Respiratory rehabilitation in patients recovering from severe acute respiratory syndrome: A systematic review and meta-analysis

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ABSTRACT

Background: With an increase in published reports on respiratory rehabilitation (RR) in severe acute respiratory syndrome (SARS), there is a need for a meta-analysis and systematic review to measure the effects of the RR in SARS.

Objective: Objective of the review was to evaluate the efficacy and safety of RR in patients recovering from SARS.

Methods: PubMed/ MEDLINE, CENTRAL, EMBASE, and Clinical Trial Registries were systematically searched (between January 1, 2003, to July 31, 2021) to identify all patients who received RR, at least for six days, following SARS. The primary outcome was exercise capacity [6-meter walking distance (6-MWD)], and secondary outcomes were change in pulmonary function test (PFT) parameters, activities in daily livings (ADLs), and quality of life (QoL). Meta-analysis was performed by using RevMan 5.4.

Results: Twenty-one observational studies, including eight comparative studies, were included. Eight comparative studies participated in quantitative meta-analysis. The intervention group, who received RR, improved significantly in exercise capacity (6-MWD) [mean difference (MD):45.79, (95% CI:31.66−59.92)] and PFT parameters, especially in forced vital capacity (FVC%) [MD:4.38, (95% CI:0.15−8.60)], and diffusion lung capacity for carbon monoxide (DLCO%) [MD:11.78, (95% CI:5.10−18.46)]. The intervention group failed to demonstrate significant improvement in ADLs and QoL outcomes. No significant adverse events were reported during the intervention.

Conclusion: Respiratory rehabilitation can improve exercise capacity and PFT parameters in patients recovering from SARS infection. The RR does not cause serious adverse events. Clinical trials to determine the best RR program (in terms of initiation, duration, and components) in SARS and its treatment efficacy, both in the short and long- term are needed.

Introduction

Severe acute respiratory syndrome (SARS) is a serious health concern, a rapidly progressive respiratory syndrome, which is caused by severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and coronavirus-2 (SARS-CoV-2). SARS-CoV was identified as a global threat in 2003 (SARS-CoV-1) and 2019 (SARS-CoV-2).[1,2]

The lung injury in SARS is caused either due to direct viral effects or immune pathogenic factors.[1] Approximately 20 to 30% of patients with SARS may require intensive care unit (ICU) treatment, including mechanical ventilation.[2] The lung damage in SARS-CoV is mainly characterized by diffuse alveolar damage, which ultimately can lead to either pleural effusion, pulmonary edema, and or consolidation/ fibrosis of the lung.[1]

It is already evident from the literature that respiratory rehabilitation (RR) may improve dyspnoea, functional capacity, and health-related quality of life (QoL). Despite this widespread clinical acceptance and demonstration of the therapeutic potential of the RR in chronic obstructive lung diseases, there is uncertainty about the precise therapeutic efficacy of the RR in patients recovering from SARS CoV infection.

Recently many reviews, consensus reports, guidelines, expert opinions have been published on recommending RR in patients recovering from SARS-CoV infection.[3−10] However, most of these reviews are based on previous experience managing other chronic

lung diseases, not on patients' research data on SARS infection. Therefore, it is essential to accumulate data for RR programs' evidence, clarify the benefit, and strengthen its rationale for incorporating standard clinical management in patients with SARS-CoV infection.

In this review, we summarised all the available literature and determined the efficacy and safety of the RR following SARS infection.

Methods

The review was performed according to the PRISMA-P 2015 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[11,12] The study protocol was registered prospectively in the International Prospective Register of Ongoing Systematic Reviews (Systematic review registration – PROSPERO 2021: CRD42021255409).

Inclusion and exclusion criteria

Observational studies of any kind [randomized controlled trials (RCT), nonrandomized clinical trials (non-RCT), studies with cohort design (prospective or retrospective), or case series (with minimum of 5 participants)], published as an article or as a pre-print, were eligible for inclusion. Duplicate studies, case series with less than 5 participants, case reports, meta-analyses, review articles, consensus documents, comments, opinion articles, and letters not presenting the original data were excluded from this review. Articles written in languages other than English were excluded.

Participants

Patients, with any age, with (1) SARS either due to SARS-CoV-1 or SARS-CoV-2 infection, (2) who underwent RR for at least six days, (3) who were admitted and treated in an inpatient hospital (irrespective of severity) for the acute management of SARS, were included in this review.

Intervention

Respiratory rehabilitation (RR) consisting of 'aerobic exercises (endurance training)' and/or 'respiratory muscle training (RMT) exercises' was considered the primary treatment for SARS-CoV infection. Respiratory rehabilitation, which was administered only after the diagnosis of SARS, was included in this review. No restriction was placed based on rehabilitation technique (components of RMT or aerobic /endurance training), exercise frequency/ schedule, exercise duration, and rehabilitation set-up (ICU/ inpatient /outpatient/ home).

Comparison

Research articles, with or without having any control group (only intervention group), were included in this review. For the quantitative meta-analysis, it was mandatory to have a control/ comparison group. Control groups involved 'any interventions other than RR (an education program/ video program)' or 'no intervention' along with standard medical care for SARS. For descriptive/narrative analysis, it was not mandatory to have a comparison group.

Outcomes

Exercise capacity (endurance), measured by 'six-minute walk distance (6-MWD) in meters', was used to assess the primary outcome. Secondary Outcomes were (1) pulmonary function test (PFT) parameters [(measured by forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), carbon monoxide diffusion capacity (DLCO), and FEV1/FVC]; (2) Activities of daily living (ADL) scores [measured by function independence measure (FIM) scale]; (3) Health-related quality of life (QoL) scores [measured by any standard QoL scales (Short Form-12 (SF-12), Short Form-36 (SF-36), EuroQuality-5Dimensions-3Levels (Eq-5D-3 L), St. George Respiratory Questions (SGRQ)]; (4) Mortality [measured by the number of deaths due to RR].

The FIM instrument comprises of 18 items; 13-items [self-care (6-items), sphincter control (2-items), transfer (3-items), locomotion (2-items)] to assess motor-ADL (subscale) and 5-items [communication (2-items), social cognition (3-items)] to measure cognitive-ADL (subscale).[13-15]

The short-form health survey (SF-12), one of the most widely used tools,[16] measures health-related QoL. The SF-12 is a reduced version of the SF-36 scale, and it covers the same 8-health dimensions as the SF-36 but with substantially fewer questions (12-questionnaire).[16-18] EuroQuality-5Dimensions-3Levels (Eq-5D-3 L) (0−100 points; 0: worst and 100: best health-related QoL) is a valid tool to measure QoL domains involving mobility, self-care, usual care, pain/discomfort, and anxiety/ depression.[19,20] St. George's Respiratory Questions (SGRQ) is used to measure health impairments (HRQoL) in airway diseases. It has three components- dyspnoea, activity, and impacts (on daily life). The total score (0−100) indicates overall health and perceived wellbeing. The higher the SGRQ score, the more limitations are.[21,22]

Search strategy

A comprehensive systematic literature search was performed in MEDLINE/ PubMed, CENTRAL, EMBASE, Clinical Trial Registries, medRxiv, and Research Square to find the published and unpublished research articles (clinical trials and observational studies) on RR following SARS-CoV infections (SARS-CoV-1 and SARS-CoV-2). The search strategy was developed from January 1, 2003, to July 31, 2021. The reference lists of published articles were also searched manually.

The relevant keywords and MeSH terms, which were used during the literature search, were "severe acute respiratory syndrome" OR "SARS" OR "SARS-CoV" OR "SARS-CoV-1" OR "SARS-CoV-2" OR "Coronavirus" OR "coronavirus" OR "COVID" OR "COVID-19" AND "rehabilitation" OR "respiratory rehabilitation" OR "respiratory muscle training" OR "Respiratory therapy" OR "pulmonary rehabilitation" OR "physiotherapy" OR "physical therapy" OR "physical intervention" OR "exercise" OR "exercises."

Data collection and analysis

Selection of studies
According to the inclusion and exclusion criteria, two reviewers (A.B.and M.K.S) independently searched the articles and identified them as included, excluded, or uncertain. The full-text article was obtained and reviewed for eligibility based on the inclusion criteria in case of uncertainty.

Data extraction and management
Two reviewers (A.B. and M.K.S.) extracted the data independently with a standardized data collection form, including (1) author, year, setting (country, ICU, inpatient (IPD), Out-patient (OPD), home) (2) participants (number, mean age and gender, type of viral infections, and severity of the disease, (3) inclusion and exclusion criteria, (4) intervention (components of RR, frequency, intensity, and duration), (5) results (outcome measures, effect, significance) (6) safety (adverse events, mortality due to intervention). Any discrepancies during the selection and data collection were resolved by discussion and consensus. For studies with more than one-time point to observe and assess, the outcome data assessed at the end of intervention (RR) was included.

