The effect of exercise rehabilitation on COVID-19 outcomes: a systematic review of observational and intervention studies

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Received: 17 April 2022 / Accepted: 19 May 2022 / Published online: 28 June 2022
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Abstract
Purpose Disturbance to physical and psychological characteristics among COVID-19 survivors are not uncommon complications. In the current systematic review, we aimed to investigate the role of exercise rehabilitation programs, either in acute or post-acute phase, on COVID-19 patients’ outcomes.

Methods A systematic search was conducted in November 2021 of Web of Sciences, PubMed-Medline, Google Scholar, and Scopus. Observational and intervention studies on COVID-19-infected patients undergoing a rehabilitation program including any type of exercise were included if they reported physical or psychological factors as outcomes. The Cochrane risk of bias tool for randomized controlled trials and Joanna Briggs Institute (JBI) critical appraisal checklist were used by two independent reviewers.

Results A total number of 469, and 957 patients were included in 9 intervention studies, and 14 observational studies, respectively. Most factors reported by studies as outcomes fell in the categories of exercise capacity, respiratory function, as well as psychological aspects. The reported outcomes in almost all studies, disclosed the overall beneficial role of exercise rehabilitation in improving the outcomes.

Conclusion The current review demonstrated that exercise rehabilitation generally could have a beneficial role in improvement of both physical and psychological related outcomes. As the best onset time, and FITT components are not yet completely clear, further large, well-designed RCTs are suggested to provide details of exercise rehabilitation program.

Keywords Exercise · Rehabilitation · SARS-Cov-2 · COVID-19 · Systematic review

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| BI | Barthel index |
| CPET | Cardio-pulmonary exercise test |
| DLCO | Diffusing capacity for carbon monoxide |
| FEV1 | Force expiratory volume in 1 s |
| FITT | Frequency, intensity, time and type |
| FVC | Forced volume capacity |
| hACE-2 | Human angiotensin-converting enzyme-2 |
| MCID | Minimal clinically important difference |
| MEP | Maximum expiratory pressure |
| mMRC | Modified Medical Research Council |
| MP | Maximum inspiratory pressure |
| NICE | The National Institute for Health and Care Excellence |
| PEFR | Peak expiratory flow rate |
| PEmax | Maximum expiratory pressure |
| PLmax | Maximum inspiratory pressure |
| PRISMA | The Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| ROBVIS | Results of the risk of bias visualization |
| SARS | Severe acute respiratory syndrome |
| SPPB | Short physical performance battery |
| STS | Step test score |
| STSS | Sit to stand score |
| TLC | Total lung capacity |
| TLCO% | Transfer factor for lung carbon monoxide |
| 6MWT | Six minutes’ walk test |
| 30STS | Thirty-second sit-to-stand test |

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**Introduction**

By the end of February 2021, more than 430 million people have been recognized as confirmed cases with SARS-CoV2 infection. In addition, after almost 2 years of COVID-19 pandemic, this ongoing public health problem has been responsible for more than 5.9 million deaths globally [1].

As the number of confirmed cases with COVID-19 increases, the pressure posed to global health and economy will become more evident [2, 3]. Not only is this due to increase in mortality, but also the result of increase in long-term health consequences among recovered cases [3].

A significant number of patients with COVID-19 suffer from prolonged symptoms [4]. Existing research indicates that patients with different age group as well as diverse severity of disease may experience persistent symptom [5].

Although the evidence suggests that efficacious and trustworthy vaccines may play a crucial role in terminating the pandemics [6], potential of high mutation rate within SARS-CoV-2 genome could make it more challenging [7]. Furthermore, long COVID still seems to exist as a significant complication of the disease [5].

Finding the most effective therapeutic interventions is still emerging with a variety of ongoing studies [8]. Besides that, it is likely, along with the primary prevention i.e., using vaccine, to combat the pandemic [7], the rehabilitation programs as a tertiary prevention could help to alleviate the huge health adverse effects due to COVID-19 [9], and to decrease the disease burden [10].

The evidence suggest that exercise could play a fundamental role in rehabilitation and restoring the normal life among COVID-19 survivors. In this sense, improvement in lung function, immunity enhancement by cytokine regulation, reduction in oxidative stress, as well as intestinal flora modulation were theoretically introduced [2]. On the other hand, inactivity has proposed as a novel risk factor for increasing COVID-19 duration [11]. In addition, sports participation was associated with lower rate of COVID-19 complication [12].

