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Natural Course of Muscular Strength, Physical Performance, and Musculoskeletal Symptoms in Hospitalized Patients with COVID-19

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PII: S0003-9993(22)01589-1
DOI: https://doi.org/10.1016/j.apmr.2022.09.001
Reference: YAPMR 58629

To appear in: *Archives of Physical Medicine and Rehabilitation*

Received date: 17 February 2022
Revised date: 16 August 2022
Accepted date: 3 September 2022

Please cite this article as: Ayça Utkan Karasu MD , Levent Karataş MD , Yeşim Yıldız MD , Zafer Günendi MD , Natural Course of Muscular Strength, Physical Performance, and Musculoskeletal Symptoms in Hospitalized Patients with COVID-19, *Archives of Physical Medicine and Rehabilitation* (2022), doi: https://doi.org/10.1016/j.apmr.2022.09.001

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Running title: COVID-19 and Muscular Strength

Natural Course of Muscular Strength, Physical Performance, and Musculoskeletal Symptoms in Hospitalized Patients with COVID-19

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Acknowledgment: None

Conflict of interest: None

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Clinical Trials registiration number: NCT04784546

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Abstract

Objective

To investigate the course of muscle strength, musculoskeletal symptoms and physical performance over time in hospitalized COVID-19 patients, and their relationship with disease severity at admission.

Design

Prospective cohort study.

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Setting

Pandemic clinic of Gazi University Hospital, Ankara, Turkey.

Participants

76 adult COVID-19 patients (age >18 years) were enrolled in the study between March 2021 and May 2021. The participants were grouped as “mild”, “moderate”, and “severe” according to clinical and radiological findings.

Outcome measures

The fraction of inspired oxygen (FiO2), oxygen saturation (SpO2), hand grip strength (HGS), 5-times sit and stand test (5XSTS), modified Borg scale at rest (mBorg-rest), modified Borg scale during activities of daily living (mBorg-ADL), Barthel index, and visual analog scale for myalgia (myalgia-VAS) values were recorded on the first day of hospitalization and in the

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first, third, and twelfth weeks. Outcome measures were compared between disease severity groups. In addition, the changes in these outcome measures over time were also examined.

Results

There were 15 (19,7%) participants in the mild, 20 (26,3%) in the moderate, and 41 (53,9%) in the severe groups. At the baseline evaluation, SpO2 ($p<0.001$), FiO2 ($p<0.001$), 5XSTS ($p=0.002$), mBorg-rest ($p=0.016$), and mBorg-ADL ($p<0.001$) were different in three groups but there were no differences for HGS, Barthel index, myalgia VAS score. HGS, 5XSTS, myalgia-VAS and mBorg-ADL scores improved significantly over time in all groups ($p<0.001$, $p\leq0.001$, $p<0.001$ respectively). At the end of 12 weeks, only 5XSTS was different between the groups. 5XSTS was significantly longer in the severe group ($p=0.010$).

Conclusion

Although significant improvement was observed in the muscle strength, physical performance and musculoskeletal symptoms of patients with COVID-19 over time, the

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physical performance of these patients did not reach normal standards. We conclude that post-COVID-19 rehabilitation programs are needed to optimize the physical performance of the patients.

Key Words: COVID-19, Hand Strength, Sarcopenia, Physical Functional Performance, Muscle Strength

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List of abbreviations:

COVID-19: coronavirus disease 2019

CRP: C-reactive protein

CT: computed tomography

FiO2: fraction of inspired oxygen

HGS: hand grip strength

ICU: intensive care unit

mBorg-ADL: modified Borg scale during activities of daily living

mBorg-rest: modified Borg scale at rest

myalgia-VAS: visual analog scale for myalgia

SpO2: oxygen saturation

VAS: visual analog scale

WBC: white blood cell

5XSTS: 5 times sit and stand test

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The clinical presentation of COVID-19 ranges from asymptomatic illness to mild flu symptoms, pneumonia accompanied by acute respiratory failure or acute respiratory distress syndrome requiring intensive care unit admission, and death [1]. According to Centers for Disease Control and Prevention data, approximately 14% of patients required hospitalization [2].

Accumulating evidences have showed that the musculoskeletal symptoms can occur during the infection, even before the common respiratory symptoms begin (dry cough, nasal congestion, sore throat and dyspnea). Fatigue, arthralgia, myalgia, and muscle weakness are common symptoms in COVID-19 [3, 4]. The prevalence of myalgia has been reported between 11% to 50% in large cohort studies, regardless of disease severity [5, 6]. Even months after recovery, patients still complain of musculoskeletal symptoms such as fatigue and muscle pain [7].

Muscle weakness and exercise intolerance in COVID-19 patients are multifactorial. The most commonly accepted factors are systemic inflammation, forced physical inactivity or disuse, hypoxemia, malnutrition, and certain medications [8].