For continuous outcomes, mean values, standard deviation (SD), and total participants were extracted. For dichotomous outcomes, the total number of events and total participants were extracted. If mean and SD were not reported in the particular study, it was calculated manually from the reported indicators. If data were not available or written in an unusable way, the specific research was excluded from meta-analysis, and the data were presented descriptively.

Data analysis

Only comparative ('RR' versus 'No RR') studies [clinical trials and comparative observational studies] were included in the meta-analysis. Meta-analysis was performed by Review Manager software (Rev-Man 5.4) (The Cochrane Collaboration, Copenhagen, Denmark). As per the recommendation of the Cochrane handbook, during analysis, the random-effects model analysis was utilized, as there could be heterogeneity (none of the studies applied the same set of RR) among the original studies, which might not be evident in the data.

Assessment of risk of bias

The methodological quality of the comparative studies was assessed with the Newcastle -Ottawa scale (NOS),[23] which is being used to measure the risk of bias of observational (non-randomized) studies. A score >7 on NOS was considered a high-quality study. The higher the total NOS, the lower the risk of bias was.[23] Two reviewers (A.B. and M.K.S.) independently extracted data and performed the risk-of-bias assessment. Disagreements between these two reviewers were resolved by discussion with a third reviewer (J.S.).

Measurement of treatment effects

The outcome measures of interest, exercise capacity/ endurance (6-MWD), change in PFT parameters, ADL and QoL scores were presented as continuous data, and mortality events (deaths during study period) were presented as categorical data.

For quantitative meta-analysis of comparative studies (to measure the treatment effect), either 'the mean differences (MD)' or 'the standardized mean difference (SMD)' with corresponding 95% confidence intervals (CIs) was used to calculate the effect sizes of continuous outcomes measures. The significance level was fixed at $P < .05$.

Data from non-comparative observational studies or case series were presented and discussed narratively. In non-comparative studies, the therapeutic efficacy of RR (change in outcome) was considered significant if there was a significant change (p<0.05) following RR.

The overall efficacy of the RR was assessed according to the criteria recommended by the French Haute Autorité de la santé,[24] which is being used to evaluate the level of scientific proof. The levels of evidence were categorized into four classes, ranging from level-1 (well-powered, randomized, comparative trials) to level-4 (comparative studies with marked biases and retrospective studies).[24]

Results

The outcome of the electronic search

A total of 4211 articles were retrieved from January 1, 2003, to July 31, 2021. After excluding the irrelevant (not matching the inclusion and exclusion criteria) and duplicate reports, 21-articles[21-45] were included in this review (Fig. 1).

Out of 21-articles,[25−45] eight[25−32] were comparative ('RR' versus 'No RR') studies, and thirteen[33−45] were non-comparative (only intervention (RR) group) studies. Among comparative studies, five[25−29] were clinical trials, three[30−32] were cohort studies (two-studies[30,32] with prospective-cohort, and one[31] with retrospective-cohort design).

Only comparative studies (8-articles)[25−32] were included for the quantitative meta-analysis. However, all observational studies (21-articles)[25−45] were included for descriptive and qualitative analysis.

Characteristics of all included studies

Characteristics of all included studies where RR was undertaken have been presented in Table 1. Irrespective of the study design, 996 patients (21-articles) received RR. The mean age of the patients, who received RR following SARS, ranged from 37.1 to 70.5 years.

Respiratory rehabilitation was conducted in an inpatient (IP) setting (12-studies),[28,29,33,36,38−45] in ICU setting (3-studies),[31,32,34] in OPD (3-studies),[26,27,37] and in home (3-studies)[25,30,35] settings. The duration of RR ranged from 1-week to 6-weeks.

Each study used a different protocol for the RR (exercise schedule). Components of the RR used in each study have been presented in Table 1. The intensity, duration, and frequency of exercises (in the RR) were individualized, according to each patient's physical capacity and medical stability. Among the various RR techniques, respiratory muscle training (RMT) was included in 16-studies,[25,26,28−31,33,34,36,38−43,45] aerobic exercises/ endurance training in 19-studies[25−28,30−39,41−45] and strength/resistance training in 12-studies.[25,27,30,33,36−39,41−43,45] Besides these techniques (RMT, aerobic/ endurance training, and strength/resistance training), relaxation, occupational therapy, energy conservation techniques, and psychological support were incorporated in a few research articles as part of the RR.

Quantitative analysis (Meta-analysis) of comparative studies

In the quantitative meta-analysis, only eight comparative studies (334 participants received respiratory rehabilitation (RR), and 319 received 'No RR') were included.

The mean age of patients, who were included in the meta-analysis, were ranged from 37.1 years to 70.4 years. One-hundred thirty-three patients reported SARS secondary to SARS-CoV-1, and 461 reported SARS secondary to SARS-CoV-2.

The quality assessments (the risk of bias) of individual articles (included in the meta-analysis) have been presented in [**Table 2**].

Change in 6-MWD

Exercise capacity (endurance) was reported in five-comparative studies.[25−28,31] Pooled analysis from these 5-comparative studies[25−28,31] (222 received 'RR', 213received 'No RR'), reported mean difference (MD) of 6-MWD: 45.79 m (95% CI: 31.66 to 59.92 m, I^2= 38%). (Fig. 2) After excluding the retrospective study (Qi Di),[31] the mean difference in 6-MWD reached 53.07 m (95% CI: 39.23.7 to 66.9 m), and heterogeneity was reduced to 0%.

Thus, irrespective of inclusion or exclusion of the study by Qi Di et al.,[31] the mean difference in 6-MWD between two groups (active intervention versus control) remained significantly in favor of the RR group.

Change in PFT parameters

The PFT parameters were reported in 4-articles.[25,26,29,31] Researchers expressed the PFT-parameter data in (% pred) and (absolute volume) values to examine the effect on PFT parameters. In 2-articles,[29,31] the PFT parameters were expressed in (% pred) value, and in another two-articles,[25,26] PFT parameters were presented in absolute volume (liter). They (% pred and liter) were analyzed separately.

The pooled data from the two-studies,[29,31] where the PFT parameters were expressed in [FVC (% pred), FEV1 (% pred), FEV1/ FVC (%) and DLCO (% pred)], showed MD in FVC (% pred) 4.38 (% pred) (95%
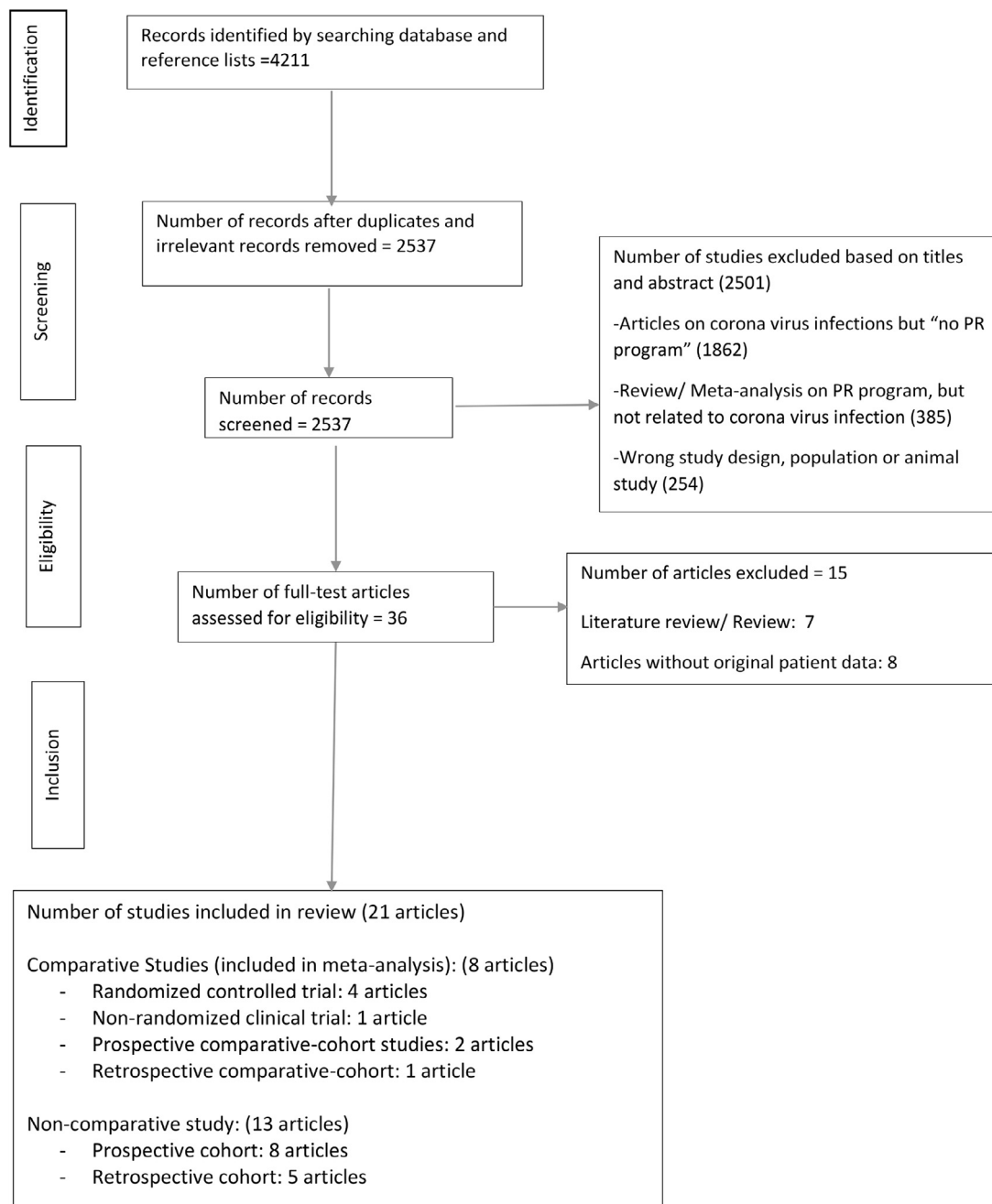
Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the study selection process.

