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Effect of pulmonary rehabilitation approaches on dyspnea, exercise capacity, fatigue, lung functions and quality of life in patients with COVID-19: A Systematic Review and Meta-Analysis

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Yours Sincerely,

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Abstract

Objective: To qualitatively synthesize and quantitatively evaluate the effect of pulmonary rehabilitation (PR) on dyspnea, lung functions, fatigue, exercise capacity, and quality of life (QoL) in patients with COVID-19.

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Data sources: PubMed, Web of Science, and Cochrane databases were searched from January 2020 to April 2022.

Data Selection: Randomized controlled trials (RCTs) assessing the effect of PR on dyspnea, lung functions, fatigue, exercise capacity, and QoL in patients with COVID-19.

Data Extraction: The mean difference (MD) and a 95% CI were estimated for all the outcome measures using random effect models. The following data were extracted by two independent reviewers: 1) first author; 2) publication year; 3) nationality; 4) number of patients included 5) comorbidities; 6) ventilatory support; 7) length of inpatient stay; 8) type of PR; 9) outcome measures; and 10) main findings. The risk of bias was evaluated using the cochrane risk of bias tool.

Data Synthesis: A total of 8 RCTs involving 449 participants were included in the review. PR was found to be significantly effective in improving dyspnea (5 studies, SMD -2.11 [95% CI, -2.96 to -1.27; p<0.001]) and exercise capacity (MD 65.85 m [95% CI, 42.86 to 88.83; p<0.001]) in patients with both acute and chronic COVID-19 with mild to severe symptoms whereas, fatigue (MD -2.42 [95%CI, -2.72 to -2.11, p<0.05]) and lung functions (MD 0.26 L [95%CI, 0.04 to 0.48, p<0.05]) were significantly improved in acute COVID-19 patients with mild symptoms. The effect of PR on QoL was inconsistent across studies. PR was found to be safe and feasible for patients with COVID-19.

Conclusion: Evidence from studies indicates that PR program is superior to no intervention in improving dyspnea, exercise capacity, lung functions, and fatigue in patients with COVID-19. PR appears to be safe and beneficial for both acute and chronic COVID-19 patients.

Keywords: COVID-19, Pulmonary Rehabilitation, SARS-COV-2, Dyspnea, Exercise Capacity.

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List of Abbreviations:

Acute COVID-19: People with a confirmed diagnosis of COVID-19 (Active Covid-19) .

COVID-19: Coronavirus disease 2019.

Chronic COVID-19: People who have recovered from COVID-19 but have long-term effects of COVID-19 or have symptoms for far longer than would be expected.

COPD: Chronic obstructive pulmonary disease.

Eq-5D-3L: EuroQuality-5Dimensions-3 Levels questionnaire

FVC: Forced vital capacity

L: liters

MCID: Minimal clinical important difference

PR: Pulmonary rehabilitation.

QoL: Quality of life.

RCTs: Randomized controlled trials.

SF-12: Short-Form Health Survey-12 .

SF-36: Short-Form Health Survey-36.

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SGRQ: St. George's Respiratory Questionnaire.

Telerehabilitation: Pulmonary rehabilitation delivered via an online platform.

WHO: World Health Organization.

6MWT: 6-minute walk test.

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1. Introduction

According to the world health organization (WHO) coronavirus disease 2019 (COVID-19) has affected more than 237 countries, and more than 517 million people have been infected across the globe, causing the deaths of more than 6 million people (as of November 09, 2022) [1]. The clinical manifestations of COVID-19 were heterogeneous, most of the cases (81%) have no or mild pneumonia that did not require any specific medical treatment and can be managed at home. Severe (14%) and critical (5%) cases develop severe pneumonia and respiratory illness which require in-hospital treatment and are more likely to have long-term effects [2, 3]. Almost 3% of severe COVID-19 cases may progress to death [4].

Previous studies started using the term "Long COVID" for people who have recovered from COVID-19 but have long-term effects of COVID-19 or have symptoms for far longer than would be expected [5, 6]. Computed tomography of patients recovered from COVID-19 showed abnormal lung findings and impaired lung functions even 30 days after discharge from hospital [7]. Further investigation revealed that lung damage results in impaired pulmonary function, decreased strength of limb muscles, and reduced exercise capacity [8]. Some patients reported cough, dyspnea, fatigue, and decreased functional capacity even 8 weeks after discharge from hospital [5, 7, 9, 10]. According to a study, 39% of patients who recovered from COVID-19 perceived a decrease in their overall health [11]. In recent days the number of patients who recovered from COVID-19 has increased[12], and due to the long-lasting effect of COVID-19, it is crucial to explore novel approaches to help ameliorate the residual symptoms.

Pulmonary rehabilitation (PR) including exercise training, education, and behavioral changes can improve the physical and psychological condition of patients with COVID-19[5]. Several guidelines for COVID-19 rehabilitation were published by the World Health Organization [13], Chinese Medical Association of Rehabilitation [14], and European Respiratory Society/American Thoracic Society [15]. These clinical guidelines recommended PR for the management of the long-term effects of critical illness associated with COVID-19. Previous studies reported that the supervised PR program is safe and effective in improving exercise capacity, lung functions, exertional dyspnea, psychological function, and quality of life (QoL) in both mild/moderate and severe/critical COVID-19 patients [16-20]. As COVID-19 is a new disease, there is insufficient data in the literature on the pathways for recovery from severe complications. PR might have an important role in reducing the long-term effects of COVID-19. To date, the effect of PR on respiratory and physical functions in patients with COVID-19 is not well established. Therefore, we

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aimed to conduct a systematic review and meta-analysis to synthesize the evidence about the effectiveness of PR on dyspnea, exercise capacity, lung functions, fatigue, and QoL in patients with COVID-19.