COVID-19 infection causes acute and severe inflammation. The inflammatory response may include cytokine storm with extremely high levels of proinflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [9]. Severe inflammation can cause multiple organ damage, including not only the lungs but also the muscles. Another

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factor that causes muscle weakness and exercise intolerance in these patients is immobility and prolonged bed rest. Immobilization causes significant changes in muscle mass. It can also lead to metabolic dysfunction and worsening of functional status [10]. Insufficient food intake may also cause muscle weakness and exercise intolerance in COVID-19 patients. Intense inflammation and proanorectic effect of hypoxia, together with loss of appetite, loss of taste and smell, may cause decreased consumption of nutrients. In addition, severe inflammation accompanying tissue ischemia increases caloric needs [10].

Regardless of the causes, it is important to monitor and evaluate the musculoskeletal symptoms and physical performance during the course of the disease and after discharge in COVID-19 patients. There are few studies evaluated musculoskeletal symptoms and physical performance in COVID-19 patients who do not need intensive care, during hospitalization or after discharge [5, 11]. None of these studies investigated how musculoskeletal symptoms and physical performance changes during the disease process and whether discharged patients may achieve their ideal physical performance. It is important to know the effect of disease severity on the performance of patients during hospitalization and after discharge. Thus, appropriate rehabilitation programs can be designed for patients with physical performance deterioration.

The aim of this study is to evaluate the relationship between disease severity and muscle strength, musculoskeletal system symptoms and physical performance in hospitalized patients with COVID-19, and to examine the change of these clinical parameters throughout the course of the disease.

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Methods

Study Design and Participants

This prospective cohort study was conducted in the pandemic clinic of Gazi University Hospital, which was designated as a COVID-19 hospital by the Turkey Ministry of Health. A total of 76 consecutive hospitalized polymerase chain reaction positive COVID-19 patients were enrolled in the study between March 2021 and May 2021. Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Gazi University clinical research ethics committee (Decision number: 118, February 17th, 2021). This study was registered in ClinicalTrials.gov (number NCT04784546). Pediatric, pregnant, critically ill patients who were admitted initially to ICUs, patients who had neuromuscular, orthopedic, rheumatic diseases or cancer, and those who did not agree to participate were excluded.

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Procedures

Demographic data, hospital length of stay, comorbidities, medications used for COVID-19 treatment, laboratory findings [C-reactive protein (CRP), ferritin, D-dimer, white blood cell (WBC) count, lymphocyte count] at hospitalization were recorded. FiO2, SpO2 HGS, 5XSTS, mBorg-rest, mBorg-ADL, Barthel index, and myalgia-VAS were evaluated on the first day of hospitalization. Measurements were repeated at the 1st, 3rd, and 12th weeks. All assessments were performed by the same physical medicine and rehabilitation specialist. The tests were carried out in the patient's room at bed side during hospitalization. Post-discharge evaluations were carried out in the outpatient clinic.

Participants were categorized into mild, moderate or severe groups according to WHO classification. Mild COVID-19 defines as respiratory symptoms without evidence of pneumonia or hypoxia, while moderate or severe infection defined as presence of clinical and radiological evidence of pneumonia. In moderate cases, SpO2 ≥90% on room air while one of the following was required to define the severe cases: respiratory rate >30 breaths/min or SpO2 <90% on room air [12, 13].

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Outcome Measures

Information about outcome measures is presented in Table 1.

Table 1. Outcome measures.

Data analysis

Statistical analyses were made using the IBM SPSS Statistics 20.0 software package (SPSS Inc., Chicago, IL, USA)[b]. The Kolmogorov-Smirnov or Shapiro-Wilk tests were used to test for normal distribution. Numerical variables are expressed as mean±standard deviation. Categorical variables are given as numbers and percentages. Numerical variables were compared using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, and categorical variables were compared using Chi-square or Fisher's exact tests. The variation of independent variables over time was evaluated using Friedman test. Wilcoxon signed rank test was used for post hoc pairwise comparisons. Statistical significance was set at $p<0.05$($p<0.008$ for post hoc pairwise comparisons).

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Results

Seventy-six participants were included in the study between March 2021 and May 2021 (Figure 1). At the baseline evaluation, the distribution of mild, moderate, and severe disease was n=15 (19.7%), n=20 (26.3%), and n=41 (53.9%), respectively. Some clinical and demographic characteristics of the participants are summarized in Table 2. During the follow-up, 6 participants of severe disease group were transferred to ICU after the 3rd week. Three of them deceased. All other participants discharged from hospital and they were independent in their daily living activities at the end of the 12th week.

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Figure 1. Study flowchart

Table 2. Clinical and demographic characteristics of the study population according to disease severity.