CI: 0.15 to 8.60, I^2= 21%)] (Fig. 3A), in FEV1 (% pred) [MD: 4.14 (% pred) (95% CI: -3.09 to 11.36, I^2= 74%)] (Fig. 3B), in FEV1/FVC (% pred) [MD: 3.48 (% pred) (95% CI: -3.58 to 10.55, I^2= 58%)] (Fig. 4A) and in DLCO% [MD: 11.78 (% pred) (95% CI: 5.10 to 18.46, I^2= 58%)] (Fig. 4B).

Li J et al.,[25] Liu K et al.[26] in their RCTs (n=179) reported PFT parameter (FVC and FEV1) in absolute volume (liter)). The pooled data from these 2-studies[25,26] showed improvements in favor of active intervention (RR program) group, both in FVC (liter) [mean difference: 0.14 l (95% CI: -0.11 to 0.40 l] (**Fig S1**) and FEV1 (liter) [MD: 0.16 l (95% CI: 0.05 to 0.27 l)] (**Fig S2**).

Change in activities of daily livings (ADLs)

To explore whether RR had an effect on ADL, the FIM scores were included. The FIM scores were reported in 2-articles.[26,31] The pooled data from these 2-studies[26,31] demonstrated that the MD of FIM scored 3.68 points (95% CI: -2.93 to 10.30), I^2= 67%] (**Fig S3**).

Change in Quality of Life (QoL)

The Health-related QoL was assessed in 6-articles.[25-27,29,31,32] In four articles (164 received 'RR', 159 received 'No RR'),[25-27,32] the QoL was assessed with a short form-general health survey (either with SF-36 or SF-12) questionnaires. In one article, it (QoL) was assessed with 'EuroQuality-5Dimensions-3Levels' questionnaires[29] and in another article with 'St. George Respiratory Questions' questionnaires.[31]

The short form-general health survey questionnaires (SF-36 and SF-12) QoL scale does not have a single total QoL score.[18] Therefore, the short-form general health survey questionnaires [SF-36 and SF-12] were assessed separately.

Table 1
Characteristics of the included studies (21 articles).

Author Year	Type of Study	Study design	Characteristics of participants	Sample size	Age Year (SD) Male: Female	The onset of RR (from SARS)	Respiratory Rehabilitation				Outcomes
							Setting	Components	Period (week)	Number of sessions/ Session duration	
Liu K 2020[26]	Prospective	RCT	Patients with SARS (SARS-CoV-2) RR program was started after hospital discharge	RR: 36 Control: 36	69.15(7.8) Years M: F: 49:23	NR	OPD	Respiratory muscle training: RMT with Hand-held resistance device (Threshold PEP): 3 sets/10 breaths/60% MEP); Cough Ex: 3 sets/10 active coughs; DPH Muscle training (30 contractions, placing a weight 1–3 kg on the anterior abdominal wall). Home exercises: pursed lip breathing, coughing training (30 sets/ day) Aerobic exercise/ endurance training: supervised stretching exercises	6	Home exercises daily [10 min/ day] along with supervised respiratory rehab training 2 sessions/ week	PFT (FEV1, FVC, DLCO); Exercise capacity (6-MWD); ADL(FIM); QoL (SF-36); Anxiety (SAS); Depression (SDS)
Lau HM-C 2005[27]	Prospective	RCT	Patients with SARS (SARS-CoV-1) RR program was started after hospital discharge	RR: 71 Control: 62	37.1(10.23) Year M:F: 45:88	NR	OPD	Aerobic exercises/ endurance training: Ergometer (UL/ LL), stepper, or treadmill (total of 30–45 min) Strength training: Resistance training (UL/ LL); 1 set of 10–15 repetitions x 3 sets	6	4–5 sessions / week [each session consisted of 1–1.5 h]	Exercise capacity (6-MWD); Chester step test, muscle strength test (hand held dynamometer); QoL (SF-36)
Lyadov KV 2020[28]	Prospective	RCT	Patients with SARS (SARS-CoV-2) [on oxygen support] RR program was started in acute hospital set-up	RR: 73 Control: 73	59.7(14.9) Year M:F: 81:65	NR	IPD	Respiratory muscle training: Breathing exercises (as per protocol) Aerobic exercise/ endurance training: Stretching and ROM exercises (as per protocol)	1	4–6 times / day	Oxygenation Index, Self-service status, Mortality
Li J 2021[25]	Prospective	RCT	Patients with SARS (SARS-CoV-2) RR program was started after hospital discharge	RR: 59 Control: 60	50.61(10.98) Year M:F: 53:66	70 days (16.85)	Home	Respiratory muscle training: Diaphragmatic breathing exercises Breathing control and thoracic expansion exercise, Aerobic exercises/ endurance training: brisk walking, running, treadmill Strength training: lower limb muscle strength	6	3–4 sessions / week [each session consisted of 40–60 min]	Exercise capacity (6-MWD); PFT (FEV1, FVC, DLCO); QoL (SF-12); Perceived dyspnea
Abodonya AM 2021 [29]	Prospective	Non-RCT	Patients with SARS (SARS-CoV-2) [weaned off from mech. Vent.] RR program was started in post-acute stage	RR: 21 Control: 21	48.05(8.86) year M: F 33:9	NR	IPD	Respiratory muscle training: Inspiratory muscle training with threshold inspiratory muscle trainer (Respironics). [each session is consisted of 6 inspiratory cycles/50% of MIP]	2	2 sessions daily, 5 days a week	Exercise capacity (6MWD); PFT (FEV1, FVC); Dyspnea severity index (DSI); QoL (EQ-5D-3L)
Ozyemisci-Taskiran O 2021[32]	Prospective	Comparative, cohort, study	Patients with SARS (SARS-CoV-2) [Severely and critically ill, in ICU] RR program was started in post-acute stage (ICU)	RR: 17 Control: 17	70.42(11.3) years M:F 24:11	6 days	ICU	Aerobic exercise/ endurance training: Mobility training- sitting, standing, walking Stretching exercise, ROM exercises: 10–15 repetitions, 15 min / day Others: NMES (complex Rehab 400) to bilateral Quadriceps and Tibialis Anterior muscle	4	6 days / week	Composite MRC score, QoL (SF-36)
Martin I 2021[30]	Prospective	Cohort, comparative study	Patients with SARS (SARS-CoV-2) RR program was started after hospital discharge	RR: 14 Control: 13	61.5(10.5) years M: F 17:10	2–3 weeks	Home [Tele-rehab]	Respiratory muscle training: Pulmonary rehabilitation program of 20 minutes' duration Aerobic exercise/ endurance training: Aerobic exercises of 30 minutes' duration Strength training: Resistance training (upper and lower limbs); 1 set of 8–12 repetitions x (2–3) sets	6	5 days / week	Exercise capacity (One minute sit –to—stand test (STST)), Dyspnea severity
Qi D 2021[31]	Retrospective	Cohort, comparative study	Patients with SARS (SARS-CoV-2) [Severely and critically ill, in ICU] RR program was started in post-acute stage (ICU)	RR: 43 Control: 37	64.9(17.0) years M: F 48:32	Within 72 h of admission to ICU	ICU	Respiratory muscle training: Pursed lip, deep breathing exercises, breathing exercises through PEP device (Acapella Choice), chest physiotherapy by percussion & vibration technique Aerobic exercise/ endurance training: Mobility training including bed mobility, sitting & transfer training and stretching exercise Others: Position management and prone positioning ventilation	3–4	Physical therapy: 30 minutes / day Breathing exercises: four times / day	PFT (FEV1, FVC, DLCO); Exercise capacity (6-MW); ADL (FIM, BI); QoL (SGRQ)

