Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Does pulmonary rehabilitation improve pulmonary function and quality of life among long COVID patients with residual pulmonary symptoms?

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RECOMMENDATION

We recommend individualized pulmonary rehabilitation with pre-intervention medical clearance for long COVID patients who show residual respiratory symptoms *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

The panel recommends that the start and duration of pulmonary rehabilitation of each patient should be individualized depending on the assessment of a pulmonologist. Studies showed that the assessment of pulmonary rehabilitation among long COVID patients should start at least 6 months after their hospital admission and last for as long as 6 weeks. However, recommendations on when the assessment for pulmonary rehabilitation should start differ across professional medical societies. An international task force with representation from the European Respiratory Society and the American Thoracic Society recommends that the assessment should be done 6-8 weeks after hospital discharge in order to identify patients who will have residual symptoms. In addition, pulmonary rehabilitation for other disease conditions lasts for 6-9 weeks.

Key Findings

We found one randomized controlled trial that investigated the effect of pulmonary rehabilitation (PR) among long COVID patients with residual respiratory symptoms. The study was found to have a moderate risk of bias due to absence of blinding for both patients and outcome assessors and unclear allocation process. They also enrolled only participants above 65 years of age. Based on moderate quality of evidence, pulmonary function tests of those who received pulmonary rehabilitation significantly improved. Quality of life and anxiety scales also significantly differed between groups, with improvement noted in the PR group compared to no PR. There was no significant difference for depression and activities of daily living between groups and within groups before and after the intervention. The RCT did not report any adverse events; indirect evidence from PR done on COPD patients likewise showed no to low number of adverse events which did not hinder the feasibility and safety of the procedure of pulmonary rehabilitation.

Introduction

COVID-19 patients suffer long term effects after the acute phase of the infection, a condition now known as long COVID. Other terms referred to this condition are post-acute COVID-19 syndrome,

post-acute sequelae of COVID and long-haul or long-tail COVID. This group includes patients suffering from symptoms four to twelve weeks after the acute phase (ongoing symptomatic COVID-19) and those suffering symptoms for >12 weeks past the onset of infection (post-COVID-19 syndrome) [1]. Pulmonary rehabilitation (PR) is a multidisciplinary approach used in improving functional status of patients who are suffering/suffered pulmonary diseases such as interstitial lung disease, chronic obstructive pulmonary disease and even SARS infection [2,3].

Review Methods

We searched for articles that investigated long COVID patients (P) who underwent respiratory rehabilitation (I) to improve patients' pulmonary function and quality of life (O). We performed a systematic literature search in online databases such as MEDLINE, Cochrane, and Google Scholar. Additional searches in MedRxiv, BioRxiv, clinicaltrials.gov , and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used mesh terms for "long COVID," "post-COVID," "respiratory rehabilitation," and "pulmonary function". References from review articles were also manually searched for additional articles. We also performed a free search. Letters, narrative reviews, and case reports were excluded. Studies that did pulmonary rehabilitation while patient is still admitted at the ICU were also excluded.

Results

Efficacy

Our initial search yielded 215 articles from which we obtained one randomized control trial (RCT) which fit our inclusion criteria. Liu et. Al. [4] investigated the effect of pulmonary rehabilitation which included respiratory muscle training, cough exercise, diaphragmatic training, stretching exercise and home exercise among long COVID patients at least 6 months after their hospital admission (N= 76, intervention group n= 38). Participants were all above 65 years old and those who received the intervention underwent their regimen once a day for ten minutes, with two sessions per week for 6 weeks.

Primary outcome was the respiratory function reported as forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and diffuse lung capacity for carbon monoxide (DLCO) pre-PR and six weeks post-PR. (Table 1). Patients receiving PR had statistically significant improvement in all pulmonary function tests compared to the control group, as well as post-PR pulmonary parameters compared to pre-PR. Among the secondary outcomes, those who received PR had significant improvement in quality of life (assessed using the Short Form-36 questionnaire) compared to those who did not (p value <0.05 among all eight domains: (physical health, body role function, physical pain, general health, energy, social function, emotional role function, mental health). Anxiety and depression scores improved post-intervention in the PR group, but only the anxiety scores were statistically significant within and between the groups compared. Activities of daily living (ADL) assessed using the Functional Independence Measure (FIM) on the other hand showed no significant difference among and between groups pre and post-PR.

This RCT was appraised to have a moderate risk of bias because blinding was not possible for the participants. Outcome assessors were also not blinded and the allocation process was not mentioned. This study is also limited by the population, which investigated only patients aged 65 years or older.