Clinical findings according to disease severity are given in Table III. There was a statistically significant difference in 5XSTS at baseline, 1st week, and 12th week between disease severity groups ($p<0.05$). The mBorg-rest and mBorg-ADL scores were also different at baseline and 1st week between disease severity groups ($p<0.05$). FiO2 and SpO2 were different at baseline, 1st week, and 3rd week evaluations between disease severity groups ($p<0.001$). There were no significant differences between the disease severity groups for the other parameters (HGS, Barthel index, myalgia) (Table 3). Comparison of HGS and 5XSTS with age and gender specific normative data (50th percentile) is shown in Figure 2.

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Table 3. Comparison of muscle strength, functional independence, myalgia severity, fatigue, dyspnea, FiO2, and SpO2 according to disease severity.

Figure 2. Change of HGS and 5XSTS tests over time.

5XSTS values were different at baseline, 1st week and 12th week between the disease severity groups. Post-hoc pairwise comparisons revealed that the mild group had better 5XSTS scores than both the moderate and severe groups at the baseline evaluation (p=0.025 and p=0.001, respectively). There was statistically significant difference for 5XSTS in mild and severe groups at the 1st and 12th week comparisons (p=0.001 and p=0.008, respectively).

mBorg-rest values were statistically different between the mild and severe groups at baseline and at 1st week (p=0.013 and p=0.003, respectively). mBorg-ADL was different in the mild and moderate groups and in the mild and severe groups at baseline evaluations (p=0.012 and p<0.001, respectively). At the 1st week, there was a difference between both the mild and severe groups and between the moderate and severe groups (p<0.001 and p=0.017, respectively). At the 3rd week, there was only a difference between the mild and severe groups (p=0.016). By the 12th week, there was no difference between the groups for mBorg-ADL.

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There was a statistically significant increase in the HGS over time in all groups (mild: $X^2(3)=23,674$, $p<0.001$; moderate: $X^2(3)=16,815$, $p=0.001$; severe: $X^2(3)=40,079$, $p<0.001$). There was a significant decrease in the 5XSTS scores over time in each group ($p\leq0.001$). The Barthel index increased gradually over time only in the severe group ($X^2(3)=13.071$, $p=0.004$). However, there was no difference for paired comparisons ($p>0.008$). Myalgia-VAS scores decreased over time in each group (mild group: $X^2(3)=20.631$, $p<0.001$; moderate group: $X^2(3)=19.388$, $p<0.001$; severe group: $X^2(3)=15.400$, $p=0.002$), but there was no statistically significant difference in paired comparisons ($p>0.008$). The change in the mBorg-rest score over time in the moderate and severe groups was found to be statistically significant (moderate group: $X^2(3)=32.899$, $p<0.001$; severe group: $X^2(3)=53.013$, $p<0.001$). The change was significant in mBorg-ADL scores over time in all three disease severity groups (mild group: $X^2(3)=16.657$, $p=0.001$; moderate group: $X^2(3)=40.451$, $p<0.001$; severe group: $X^2(3)=78.149$, $p<0.001$).

The weeks in which the change in outcome measures over time was statistically significant are summarized in the Table IV.

Table 4. Significant changes in outcome measures over time.

Baseline and 12th week HGS and 5XSTS values were compared with age and gender-specific normative data. At baseline, HGS was in normal ranges in all participants in the mild group but it was low in 5.3% of the moderate group and in 14.6% of the severe group. At the 12th

week, HGS values were in normal ranges in mild and moderate groups and it was low in 7.9% of participants in the severe group. However, these changes over time in HGS were not significant in moderate and severe groups (p=0.317 and p=0.180). In the baseline evaluation, the 5XSTS performances (according to age and gender-specific normative data) were slower in 53.3% of the participants in the mild group, in 84.2% of the participants in the moderate group, and in 76.7% of the participants in the severe group. At the end of the 12th week, these values were 40.0%, 57.9% and 54.1%, respectively. Although this change was not significant in the mild group (p=0.157), it was significant in the moderate and severe groups (p=0.025 and p=0.007).

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Discussion

In our study, there were significant differences in hospital length of stay, BMI, laboratory findings (CRP, ferritin, lymphocytes, SpO2, FiO2), 5XSTS, mBorg-rest, and mBorg-ADL at the baseline evaluation according to disease severity. However, there were no difference for other clinical variables such as HGS, Barthel index and myalgia. Our study showed that there was significant improvement in all clinical parameters in all groups over time. HGS increased significantly, and 5XSTS, myalgia-VAS, and mBorg-ADL scores decreased.