As the deterioration in physical and psychological characteristics among COVID-19 survivors are not uncommon complications [10], we aimed in this systematic review to investigate the role of exercise rehabilitation programs, either in acute or post-acute phase, on physical and psychological outcomes among COVID-19 patients.

**Methods**

This systematic review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The protocol was registered to PROSPERO (CRD42022301087).

**Search strategy**

Web of Sciences, PubMed-Medline, Google Scholar, and Scopus were searched systematically between December 2019 and November 2021 in English language. The combination of (“physical activity” OR “exercise” OR “physical inactivity” OR “sedentary behavior” OR “life-style” OR “sports”) with (“COVID-19” OR “SARS-CoV-2” OR “SARS-CoV-2”) were defined as the search strategy.

**Inclusion and exclusion criteria**

All published observational and intervention studies on COVID-19-infected patients undergoing an exercise rehabilitation program were included if they met the following inclusion criteria: 1—Studies conducted on patients with confirmed diagnosis of COVID-19 regardless of the severity, either with or without comorbidity. 2—Rehabilitation programs included any type of exercise regardless of onset time, and duration of program. 3—Studies have reported either physical or psychological factors as outcome. All other study types (e.g., case reports, case series, qualitative, reviews, commentaries and editorials) were excluded.

**Eligibility and data extraction**

The title and abstract of studies, found based on the above strategy, were screened by two independent investigators (FH & BM) and a third one (MS) as consultant in specific disagreement cases. Full texts of eligible studies were reviewed.

The previously designed data extraction sheet including the name of first author, study design, sample size, methodology, sex and age range of patients, onset and type of rehabilitation, outcome definition and assessment time was used.

**Quality assessment**

For intervention and observational studies, the Cochrane risk of bias tool for randomized controlled trials [14] and Joanna Briggs Institute (JBI) [15] critical appraisal checklist were
used, respectively. Two independent reviewers (BM & BT) were involved in quality assessment.

**Results**

As seen in Fig. 1, 5035 studies were identified initially through Web of Sciences, PubMed-Medline, Google Scholar, and Scopus databases. After duplicate removal, 3332 studies were remained. Title/abstract screening excluded another 3245 studies and 87 studies were selected for full-text review. Finally, 23 studies including fourteen observational and nine intervention studies met the inclusion criteria. Most factors reported by studies as outcomes fell in the categories of exercise capacity, respiratory function, as well as psychological aspects.

Risk of bias assessment revealed variation in scores of different domains through all studies. Table 1 and Fig. 2 illustrate the results of quality assessment of observational, and intervention studies, respectively. Results of The Risk of Bias VISualization (ROBVIS) [16] was utilized to demonstrate the results of quality assessment of intervention studies.

**Intervention studies**

A total number of 469 patients were included in nine intervention studies [17–25] (Table 2). The duration of rehabilitation programs was within the range of 5–42 days. Acute and post-acute rehabilitation were considered in six and three studies, respectively.

According to the National Institute for Health and Care Excellence (NICE), acute and post-acute phases were defined as within the first 4 weeks of symptoms onset, and more than 4 weeks of symptoms onset, respectively [26]. However, acute phase was considered as the first 40 days of...
symptoms onset in studies by Gonzalez-Gerez et al. [18], and Rodriguez-Blanco et al. [24]. This discrepancy was due to problems related to diagnostic testing caused by collapses in their health systems.

The reported outcomes in eight studies of nine disclosed the overall beneficial role of exercise rehabilitation in improving the outcomes.

Five studies by Gonzalez-Gerez et al. [18], Liu et al. [21], Mohamed et al. [22], Ozlu et al. [23], and Rodriguez-Blanco et al. [24] demonstrated the beneficial effects of acute exercise rehabilitation among COVID-19 patients. The reported severity was within mild to moderate in these studies.

In studies by Abodonya et al. [17], Liu et al. [20], and Tang et al. [25] exercise rehabilitation in post-acute phase was significantly effective in improving the physical (including both exercise capacity, and respiratory function) and psychological outcomes among the patients with either mild-to-moderate severity or severe to critically ill.

Andre et al. revealed that inpatient rehabilitation (including unsupervised physical activity) among older hospitalized patients with COVID-19 was ineffective to improve neither exercise capacity nor psychological aspects [19].

### Rehabilitation and exercise capacity

Six minutes’ walk test (6MWT), and thirty-second sit-to-stand test (30STS) were the most common tests evaluated as exercise capacity in included studies. The results demonstrated a significant improvement in favor of rehabilitation group. Sit to stand test, semi-tandem and side by side stand, as well as walking speed were considered as outcomes in study by Andre et al. [19] They have not reported significant difference between two groups.