Table 1 (Continued)

Author Year	Type of Study	Study design	Characteristics of participants	Sample size	Age Year (SD) Male: Female	The onset of RR (from SARS)	Respiratory Rehabilitation				Outcomes
							Setting	Components	Period (week)	Number of sessions/ Session duration	
Gloeckl R 2021[33]	Prospective	Observational, cohort study	Patients with SARS (SARS-CoV-2) [irrespective of severity] RR program was started in acute stage	RR:50	58.65(7.93) years M:F 22:28	61(40−108) days [severe/ critical] 178 (127−217) days [mild/ moderate]	IP	Respiratory muscle training: breathing ex, cough technique, mucus clearance, connective tissue massage and energy conservation technique = 30 min/ session Aerobic exercises/ endurance training: Cycle ergometer (10−20 min/ day), aerobic exercises (calisthenics, Nordic walking or aqua fitness − 30 minutes' session) Strength training: Resistance training − leg press, knee extension, pull down & push up: (15−20 repetitions/set); Total of 3 sets/ dayOthers: Relaxation technique (QiGong or progressive muscle training), Occupational therapy, Psychological support	3	Respiratory Physiotherapy [30 minutes' session]: 2−4 (sessions) times/ 5 day/ week Endurance training: 5 days/ week Strength training: 5 days / week ADL training [30 minutes session]: 4−5 (sessions) times/ week	Exercise capacity (6-MWD, ESWT); PFT (FVC, FEV1, TLC, DLCO); QoL (SF-36); Anxiety (GAD-7); Depression (PHQ-D)
Li L 2021[34]	Prospective	Observational, Cohort study	Patients with SARS (SARS-CoV-2) [Severely and critically ill. in ICU] RR program was started in post-acute stage (ICU)	RR:13	66.9(16.1) years M:F: 6:7	NR	ICU	Respiratory muscle training: Upright positioning for 20 min, ACBT, IMT, PEP device (Acapella Portex): set of 8 breaths for 10 min/ 3 times per day, percussion and vibration to chest wall: twice each day, threshold IMT by device (Digi IMT S2) 4 sets of 8 breaths daily at 30% or 50% MIP Aerobic exercise/ endurance training: Ambulation training (Walking exercises), bed mobility training,	2	Daily twice daily	PaO2/FiO2 ratio, PEFR, MIP, Modified Borg Dyspnea scale, De Morton Mobility Index, ADL (MBI), Walking distance
Tang Y 2021[35]	Prospective study	Observational, cohort study	Patients with SARS (SARS-CoV-2) RR program was started after hospital discharge	RR:33	43.2(10.4) years M:F 17:16	NR	Home	Aerobic exercise/ endurance training: Liuzijue exercise technique [Traditional Chinese exercise, consisting of abdominal breathing pursed-lip breathing with uttering 6 different sounds, along with corresponding to body movements) [RMT and aerobic exercises]	4	Once daily for 20 min for 4 weeks	Exercise capacity (6-MWD); QoL (SF-36), USG (Diaphragm thickness,) Psychological assessment (HAMD, HAMA)
Spielmanns M 2021[36]	Prospective	Cohort study	Patients with SARS (SARS-CoV-2) RR program was started at acute stage	RR:99	67.72(10.23) years M: F 22: 28	NR	IP	Respiratory muscle training: Inspiratory muscle training (pursed-lip breathing, secretion mobilization & diaphragmatic breathing), controlled cough exercises, an energy conservation technique Aerobic exercise/ endurance training: In-bed cycling (RECK-Technik GmbH & Co. KG Medizintechnik), Cycling ergometer, Treadmill, Gymnastics, Walking (indoor & outdoor) Strength training: Resistance training − Upper & lower limbs (3−4 times / week) 3 series X 8−12 repetitions per exercise Others: A relaxation technique (Progressive muscle training) Educational session (self-management and coping strategy)	3	Respiratory therapy: 30 min/ session/ 3 times/ week Endurance: 10−30 min/ session/ 5−6 times/ week Gymnastics: 45 min/ session/ 5−6 times/ week Outdoor walking: 45 min/ session/ 2−3 times/ week Strength training: 30 min/ session/ 3−4 times/ week Relaxation training: 45 min/ session/ 2 times/ week	Exercise capacity (6-MWD); PFT (FVC, FEV1, TLC, DLCO); ADL (FIM); QoL (CRQ, Feeling thermometer); HADS
Daynes E 2021[37]	Prospective	Cohort study	Patients with SARS (SARS-CoV-2) RR program was started after hospital discharge	RR: 30	58(16) years M: F: 16:14	125(54) days	OPD	Aerobic exercise/ endurance training: Walking, treadmill training Strength training: Resistance training (upper & lower limbs) Others: Educational program	6	2 supervised sessions / week	Incremental and endurance shuttle walking test (ISWT/ESWT); QoL (EQ5D); MoCA: Anxiety (HADS); CAT; FACIT
Bertolucci F 2021[38]	Prospective	Cohort studies	Patients with SARS (SARS-CoV-2) RR program was started after acute stage	RR:39	67.8(10.8) years M:F: 24:15	46.4(20.9) days	IP	Respiratory muscle training: Diaphragmatic breathing exercise, controlled breathing ex, Breathing exercises by PEP devices Aerobic exercise: Walking Strength training: Resistance training (upper & lower limbs) Others: ROM exercises, postural training, balance and coordination exercises	3−4	NR	ADL (BI); Functional ambulation capacity (FAC)

Table 1 (*Continued*)

Author Year	Type of Study	Study design	Characteristics of participants	Sample size	Age Year (SD) Male: Female	The onset of RR (from SARS)	Respiratory Rehabilitation				Outcomes
							Setting	Components	Period (week)	Number of sessions/ Session duration	
Chikhanie Y Al 2021[39]	Prospective	Cohort studies	Patients with SARS (SARS-CoV-2) RR program was started after the acute stage	RR: 21	70.9(10.6) years M:F 14:7	23.4(8.5)	IP	Respiratory muscle training: Pulmonary rehab program Aerobic exercises/ endurance training: Walking, cycling and gymnastics, Strength training: Resistance training (upper & lower limbs) Others: balance exercise.	4	NR	PFT (FEV1, FVC); Exercise capacity (6-MWD); Walking performance (Tinetti balance test); Muscle strength (Handgrip, Quadriceps)
Busching G 2021[40]	Retrospective		Patients with SARS (SARS-CoV-2) [Severe and critically ill, acute stage]	RR: 51	65.8(11.7) years M:F: 38:13	NR	IP	Respiratory muscle training Details: Not reported	3	NR	Exercise capacity (6-MWD); QoL (chronic respiratory questionnaire (CRQ)); ADL(FIM)
Zampogna E 2021[41]	Retrospective	Data-analysis	Patients with SARS (SARS-CoV-2) RR program was started after the acute stage	RR:140	70.1(12.4) years M: F: 95:55	48.2(22.8) days	IP	Respiratory muscle training: Chest physiotherapy by bronchial hygiene technique. Aerobic exercises/ endurance training: Mobility training, active exercises, walking, peripheral limb muscle activities, shoulder and full arm circling, calisthenics, balance exercise, cycle ergometer Strength training: Resistance training	3	20−30 min/ daily	Exercise capacity (6-MWD); Short physical performance battery (SPPB); ADL (BI)
Hermann M 2020[42]	Retrospective	Cohort	Patients with SARS (SARS-CoV-2) RR program was started after the acute stage	RR: 28	66.04(9.3) years M:F: 14:14	19.3(10.7) days	IP	Respiratory muscle training: Pursed lip breathing, secretion mobilization, diaphragmatic breathing, controlled cough exercises Aerobic exercises/ endurance training: Supervised in- and out- door walking, stationary bicycle Strength training: Resistance training 3 × 20 repetitions per exercise with (max load) Others: Educational sessions- self-management and coping strategy, energy conservation technique	3	5−6 days / week	Exercise capacity (6-MWD); QoL (CRQ), ADL (FIM); PFT (FEV1, FVC, DLCO); CIRS; Anxiety (HADS); FT
Udina C 2021[43]	Prospective	Cohort study	SARS infection in the post-acute stage	RR: 33	66.2(12.8) years M: F 14:19	NR	IP	Respiratory muscle training: Breathing exercises, manual therapy Aerobic exercises/ endurance training: step, cycle, ergometer or walking − (5−15 min), Balance exercises- static and dynamic balance training (2 exercises (walking with obstacles, changing directions or on the unstable surface) Strength training: Resistance training - upper & lower limbs (2−4 exercises), 1−2 sets X 10 repetitions	1	30 minutes/ day 7 days/ week	Exercise capacity (6-MWD); ADL (BI); SPPB, Single leg stance test
Sakai T 2020[44]	Retrospective	Cohort study	SARS infection in the post-acute stage	RR: 25	72 (43−95) years (median (range) M:F 19:6	19(6−31) (median (range)	IP	Aerobic exercise/ endurance training Others: ADL training	2−3	20 min/ twice daily	ADL (BI)
Piquet V 2021[45]	Retrospective	Chart review	SARS infection in the post-acute stage	RR: 100	66(22) years M:F 66:34	20.4(10.0) days Mean (SD)	IP	Respiratory muscle training: Diaphragmatic breathing Aerobic exercises/ endurance training: Bicycle ergometer Strength training: Body weight exercises (sit to stand, tiptoe squad, squats), elastics, weights (approx. 3 sets X 10 repetitions of each exercise) Others: Group sessions, occupation therapy, psychological counseling	1−2	20 min / day	ADL (BI); Borg exertion score, post-sit-to-stand respiratory rate

