

OVERVIEW OF SYMPTOMS OF ONGOING SYMPTOMATIC AND POST-COVID-19 PATIENTS WHO WERE REFERRED TO PULMONARY REHABILITATION - FIRST SINGLE-CENTRE EXPERIENCE IN CROATIA

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SUMMARY

Background: Coronavirus-2 pandemic has changed the functioning of health systems worldwide. It is not yet fully known which symptoms of the disease are most commonly presented in patients referred for pulmonary rehabilitation. Our aim was to investigate the profile of patients referred for pulmonary rehabilitation; what symptoms they had during the acute phase of the disease and what symptoms were still present at the start of pulmonary rehabilitation.

Subjects and methods: Study included ongoing symptomatic and post-COVID patients who attended standard, in person pulmonary rehabilitation program. Patients had COVID-19 disease at least four weeks before attending pulmonary rehabilitation. Patients completed questionnaires of self-reported somatic deficits during acute and post-COVID-19 stage as well as questionnaires regarding their psychological symptoms. Pulmonary function test, expiratory and inspiratory muscle strength, hand grip strength and six-minute walk test was performed prior and after pulmonary rehabilitation.

Results: Study included 63 patients (32 male, 31 female), with mean age of 52.9 years. During acute COVID-19, majority of patients complained of fatigue, cough, dyspnea, myalgia and headache. More than 85% of patients reported pulmonary deficits during ongoing symptomatic and post-COVID-19 stage. Emotional distress and anxiety levels were significantly elevated in acute stage, while depression, anger and the need for help was not significantly elevated. All reported symptoms were significantly reduced in post-COVID-19 stage. There was statistically significant difference in six-minute walk distance, inspiratory and expiratory muscle strength and hand grip strength between first and final testing.

Conclusions: Results of our study are similar with previous studies, the most common symptoms during acute phase were fatigue, cough and dyspnea and fatigue and respiratory problems during ongoing symptomatic and post-COVID stage. Emotional distress diminishes significantly in post-COVID stage. Further larger studies are needed to clarify which acute disease symptoms are predominant in patients referred to pulmonary rehabilitation and cause prolonged discomfort.

Key words: COVID-19 - post-acute COVID-19 syndrome - pulmonary rehabilitation

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INTRODUCTION

A novel disease named coronavirus disease (COVID-19) by the World Health Organization (WHO), broke out in Wuhan, Hubei in December 2019 and spread rapidly to other provinces in China, as well as to many countries around the world (Zhu et al. 2020, Grigoletto et al. 2020). On 11 March 2020, one year ago, the WHO declared the COVID-19 outbreak a pandemic, which is still actual. So far (March 1, 2021) there is more than 11 million confirmed cases and almost 2.5 million deaths (WHO 2021). People infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) most frequently present with respiratory tract infection and symptoms such as fever, cough, fatigue, sputum production, dyspnoea, sore throat, and headache (Guan et al. 2020, Guo et al. 2020, Rodriguez-Morales et al. 2020). The virus can cause a spectrum of disease from mild upper respiratory symptoms to severe life-threatening pneumonia. The WHO estimates that 80% of cases are asymptomatic or mild and 20% of cases are severe (with 5% considered critical [i.e. requiring ventilation and life support]) (WHO, 2020). Although there are no widely accepted definitions of the

stages of COVID-19 recovery, one of the categories that are frequently used are: „acute COVID-19“: symptoms of COVID-19 for up to 4 weeks following the onset of illness, „ongoing symptomatic COVID-19“: symptoms of COVID-19 from 4 to 12 weeks following the onset of illness; „post-COVID-19“: symptoms that develop during or after COVID-19, continue for ≥ 12 weeks, not explained by an alternative diagnosis (NICE guidelines, 2020). These stages reflect symptomatic recovery, and are not related to active viral infection and infectivity. It is still not clear if COVID-19 will leave permanent lung and/or physical damage and, if so, to what extent. Alterations of lung tissue such as ground-glass opacities, consolidation, vascular thickening, bronchiectasis, pleural effusion, crazy paving pattern and irregular solid nodules (Wu et al. 2020), may progress in over 80% of patients (Pan et al. 2020). In previous limited studies of follow up of patients with COVID-19, there were mild reduction in pulmonary function tests and six-minute walk test distance (6MWD). A mild reduction was found in diffusing capacity of the lungs for carbon monoxide (DLCO) (Torres-Castro et al. 2020, Daher et al. 2020). There were relevant limitations of the walk distance during six-