### Rehabilitation and respiratory function

Spirometry outcomes and dyspnea scale were considered as the most common outcomes. Spirometry-related factors consisted of force expiratory volume in one second (FEV1), forced volume capacity (FVC), FEV/FVC%, and transfer factor for lung carbon monoxide (TLCO%). Borg scale and modified Medical Research Council (mMRC) were considered as dyspnea scale in two and one studies, respectively. All factors were significantly improved in favor of rehabilitation group.

### Rehabilitation and psychological aspects

Outcomes in this field generally were related to the quality of life, anxiety, and depression measured via questionnaire-based approach.

### Other outcomes

Only in one study, blood immune markers including leukocytes, lymphocytes, interleukins, IgA, and TNF-alpha were considered as outcomes. Although only changes in leukocytes, lymphocytes and IgA were reached statistical difference, improvement in all investigated factors was seen. All

| Table 1 | Results of quality assessment of included observational studies using the Joanna Briggs Institute (JBI) critical appraisal checklist |
|---------|---------------------------------------------------------------|
| Study   | Q1  | Q2  | Q3  | Q4  | Q5  | Q6  | Q7  | Q8  | Q9  | Q10 | Q11 |
| Cross-sectional | | | | | | | | | | | |
| Evaraerts et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Yes | Yes | Yes |
| Maniscalco et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Yes | Yes | Yes |
| Olezene et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Yes | Yes | Yes |
| Rosen et al. 2020 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Yes | Yes | Yes |
| Zampogna et al. 2021 | Yes | Yes | Yes | Yes | No  | No  | Yes | Yes | Yes | Yes | Yes |
| Zhang et al. 2021 | Yes | Yes | Yes | Yes | No  | No  | No  | No  | Yes | Yes | Yes |
| Cohort | | | | | | | | | | | |
| Chikhanie et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Daynes et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Hameed et al. 2021 | Yes | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Jiandani et al. 2020 | Yes | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Li et al. 2021 | No  | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Martin et al. 2021 | Yes | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Udina et al. 2021 | Yes | Yes | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
| Zha et al. 2020 | No  | No  | Yes | Yes | No  | No  | Yes | Yes | Not applicable | Yes | Yes | Yes |
differences were in favor of exercise rehabilitation except TNF-alpha [22].

**Observational studies**

A total number of 957 patients were included in 14 observational studies [27–40] (Table 3).

The duration of rehabilitation programs was within the range of 1–42 days. Acute and post-acute rehabilitation were considered in five and nine studies, respectively. The reported outcomes in all studies disclosed the overall beneficial role of exercise rehabilitation in improving the outcomes. All types of disease severity from mild to severe and critically ill patients were included in the studies. Only one study dealt with the rehabilitation of patients with persistent symptoms.