Table 1. Differences among those who received pulmonary rehabilitation (PR) and no PR (reported as mean difference, 95% CI, p-value)

	PR vs no PR	Control (pre vs 6 wks after)	PR (pre vs 6 wks after)
FEV1 (MD in L)	-0.18 (95%CI -0.31 to -0.05, p <0.05)	0.13 (0.02 to 0.24, p=0.02)	0.34 (0.26 to 0.42, p <0.05)
FVC(MD in L)	-0.28 (-0.48 to -0.08, p<0.05)	0.31 (0.07 to 0.55, p=0.01)	0.57 (0.34 to 0.80, p <0.05)
FEV1/FVC (MD %)	-6.96 (-9.81 to -4.11, p <0.05)	0.79 (-2.0 to 3.58, p =0.564)	7.7 (4.87 to 10.55, p<0.05)
TLCO (MD %)	-15.1 (-20.98 to -9.22, p <0.05)	2.3 (-3.51 to 8.11, p =0.43)	17.8 (12.4 to 23.2, p <0.05)
Exercise capacity (6min walk test,m)	-55.1 (-90.4 to -19.77, p <0.05)	1.5 (-33.73 to 36.73, p=0.93)	49.6 (14.2 to 85, p <0.05)
ADL (FIM)	-0.5 (-5.3 to 4.35, p =0.84)	-0.4 (-5.16 to 4.36, p=0.87)	0.2 (-5.32 to 5.73, p =0.07)
Quality of life (FIM)	Across 8 domains, significant improvement within groups, and in between groups after 6 weeks, p<0.05		
Anxiety	7.5 (4.38 to 10.6, p<0.05)	-0.9 (-4.26 to 2.46 p=0.6)	-8.9 (-12.22 to -5.58, p<0.05)
Depression	1.3 (-1.68 to 4.2, p=0.39)	-0.1 (-3.39 to 3.19, p=0.95)	-1.9 (-5.09 to 1.29, p=0.24)

Safety

Liu et al. did not report adverse events in their study. Indirect evidence showed PR to be generally safe and feasible. He et al. reported that no adverse events were observed in the conduct of their RCT comparing PR versus no PR for the improvement of dyspnea, endurance capacity, and health-related quality of life in patients with chronic obstructive pulmonary disease (COPD) in acute exacerbation [5]. Pleguezuelos et al., used limb warm-up and aerobic exercises in their study for PR, reported two major complications (defined as warranting discontinuation of PR), both in patients with previous hypertension, diabetes and dyslipidemia: acute coronary syndrome in a 71-year-old patient, and a debut of cardiac arrythmia in a 60-year-old patient. They reported the incidence of major complications as 2.7/10,000 hours of PR (n=291). Minor complications were noted: three individuals with acute low back pain and two with increased sensation of dyspnea (incidence of 6.5/10 000 hours) of physical exercise [6].

Recommendations from Other Groups

The WHO recommends that patients who experience persistent symptoms or disability after discharge from the hospital should be screened for physical, mental and cognitive impairments, and those deemed to have rehabilitation needs should be given such, tailored to the needs of individual patients [5]. No specific recommendation or guideline was further provided. An international task force composed of a European Respiratory society and the American Thoracic Society recommends assessment of respiratory function and exercise capacity 6 to 8 weeks after hospital discharge and provide those in need with a comprehensive individualized rehabilitation program including pulmonary rehabilitation if necessary [6]. An Indian Society recommends different respiratory exercises for post-COVID patients 3-6 weeks after discharge depending on the severity of the patient's COVID-19 infection [7]. Exercises should include respiratory exercise endurance, strength training, energy conservation and patient education.

Research Gaps

There are currently nine registered ongoing clinical trials that investigate the effect of respiratory exercises among previously admitted COVID-19 patients.

References

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Appendix 1. Characteristics of Included Studies

Authors	Country	Population	Intervention	Control	Outcomes
Liu 2020	China	Previously admitted COVID-19 patients aged >65 years old recruited 6 months after the onset of infection	Respiratory rehabilitation 2 sessions per week for 6 weeks, each session held once a day for 10 minutes	No respiratory rehabilitation	Respiratory function (FEV1, FVC, FEV1/FVC, DLCO)

Appendix 2. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pulmonary rehabilitation	no rehabilitation	Relative (95% CI)	Absolute (95% CI)		
FEV1												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 0.18 higher (0.05 higher to 0.31 higher)	⨁⨁⨁◯ MODERATE	
FVC												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 0.28 higher (0.08 higher to 0.28 higher)	⨁⨁⨁◯ MODERATE	
FEV1/FVC												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 6.96 higher (4.11 higher to 9.81 higher)	⨁⨁⨁◯ MODERATE	
DLCO												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 15.1 higher (9.22 higher to 20.98 higher)	⨁⨁⨁◯ MODERATE	
6min walk test												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 55.1 higher (19.77 higher to 90.4 higher)	⨁⨁⨁◯ MODERATE	
functional independence measure												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pulmonary rehabilitation	no rehabilitation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious	none	38	38	-	MD 0.5 higher (4.35 lower to 5.3 higher)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. allocation concealment unclear, no blinding