minute walk test (Daher et al. 2020, Curci et al. 2020). In one Chinese follow up study impaired diffusing capacity, lower respiratory muscle strength and lung imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more total lung capacity (TLC) decrease and 6MWD decline (Huang et al. 2020). Persistent physical symptoms following acute COVID-19 are common, and typically include fatigue, dyspnea, chest pain, and cough (Polastri et al. 2020). Patients recovering from COVID-19 may also have additional psychological (eg, anxiety, depression, post-traumatic stress disorder [PTSD]) and cognitive (eg, poor memory and concentration) symptoms, similar to the syndrome experienced by patients recovering from other critical illnesses, known as post-intensive care syndrome (PICS). Several observational series describe persistent symptoms in patients following acute COVID-19, with one-third or more experiencing more than one symptom (Carfi et al. 2020, Xiong et al. 2021, Goërtz et al. 2020, Halpin et al. 2021). It is well known from studies in patients with COPD that home-based unsupervised exercise training is not improving exercise performance in comparison to a comprehensive supervised programme (Ries et al. 1995). In addition, patients suffering from post-intensive care syndrome (PICS) are facing not only physical but also cognitive and psychosocial impairments. Therefore, these conditions should be targeted in a multidisciplinary programme (Brown et al. 2019), such as pulmonary rehabilitation according to its definition (Spruit et al. 2019), by covering the specific needs of patients suffering from post-intensive care syndrome in COVID-19 patients (Siddiq et al. 2020). Preliminary data from China support this assumption (Liu et al. 2020). To define a rehabilitation programme for post-COVID-19 patients, mirroring the algorithm of pulmonary rehabilitation for patients with chronic respiratory conditions is an evidence-based, well recognised, widely accepted available option (Polastri et al. 2020).

The aim of our study was to investigate the profile of patients referred for pulmonary rehabilitation, what symptoms they had during the acute phase of the disease, and what symptoms were still present at the start of pulmonary rehabilitation.

SUBJECTS AND METHODS

Subjects

This study included post-COVID disease patients who attended standard in-person pulmonary rehabilitation program (PRP) five days a week, for three weeks. Patients were SARS-CoV-2 positive and had COVID-19 disease at least four weeks before attending pulmonary rehabilitation.

Methods

The program comprised three weeks of physical training combined with multidisciplinary education and individual approach. Patients attended one supervised sessions five days weekly. The first visit included initial screening with familiarization to all testing procedures and questionnaire of self-reported deficits during acute and post-COVID-19 phase. Patients were asked to complete our questionnaire about acute COVID disease symptoms and prolonged deficits after COVID disease. Psychological evaluation was done using a clinical interview and questionnaires assessing emotional distress during acute (the patients were asked to recall the intensity of presented psychological symptoms) and post-COVID-19 stage. The examined variables were: *Emotional distress, Anxiety, Depression, Anger, Need for help*. The second visit included pulmonary function testing, basic anthropometric measurements, hand grip muscle strength testing with dynamometer and 6-minute walking test (6MWT). Cardiopulmonary testing (CPET) was performed in patients with suspected cardiac and pulmonary defects that were not diagnosed previously. After three weeks of pulmonary rehabilitation patients repeated pulmonary function testing of inspiratory and expiratory muscle strength, hand grip strength and 6MWT.

Pulmonary function testing was performed with the Schiller LFX8 spirometer, spirometry was done by American Thoracic Society and European Respiratory Society standards (Brusasco et al. 2005, Miller et al. 2005), with standardization of protocols and quality control procedures ERS93&GLI2017. The highest FEV1 and FVC values of at least 3 acceptable spirometric maneuvers and the largest FEV1/FVC from a technically acceptable curve were used for analysis. Total lung capacity and Raw (measure of airway obstruction) were recorded using a body plethysmograph. Diffusing lung capacity for carbon monoxide, carbon monoxide transfer coefficient (KCO) and alveolar volume (VA) were measured by the single-breath method, according to the recommendations of the American Thoracic Society and European Respiratory Society standards. We also measured maximum static inspiratory pressure (PImax) or maximum static expiratory pressure (PEmax). All subjects used this simple method to gauge inspiratory and expiratory muscle strength. The 6-minute walking test was performed indoor using a 30 m walking course. Patient preparation and measurements were performed according to the ATS/ERS statement (Crapo et al. 2002, Enright PL 2003).