ACBT = Active cycle of breathing technique, ADL = Activities of daily living, BI= Barthel index, CIRS= Cumulative illness rating scale, CAT= chronic obstructive pulmonary disease (COPD) assessment test, DLCO= Diffusing capacity of lung for carbon monoxide, Eq-5D-3L = EuroQuality-5Dimensions-3Levels, FACIT= Functional assessment of chronic illness therapy fatigue scale, FVC= forced vital capacity, FEV1= Forced expiratory volume in 1 s, FIM = Functional independence measure, GAD-7= Generalized anxiety disorder-7; F= Female; FT= Feeling thermometer, HADS= Hospital anxiety and depression scale; IMT = Inspiratory muscle training, M= Male; MEP= Maximal expiratory mouth pressure, MIP= maximal inspiratory pressure, 6-MWD= 6 min walking distance, MoCA= Montreal cognitive assessment, MBI= Modified Barthel Index, PEP = Positive expiratory pressure, PFT: Pulmonary function test; RMT= respiratory muscle training, PHQ-D= Patient health questionnaire, ROM = Range of motion, RCT = Randomized controlled trial, RR = Respiratory rehabilitation, TLC= Total lung capacity, SGRQ = St. George Respiratory Questions, SD = standard deviation, SAS = Self-rating depression scale; SDS=Self-rating anxiety scale, SARS = Severe acute respiratory syndrome, SPPB= Short physical performance battery.

Table 2
The quality assessment (the risk of bias) of comparative studies by 'New castle Ottowa Scale (NOS)'.

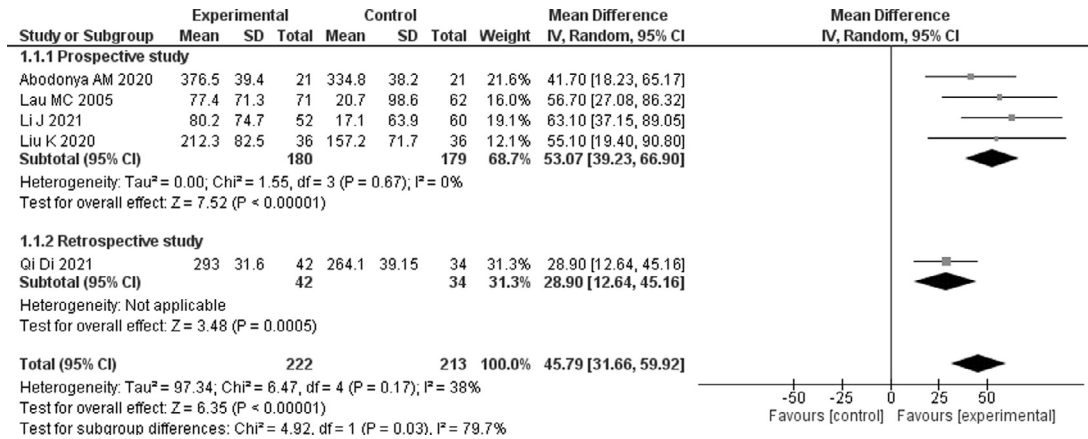| Study	Selection				Comparability		Outcome			Total quality score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	
Liu K 2020[26]	*	*	*	*	*	*	*	*	*	9
Lau HM-C 2005[27]	*	*	*	*	*	*	*	*	*	9
Li J 2021[25]	*	*	*	*	*	*	*	*	*	9
Lyadov KV 2020[28]	*	*	*	*	*	-	*	-	*	7
Abodonya AM 2021[29]	*	*	*	*	*	*	*	*	*	9
Ozyemisci-Taskiran O 2021[32]	*	*	*	*	*	*	*	*	*	9
Martin I 2021[30]	*	*	*	*	*	*	*	*	*	9
Qi D 2020[31]	*	*	*	*	*	*	*	*	*	9

Fig 2. The forest plot for included studies pooled together using a random-effects model for assessing exercise capacity [6-min walking distance (6-MWD)] immediately after intervention: comparison between respiratory rehabilitation (RR) (experiment) and control interventions.

Fig 3. A: The forest plot for included studies pooled together using a random-effects model for assessing forced vital capacity (FVC: % pred) immediately after intervention: comparison between respiratory rehabilitation (RR) (experiment) and control interventions.

B: The forest plot for included studies pooled together using a random-effects model for assessing forced expiratory volume in 1 s (FEV1: % pred) immediately after intervention: comparison between respiratory rehabilitation (RR) (experiment) and control interventions.

Table 3

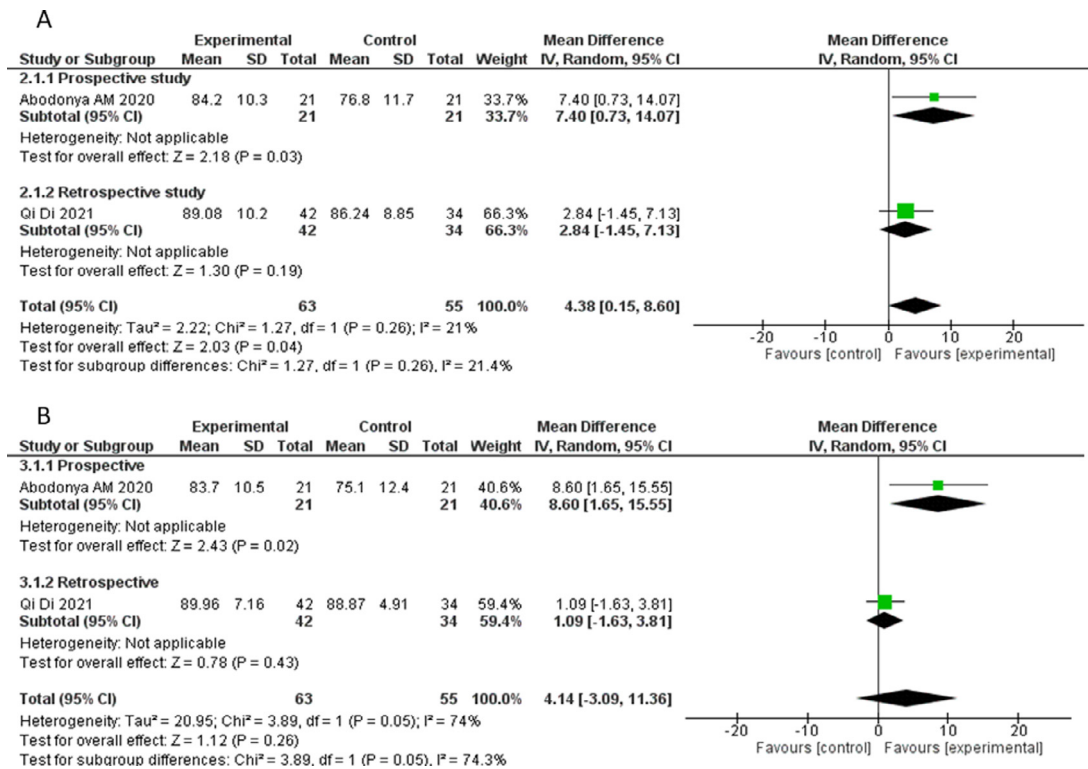Clinical outcome of non-comparative studies (change in outcome parameters following respiratory rehabilitation (RR)).