**Rehabilitation and exercise capacity**

Factors related to aerobic capacity, as well as strength and balance capacity were measured as outcomes in this field. Aerobic capacity-related factors, including 6MWT, shuttle
| Author and year | Design                      | Sample size (intervention/control ratio) | Age (year); mean (SD) | Participants                        | Exercise rehabilitation versus comparator | Rehabilitation duration | Onset of rehabilitation | Outcome(s)                                                                 |
|-----------------|-----------------------------|------------------------------------------|------------------------|-------------------------------------|------------------------------------------|-------------------------|-------------------------|----------------------------------------------------------------------------|
| Abodonya et al. 2021 [17] | Pilot clinical trial          | 42 (ratio: 1:1)                          | 48.05 (8.85)           | ICU admitted patients                | IBE + IMT [6 inspiratory cycles, threshold load with 50% of the MIP] vs. IBE | 2 weeks                 | Post-acute phase           | Exercise capacity (walking distance in 6MWT) \(P=0.028\)                 |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | Psychological aspect (Eq-5D-3L score) \(P=0.021\)                     |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | Respiratory function (FEV1%, FVC, DSI) \(P=0.041, P=0.043, P=0.032\) |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | All significant in favor of IMT group                                    |
| Andre et al. 2021 [19]   | Pilot clinical trial          | 11                                       | 86.6 (6.3)             | Hospitalized patients                | MATCH intervention: unsupervised validated physical activity | Mean: 9.3 days           | Acute phase              | Exercise capacity (including Sit to stand test, semitandem and side by side stand, walking speed) |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | Psychological aspects (including ADL, HAD anxiety/depression) Non-significant |
| Gonzalez-Gerez et al. 2021 [18] | Pilot randomized clinical trial | 38 (ratio: 1:1)                          | 40.79 (9.84), Control: 40.32 (12.53) | Mild cases                          | Home breathing exercise vs. control | 7 days                  | Acute phase              | Exercise capacity (including 6MWT, 30STST)                               |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | Respiratory function (including MD12, Borg Scale)                      |
|                 |                             |                                          |                        |                                     |                                          |                         |                         | All significant in favor of exercise group \(P<0.05\)                   |
| Author and year       | Design                        | Sample size (intervention/control ratio) | Age (year); mean (SD) | Participants                                      | Exercise rehabilitation versus comparator                                                                 | Rehabilitation duration | Onset of rehabilitation | Outcome(s)                                                                 |
|----------------------|-------------------------------|------------------------------------------|-----------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|----------------------------------------------------------------------------|
| Liu et al. 2020 [20] | Randomized clinical trial     | 72 (ratio: 1:1)                          | Intervention: 69.4 (8), Control: 68.9 (7.6) | Hospitalized patients                             | Respiratory muscle training, cough exercise, diaphragmatic training, stretching, and home exercise, (two sessions/week, once a day for 10 min) vs. no rehabilitation | 6 weeks                 | Post-acute phase          | Exercise capacity (including 6MWT), Psychological aspects (including SF36, SAS), Respiratory function (including FEV1, FVC, FEV/FVC%, TLCO%) All significant in favor of intervention group ($P < 0.05$) |
| Liu et al. 2021 [21] | Randomized clinical trial     | 140 (ratio: 1:1)                         | NA                    | Hospitalized mild COVID-19                       | Group psychological intervention + pulmonary rehabilitation exercise (including five-tone breathing and Baduanjin exercises) vs. conventional nursing methods | 1 month                 | Acute phase              | Psychological aspects (including SAI [$P < 0.001$] and PSQI Scores [$P < 0.01$]) All significant in favor of intervention group |
| Mohamed et al. 2021 [22] | Pilot randomized clinical trial | 30 (ratio: 1:1)                          | Intervention: 44.56 (4.25), Control: 35.25 (3.96) | Mild and moderate cases                          | Aerobic exercise with moderate intensity (3 sessions per week with duration of 40 min)                   | 2 weeks                 | Acute phase              | Psychological aspects (WURSS), blood immune biomarkers significant difference (WURSS, leukocyte, lymphocyte, and IgA) and non-significant difference (IL-6, IL-10, TNF-alpha) in favor of intervention group |
| Author and year       | Design                      | Sample size (intervention/control ratio) | Age (year); mean (SD) | Participants                                                                 | Exercise rehabilitation versus comparator                                                                 | Rehabilitation duration | Onset of rehabilitation | Outcome(s)                                                                 |
|---------------------|-----------------------------|------------------------------------------|----------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------|
| Ozlu et al. 2021 [23] | Randomized clinical trial    | 67 (ratio: 33:34)                         | Intervention: 36.48 (11.63) Control: 33.15 (11.90) | Hospitalized COVID-19 patients                                                  | The progressive and supervised muscle relaxation training, (twice a day) vs. routine care                          | 5 days                  | Acute phase             | Psychological aspects (including SAI, RCSQ) All significant in favor of intervention group ($P < 0.05$) |
| Rodriguez-Blanco et al. 2021 [24] | Pilot randomized clinical trial | 36 (ratio: 1:1)                           | Intervention: 39.39 (11.74) Control: 41.33 (12.13) | Mild-to-moderate cases                                                        | Resistance and strength training vs. control                                                                      | 1 week                  | Acute phase (within the first 40 days), outpatient                      | Exercise capacity (including 6MWT, 30STST) Respiratory function (Borg Scale) All significant in favor of exercise group ($P < 0.05$) |
| Tang et al. 2021 [25]  | Clinical trial              | 33                                       | 43.2 (10.4)          | 28 mild/moderate, 5 severe/critical cases                                     | Liuzijue exercise (a type of traditional Chinese mind body exercise including breathing training), once a day, 20 min | 4 weeks                 | Post-acute phase          | Exercise capacity (walking distance in 6MWT $[P = 0.02]$) Psychological aspects (including QOL: SF36-PF $[P = 0.014]$, SF36-RP $[P = 0.009]$, Anxiety: HAMA $[P < 0.001]$, Depression: HAMD $[P = 0.0032]$) Respiratory function (including MIP $[P < 0.001]$, PIF $[P < 0.001]$, diaphragmatic movement in deep breathing $[P = 0.009]$, Dyspnea: mMRC $[P = 0.022]$) All significant in favor of intervention group |
test, cardio-pulmonary exercise test (CPET), sit to stand score (STSS), step test score (STS), and 10-m walk test were measured in seven studies. Significant improvement in hand grip and quadriceps muscle strength reported in cohort and cross-sectional studies on 21, and 22 patients with severe–critically ill COVID-19, respectively. Tinetti balance test, Berg Balance Scale, Short Physical Performance Battery (SPPB), and Barthel Index (BI) were considered as balance factors in included studies. The overall results demonstrated significant improvement in favor of rehabilitation groups.