We obtained chest imaging and electrocardiography (ECG). Additional tests, such as echocardiography, holter monitoring and CPET were necessary in selected patients. In patients with persistent cardiac symptoms, particularly palpitations or symptoms of dysautonomia, despite an unremarkable ECG, we performed extended

Table 1. Descriptive statistics prior pulmonary rehabilitation and after pulmonary rehabilitation

	Mean ± SD
Age (years)	52.9 ± 15.53
FVC (L)	4.01 ± 1.31
FVC (%)	98.62 ± 20.51
FEV1 (L)	3.12 ± 0.99
FEV1 (%)	92.93 ± 23.30
FEV1/FVC (%)	76.64 ± 9.93
DLCO (%)	61.43 ± 19.77
KCO (%)	73.14 ± 18.11
VA (%)	81.71 ± 21.77
Raw (kPa/L/s)	0.25 ± 0.10
TLC (%)	96.91 ± 25.72
RV/TLC	29.42 ± 11.77
6MWD1 (m)	410.04 ± 145.29
6MWD1 (%)	70.10 ± 23.84
6MWD2 (m)	441.97 ± 181.69
6MWD2 (%)	72.93 ± 30.65
Δ6MWD (m)	33.04 ± 45.76
Hand grip1 (N)	79.34 ± 83.91
Hand grip2 (N)	96.82 ± 72.77
ΔHand grip (N)	17.48 ± 57.29
PI _{max} 1 (cmH ₂ O)	71.40 ± 31.12
PI _{max} 1 (%)	65.72 ± 28.73
PI _{max} 2 (cmH ₂ O)	85.56 ± 36.67
PI _{max} 2 (%)	79.10 ± 34.32
ΔPI _{max} (cmH ₂ O)	10.20 ± 14.10
PE _{max} 1 (cmH ₂ O)	89.07 ± 37.12
PE _{max} 1 (%)	93.61 ± 65.9
PE _{max} 2 (cmH ₂ O)	98.00 ± 44.62
PE _{max} 2 (%)	91.44 ± 40.82
ΔPE _{max} (cmH ₂ O)	7.93 ± 12.56

FVC – forced vital capacity; FEV1 – forced expiratory volume in one second; DLCO – diffusing capacity of lung for carbon monoxide; KCO – carbon monoxide transfer coefficient; VA – alveolar volume; Raw – airway resistance; RV/TLC – residual volume / total lung capacity; TLC – total lung capacity; 6MWD – six-minute walk distance; PI_{max} – maximum static inspiratory pressure; PE_{max} – maximum static expiratory pressure; *Paired T-test p < 0.05

holter monitoring. If dyspnea remained unexplained after all these test, we referred to CPET. CPET may identify the etiology of symptoms and may also identify those who may benefit from pulmonary or physical rehabilitation (eg, patients with deconditioning). CPET provides an integrated evaluation of the cardiorespiratory system during exercise (Parshall et al. 2012).

Statistical Analyses

Statistical analyses was performed with SPSS Version 11.0 statistic software package. Data analysis was performed using descriptive statistics and paired

T-test. A p value (2-sided) < 0.05 was considered to indicate a statistically significant difference in all comparisons.

RESULTS

This study included 63 patients (32 male and 31 female), with mean age of 52.9 years who attended standard PRP five days a week, for three weeks after COVID-19 disease. Majority of the patients were admitted four and more weeks after the disease. In 14.1% patients were admitted after four weeks, in 39.1% after 4-8 weeks, in 31.3% 8-12 weeks, in 10.9% 3-4 months and in only 3.1% 4 and more months after the disease onset (Figure 1). Fatigue, cough and dyspnea were three most frequent symptoms with 87.5%, 78.1% and 71.9% patients reported (Figure 2). Average length of high fever was 8 days, and the highest temperature measured was 40.8°C. Oxygen therapy was applied in 40% of patients and a small number of them were on mechanical ventilation (8%). More than 85% of patients reported pulmonary deficits during ongoing symptomatic period and post-COVID-19 (Figure 3). Functional and pulmonary function test results of testing prior and after pulmonary rehabilitation are listed in Table 1. There were statistically significant difference in six-minute walk distance, inspiratory and expiratory muscle strength, hand grip muscle strength between first and final testing. During acute phase, Emotional distress and Anxiety were significantly elevated, which, together with all other reported psychological symptoms, reduced significantly in post-COVID-19 stage.