COVID-19 is primarily a respiratory disease but it also affects the musculoskeletal system. Fatigue, myalgia, and arthralgia are common symptoms in COVID-19 patients [14]. Limited data are available on the relationship between these symptoms and the severity of the disease [5, 11]. Myofiber necrosis and atrophy secondary to severe COVID-19 have been demonstrated before [15]. Therefore, it may be reasonable to evaluate the change in muscle strength and physical performance during the disease course. There are previous studies evaluating muscle strength in COVID-19 [16]. Kara et al. reported that the HGS was lower in the severe COVID-19 patients [16]. However, in our study, we did not observe such a difference in the mild, moderate, and severe patients, both during hospitalization and during the 12-week follow-up. This may be related to the fact that the groups in our study were similar in terms of important risk factors such as age, sex, and comorbidities. Another possible explanation for this may be that critically ill patients, who are at higher risk for myofiber necrosis and atrophy, were not included in our study. Although our study did not include a healthy

control group, HGS assessments of nearly all patients were found to be normal according to age and sex-related normative HGS data at the end of the 12-week follow-up [17].

There are studies investigating physical performance of COVID-19 patients in the ICU during and after infection. Medrinal et al. reported that severe muscle weakness persists 1 month after discharge from ICU [18]. Muscle weakness after ICU admission is a common problem. The incidence of ICU-acquired weakness depends on age, sex, primary disease, and treatment. Muscular atrophy develops in up to 70% of older patients in the ICU [19] . Our study group consisted of non-ICU COVID-19 patients. Therefore, muscular atrophy may not have occurred in our participants. This may be the reason why the HGS and 5XSTS results improved in all groups over time.

Although there was no difference between the disease severity groups in HGS, there was a difference in 5XSTS. There could be several reasons for this. HGS assesses general muscle strength and measures isometric muscle strength in the upper extremity [20]. However, 5XSTS tests transitional movements, functional mobility, balance, and lower extremity strength [21]. Although there is no significant difference in muscle strength according to disease severity in these patients, there may be a difference in transitional movements, balance, and functional mobility. It was observed that 5XSTS scores improved considerably in all groups over time. However, the difference between the groups was still evident after 3 months of follow-up. Therefore, we think that rehabilitation programs are necessary to improve functional mobility and physical performance in hospitalized COVID-19 patients.

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Borg scale scores have been suggested to be valid for monitoring and prescribing exercise intensity regardless of sex, age, exercise mode, physical activity level, and coronary artery disease status [22]. In our study, the modified Borg scale was used to measure the perceived exertion during activities of daily living and rest. We observed that the mBorg scales were affected by the disease severity. Modified Borg scale was higher in severe group at the baseline evaluation. Parallel to the improvement in patients, mBorg gradually improved during the 12-week follow up. We think that the mBorg can be evaluated together with clinical findings (such as O2 saturation) and used to manage the pulmonary rehabilitation in patients with COVID-19.

There are previous studies in which the Barthel index was used to evaluate functional independence of COVID-19 patients [23-25]. Cuerda et.al stated that functional independence decreased significantly in COVID-19 patients treated in the ICU [23]. Hosoda et.al reported that functional decline in COVID-19 was not related to disease severity [25]. However, the samples of these two studies are very different from each other. First study included only the patients who were treated in the ICU but there were mild and moderate COVID-19 patients in the second study. In our study, Barthel index scores were similar in different disease severity groups at all time points and there was improvement over time only in the severe group. We think that there is no difference over time in mild and moderate disease groups because all measurements are normal or very close to normal at all time points. So, it would be more appropriate to use this scale only in the severe COVID-19 patients.

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There is not a standard rehabilitation program for COVID-19 patients. The need for rehabilitation may depend on the severity of the disease, length of stay in the hospital and/or ICU because these conditions will affect the physical performance of the patients. Patient's cardiopulmonary capacity may be the limiting factor during rehabilitation. Therefore, a complete cardiopulmonary evaluation should be performed. All patients requiring rehabilitation following COVID-19 should have a functional assessment to reveal residual musculoskeletal impairments in order to determine appropriate rehabilitation. Implementation of a multidisciplinary rehabilitation program is ideal.

In post-COVID-19 rehabilitation, it is recommended to start physical activity immediately and to gradually increase regular daily activity for full functional recovery [26, 27]. The duration and frequency of daily activities and physical rehabilitation should be adjusted according to the patient's performance. A multicomponent exercise program including aerobic, resistance, balance, coordination, and mobility training exercises is safe and well tolerated [28].

The patient's physical performance can be assessed with scales like those we used in our study and the intensity of physical rehabilitation may be adjusted individually. Close monitoring will be required to prevent worsening of respiratory symptoms. During pandemic, post-COVID-19 rehabilitation can be delivered in the hospital, in the outpatient clinic or at home, depending on the needs of the patient. During the pandemic, the number of patients undergoing rehabilitation was reduced to prevent infection transmission. Rehabilitation clinics were converted into pandemic clinics when necessary. For these reasons, patients' access to rehabilitation has decreased. Appropriate patient selection is

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very important in order to use limited rehabilitation opportunities rationally and to ensure that patients in need of post-COVID rehabilitation have access to these treatments. For this reason, it is important to choose practical, low-cost and effective methods those can be used to identify patients who needs rehabilitation. We think that 5XSTS and mBorg scale together with clinical findings can be used to determine rehabilitation needs and to monitor progression in the rehabilitation process.