2. Methods

Protocol and Registration

The study was conducted in accordance with the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [21]. The study protocol was designed a priori according to PRISMA guidelines. The systematic review is registered on Open Science Framework (https://osf.io/9ebtg/) (DOI 10.17605/OSF.IO/9EBTG).

Search strategy

Literature Search included the following electronic bibliographic databases: PubMed, Web of Science (WOS), and Cochrane Central Register of Controlled Trials (Cochrane CENTRAL). Three reviewers (I.A, R.M, and Z.Y) independently searched the literature for english articles (spoken language of authors), which were published between January 2020 and April 2022, according to each specific keyword, adopting the strategy depicted in the supplementary file, Appendix 1. The following keywords were employed: “Coronavirus disease 2019 or COVID-19”, “Exercise”, “Pulmonary Rehabilitation”, “Telerehabilitation”, “Physiotherapy”, “Rehabilitation”, “Fitness”, and “Recovery”. Initially, three of the reviewers (I.A, R.M, and Z.Y) independently screened all titles, abstracts, and full texts for eligibility. Any discrepancies identified during the screening process were resolved through a consensus meeting (I.A, R.M, Z.Y, and IY). In order to identify further articles,

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secondary searches were performed by manually screening of bibliographies of identified articles and tracking the citing articles to identify studies that were not identified by the database search.

Selection criteria

We included only those randomized controlled trials (RCTs) which have determined the effect of "pulmonary rehabilitation" on dyspnea, exercise capacity, lung functions, fatigue, and QoL in patients with acute and/or chronic COVID-19.

Types of Participants

Studies were included that recruited patients with a confirmed diagnosis of COVID-19 (Acute COVID-19) or patients who recovered from COVID-19 but have long-term effects of COVID-19 or have symptoms for far longer than would be expected (Chronic COVID-19). The eligibility of the study was confirmed by reviewing the inclusion criteria of the study.

Types of Interventions

Studies determining the effects of PR in COVID-19. We grouped PR according to the mode of delivery: telerehabilitation (PR delivered via an online platform) and face-to-face PR.

Types of Comparators

We included those studies which have one control group. In the multi-arm study design, all comparators were included.

Types of Outcomes

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Mean change from baseline to post-intervention of outcomes related exercise capacity (6-minute walk test (6MWT)), lung functions (Forced vital capacity (FVC)), dyspnea (Dyspnea severity index (DSI), multidimensional dyspnea, Dyspnea 12 (D-12), modified Medical Research Council (mmRC)), fatigue (Borg scale of perceived exertion), and quality of life (Short-Form Health Survey-12 or 36 (SF-12, SF-36), St. George's Respiratory Questionnaire (SGRQ), and EuroQuality-5Dimensions-3Levels questionnaire (EQ-5D-L3)) were included. Articles that do not demonstrate the FVC in liters (L) were excluded from the meta-analysis. We have also determined any adverse or unexpected symptoms experienced by patients during PR.

We excluded studies (i) addressing other coronavirus diseases (severe acute respiratory syndrome [SARS] or Middle East respiratory syndrome [MERS]); (ii) studies written in a language different from English; (iii) full-text unavailability (i.e. posters and conference abstracts); and, (iv) review papers and letter to the editor.

Risk of bias assessment

Cochrane Risk of Bias assessment tool (Review Manager version 5.4.1) was used to determine the risk of bias of RCTs [22, 23]. The assessment tool includes random sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, intention-to-treat analysis, and description of exclusions and losses. Each domain was categorized as “Unclear”, “Low” or “High” bias risk. Studies were considered moderate to high quality if there was a low risk of bias in three or more than three domains [22]. Visual inspection of the funnel plots and Egger’s regression asymmetry tests were used to assess publication bias [24].

Data extraction

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The main characteristics of the selected studies were summarized in microsoft excel table. The following data were extracted: 1) first author; 2) publication year; 3) nationality; 4) population and number of patients included; 5) comorbidities; 6) ventilatory support; 7) length of inpatient stay; 8) type of PR; 9) outcome measures; and 10) main findings. Data extraction and quality assessment were independently performed by two reviewers (I.A and Z.Y), and inconsistencies were solved by consensus or by involving a third reviewer (I.Y).

Statistical Analysis

The results of the included studies were reported as mean and standard deviation or median and interquartile range. When data were provided as median and range, we converted median and interquartile range to mean and standard deviation using appropriate statistical formulas[25, 26]. WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to extract numerical data from figures. If the data could not be retrieved from the selected publications, requests were made to corresponding authors to provide the necessary data. We calculated the mean difference (MD) and their 95% confidence interval (CI) for studies that used the same outcome measure, whereas standard mean difference (SMD) and their 95% confidence interval (CI) were calculated for the studies that did not use the same outcome measure to evaluate the same construct. The I^2 statistic was used to assess the statistical heterogeneity of the included studies. The value of I^2 statistic above 25% indicates small, above 50% indicates moderate and more than 75% indicates a high degree of heterogeneity[27].Random effect model (if I^2 >50%) and Fixed effect model (if I^2 <50%) were used to determine the variability between the studies and to determine their effect on the intervention. A P-value of ≤0.05 is considered significant. Subgroup analyses to explore possible sources of heterogeneity were also performed. All the statistical analyses were performed using the "metaan" function in STATA (version 16.0, StataCorp LP, College Station, TX, USA).