DISCUSSION

During the acute COVID-19, majority of our patients complained of fatigue, cough, dyspnea, myalgia and headache (Figure 2) which is similar to other studies (Rodriguez-Morales et al. 2020). Many authors describe persistent symptoms in patients following acute COVID-19 such as fatigue (15 to 87%), dyspnea (10 to 71%), chest pain or tightness (12 to 44%), cough (17 to 26%) (Mikkelsen et al. 2021). Chopra and coauthors find that among 1600 patients in United States hospitals with acute COVID-19, at 60 days after discharge 33% reported persistent symptoms and 19% reported new or worsening symptoms, and almost 40% of patients were unable to return to normal activities at 60 days following hospital discharge (Chopra et al. 2020). In another study (approximately 1300 hospitalized COVID-19 patients discharged to home) authors also find that persistent symptoms can affect functional ability. Only 40% of patients were independent in all activities of daily living at 30 days despite home health services (Bowles et al. 2020). After at least four weeks because of persistent physical symptoms following acute COVID-19

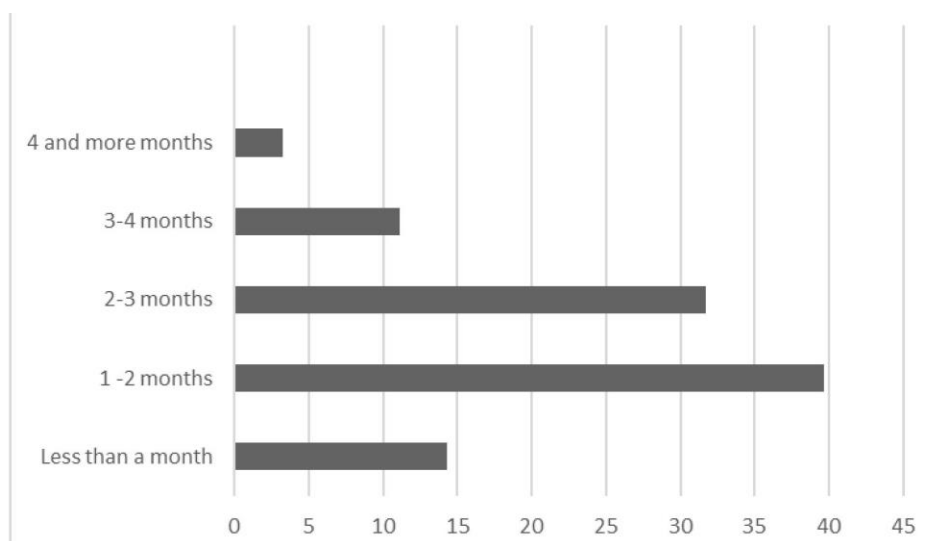


Figure 1. Time after illness onset and starting with pulmonary rehabilitation

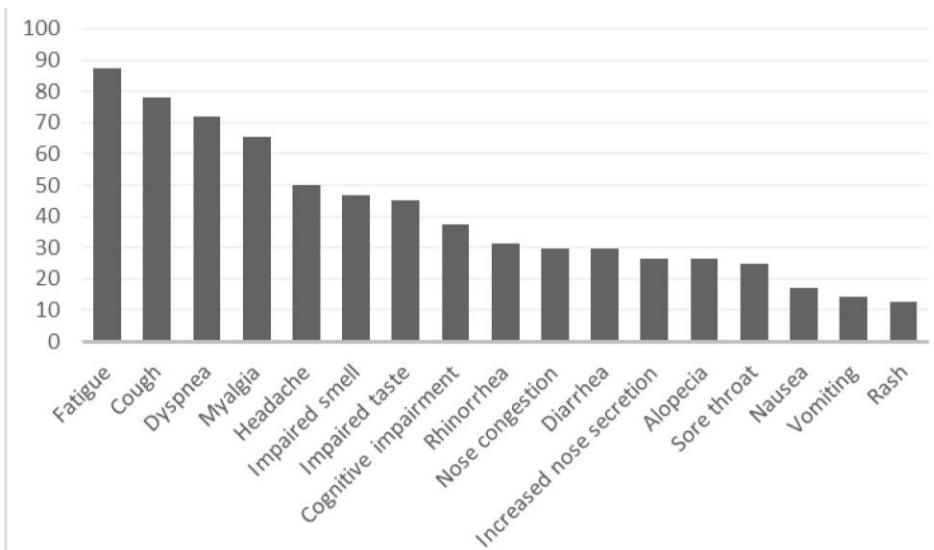


Figure 2. Percentage of acute COVID-19 symptoms

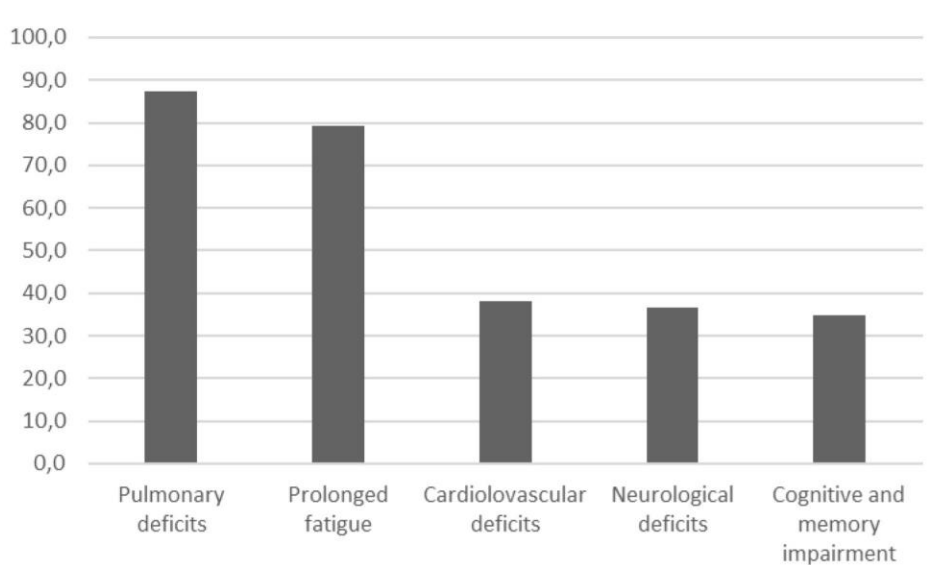


Figure 3. Percentage of deficits during ongoing symptomatic and post-COVID-19 phase

our patients were referred for rehabilitation. During acute COVID-19 87.5% of patients developed fatigue and at the time of referring to the pulmonary rehabilitation 79,4% of patients had prolonged fatigue. Lung problems as shortness of breath on exertion, dyspnea, pain on deep breathing, coughing, feeling that he cannot breathe completely, shallow breathing, feeling of catching air were reported by 87.3% of patients. More than a third of patients (38.1%) also had heart problems like increased systolic and diastolic pressure, tachycardia, chest pressure. Neurological difficulties in the form of clumsiness, twitching of the