Study Limitations

One of the limitations of our study is the relatively small number of patients. The main reason for this is that the study was conducted in a single center. Due to the ongoing pandemic, the man-power and working time that could be allocated to the study were limited. The lack of a control group including healthy individuals is also a limitation. A comparison with healthy individuals in the study could be useful in demonstrating the change in physical performance due to COVID-19 infection. However, sometimes there were lockdowns in the country, and healthy individuals were asked not to visit hospitals as much as possible. Another limitation is that critical COVID-19 patients are not included. Our study focuses on physical performance in patients with COVID-19; however, it should be kept in mind that most of the tests we evaluated cannot be used efficiently in critically ill patients, almost all of whom are treated in the ICU.

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Conclusions

Borg scale and 5XSTS were affected by disease severity in the early period. After 12 weeks, the physical parameters improved considerably in most of the mild, moderate, and severe COVID-19 patients. We observed that HGS was normal in almost all patients at the end of 12 weeks. However, 5XSTS tests were still slow in most of the patients. These results suggest that muscle strength improves over time, but rehabilitation programs are needed to improve functional mobility and physical performance in hospitalized patients with COVID-19.

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References

1. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52(11):549-57.
2. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(24):759-65.
3. Baj J, Karakula-Juchnowicz H, Teresinski G, Buszewicz G, Ciesielka M, Sitarz R, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med. 2020;9(6).
4. Cipollaro L, Giordano L, Padulo J, Oliva F, Maffulli N. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. J Orthop Surg Res. 2020;15(1):178.
5. Paneroni M, Simonelli C, Saleri M, Bertacchini L, Venturelli M, Troosters T, et al. Muscle Strength and Physical Performance in Patients Without Previous Disabilities Recovering From COVID-19 Pneumonia. Am J Phys Med Rehabil. 2021;100(2):105-9.
6. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurol Sci. 2020;41(11):3039-56.
7. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32.
8. Soares MN, Eggelbusch M, Naddaf E, Gerrits KHL, van der Schaaf M, van den Borst B, et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. J Cachexia Sarcopenia Muscle. 2022;13(1):11-22.
9. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. Front Immunol. 2020;11:1708.
10. Piotrowicz K, Gasowski J, Michel JP, Veronese N. Post-COVID-19 acute sarcopenia: physiopathology and management. Aging Clin Exp Res. 2021;33(10):2887-98.
11. Tuzun S, Keles A, Okutan D, Yildiran T, Palamar D. Assessment of musculoskeletal pain, fatigue and grip strength in hospitalized patients with COVID-19. Eur J Phys Rehabil Med. 2021;57(4):653-62.
12. WHO. Clinical management of COVID-19: interim guidance 27 May 2020 2021 [Available from: https://apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf.
13. Xiao J, Li X, Xie Y, Huang Z, Ding Y, Zhao S, et al. Maximum chest CT score is associated with progression to severe illness in patients with COVID-19: a retrospective study from Wuhan, China. BMC Infect Dis. 2020;20(1):953.
14. Vaishya R, Jain VK, Iyengar KP. Musculoskeletal manifestations of COVID-19. J Clin Orthop Trauma. 2021;17:280-1.
15. Leung TW, Wong KS, Hui AC, To KF, Lai ST, Ng WF, et al. Myopathic changes associated with severe acute respiratory syndrome: a postmortem case series. Arch Neurol. 2005;62(7):1113-7.
16. Kara O, Kara M, Akin ME, Ozcakar L. Grip strength as a predictor of disease severity in hospitalized COVID-19 patients. Heart Lung. 2021;50(6):743-7.
17. Landi F, Calvani R, Martone AM, Salini S, Zazzara MB, Candeloro M, et al. Normative values of muscle strength across ages in a 'real world' population: results from the longevity check-up 7+ project. J Cachexia Sarcopenia Muscle. 2020;11(6):1562-9.
18. Medrinal C, Prieur G, Bonnevie T, Gravier FE, Mayard D, Desmalles E, et al. Muscle weakness, functional capacities and recovery for COVID-19 ICU survivors. BMC Anesthesiol. 2021;21(1):64.
19. Wang W, Xu C, Ma X, Zhang X, Xie P. Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. Front Med (Lausanne). 2020;7:559789.
20. Ekiz T, Kara M, Ozcakar L. Measuring grip strength in COVID-19: A simple way to predict overall frailty/impairment. Heart Lung. 2020;49(6):853-4.