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3. Results

Study Selection

A total of 2532 papers were retrieved from the selected electronic databases. In addition, five studies were identified by hand-searching the included papers' reference lists. Six hundred and forty-eight duplicate studies were identified through an endnote duplicate citation checker and were removed. Consequently, 1889 identified records were screened for title and abstract by two independent reviewers for eligibility, of which 1828 were excluded. The remaining 61 articles were screened for full text and eight studies [18, 28-34] were included in the review for final evaluation, as illustrated by the PRISMA flowchart in Figure 1.

****Figure 1 Here****

Study Characteristics

The main characteristics of these studies are described in detail in Table 1. Among the selected RCTs, five studies[18, 28, 30, 33, 34] have determined the effect of PR on patients with acute COVID-19 whereas three studies [29, 31, 32] determined on patients with chronic COVID-19. The selected studies were examined in terms of study quality, purpose of the studies, study characteristics, outcome measures, and main results.

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A total of 449 subjects were analyzed, of which 257 were acute COVID-19 and 192 were chronic COVID-19 patients. Regarding mode of treatment, three studies [18, 31, 34] delivered PR face-to-face while 5 studies [28-30, 32, 33] delivered via telerehabilitation. The number of sessions delivered via telerehabilitation varies between 1 and 12 whereas the number of sessions delivered face-to-face varied between 2 and 6 weeks.

Seven studies [18, 28-33] investigated the exercise capacity using the 6-minute walk test while five studies [30, 31, 33-35] reported the effect of PR on dyspnea. Four studies [18, 29, 31, 32] have determined the effect of PR on lung functions, four studies [28, 30, 33, 35] on fatigue, and four studies[18, 29, 31, 34] on quality of life. The length of in-patient stay varies between 19.7[31] to 26.18[29] mean days and the patients who used ventilatory support during their active course of disease ranged between 42[31] to 103[29] days. PR varies between 1[28] to 6[18] weeks with 2-5 sessions per week for acute COVID-19 and 2[31] to 12[32] weeks with 2-5 sessions per week for chronic COVID-19.

**** Table 1 Here****

Details of Intervention:

Although PR varied in detail, six trials used respiratory muscle exercise with or without endurance training[18, 29-31, 33, 34]. Two studies[18, 31] used device-based threshold positive expiratory pressure, and four studies[29, 30, 33, 36] used airway cleaning exercises to improve mucus clearance. Lower limb muscle strength exercises were used in one study to improve muscle mass and strength, and stretching activities were used in another study to improve body posture and flexibility[18, 29].

Risk of bias

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More than 75% of RCTs presented with random sequence generation and concealment of allocation. All the selected RCTs have blinded the outcome assessors and have described the reason for exclusions and losses. Only 50% of studies have blinded the personal and participants and only 25% of studies performed the intention to treat analysis (Supplementary file, Figure 1-a). All of the selected RCTs were of moderate to high quality (Supplementary file, Figure 1-b). Egger's regression asymmetry test shows no evidence of publication bias (p =0.32).

Effects of pulmonary rehabilitation

Exercise Capacity

Seven studies [18, 28-33] compared PR versus control in exercise capacity (6MWT). The PR produced significant improvement in exercise capacity in patients with COVID-19 as compared to the control group (8 studies, MD 65.85 m [95% CI, 42.86 to 88.83; p<0.001]) with a high degree of heterogeneity (I^2=80%) (Figure 2). The sub-group analysis according to the stage of disease revealed that PR is effective in improving exercise capacity in both acute (5 studies, MD 82.69 [95% CI, 56.30 to 109.07, p<0.001]) and chronic COVID-19 patients (3 studies, MD 44.16 [95% CI, 20.30 to 68.02, p<0.001]) as compared to control group (Figure 2). However, the improvement in patients with COVID-19 patients is significantly better than the patients with chronic COVID-19 (p=0.03). Both mild (6 studies, MD 72.30 [95%CI, 42.76 to 101.85, p<0.001]) and moderate/severe (2 studies, MD 49.63 [95%CI, 25.96 to 73.31, p<0.001]) patients can get benefits from PR program and PR program is superior to no intervention in improving exercise capacity in patients with COVID-19 (Figure 2). Both face-to-face (2 studies, MD 41.46 [95%CI, 24.28 to 58.63, p<0.001]) and telerehabilitation (6 studies, MD 75.95 [95%CI, 49.05 to 102.84, p<0.001]) PR program is

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effective in improving exercise capacity in patients with COVID-19. Patients can get significant benefits, as compared to no intervention, from even two weeks of PR program (5 studies, MD 78.15 [95%CI, 48.21 to 108.09, p<0.001]) (Figure 2).

****Figure 2 Here****

Dyspnea

Five studies [30, 31, 33-35] compared PR versus control in dyspnea. The PR has resulted in a significant reduction in dyspnea in patients with COVID-19 as compared to the control group (5 studies, SMD -2.11 [95% CI, -2.96 to -1.27; p<0.001]) (Figure 3). Both mild and moderate/severe patients can get benefits from face-to-face and telerehabilitation PR programs and PR program is superior to no intervention in reducing dyspnea in patients with both acute (4 studies, SMD -2.42 [95% CI, -3.12 to -1.71, p<0.001]) and chronic COVID-19 (1 study, MD -0.88 [95% CI, -1.51 to -0.26, p<0.05]) (Figure 3). Patients can get significant benefits, as compared to no intervention, from even two weeks of PR program (4 studies, MD -5.02 [95% CI, -6.54 to -3.51; p<0.001]) (Figure 3).