extremities, slightly impaired hearing and vision, trembling of the hands were reported by 36.5% of patients. Problems with memory and concentration with psychological problems, depression were present in 34.9% of patients. They mostly complained of forgetfulness, hallucinations, memory holes, fear of re-infection, fear of being in the hospital. They were also noticed during rehabilitation and emotional outbursts (crying and aggression) in retelling the course of the disease. Our results are comparable with other similar studies that investigated post-COVID symptoms (Daher et al. 2020, Carfi et al. 2020). During rehabilitation, we noticed very good patient compliance. Patients felt safe while exercising because they were in a hospital setting and with medical professionals.

All patients referred to pulmonary rehabilitation started a modified, personalized pulmonary rehabilitation (the team includes a pulmonologist, psychologist, respiratory physiotherapist, general physiotherapist, respiratory nurse, nutritionist). Part of the patients were first hospitalized as acute COVID-19 and then transferred directly to inpatient pulmonary rehabilitation, but the majority of patients were referred from an outpatient clinic. The pulmonary rehabilitation program was individualized for each patient depending on the findings of pulmonary functions, functional outcomes, age, gender, and previous level of fitness of the patient. The average age was 52.90 years. The basic rehabilitation program for COVID-19 patients was based on a pulmonary rehabilitation program for COPD patients (Corhay et al. 2014).

All patients had chest X-ray and/or CT pulmonary angiography. Majority of patients in the acute COVID-19 received therapy with corticosteroids, antibiotics, antivirals, oxygen therapy. Oxygen therapy was applied in 40% of patients. Majority of patients was initially on high-flow oxygen therapy, and a small number of them were on mechanical ventilation (8%). Patients who were not hospitalized and had a lot of symptoms in the post-COVID-19 phase were therefore referred for rehabilitation.