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21. Lord SR, Murray SM, Chapman K, Munro B, Tiedemann A. Sit-to-stand performance depends on sensation, speed, balance, and psychological status in addition to strength in older people. J Gerontol A Biol Sci Med Sci. 2002;57(8):M539-43.
22. Ogura A, Izawa KP, Tawa H, Kureha F, Wada M, Harada N, et al. Impact of the COVID-19 pandemic on phase 2 cardiac rehabilitation patients in Japan. Heart Vessels. 2021;36(8):1184-9.
23. Cuerda C, Sanchez Lopez I, Gil Martinez C, Merino Viveros M, Velasco C, Cevallos Penafiel V, et al. Impact of COVID-19 in nutritional and functional status of survivors admitted in intensive care units during the first outbreak. Preliminary results of the NUTRICOVID study. Clin Nutr. 2021.
24. Trevisson-Redondo B, Lopez-Lopez D, Perez-Boal E, Marques-Sanchez P, Liebana-Presa C, Navarro-Flores E, et al. Use of the Barthel Index to Assess Activities of Daily Living before and after SARS-COVID 19 Infection of Institutionalized Nursing Home Patients. Int J Environ Res Public Health. 2021;18(14).
25. Hosoda T, Hamada S. Functional decline in hospitalized older patients with coronavirus disease 2019: a retrospective cohort study. BMC Geriatr. 2021;21(1):638.
26. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med. 2020;54(16):949-59.
27. Demeco A, Marotta N, Barletta M, Pino I, Marinaro C, Petraroli A, et al. Rehabilitation of patients post-COVID-19 infection: a literature review. J Int Med Res. 2020;48(8):300060520948382.
28. Wang TJ, Chau B, Lui M, Lam GT, Lin N, Humbert S. Physical Medicine and Rehabilitation and Pulmonary Rehabilitation for COVID-19. Am J Phys Med Rehabil. 2020;99(9):769-74.

Suppliers:

a. Jamar Hydraulic Hand Dynamometer (JA Preston Corporation, New York, USA).

b. IBM SPSS Statistics 20.0 software package (SPSS Inc., Chicago, IL, USA).

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Figure 1. Study flow chart

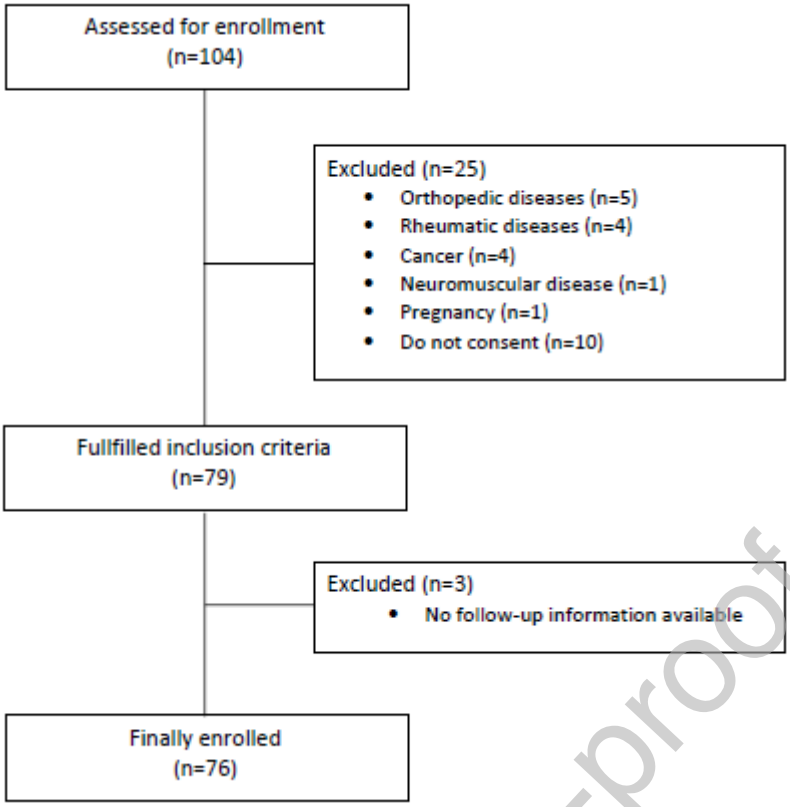


Figure 2. Change of HGS and 5XSTS tests over time.



Abbreviations: HGS, hand grip strength; 5XSTS, 5 times sit and stand test.

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Table 1. Outcome measures.