****Figure 3 Here****

Lung Functions

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Four studies [18, 29, 31, 32] compared PR versus control in FVC. No significant difference was found between the PR and control group (3 studies, MD 0.12 L [95%CI, -0.05 to 0.29, p>0.05]) with a small degree of heterogeneity (I^2 =36%) (Figure 4). Sub-group analysis revealed that only face-to-face PR (1 study, MD 0.26 L [95%CI, 0.04 to 0.48, p<0.05]) is effective in improving FVC in acute patients with mild symptoms. No significant difference was found between telerehabilitation and control group in improving FVC in chronic patients with severe symptoms (2 studies, MD 0.03 L [95%CI, -0.11 to 0.17, p>0.05]) (Figure 4). One trial[31] reported FVC % predicted value and was excluded from the analysis.

****Figure 4 Here****

Fatigue

Four studies[28, 30, 33, 35] have determined the effect of PR on fatigue using the Borg Rating of Perceived Exertion (RPE) scale. They have determined the effect of PR delivered via telerehabilitation on fatigue in acute patients with mild symptoms. A significant difference in favor of PR was found in reducing fatigue as compared to control group (4 studies, MD -2.42 [95%CI, -2.72 to -2.11, p<0.05]) (Figure 5).

****Figure 5 Here****

Quality of Life

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Four studies [18, 29, 31, 34] have determined the effect of PR on QoL, using varied inventories, including SF-36, SF-12, SGRQ and Eq-5D-3L. Liu et al., [18] adopted the SF-36 scale but did not report the overall score, and was excluded from the analysis. No significant difference was found between the PR and control group (3 studies, SMD 1.18 [95%CI, 0.46 to 2.81, p>0.05]) (Figure 6). However, Sub-group analysis revealed that face-to-face PR for 2 weeks is effective in improving QoL in patients with COVID-19 (1 study, SMD 2.89 [95%CI, 2.04 to 3.75, p<0.05]) (Figure 6).

****Figure 6 Here****

Safety of PR program

Five studies [28-30, 32, 33] (60% in acute COVID-19 patients and 66% in chronic COVID-19 survivors) reported data on safety and feasibility; however, in those that did, no adverse events related to PR were reported. PR was found to be safe and feasible for acute/chronic patients with COVID-19.

4. Discussion

This is the first systematic review and meta-analysis that included eight randomized controlled trials with 449 participants evaluating the safety and efficacy of PR in patients with acute and/or chronic COVID-19. Our meta-analysis revealed that the PR program is safe and effective in improving exercise capacity and dyspnea in patients with both acute and chronic COVID-19 with mild to severe symptoms

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whereas, fatigue and FVC were significantly improved in acute COVID-19 patients with mild symptoms and PR superior to no exercise program. However, the effect of PR on QoL was inconsistent across studies.

Regardless of the types of interventions (face-to-face or telerehabilitation, device-based/airway cleaning exercise or not, endurance/aerobic training or not), all studies found that PR significantly improved exercise capacity, despite significant heterogeneity in baseline 6-MWT data. The effect size produced by PR on exercise capacity (65.85 m) exceeded the minimal clinical important difference (MCID) of 25–30 m for 6MWT in patients with chronic obstructive pulmonary disease (COPD), given MCID for COVID-19 has not been established yet[3]. The effect was also comparable to 56.7 m for patients recovered from SARS[37] and 43.9m for patients with COPD with severe lung impairments[38]. The sub-group analysis revealed that the improvement in exercise capacity in patients with acute COVID-19 is higher than in patients with chronic COVID-19 (82.69 m vs 44.16 m). The reason for this might be that there is more room/space for natural recovery and improvement in the acute stage of disease and early inpatient PR is usually associated with substantial motor, respiratory, and functional improvement in patients with COVID-19 [16, 20, 39, 40]. Therefore, it is recommended to start PR as early as possible to achieve large and more sustained benefits. Patients with mild and moderate/severe symptoms can also get benefits from the PR program. The pooled mean difference for patients with moderate/severe symptoms is greater than for COPD patients with severe lung impairments (49.63 vs 43.9m) [38].

Shortness of breath is observed due to the damage and inflammation caused by COVID-19 at the cellular level, and this may even continue for a while after the disease. Our analysis showed that dyspnea is significantly reduced in acute and chronic patients with COVID-19 having mild and moderate/severe symptoms after PR as compared to control. Our sub-group analysis revealed that PR effectively reduced

dyspnea in both acute COVID-19 (-5.34) and chronic COVID-19 patients (-3.60). PR is also effective in reducing the rate of perceived exertion in patients with COVID-19. The results are in line with previous studies which reported that PR resulted in improvements with large effect sizes in dyspnea, physical capacity, quality of life, fatigue, and depression in both mild/moderate and severe/critical COVID-19 patients [3, 18, 20]. The decrease in dyspnea perception during exercise training might be due to physiological adaption to exercise training[3].