**Rehabilitation and respiratory function**

Dyspnea scores including Borg dyspnea scale, and spirometry factors including FEV1%, FVC%, total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), P/F ratio, peak expiratory flow rate (PEFR), maximum inspiratory pressure (PImax), maximum expiratory pressure (PEmax), as well as acute symptoms and oxygen requirement were considered as parameters of respiratory function in included observational studies.

**Rehabilitation and psychological aspects**

Questionnaire-based measurement of quality of life, anxiety, and depression were generally regarded as psychological outcomes. Improvement in psychological aspects were observed in all studies, although statistical significance was not reached in some studies.

**Discussion**

The current systematic review aimed to figure out the role of exercise rehabilitation on COVID-19 patients’ outcomes. Results of included studies generally have revealed the benefits of exercise rehabilitation. Overall, both physical and psychological related outcomes have improved by exercise rehabilitation.

The results are contrary to that of Connoly et al. who found that the benefit of post-discharge exercise-based rehabilitation on exercise capacity and health-related quality of life among 483 ICU survivors were inconclusive [41], but are broadly consistent with earlier systematic review study conducted by Goodwin et al., which has postulated that exercise and mobilization could have a substantial role in improving the outcomes among critical care admitted patients with severe respiratory illness. As they generalized the results to the cases with COVID-19 infection, they have concluded that exercise could make a significant
### Table 3: Summary of observational studies

| Author and year | Design | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes |
|-----------------|--------|----------------------------------|---------------------------------------|--------------|------------------------------------------------------|-------------------------|------------------------|----------|
| Chikhanie et al. (27) 2021 | Cohort | 42 including 21 COVID patients | 70.9 (10.6) | Severe COVID patients with at least one comorbidity including obesity, diabetes, cardiovascular, respiratory as well as cancer | Respiratory exercises, strengthening, and balance training. In some cases, walking, cycling and gymnastics may also be done | Mean: 27.6 (14.2) days | Post-acute phase | Significant ($P < 0.05$) improvement in Exercise capacity (Tinetti balance test, 6MWD, Handgrip and Quadriceps isometric (Kg)), Psychological aspects (Fatigue, Anxiety, Depression), and Respiratory function (FEV1%, FVC%, PImax, PEmax) Non-significant improvement in Psychological aspects (Quality of life, post-traumatic stress), Respiratory function (Percent of patients needed Oxygen therapy, Minimal SpO2 (%), End-of-test dyspnea (Borg)) |
| Author and year | Design     | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants                                                                 | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes                                                                 |
|-----------------|------------|----------------------------------|---------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------|------------------------|--------------------------------------------------------------------------|
| Daynes et al. 2021 [28] | Cohort     | 30                               | 58                                   | 26 hospitalized patients (21 patients with mechanical ventilation)             | Two sessions weekly, supervised rehabilitation program including aerobic exercise (walking/treadmill based), strength training of upper and lower limbs and online educational discussions | 6 weeks                 | Post-acute (mean of 125 days post infection) | Significant improvement in Exercise capacity (Incremental Shuttle Walking Test $P<0.01$, Endurance Shuttle Walking Test $P<0.01$) Psychological aspects (Montreal Cognitive Assessment $P<0.01$ Non-significant in Hospital Anxiety and Depression Scale $P=0.5$ Hospital Anxiety and Depression Scale $P=0.1$) |
| Everaerts et al. 2021 [29] | Cross-sectional | 22                               | 54.5 (47–61)                         | Hospitalized patients (15 ICU admitted patients)                              | Progressive endurance and resistance training including treadmill, cycle/arm ergometer, stair climbing, step, leg and chest press | 12 weeks                | Acute phase            | Significant improvement in Exercise capacity (including 6MWD, hand grip force, quadriceps force, work load and peak VO2 via CPET) and Respiratory function (including FEV1, TLC, DLCO, MIP, MEP). $P<0.05$ Deterioration in Psychological aspects (including HADS anxiety and depression score, MoCA, return to work) |
Table 3 (continued)