Reference	Status of the persons	Number (n=)	Outcome Measurement		Main findings	Level of evidence
			Pre	Post		
Gloeckl R 2021[33]	Severe to critical SARS (COVID-19)	26	6MWD: Median 344 (IQR= 244-392) meter PFT Parameters [median (IQR)]: FVC: 75.1(59.8-90.6) FEV1: 79.1(65.8-99.7) DLCO: 55.8(37.2-63.0) QoL: SF-36 [Phys. Comp] 30.2(22.7-36.8) SF-36 [Mental Comp]38.5(30.1-52.8)	6MWD: Median 468 (IQR= 374-518) meter PFT Parameters [median (IQR)]: FVC: 86.4(67.6-96.3) FEV1: 94.8(80.9-106.2) DLCO: 59.5(37.8-70.9) QoL: SF-36 [Phys. Comp.] 34.7(30.2-41.3) SF-36 [Mental Comp.] 52.9(32.0-58.2)	6-MWD: (3 week) Significant Improvement by [median= 124(IQR= 75-145) meter] (p <.001) PFT Parameters (3 week): FVC: Significant improvement by 11.3(1.0-16.9) (p <0.001) FEV1: Significant improvement by 15.7(3.7-17.5) (p <0.001) DLCO: Significant improvement by 3.7(-0.5-12.7) (p <0.001) QoL: (3 week) SF-36 [Phys. Comp]: No significant improvement; 4.5(0.5-9.5) (p >0.05) SF-36 [Mental Comp]: Significant improvement by 14.4(-0.6-24.5) (p <0.001)	Level 2
	Mild to moderate SARS (COVID-19)	24	6MWD: Median 509(IQR= 426-539) meter PFT Parameters [median (IQR)]: FVC: 80.0(59.2-90.9) FEV1: 83.3(65.5-101.1) DLCO: 57.0(50.0-65.5) QoL: SF-36 [Phys. Comp] 31.8(26.2-35.7) SF-36 [Mental Comp] 48.6(37.2-53.8)	6MWD: Median 557(IQR= 463-633) meter PFT Parameters [median (IQR)]: FVC: 87.7(67.0-98.9) FEV1: 95.1(84.0-106.8) DLCO: 61.5(50.0-76.3) QoL: SF-36 [Phys. Comp] 31.7(31.7-42.0) SF-36 [Mental Comp] 54.2(52.5-56.7)	6-MWD: (3 week) Significant improvement by [median 48(IQR= 35-113) meter] (p <0.001) PFT Parameters: (3 week) FVC: Significant improvement by 7.7(1.0-17.8) (p<0.01) FEV1: Significant improvement by 11.8(3.3-18.1) (p <0.001) DLCO: Improvement by 4.5(-1.8 -16.5) (p >0.05) QoL: (3 week) SF-36 [Phys. Comp] No significant Improvement, -0.1(-4.0- 9.9) SF-36 [Mental Comp]: Improvement by 5.6(1.4 -9.2) (p >0.05)	
Li Lei 2020[34]	severe and critical SARS (COVID-19)	13	6MWD: NR PFT Parameters: NR ADL [Median (Range)]: MBI: 55 0-70)	6MWD: NR PFT Parameters: NR ADL [Median (Range)]: MBI: 75(30-100)	6-MWD: Not assessed PFT Parameters: Not assessed ADL (2 weeks): MBI: increased significantly (p <0.05)	Level 2
Tang Y 2021[35]	Persons with COVID 19 discharged from Hospital	33 (Mild/ moderate: = 28; Severe/ critical = 5)	6MWD: NR PFT Parameters: NR QoL: SF-36 [Phys. Comp]: NR SF-36 [Mental Comp]: NR	6MWD: values not mentioned PFT Parameters: NR QoL: SF-36 [Phys. Comp]: NR SF-36 [Mental Comp] NR	6-MWD: (4 weeks): Improved by [mean=17.22(SD= 43.78) meter] (p= 0.20) QoL (4 weeks) SF-36 [Phys. Comp]: Significant improvement (p=.014) SF-36 [Mental Comp]: No significant improvement (p>0.05)	Level 2
Spielmann M 2021[36]	Post COVID-19 patients, discharged from Hospital	99	6-MWD: [mean (SD)] 176(141) meters FVC: 74.1(37.6) FEV1: 74.9(38.9) DLCO: 61(38.6) ADL: [mean (SD)] FIM: 100(15.1)	6-MWD: [mean (SD)] 357(132.0) meter FVC: NR FEV1: NR DLCO: NR ADL: [mean (SD)] FIM: 111(15.0)	6-MWD: [mean (SD)] (3 weeks) Significant improvement by 180 (101.0) meters (p<0.0001) PFT Parameters (3 weeks): NR ADL: (3 weeks) FIM: Significant Improvement by 11(10) points (p<0.0001)	Level 2
Daynes E 2021[37]	Post COVID-19 patients, discharged from Hospital	30	6-MWD: NR QoL [Mean (SD)] EQ5D: 62(18)	6-MWD: NR QoL [Mean (SD)] EQ5D: 70(21)	6-MWD: Not assessed QoL: [6 weeks) EQ5D: Improvement by 8(19) (p= 0.05)	Level 2
Bertolucci F 2021[38]	Sub-acute SARS (COVID-19)	39	ADL: [median (IQ] Barthel Index (BI) 7.5(0-10)	ADL: [median (IQ] BI: 65(60-85)	Functional measures:(3-4 weeks) BI: Significant improvement (p<0.01)	Level 2
Chikhanie YA 2021[39]	sub-acute SARS (COVID-19)	21	6-MWD: [mean (SD)] 138.7(144.4) meter PFT Parameters: [mean (SD)] FVC: 59.1(15.2) FEV1: 66.7(16.0) QoL [mean (SD)] SGRQ: 37.2(22.8)	6-MWD: [mean (SD)] 343.4(139.6) meter PFT Parameters: [mean (SD)] FVC: 72.9(15.2) FEV1: 81.2(14.2) QoL [mean (SD)] SGRQ: 22.3(15.9)	6-MWD: (4 weeks) Significant improvement (p<0.001) PFT Parameters: (4 weeks) FVC: Significant improvement <0.05 FEV1: Significant improvement <0.05 QoL (4 weeks) SGRQ: improvement present, but p >0.05	Level 2
Busching G 2021[40]	Severe & critical SARS (COVID 19)	51	6-MWD: [mean (SD)] 336.2(169.3) meter ADL: [mean (SD)] FIM: 97.3(17.4) QoL: [mean (SD)] CRQ: 91.7(19.8)	6-MWD: [mean (SD)] 484.4(146.6) meters ADL: [mean (SD)] FIM: 115.8(14.0) QoL: [mean (SD)] CRQ: 105.8(18.0)	6MWD: (3 weeks) Improvement by 132.8(92.9) meter (p<0.001) ADL: (3weeks) FIM: Improvement by 18.0(11.4) meter (p<0.001) QoL: (3 weeks) CRQ: Significant improvement by 15.5(15.2) (p <0.001)	Level 4
Zampogna E 2021[41]		140				Level 4

Table 3 (*Continued*)