COVID-19 has a direct association with peripheral muscle and respiratory muscle integrity and is characterized by impaired lung functions[7]. Patients discharged after a severe illness due to COVID-19 may experience post-intensive care syndrome that impacts the mental health and quality of life of patients[41]. Studies reported FVC (parameter for the ventilation capacity) and QoL, in different formats with conflicting results. There was no significant difference between the PR and control group in improving FVC and QoL. However, sub-group analysis revealed that face-to-face PR is effective in improving FVC and QoL in patients with COVID-19. The reason for this might be that majority of the included studies delivered PR via telerehabilitation and different types of telemonitoring options (e.g., mobile phone, videoconference, WeChat voice calls, text messages, and YouTube) may have influenced the telerehabilitation outcomes. Also, the included studies presented heterogeneity in participants' demographic and clinical characteristics, stage, and severity of disease. Further RCTs are required for a robust conclusion on the effect of PR on FVC and QoL.

Study limitations, strengths, and future implications

To the best of our knowledge, this is the most comprehensive systematic review with meta-analysis that determined the effect of PR on exercise capacity, lung functions, dyspnea, fatigue, and QoL in patients with COVID-19. The most important limitation of this review is that it

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cannot draw conclusions about the mechanisms of PR because there was methodological and clinical heterogeneity among the included studies regarding duration and intensities of PR, number of sessions, and level of initial severity. This may be due to the fact that the optimal PR protocol for COVID-19 still has yet to be established and different forms of PR with different duration may produce some bias. Secondly, participants across studies varied in underlying comorbidities and age. Future studies are required with higher methodological quality, larger sample sizes, and other relevant outcomes such as satisfaction, level of functional independence, peripheral and/or respiratory muscle strength, costs, and mortality to better understand the role of PR in the management of respiratory and physical disorders caused by COVID-19.

5. Conclusion

Evidence from studies indicates that PR program is superior to no intervention in improving dyspnea, exercise capacity, lung functions, and fatigue in patients with COVID-19. PR appears to be safe and beneficial for both acute and chronic COVID-19 patients. Accordingly, PR appears to be valuable in the management of both mild/moderate and severe/critical COVID-19.

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Tables and figures

Figure legends

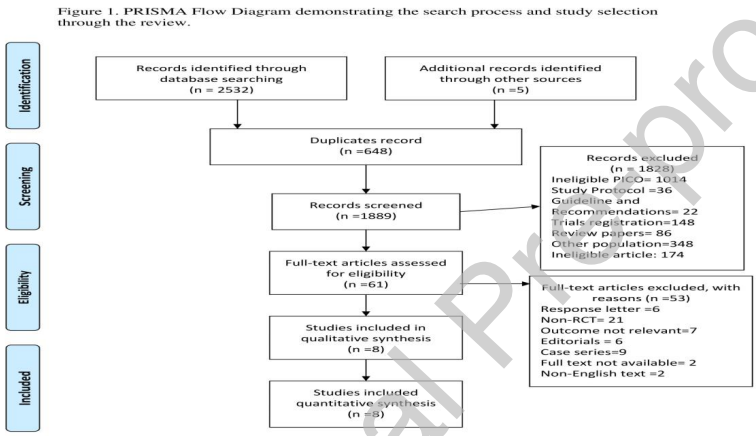


Figure 1: PRISMA flow diagram demonstrating the search process and study selection through the review.

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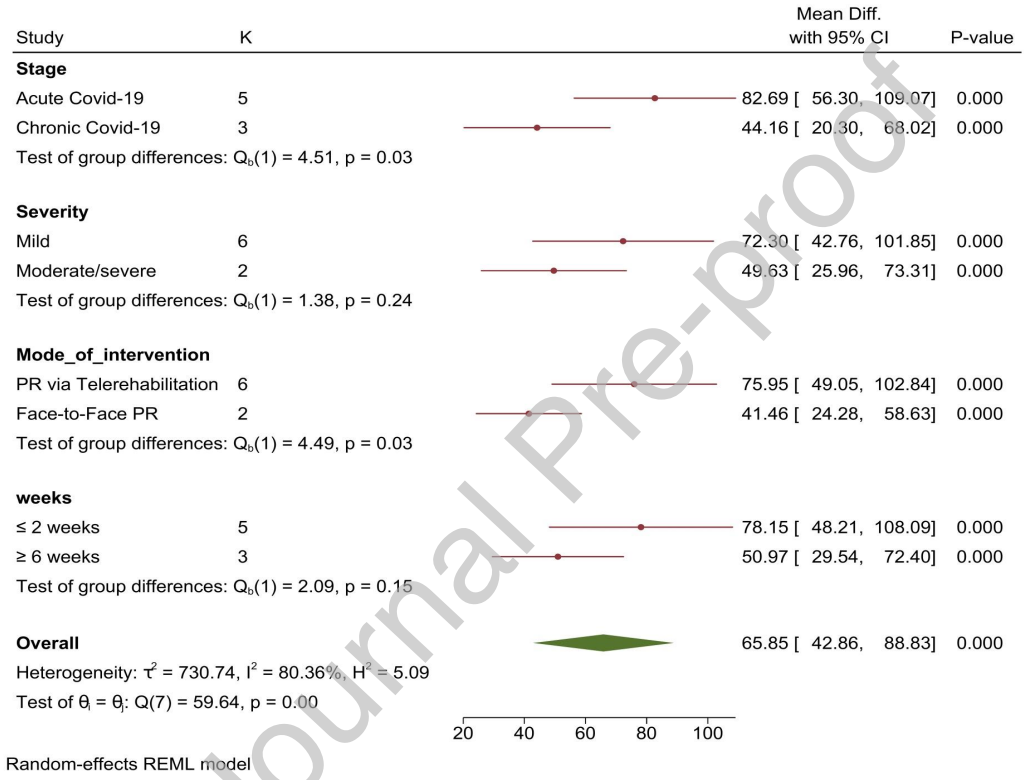


Figure 2: Mean difference of change in 6-MWT between 7 studies after intervention from baseline.