| Author and year       | Design | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes |
|-----------------------|--------|----------------------------------|---------------------------------------|--------------|--------------------------------------------------------|--------------------------|--------------------------|----------|
| Hameed et al. 2021    | Cohort | 106 (44: VPT/25: HPT/17:IE/20: no rehabilitation) | VPT: 60 (14), HPT: 57 (14), IE: 59 (20), none: 58 (18) | Persistent COVID-19 patients including mild to critically severe cases | Tele-medicine rehabilitation program including VPT, HPT, IE Vs. no rehabilitation | 2 weeks | Post-acute phase | Data on 53 patients with follow-up visits showed improvement in Exercise capacity (STSS, STS) in VPT, and HPT groups. In addition, STS changes were significant in IE group. Neither STSS changes nor STS changes were significant among patients with no rehabilitation |
| Jiandani et al. 2020  | Cohort | 278                              | ICU: 54.82 (13.09), SDU: 51.71 (14.57) | COVID-19 patients admitted in ICU and a step-down unit (SDU) of the hospital | Position change, Respiratory physiotherapy consist of deep breathing exercises, paced breathing, active cycle of breathing technique (ACBT), and diaphragmatic breathing | 7 days | Post-acute phase | Significant improvement in ICU mobility score (IMS) among ICU patients ($P=0.00$) and SDU patients ($P=0.00$) |
| Li et al. 2021        | Cohort | 13                               | Age range (50–85) | Severe and critical COVID-19 cases | Respiratory physiotherapy, positioning, mobility and IMT exercises | A range of 3–21 days, 2 sessions of 30–40 min in a day | Acute phase | Improvement in Respiratory function (P/F ratio, PEFR, MIP, and Borg Dyspnea Scale), and Functional outcomes (Medical Research Council Sum Score, the Physical Function in Intensive Care Test score, De Morton Mobility Index, and Modified BI) |
| Author and year | Design  | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes |
|-----------------|---------|---------------------------------|--------------------------------------|--------------|------------------------------------------------------|--------------------------|-------------------------|----------|
| Maniscalco et al. 2021 [33] | Cross-sectional | 95 (49 without comorbidity, 46 with comorbidity) | Comorbid patients: 65.3 (1.2), non-comorbid patients: 61.5 (1.6) | COVID-19 patients with and without comorbidity | 6 sessions/week: pulmonary rehabilitation program including progressive exercise training (upper and lower extremity strength and flexibility training, treadmill and outdoor walking and stationary cycling at moderate-to-high intensity according to dyspnea and fatigue symptoms), dietary and psychosocial counselling | 5 weeks (30 sessions) | Post-acute phase | Improvement in Exercise capacity (6MWD) and Respiratory function (FEV1, FVC, and DLCO%) in both groups of patients with or without comorbidity |
| Martin et al. 2021 [34] | Cohort | 27 (14: 13) | 61.5 (10.5) Case: 60.8 (10.4), control: 61.9 (10.7) | Severe, and critically ill cases | The synchronous telerehabilitation program including endurance exercises, upper and lower body strength training. Encouragement to perform unsupervised exercises three times a week, using the provided templates | 6 weeks | Post-acute phase | Significant difference of exercise capacity (STST change) between rehabilitation group and control ($P=0.004$) Non-significant difference of respiratory function (dyspnea) between rehabilitation group and control ($P=0.56$) |
| Author and year          | Design      | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes                                                                 |
|-------------------------|-------------|---------------------------------|--------------------------------------|--------------|------------------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------|
| Olezene et al. 2021     | Cross-sectional | 29                              | 60 (50.5–67.5)                       | Severe       | At least three hours per day, five days per week, individualized rehabilitation | Mean: 16.7 ± 7.8 days   | Post-acute phase          | Significant improvement in Exercise capacity (including Berg Balance Scale $P < 0.001$, 10-m walk test $P < 0.0001$, 6 MWTD $P < 0.001$, gait speed $P < 0.001$), Functional independence (including transfer and ambulation independence $P < 0.001$), and Functional communication measures. $P < 0.05$ |
| Rosen et al. 2020       | Cross-sectional | 12                              | Median: 56                          | COVID-19 inpatients | Inpatient telerhabilitation (included patient education, therapeutic exercises, and breathing techniques) | 1–2 sessions            | Acute phase              | None of the patients required increased oxygen supplementation or medical care after rehabilitation |
| Udina et al. 2021       | Cohort      | 33                              | 66.2 (12.8)                         | Survived COVID-19 patients. 60.6% of them were ICU admitted | A 30-min daily multicomponent exercise training including resistance, endurance and balance training | Up to 10 days           | Post-acute phase          | Significant improvement in Exercise capacity (including SPBB, BI, ability to walk unassisted, and single leg stance). $P < 0.05$ |
| Author and year              | Design    | Sample size (case/control ratio) | Age (years) [mean (SD)/median (IQR)] | Participants                                                                 | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes                                                                 |
|-----------------------------|-----------|----------------------------------|--------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------|
| Zampogna et al. 2021 [38]   | Cross-sectional | 140                              | 71 (61.5–78)                         | Recovered patients with negative RT-PCR test for SARS-CoV-2                    | Individually tailored training including both group and personal exercise programs with one or more of the following trainings; mobilization, active exercises and free walking, limb muscle activities, shoulder, and full arm circling, callisthenic, strengthening, balance exercise, paced walking, cycle-ergometer at low-intensity exercises (<3.0 METs), and chest physiotherapy | Median: 24.0 (19.0–34.0) days, 60 (38–84) sessions, 2.8 (1.0–3.8) daily sessions | Post-acute phase | Significant improvement in exercise capacity (including SPPB, \( P < 0.00 \) and BI, \( P < 0.001 \)) were identified. Also, the authors revealed significant reduction (\( P < 0.001 \)) in the proportion of patients were unable at admission to stand, to rise from a chair, and to walk |
| Zha et al. 2020 [39]        | Cohort    | 60                               | 54 (38–62)                           | mild, and no CT evidence of pneumonia on admission                           | The modified rehabilitation exercise (MRE), including Overhead Chest and Shoulder Stretch, Heel Raises and Upper Body Acupressure, Upper Body Rotation, and Hand Acupressure Massage | NA                      | Acute phase              | Improvement in All respiratory symptoms (including dry cough, productive cough, difficulty in expectoration and dyspnea) |
contribution to improve the physical outcomes. However, their finding regarding quality of life was under debate [42].