Pulmonary function test of our patients showed no limitations in spirometry and body plethysmography but it showed mild reduction in diffusing capacity of the lungs

for carbon monoxide mainly because of disorders at the level of the alveocapillary membrane. Compared to previous studies (Torres-Castro et al. 2020, Daher et al. 2020), our tests are better, probably because in our study there was a higher number of patients who were treated on an outpatient basis during acute COVID-19 disease and did not have a severe form of the disease. Our 6MWT results are satisfactory, better than in previous studies (Daher et al. 2020, Curci et al. 2020), which, however, were mostly based on early inpatient rehabilitation and these patients had limiting 6MWT results. Our results show reduced strength of respiratory inspiratory muscles with satisfactory strength of expiratory muscles, which is comparable to a previous study (Huang et al. 2020). Functional impairment of patients surviving the COVID-19 acute phase has been poorly described, and majority of available information is inferred from patients with other clinical conditions (e.g. acute respiratory failure) (Zampogna et al. 2021). In our study functional impairment of patients surviving the COVID-19 was assessed with several diagnostic test. Cardiopulmonary condition of patients referred to pulmonary rehabilitation was assessed with pulmonary function tests, ECG and/or echocardiography and 6MWT with or without CPET.

Almost half of the patients (39,7%) were included within 1-2 months of the onset of the disease, only 14.3% were included within a period of up to one month (Figure 1). Two recent studies suggested that early, post-hospitalization rehabilitative interventions would be recommended (Belli et al. 2020, Curci et al. 2020). Our results show that the recruitment time of our patients to pulmonary rehabilitation is mostly up to 8-12 weeks.

In terms of patient's emotional reactions, most patients described some emotional distress during acute infection stage and hospitalization (acute reaction to stress) – fear of death, anxiety from infecting family members, feeling breathless and helpless which was more intense with the level of respiratory support needed. Three of them reported hallucinations in acute phase (two during high flow oxygenation and one separate from any medication or fever). Most patients who had experienced high flow or mechanical ventilation report of „new found respect for life and health“ and have elements of traumatic growth. From the clinical interviews it was visible that after the acute reaction to stress, most of our patients return to stable emotional profile, with minimal or no symptom of depression, anxiety and stress. Also, from the qualitative data from clinical interviews, we presume that the role of patient's personality and/or severity of disease along with the long-term effect on quality of life in the months to come, will determine the overall psychological wellbeing in post-COVID-19 stage. Pulmonary rehabilitation will have a great effect on these variables because it targets to restore the patient's best possible physical state.

Study limitations include a small sample size, single study location, potential bias from self-reported symptoms during illness episode (recalled data) and in ongoing symptomatic and post-COVID-19 period.

To our knowledge, this is the first study using six-minute walk test, inspiratory and expiratory muscle and hand grip strength as outcome measurements in COVID-19 patients referred to pulmonary rehabilitation. This study also showed that all patients after pulmonary rehabilitation had better respiratory muscle strength, exercise capacity and hand grip muscle strength.

CONCLUSIONS

Our aim was to investigate the profile of patients referred for pulmonary rehabilitation, what symptoms they had during the acute phase of the disease, and what symptoms were still present at the start of pulmonary rehabilitation. During rehabilitation, we noticed very good patient compliance. Patients felt safe while exercising because they were in a hospital setting and with medical professionals. The results of our study are similar with previous studies, the most common present symptoms during acute phase were fatigue, cough and dyspnea and fatigue and respiratory problems during ongoing symptoms and post-COVID stage. There were statistically significant difference in six-minute walk distance, inspiratory and expiratory muscle strength, hand grip muscle strength between first and final testing. Study limitations include a small sample size, single study location, potential bias from self-reported symptoms during illness episode and in ongoing symptomatic and post-COVID-19 stage. This is why further larger studies are needed to provide an answer to what symptoms of the acute disease patients have who are referred to pulmonary rehabilitation due to prolonged discomfort. Our study is still ongoing and we continue to recruit patients.

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Contribution of individual authors:

Tajana Jalušić Glunčić, Davorka Muršić & Latinka Basara: conception and design of the manuscript and interpretation of data, literature searches and analyses, evaluations, manuscript preparation and writing the paper.

Lana Vranić: data collection, paper drafting.

Tajana Jalušić Glunčić, Davorka Muršić, Latinka Basara, Lana Vranić, Andreja Močan, Mateja Janković Makek & Miroslav Samaržija: made substantial contributions to conception and design, participated in revising the article and gave final approval of the version to be submitted.

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