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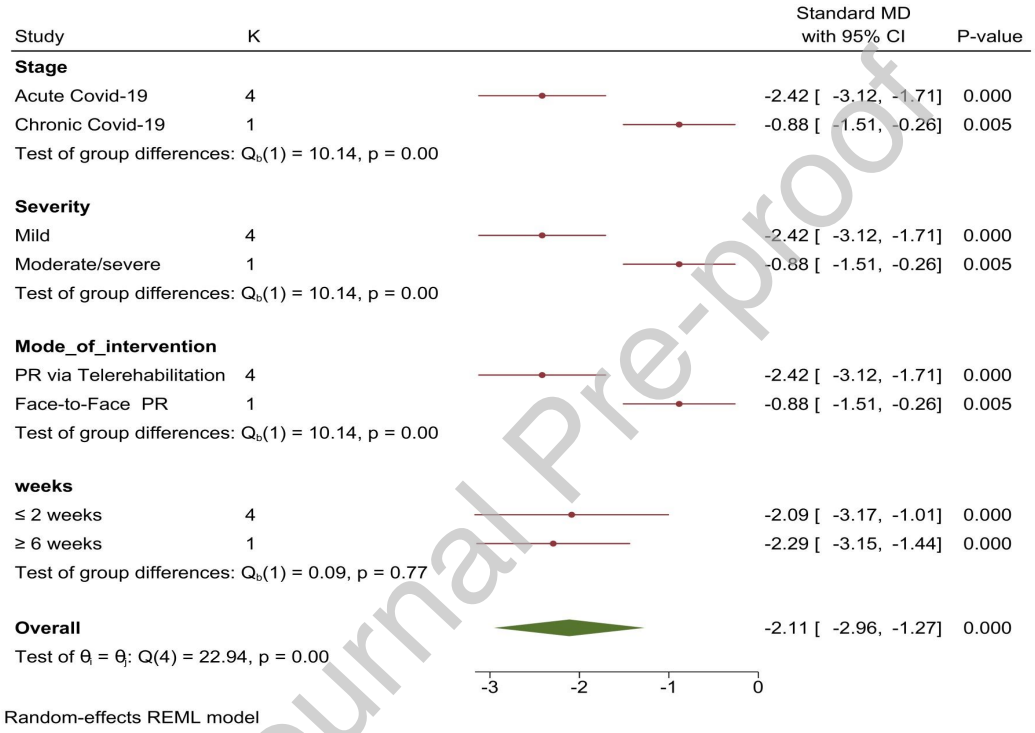


Figure 3: Standard mean difference of change in dyspnea between 5 studies after intervention from baseline.

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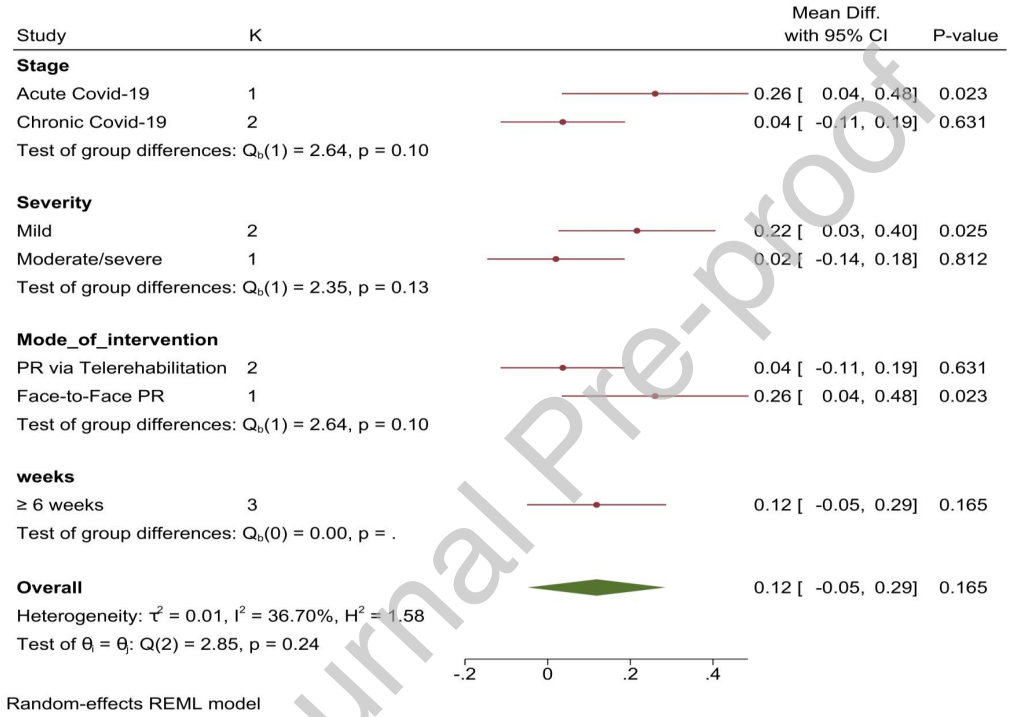


Figure 4: Standard mean difference of change in lung functions between 3 studies after intervention from baseline.