In a 2022 study by Barman et al., respiratory rehabilitation including either aerobic or respiratory muscle training has a positive effect on exercise capacity as well as pulmonary function among patients with Severe Acute Respiratory Syndrome (SARS) [43]. With respect to the minimal clinically important difference (MCID) of 20–30 m established for 6MWD, analysis of pooled data in the mentioned study revealed that 6MWD as a valid tool to determine the exercise capacity had been improved significantly higher than MCID [43]. The amount of such increase in all included studies were higher than previously reported MCID except in study by Tang et al. [25].

It is worth noting that a wide variety in the rehabilitation onset were used in included studies in our review. Although most of intervention studies focus on acute rehabilitation, post-acute rehabilitation was considered as a dominant approach in observational studies.

It seems there is still big controversy over the appropriate time of rehabilitation onset among COVID-19 patients. Chinese and Italian societies of rehabilitation did not recommend acute rehabilitation due to probable decrease in oxygen blood saturation [44, 45]. A similar conclusion was reached by Demeco et al. [46] In their study, severe and critically ill patients were recommended to postpone the respiratory rehabilitation until their status become more stable. In contrast, the results of the study by Goodwin et al. focusing on acute rehabilitation in critical care setting were pleasant [42].

The results of the current review revealed that acute rehabilitation in either mild to moderate [18, 21, 22, 24, 39, 40] or severe patients [8, 23, 29, 36] were associated with successful outcomes.

In addition, components of exercise prescription including frequency, intensity, time and type (FITT) were broadly varied through the studies. It is not yet completely clear what FITT components are of interest to COVID-19-affected patients.

Wittmer et al. have sounded a note of caution on exercise prescription for COVID-19 patients [47]. They concluded that exercise intensity must be adapted according to clinical status and stage of illness. Neither too much to be problematic nor too little to be ineffective. The challenges to determine the intensity are twofold. First, it should be compatible with patients with muscle strength decrement [48]. Second, the intensity should not be as vigorous as it poses a further pressure to respiratory system for the reason that SARS could happen to some mild-moderate patients [49].