Measure	Assessing	Procedure
HGS	Indicator of overall muscle strength. HGS was considered low if it was less than 5th percentile of the age and sex-specific peak mean values (14).	A recently calibrated Jamar Hand Dynamometer (JA Preston Corporation, New York, USA)[a] was used in the standard position recommended by the American Society of Hand Therapists (15). Measurements were repeated three times at one-minute intervals. The arithmetic average of the measurements was recorded in kilograms.
5XSTS	5XSTS is a reliable tool that can be used to assess lower limb muscle strength, balance, and functional mobility (16). 5XSTS test was considered abnormal if it was more than 95th percentile of the age and sex-specific peak mean values (14).	Participant were asked to sit in a 43-cm high chair, with their arms crossed over their chest and their back resting on the back of the chair. Then they were asked to stand up and sit down five times as fast as possible (17).
mBorg	The mBorg scale measures perceived exertion, and effort spent during physical activities (18). This scale also evaluates the severity of dyspnea at rest.	It is a numerical scale consisting of 12 items (0, 0.5, 1–10). Higher scores correspond with increasing shortness of breath In our study, the mBorg scale was used to measure perceived dyspnea and fatigue symptoms during rest and daily activities.
Barthel Index	The Barthel ADL index is a 10-item scale that is widely used in functional disability (19). It measures the performance during activites of daily living.	High scores indicate better performance in the daily life of the patients.
myalgia-VAS	A visual analog scale was used to evaluate myalgia (16).	The participants were asked to specify general muscle pain severity at the time of evaluation by indicating a position along a 10-cm long line. In VAS, 0 indicated no pain at all and 10 represented the strongest pain imaginable (18).

Abbreviations: HGS, hand grip strength; 5XSTS, 5 times sit and stand test; mBorg, modified Borg scale; myalgia-VAS, visual analog scale for myalgia.

Table 2. Clinical and demographic characteristics of the study population according to disease severity.

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	Mild (n=15)	Moderate (n=20)	Severe (n=41)	P value
Age (year)	48.2±16.7	53.7±13.1	57.0±12.7	0.106
Gender (%)				
Female (n=30)	7 (44%)	10 (50%)	13 (32%)	0.344
Male (n=46)	8 (56%)	10 (50%)	28 (68%)	
Hospital length of stay (days)	5.8±3.8	6.45±3.9	11.6±6.6	0.001*
BMI (kg/m^2)	26.1±5.4	28.7±3.5	29.4±3.9	0.032*
Comorbidities				
Hypertension	5 (33.3%)	8 (40%)	16 (39%)	0.909
Obesity	3 (20%)	5 (25%)	19 (46.3%)	0.098
Diabetes Mellitus	1 (6.7%)	4 (20%)	12 (29.3%)	0.190
Hypothyrodism	2 (13.3%)	1 (5%)	2 (4.9%)	0.500
CVD	1 (6.7%)	3 (15%)	8 (19.5%)	0.503
COPD	0 (0%)	4 (20%)	2 (4.9%)	0.054
Laboratory				
WBC ($10^3/\mu L$)	6.4±2.5	6.7±3.2	6.5±2.5	0.973
Lymphocytes ($10^3/\mu L$)	1.5±0.5	1.2±0.5	0.9±0.5	<0.001*
D-Dimer (μg/mL)	0.6±0.5	0.6±0.3	0.7±0.5	0.319
Ferritin (μ/L)	137.4±249.8	257.2±295.7	549.7±612.5	0.001*
CRP (mg/L)	33.0±39.7	55.7±38.1	82.4±76.5	0.007*
Treatment				
Antiviral	15 (100%)	20 (100%)	41 (100%)	NA
Antithrombotics	13 (87%)	20 (100%)	41 (100%)	0.015*
Steroids				
Oral	1 (6.7%)	13 (65%)	24 (58.5%)	<0.001*
Pulse	0 (0%)	1 (5%)	15 (36.5%)	
Biopharmaceutical medication	0 (0%)	0 (0%)	4 (9.8%)	0.165

NOTE. Values are presented as number (%) or mean ± SD.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; CRP, C-reactive protein.

* $p<0.05$

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Table 3. Comparison of muscle strength, functional independence, myalgia severity, fatigue, dyspnea, FiO2, and SpO2 according to disease severity.