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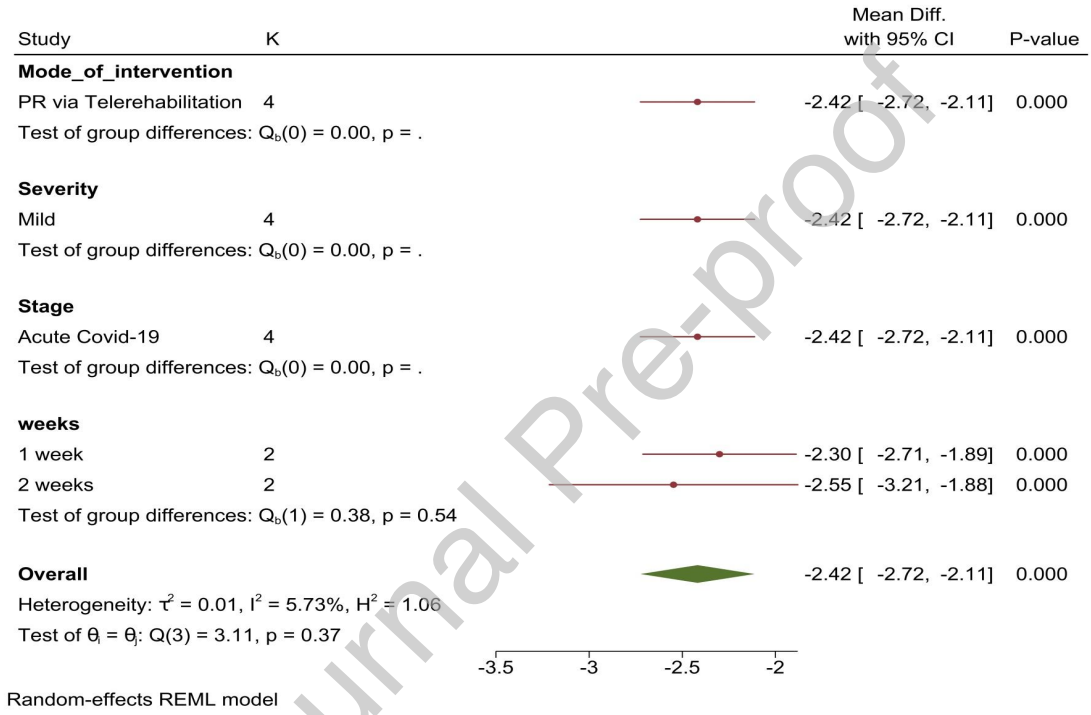


Figure 5: Mean difference of change in fatigue between 4 studies after intervention from baseline.

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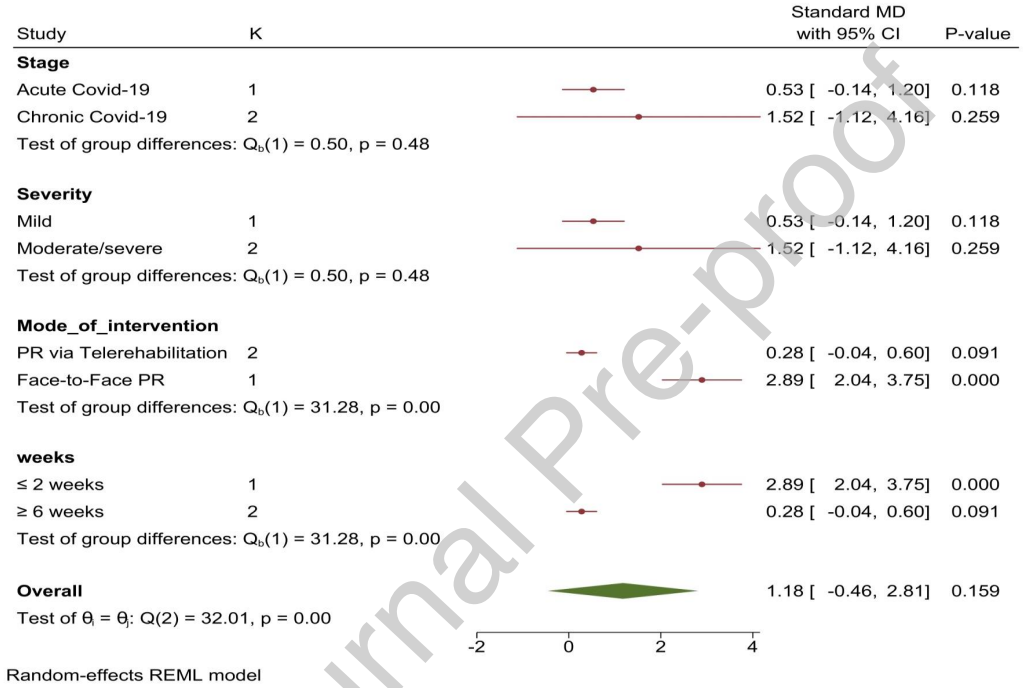


Figure 6: Standard mean difference of change in quality of life (QoL) between 3 studies after intervention from baseline.

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Table 1: Characteristics of the studies in the systematic review and meta-analysis.

Author, Country, Year, Stage, and Severity	Sample size and Comorbidities N (IG/CG)	Ventilatory support used during illness. N (IG/CG)	Length of inpatient stay Mean+SD Days	Interventions	Duration / Session	Outcomes measures	Results
Li et al., China, 2021 Chronic Moderate/severe	118 (59/61) - Heart Disease - Hypertension - Diabetes - Obesity - Lung disease	103 (49/54)	26.18 (15.25)	Pulmonary Rehabilitation	-Breathing control and thoracic expansion, aerobic exercise, and LMS exercises are specified in a 3-tiered exercise plan with difficulty and intensity scheduled to increase over time. -Exercise program was 40-60 minutes per session, with 3-4 sessions per week, for a total of 6 weeks.	- 6MWT - PFTs - HRQOL - Borg RPE - Squat Test	After 6 weeks of PR program, exercise capacity, dyspnea, lung functions, and quality of life were significantly improved in intervention group as compared to control group ($p<0.001$).