Reference	Status of the persons	Number (n=)	Outcome Measurement		Main findings	Level of evidence
			Pre	Post		
	Sub-acute (moderate to severe) SARS (COVID-19)		6-MWD: [mean (SD)] 229.0(102.5) meter ADL: [(Median (IQR)] BI: 55.0(30.0-90.0)	6-MWD: [mean (SD)] 327.9(97.8) meter ADL: [Median (IQR)] BI: 95.0(65.0-100.0)	6-MWD: (3 weeks) Significant Improvement (p=0.00) ADL: (3 weeks) BI: Significant improvement, (p <0.001)	
Hermann M 2020[42]	Post-acute phase (COVID-19)	28	6-MWD: [mean (SD)] 230.9(153.6) meter ADL: [median (IQR)] FIM:107.0(103-122)	6-MWD: [mean (SD)] 360.9(134.6) meter ADL: [median (IQR)] Function: NR	6-MWD (3 weeks): significant Improvement 30(78.0) meter (p=0.00) ADL: (3 weeks) Not assessed	Level 2
Udina C 2021[43]	Post-acute phase (COVID-19)	33	6-MWD: [mean (SD)] 158.7(154.1) meter (n=22) ADL: [mean (SD)] BI: 76.5(17.4)	6-MWD: [mean (SD)] 346.3 (111.5) meter (n=22) ADL: [mean (SD)] BI: NR	6-MWD: (1 week) improved significantly (p<0.001) (n=22) ADL: (1 week) BI: improved significantly by 18.5 (12.9) (p <0.05) (n=22)	Level 2
Sakai T 2020[44]	Post-acute phase (COVID-19)	25	6-MWD: NR PFT Parameters: NR ADL: [Median (Range)] BI: 40(0-85)	6-MWD: NR PFT Parameters: NR ADL: [Median (Range)] BI: 70(0-85)	6-MWD: NR PFT Parameters: NR ADL: (2- 3 weeks) BI: improved significantly (p <0.001)]	Level 4
PiquetV 2021[45]	Post-acute phase (COVID-19)	100	6-MWD: NR PFT Parameters: NR ADL: [Mean (SD)] BI: 77.3(26.7)	6-MWD: NR PFT Parameters: NR ADL: [Mean (SD)] BI: 88.8(24.5)	6-MWD: NR PFT Parameters: NR ADL: (1-2 week) BI: Significant improvement, p <0.001	Level 4

ACBT = Active cycle of breathing technique, ADL = activities of daily living, BI= Barthel Index, CRQ= chronic respiratory questionnaire, DLCO= Diffusion capacity of lung for carbon monoxide, Eq-5D-3L = EuroQuality-5Dimensions-3Levels, FIM = functional independence measure, FVC= forced vital capacity, FEV1= Forced expiratory volume in 1 second, IQR= interquartile range, MB = Modified Barthel Index, 6-MWD= 6 minute walking distance, NR = not reported, QoL= Quality of life, SARS = severe acute respiratory syndrome, SGRQ = St. George Respiratory Questions, SD = standard deviation, TLC= total lung capacity,

Table 4
Summary of results (outcomes) of reported articles.

SARS infection studies	Exercise Capacity			Lung function									ADL			QoL (SF-36/ SF-12)						QoL (Others)		
	6MWD			FVC			FEV1			DLCO			FIM/ BI/MBI			[SF 36/ SF 12] Physical			[SF 36/ SF 12] Mental			Overall		
	+	-	NT	+	-	NT	+	-	NT	+	-	NT	+	-	NT	+	-	NT	+	-	NT	+	-	NT
Comparative/ controlled studies [a]																								
Randomized controlled Trial	3	0	1	2	0	2	2	0	2	1	0	3	0	1	3	2	1	1	2	1	1	0	0	3
Non-randomized clinical trial	1	0	0	1	0	0	1	0	0	0	0	1	0	1	0	0	0	1	0	0	1	1	0	0
Prospective comparative cohort	0	0	2	0	0	2	0	0	2	0	0	2	0	2	0	0	1	1	0	1	1	0	0	2
Retrospective comparative cohort	0	0	1	0	1	0	0	1	0	1	0	0	0	0	1	0	0	1	0	0	1	1	0	0
Non-comparative studies [b]																								
Prospective (non-comparative) cohort	5	1	3	2	0	6	2	0	6	1	0	7	3	0	5	1	1	6		2	6	0	2	6
Retrospective (non-comparative) cohort / Chart review	3	0	2	0	0	5	0	0	5	0	0	5	4	1	0	0	0	5	0	0	5	1	0	4
Number of studies	12	1	8	5	1	15	5	1	15	3	0	18	7	5	9	3	3	15	2	4	15	3	2	15

(+): Respiratory rehabilitation (RR) efficacy evidenced, (-): RR efficacy not evidenced, NT: Not Tested,
6MWD = 6-min walk distance, FVC = Forced Vital capacity, FEV1= Forced expiratory volume in 1 s, DLCO = Diffusion capacity lung for carbon monoxide, ADL= Activities of daily living, BI = Barthel Index, MBI = Modified Barthel Index, FIM = Functional independence measure, QoL = Quality of life, SF 36= short-form health survey-36, SF 12= short-form health survey-12
[a] Efficacy of comparative studies were assessed by comparing intervention versus control arm (evidence of significant improvement/ difference was considered when $p < 0.05$)
[b] Efficacy of non-comparative studies were assessed by comparing pre −post-intervention versus (evidence of significant improvement between pre and post-treatment was considered when $p < 0.05$)
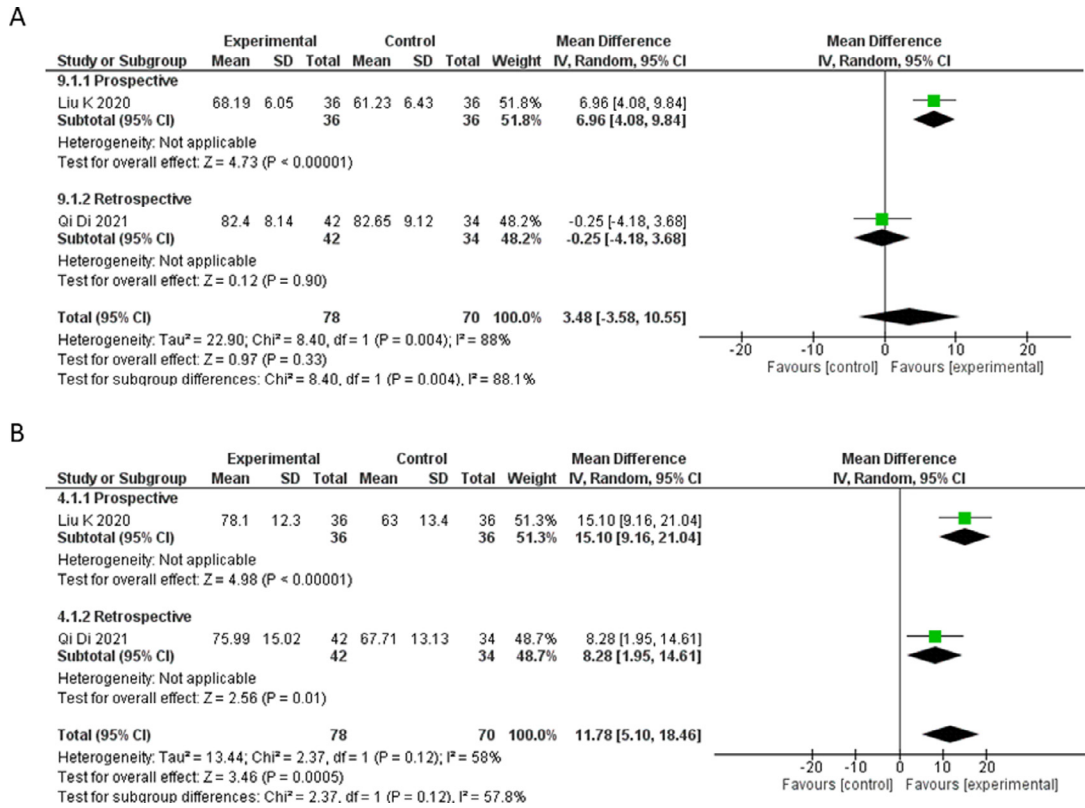
A

B

Fig 4. A: The forest plot for included studies pooled together using a random-effects model for assessing the ratio of 1 s FEV1 and FVC (FEV1/FVC: % pred) immediately after intervention: comparison between respiratory rehabilitation (RR) (experiment) and control interventions.

B: The forest plot for included studies pooled together using a random-effects model for assessing the diffusing capacity of the lung for carbon monoxide (DLCO: % pred) immediately after intervention: comparison between respiratory rehabilitation (RR) (experiment) and control interventions.

Pooled data from the four-studies,[25-27,32] where SF health questionnaires (SF-12/ SF-36) was used to measure QoL, showed the SMD of 0.79 points (95% CI: -0.17 to 1.75), I^2= 93%] in physical health (**Fig. S4**), and SMD of 0.47 point (95% CI: -0.24 to 1.19), I2= 88%] (**Fig. S5**) in mental health. The pooled data from the other 2-studies,[29,31] where QoL was expressed in total overall QoL score, ['EuroQuality-5Dimensions-3Levels' and 'St. George Respiratory Questions' questionnaires] showed the SMD of 1.35 points (95% CI: -0.08 to 2.79), I^2= 90%] between active intervention and control group (**Fig. S6**).

