a global scale, an international consensus study was conducted to achieve the adoption of a standardized framework for assessing adults with post COVID-19 condition.[97-99] However, only eleven outcomes achieved consensus for inclusion in the final core outcome set: fatigue; pain; post-exertion symptoms; work or occupational and study changes; survival; functioning, symptoms, and conditions for each of cardiovascular, respiratory, nervous system, cognitive, mental health, and physical outcomes. For several symptoms, like joint pain, olfactory dysfunction, mood or cognitive alterations, strong evidence about the optimal rehabilitative management is not present yet. In these cases, clinicians should consider the available findings integrating them in an evidence-based practice approach. Conversely, where evidence is conflicting or completely absent, the use of an "evidence relevant to" approach[11] can help clinicians and researchers to partially fill the knowledge gap and provide patients the best available evidence for their management starting from other health conditions.[100-102]

Limitations of the study

This study presents some limitations. Despite the comprehensive PICO considered, the "COVID-19 degree of severity" was not always defined and described in the studies, and often, the population included people in different disease stages and with variable disability levels. Consequently, we included all types of population in the

synthesis, and the COVID-19 degree of severity was defined using the WHO-living guidance.[19] Moreover, studies not published in English and grey literature have not been considered, while the search was limited to studies published up to the end of 2022. Consequently, the results may change in the future, as far as novel RCTs, with lower risk of bias will be available.[103]

Conclusions

Interventions that are part of comprehensive pulmonary rehabilitation approaches seem to deliver promising results on dyspnea and exercise tolerance in adults with COVID-19 and PCC. Considering the diverse nature of COVID-19 and PCC related limitations of functioning, the involvement of a multi-professional, interdisciplinary team, ensuring a thorough assessment of any body-function impairment and activity limitation before planning an individual rehabilitation project (IRP) that aims at the recovery of the optimal subjects' functioning, would be desirable.

Currently, the available evidence has several methodological limitations that reduce the certainty of evidence and the clinical relevance of findings, making it difficult to provide robust clinical suggestions for practice. Therefore, clinicians should consider transferring interventions from well-known health conditions in COVID-specific contexts to mitigate the current absence of evidence.

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The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Chiara Arienti and Maria G. Ceravolo have given substantial contributions to the conception of the manuscript. Elisa Pollini, Claudio Cordani, Francesco Negrini, Elisa Andrenelli performed the screening process. Stefano G. Lazzarini and Chiara Arienti performed data analysis and interpretation. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

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