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Liu et al., China, 2020 Acute Mild	72 (36/36) - Hypertension - Diabetes - Osteoporosis	Not reported	Not reported	Pulmonary Rehabilitation	-Respiratory muscle training (device-based: threshold PEP); Cough exercise; diaphragmatic training; stretching exercise; home exercise -10 minutes/session, 2 sessions per week for 6 weeks.	- PFTs - 6MWT - SF-36 scores - FIM - SAS anxiety - SDS depression.	After 6 weeks of pulmonary rehabilitation program, exercise capacity, lung functions, and quality of life were significantly improved in intervention group as compared to control group ($p<0.001$). The SAS and SDS scores in the intervention group decreased after the intervention, but only anxiety had significant statistical significance within and between the two groups.
Blanco et al., Spain, 2021 Acute Mild	36 (18/18)	Not reported	Not reported	Telerehabilitation	Strengthening exercise program; 60 minutes/session, one session/day, for 1 week.	- 6MWT - STST - Dyspnea	After 1 week of telerehabilitation program, exercise capacity, muscle performance, and dyspnea were significantly improved in intervention group as compared to control group ($p<0.001$).
Gerez et al., Spain, 2021 Acute Mild	38 (19/19)	Not reported	Not reported	Telerehabilitation	Breathing and airway cleaning exercise program were 60 minutes per session, with 2 sessions per day, for 1 week.	- 6MWT - 30 STST -Dyspnea	After 1 week of telerehabilitation program, exercise capacity, muscle performance, and dyspnea were significantly improved in intervention group as compared to control group ($p<0.001$).

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Pehlivan et al., Turkey, 2021 Acute Mild	34 (17/17)	3 (1/2)	Not reported	Telerehabilitation	- Breathing exercises, active breathing techniques, lower and upper limb exercises, walking and wall squat exercises, delivered as a synchronized exercise program via videoconferencing; three sessions/week, 6 weeks.	- 30 STST -Dyspnea -Fatigue - Quality of life (SGRQ)	A significant improvement was observed in intervention group in terms of dyspnea (P= 0.035), 30STS (P= 0.005),) and SGRQ scores.
Abodonya et al., Saudi Arabia, 2021 Chronic Moderate/severe	42 (21/21)	42 (21/21)	19.7±8.6	Inspiratory muscle Training+ Breathing exercise	Breathing exercise (device-based: threshold PEP) 2 times daily for 2 weeks while intervention group received additional 2 sessions of IMT daily for 5 days a week for 2 weeks.	- PFTs - DSI - HRQoL - 6MWT	Two weeks of pulmonary rehabilitation program has significantly improved exercise capacity, lung functions, and dyspnea in intervention group (FVC%, P=.047, FEV1%, P=.039, DSI, P=.001, QOL, P<.001, and 6-MWT, P<.001), whereas the control group displayed nonsignificant changes (P>.05).

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Amaral et al., Brazil, 2022 Chronic Mild	32 (12/10) -Hypertension - Diabetes -Obesity -Respiratory disease -cardiovascular disease	Not reported	Not reported	Telerehabilitation	Resistance and aerobic exercise three sessions/week and aerobic exercise five sessions/week, for 12 weeks	-6MWT -FTSTS -Grip strength -PFTs	Both groups similarly increased ($P < 0.001$) forced vital capacity (absolute and % of predicted), forced expiratory volume in the first second (absolute and % of predicted), and handgrip strength during follow-up. However, only exercise group increased MIP (24.7 ± 7.1 cmH2O, $P < 0.001$), MEP (20.3 ± 5.8 cmH2O, $P = 0.021$), and MEP % pred (14.3 ± 22.6 %, $P = 0.042$) during follow-up.
Blanco et al., Spain, 2022 Acute Mild	77 (55/22)	Not reported	Not reported	Telerehabilitation	Exp 1 = strengthening exercise program; one session/d, 7 d/week, 2 weeks Exp 2 = breathing and airway cleaning exercise program; one session/d, 7 d/week, 2 weeks	-6MWT -VASF -Dyspnea (MD-12) - 30STST -Borg scale	All the outcome measures were significantly improved in exercise group as compared to control group ($p < 0.05$). The greatest effect sizes were found in the Borg Scale (R2 = 0.548) and MD-12 questionnaire (R2 = 0.475).

Abbreviations: PFTs: Pulmonary function tests; 6MWT: Six-minute walk test; HRQOL: Health-related quality of life; SF-36 scores: Short Form 36 Health Survey Questionnaire (SF-36); FIM: Functional Independence Measure; SAS anxiety: Self-Rating Anxiety Scale (SAS); SDS

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depression: Self-Rating *Depression* Scale; 30STST: 30-second sit to stand test; DLCO: Diffusing capacity for carbon monoxide; Borg RPE: Borg Rating of Perceived Exertion; DSI: Dyspnea severity index; FTSTS: Five-time sit to stand test; MD-12: Multidimensional dyspnoea-12; VASF: Visual analogue scale Fatigue; SGRQ: Saint George Respiratory Questionnaire.

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