Appendix 3. Characteristics of Ongoing Studies

	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	Organization of Pulmonary Rehabilitation of Post-COVID-19 patient with sequelae (REHABCOVID) NCT04634318	Recruiting	Study start: December 10,2020 Estimated primary completion: December 2021	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label)	France	Known COVID-19 patient who have atleast one post-COVID-19 sequelae	Respiratory tele-rehabilitation program	Respiratory Rehabilitation program	6min walk test 1min sit to stand test Dyspnea and fatigue evaluation Anxiety and depression evaluation
2	Implementation of a respiratory physiotherapy program in post covid-19 patient through tele-assistance NCT04678700	Recruiting	Start date: March 1, 2021 Estimated primary completion: June 1, 2021	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: Experimental study composed of an intervention group and a control group The control group will receive the intervention after finishing the intervention with the experimental group. Masking: None (Open Label) Primary Purpose: Treatment	Spain	Patients with COVID-19 in the recovery period who still have subjective dyspnea	Chest physiotherapy modules	No physotherapy	Euroqil-5d quality of life tool Dyspnea scale Borg Anxiety Scale
3	SingStrong: Strong Lungs through song long covid study	Recruiting	Start: March 29, 2021 Estimated complet	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary	Ireland	Previously diagnosed COVID-19 patient with residual symptoms of shortness of breath,	Biweekly hour-long breathing and singing classes	none	COVID-19 Yorkshire Rehab Screen DePaul Symptom Questionnaire

	NCT04810065		ion: July 2021	Purpose: Treatment		disordered breathing, or reduced exercise tolerance			
4	Long term functional outcomes of COVID-19 patients treated by rehabilitation services via telehealth NCT04385901	Completed but no result posted yet	Start date: May 19,2020 Completion: February 2021 (no result posted)	Allocation: Non-Randomized Intervention Model: Parallel Assignment Intervention Model Description: Patients receiving care through the program developed by the University of Missouri Healthcare system will, if willing, return for follow up testing and be compared against a matched group that did not receive the rehabilitative treatment to see if there are short or long term differences. Masking: Double (Investigator, Outcomes Assessor) Purpose: treatment	USA	Coid-19 confirmed in the previous 6 months	Therapy intervention including speech therapy, occupational therapy, strength exercise, pulmonary strengthening and breathing exercises	Standard of care	Change in 6minute walk test Change in Qulaity of life (SF-36) Change in peak flow meter test Change in strength testing
5	Breathing Exercise After COVID-19 Pneumonia NCT04771598	Not yet recruiting	Start date: February 25, 2021 Estimated completion date: June 30, 2021	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: Randomised Controlled Study Masking: None (Open Label) Primary Purpose: Supportive Care	Turkey	Known COVID-19 patients with residual dyspnea 2 months after the diagnosis of COVID-19	Respiratory exercises	Breathing exercises	Pulmonary function tests (FEV1, FVC. FEV1/FVC, MVV) 6 min walking test

7	Effects of Respiratory muscle training in people who have had COVID-19 disease NCT04734561	Not yet recruiting	Start date: Februar y 8,2021 Primary completion: July 30,202 2	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: double-blind randomized controlled clinical trial Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	Spain	Discharged COVID-19 patients who has been diagnosed n the last 3 months	Inspiratory and expiratory muscle training group	none	Health-related quality of life Exercise tolerance Maximum respiratory pressures Inspiratory muscle endurance Forced spirometry Cognitive scale assessment Psychological assessment Upper and lower limb muscle strength
8	Home-based respiratory physiotherapy and telephone-based psychological support in severe covid-19 patients (WAYRA) NCT04649736	Recruitin g	Start date: Octiber 26,202 0 Estimat ed completion: March 30,202 1	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	Peru	50-75yr old previously diagnosed COVID-19 patients	Respiratory rehabilitation	No rehabilitatio n	6min walk distance Respiratory questionnaire PHQ-9 Anxiety assessment scale QoL assessment (SF36) Pulmonary function tests (FEV,FVC) PTSD assessment
9	The effect of chest physiotherapy on respiratory capacity and the rate of respiratory gas exchange during walking on the treadmill in patients with COVID-19 after the recovery stage IRCT20160808 029264N9	Recruitin g	Start date: 9/20/20 20 Expect ed end date: 6/20/20 21	Randomized clinital trial, parallel group assignmen, double-blinded phase 2 study	Iran	35-55 years old previously hospitalized COVID-19 patients diagnosed in the past past 1-2months	Chest physiotherapy intervention with exercises and postural/movemen t rehabilitation	No rehabilitatio n, will receive intervention after the study period	Tidal volume, residual volume, FEV1, FVC