The results of observational studies included in study by Wittmer et al. demonstrated that low-to-moderate intensity and low intensity were associated with good results in mild, and moderate COVID-19 patients, respectively. Early

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### Table 3 (continued)

| Author and year | Design | Sample size (case/control ratio) | Age (years) [mean (SD)/median [IQR]] | Participants | Exercise rehabilitation vs. comparator (if available) | Rehabilitation duration | Onset of rehabilitation | Outcomes |
|-----------------|--------|---------------------------------|-------------------------------------|-------------|----------------------------------------------------|------------------------|-----------------------|----------------------|
| Zhang et al. 2021 | Cross-sectional | 91 | NA | NA | Intensive exercise vs. control group | NA | Acute phase | Correlation between higher frequency of Baduanjin exercise and improvement in Psychological aspects including HAD anxiety (P = 0.65) and depression (P < 0.01) |

| BI | Barthel Index; CPET, Cardiopulmonary Exercise Test; DLCO, Diffusing Capacity for Carbon monoxide; FEV1, Forced Expiratory Volume in One second; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale; HAA, Hospital Anxiety and Depression Scale; HPT, Home physical therapy; IE, independent exercise program; MIP, Maximal Inspiratory Pressure; MEP, Maximal Expiratory Pressure; MoCA, Montreal Cognitive Assessment; P/F ratio, PaO2/FIO2; PEFR, Peak Expiratory Flow Rate; PEmax, Maximal Expiratory Pressure; PImax, Maximal Inspiratory Pressure; P/F ratio, PaO2/FIO2; SpO2, Pulse Oximeter Oxygen Saturation; SPPB, Short Physical Performances Battery; STS, Step Test Score; SSC, Sit To Stand Score; TLC, Total Lung Capacity; VO2, oxygen consumption; VPT, virtual physical therapy; 6MWD, 6 min walking distance |
mobilization was also related to better prognosis in severe to critical COVID-19 patients [47]. Similarly, included studies in our review revealed that progressive mild-to-moderate intensity could bring positive results.

Hassanodin et al. demonstrated that comorbidities should be considered in any rehabilitation. It is clearly affect the participation or progression of program [50]. It seems individualized rehabilitation approach is rational. According to position statement of Taiwan Academy, rehabilitation programs for patients with COVID-19 should adjusted according to clinical statuses. COVID-19 patients were categorized into the following groups: 1—mild severity without any risk factor, 2—mild severity with established risk factor, 3—moderate-to-severe severity, 4—ventilator-assisted cases without cognitive problem, and 5—ventilator-assisted cases with cognitive problem [51].

As there was a huge heterogeneity regarding the components of rehabilitation training, it is not possible to compare the results within the different frequency and duration of programs. Also, a large modes of workouts including breathing exercise, muscle relaxation training, aerobic, strengthening, stretching as well as balance training were used as exercise rehabilitation in included studies.

It is thought that the broad expression of Human Angiotensin-Converting Enzyme-2 (hACE-2) receptors in multiple organs could lead to wide extra-pulmonary manifestations in COVID-19 [52]. Most outcomes have been addressed by included studies were related to cardiopulmonary, and psychological factors. It seems the remaining extra-pulmonary manifestations including neurologic, gastrointestinal, hematologic, hepatic, and renal involvement should be more considered in future studies. Although study by Mohammed et al. demonstrated the benefits of exercise on some hematologic factors [52], the role of exercise in coagulopathy is relatively scarce. Previous research introduced the coagulopathy as the most important feature of hematologic manifestations in COVID-19 [53]. In this regard, Zadow et al. reported that mild-to-moderate exercise training might improve the coagulopathy problems associated with COVID-19. However, probably the opposite effect could be observed in high intensity exercise [54].

**Limitation**

In current study, there were huge heterogeneity in included studies. In addition to differences in FITT components of exercise, large variation in disease severity, as well as rehabilitation onset was observed. In addition, the measured outcomes were broadly different in each study. In light of these considerations, meta-analysis could not be performed. We have also included all studies determining the effect of exercise as a part of rehabilitation on COVID-19 outcomes. As the other non-exercise component of rehabilitation programs including either nutritional, or psychological consultation have been neglected, the results should be interpreted with some cautions.

**Conclusion**

Exercise rehabilitation generally could have a beneficial role in improvement of both physical and psychological related outcomes. As the best onset time, and FITT components are not yet completely clear, further large, well-designed RCTs are mandatory to provide details of exercise rehabilitation program.

**Author contributions** FH devised the project, the main conceptual ideas and proof outline. He also revised the drafted manuscript critically for important intellectual content. BM, MS, and BT contributed to study implementation. They drafted the manuscript. All the authors have read and approved the final version of the manuscript.

**Declarations**

**Competing interests** The authors declare no competing interests.

**Conflict of interest** All authors declare that they have no conflict of interest.

**Ethical approval** This study is a review type and ethical approval is not required.

**Informed consent** For this type of review study informed consent is not required.

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