Thus, irrespective of QoL outcome scales, the SMD between the two ('RR' versus 'No RR') groups remained non-significant (though there was a tendency of improvement in favor of the RR group)

Adverse events

None of the studies reported any significant adverse events (falls, arrhythmia, severe hypertension, hypotension, syncope, ischaemic heart disease, cardiac arrest, and death) during or after the RR. No dropouts were reported due to intolerance or adverse events of RR.

No deaths were reported due to active intervention (RR). However, deaths were reported due to other causes (disease itself and comorbidities) from 3-studies.[28,31,32] Irrespective of causes, there was no significant difference in deaths in both groups ('RR' versus 'No RR') [relative risk: 0.73, (95% CI: 0.19 to 2.86), I^2=39%] (**Fig. S7**), which indicated that intervention (RR) did not significantly increase or decrease the mortality rates among survivors.

Descriptive analysis of all included articles (comparative and non-comparative)

The clinical outcomes of non-comparative studies (change in outcome parameters following RR) have been presented in Table 3.

However, irrespective of study designs, all studies (21-studies) were included to summarize the overall efficacy of the RR. The summary of the overall effectiveness, according to criteria recommended by the French Haute Autorité de la santé[24] of the RR, has been presented in Table 4.

Out of 21-articles, 13-articles (9 non-comparative studies) assessed 6-MWD. Twelve articles [except one article (with level-2 evidence)] showed significant improvement (p <0.05) in 6-MWD following RR. Among the 12-articles, three articles were RCTs (Level-1 evidence),[25−27] which demonstrated the considerable change (p<0.05) in 6-MWD compared to the control intervention.

Seven-articles[25,26,29,31,33,36,39] reported the PFT parameters (FVC, FEV1, DLCO) before and after RR. Five research articles demonstrated a significant change in FVC and FEV1 parameters following RR. Three research articles[26,31,33] assessed the diffusing capacity of the lung (DLCO) following RR. All articles[26,31,33] showed considerable improvement (p<0.05) in DLCO following RR.

Discussion

This study gives an idea of the efficacy of aerobic exercises/ aerobic training and RMT exercises among patients with SARS recovering from active disease. This is the first review article on a meta-analysis on SARS and respiratory rehabilitation (RR). The present meta-analysis suggested a beneficial effect of the RR following SARS infection, especially in terms of improvement in exercise capacity (6-MWD) and pulmonary function parameters (FVC%, FEV1(liter) and DLCO%).

It is already evident that severe acute respiratory syndrome, caused by SARS CoV-1 and SARS-CoV-2, causes significant lung damage (acute lung injury), along with the involvement of other organs.[34] Acute lung injury, multi-organ involvement, prolonged bed rest, ICU care, adverse drug effects, and residual disease pathology can cause

respiratory distress, dyspnoea, and palpitation during walking and daily functional activities. Respiratory distress during walking/ activities can cause significant impairment in exercise capacity (endurance) and PFT parameters.[34]

Exercise intolerance, measured by exercise capacity, is one of the key features of acute and chronic lung diseases[9] and is associated with poor survival[46] and reduced QoL.[47] Self-paced 6-MWD is a validated tool to measure the exercise capacity following pulmonary diseases,[9,46] and it correlates with peak functional or aerobic capacity.[34,48] Chan KS et al.,[48] in their studies, reported a minimally important difference of 20−30 m in 6-MWD could be considered significant changes in exercise capacity (endurance) in patients with acute respiratory distress syndrome or acute respiratory failure. Our review found a mean difference of 45.79 m with 95% of 31.66 m to 59.92 m.

Previous Cochrane and non-Cochrane reviews demonstrated the positive effects of pulmonary rehabilitation programs on increasing exercise capacity and PFT parameters in chronic lung disease,[49−55] including chronic obstructive pulmonary disease and interstitial lung diseases. The American Thoracic Society/European Respiratory Society defined pulmonary rehabilitation as a patient-tailored, structured, comprehensive intervention that included patient assessment, exercise training, education, and behavior training as essential for pulmonary rehabilitation.[9] Pulmonary rehabilitation is usually being delivered over several weeks. During this review, we observed that many pulmonary rehabilitation program components, like education and behavioral treatment, were not instructed in many patients. In a few studies, the study duration was very short (1-week), and there was a lack of consistent, thorough assessment at baseline and follow-up visits. There were significant variations in the exercise or activity schedules, though the core components[9] of the pulmonary rehabilitation program-aerobic exercise/ endurance training and RMT exercises were included in all studies.

Any form of exercise (walking exercise, running, cycling, ergometer training, etc.) or physical activity (mobility training, treadmill training, etc.) that produces an increased heart rate and respiratory volume (to meet the increased oxygen demands in the activated muscles) is called aerobic exercise.[55] Respiratory muscle training comprises breathing exercises, airway clearance techniques, and strengthening exercises of respiratory muscles. Aerobic exercises/ endurance training cannot improve the pressure-generating capacity of the inspiratory muscles.[9,56,57] The RMT exercises, especially inspiratory muscle training (IMT), improve inspiratory muscle strength and endurance.[9,57] RMT can reduce dyspnoea and increase peak inspiratory flow.[9,58] Studies[59,60] on critically ill patients reported RMT is effective in persons with weaning failure (from mechanical ventilation). Respiratory muscle training effectively reduces the duration of mechanical ventilation and improves respiratory muscle function in ICU.[9,59,60] Ozyemisci T[32] and Li Lei[34] conducted RR training in an ICU set-up. Both[32,34] reported significant improvement in respiratory muscle function in patients recovering from active SARS following RR training.

Exercise intensity, duration, and frequency are essential factors for increasing the aerobic and RMT exercise capacities.[9,61] This review observed that in most studies, the activity schedule, duration, and intensity of exercises (RR) were planned according to each patient's oxygen saturation level, Borg dyspnoea score, body temperature, respiratory rates, and mental status.

The PFT parameters, FVC, and FEV1 largely depend on the status of the respiratory muscle function, lung compliance, and airway resistance.[55] In contrast, DLCO largely depends on lung parenchymal changes (blood flow and alveolar damage), provides information on the quantitive measurement of gas transfer in the lungs.[62] This meta-analysis could not show the consistent beneficial effects in all PFT parameters following RR training. The impact of RR is challenging to evaluate when disease (lung involvement) course, severity, and

resolution of lung pneumonia are inconsistent/ variable in a particular disease.

Exercise training is the best available means of improving muscle function.[9] However, the exact mechanisms of improving exercise capacity and PFT parameters in the SARS population are still unclear. We speculate that aerobic exercises and RMT might have improved the respiratory muscle function, inspiratory volume, expiratory reserve capacity, and reduced airway obstruction, thereby reducing the dyspnoea, improving gas exchange and fatigue on physical activities, and increasing exercise capacity and PFT parameters in patients with SARS recovering from active disease.

The previous reviews,[9,42] conducted on acute and chronic lung diseases, reported that the pulmonary rehabilitation program, as a whole or every activity, is a safe intervention, does not cause significant adverse events or increase mortality. Similarly, we also noticed that none of the studies had reported serious adverse events (including death) during the training program. However, few transient events (pulse rate, dyspnoea, drop of saturation rate) related to exercises were reported from a few patients, especially those who were admitted to ICU.

However, a few aspects should be considered during the interpretation of this study's results. (1) This study included a large number of observational studies. Among them, few were retrospective studies (Level-4 evidence); (2) The search criteria were limited to English language articles only; (3) The number of studies in each pooled analysis was significantly less. Most of the findings were reported based two-three studies; (4) There was heterogeneity between the studies. Heterogeneity was probably due to different study designs and different patients' conditions. This review included patients with various severity of SARS-CoV diseases; (5) Respiratory rehabilitation was provided at different clinical set-ups (ICU, IPD, OPD, Home). The activities of RR were not uniform across the studies. Duration and composition of RR were different in each study; (6) This review evaluated only the short-term effect (1 to 6 weeks) of RR in SARS patients. The long-term efficacy of RR was not assessed; (7) During analysis, this study did not consider other comorbidities like myopathy, neurological disorders, or femoral head necrosis during outcomes assessment.

Conclusions

This systematic review demonstrated a positive association between respiratory rehabilitation and exercise capacity and PFT parameters in patients with SARS infection. Respiratory rehabilitation did not cause significant adverse events or increase mortality in the SARS population. Among the various program schedules, aerobic exercises and RMT could be used as important techniques to improve exercise capacity and lung function. However, additional RCT is needed comparing RR and conventional treatment to determine the best RR program/ schedule (in terms of initiation, duration, and components) and to measure the accurate treatment efficacy in COVID-19 patients at different set-ups, both for short and long duration.

Declaration of Competing Interest

In this study, there were no competing interests or financial benefits to the authors.

Acknowledgments

Not applicable

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2022.01.005.

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