	Mild (n=15)	Moderate (n=20)	Severe (n=41)	P value
HGS (kg)				
Baseline	33.6±11.9	31.9±8.4	31.6±10.4	0.922
1st week	34.4±11.7	33.5±8.9	31.8±11.2	0.705
3rd week	35.7±11.8	34.0±8.9	33.7±10.8	0.935
12th week	36.3±11.5	34.3±8.8	35.2±10.1	0.915
5XSTS (sec)				
Baseline	10.7±3.2	14.7±4.6	15.0±3.6	*0.002**
1st week	11.1±1.7	12.9±3.5	14.9±4.1	*0.002**
3rd week	10.4±1.3	11.9±2.5	12.0±2.5	0.068
12th week	9.9±1.1	10.9±1.8	11.6±1.8	0.010*
mBorg-rest				
Baseline	0.5±1.4	1.4±1.7	1.5±1.8	0.016*
1st week	0.4±1.3	0.7±1.0	1.5±1.7	0.003*
3rd week	0.03±0.1	0.3±0.8	0.3±0.9	0.355
12th week	0.0±0.0	0.03±0.1	0.01±0.08	0.671
mBorg-ADL				
Baseline	0.7±1.0	2.6±2.3	3.0±1.9	<0.001*
1st week	0.3±0.6	1.3±1.5	2.7±1.9	<0.001*
3rd week	0.2±0.4	0.7±1.2	1.0±1.4	0.019*
12th week	0.0±0.0	0.1±0.3	0.2±0.3	0.123
Barthel Index				
Baseline	100±0.0	98.5±6.7	96.9±8.1	0.085
1st week	100±0.0	99.0±4.5	94.0±17.0	0.122
3rd week	100±0.0	96.5±2.2	98.1±10.5	0.675
12th week	100±0.0	99.5±2.2	100±0.0	0.266
Myalgia-VAS				

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Baseline	2.3±3.1	1.9±2.6	1.1±2.3	0.199
1st week	0.9±1.9	1.3±2.1	0.7±1.7	0.255
3rd week	0.3±0.9	0.3±0.8	0.4±0.9	0.981
12th week	0.0±0.0	0.0±0.0	0.0±0.0	NA
FiO2				
Baseline	21±0.0	21.6±2.7	29.1±6.7	<0.001*
1st week	21±0.0	21.0±0.0	33.8±18.7	<0.001*
3rd week	21±0.0	21.0±0.0	23.4±12.7	0.251
12th week	21±0.0	21.0±0.0	21.0±0.0	NA
SpO_2 (%)				
Baseline	95.7±1.5	93.7±1.8	93.4±1.6	<0.001*
1st week	95.9±1.5	95.0±1.7	93.1±2.3	0.007*
3rd week	97.1±1.3	96.8±1.1	95.6±1.9	0.007*
12th week	97.6±0.8	96.6±0.8	96.4±1.0	0.001*

NOTE. Values are presented as number (%) or mean ± SD.

Abbreviations: HGS, hand grip strength; 5XSTS, 5 times sit and stand test; mBorg-rest, modified Borg scale at rest; mBorg-ADL, modified Borg scale during activities of daily living; myalgia-VAS, visual analog scale for myalgia FiO2, fraction of inspired oxygen; SpO2, oxygen saturation.

* p<0.05

Table 4. Statistically significant changes over time.

	Group		Z value	P value
HGS	**Mild**	Baseline - 3rd week	-3.194	0.001
		Baseline - 12th week	-2.972	0.003
		1st week - 3rd week	-2.842	0.004
		1st week - 12th week	-2.938	0.003
		Baseline - 1st week	-3.099	0.002
		Baseline - 3rd week	-3.421	0.001
	Moderate	Baseline - 12th week	-3.323	0.001
	Severe	Baseline - 12th week	-3.903	<0.001
		1st week - 12th week	-4.954	<0.001
		3rd week - 12th week	-3.474	<0.001
5XSTS	**Mild**	1st week - 12th week	-3.124	0.002
	Moderate	Baseline - 1st week	-3.099	0.002
		Baseline - 3rd week	-3.421	0.001
		1st week - 12th week	-3.501	<0.001
		3rd week - 12th week	-3.340	0.001
	Severe	Baseline - 3rd week	-3.676	<0.001
		Baseline - 12th week	-4.444	<0.001

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		1st week - 3rd week	-4.587	<0.001
		1st week - 12th week	-4.954	<0.001
mBorg-rest	**Moderate**	Baseline - 3rd week	-3.209	0.001
		Baseline - 12th week	-3.197	0.001
		1st week - 12th week	--2.831	0.005
	Severe	Baseline - 3rd week	-3.443	0.001
		Baseline - 12th week	-4.575	<0.001
		1st week - 3rd week	-3.550	<0.001
		1st week - 12th week	-4.421	<0.001
mBorg-ADL	**Moderate**	Baseline - 1st week	-3.189	0.01
		Baseline - 3rd week	-3.523	<0.001
		Baseline - 12th week	-3.523	<0.001
		1st week - 12th week	-3.130	0.002
		3rd week - 12th week	-2716	0.007
	Severe	Baseline - 3rd week	-4.012	<0.001
		Baseline - 12th week	-5.177	<0.001
		1st week - 3rd week	-4.184	<0.001
		1st week - 12th week	-5.173	<0.001
		3rd week - 12th week	-4.151	<0.001

Abbreviations: HGS, hand grip strength; 5XSTS, 5 times sit and stand test; mBorg-rest, modified Borg scale at rest; mBorg-ADL, modified Borg scale during activities of daily living.

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