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Do functional capacity, fatigue and dyspnea change in the post-acute period according to severity of COVID-19?

Fatima Yaman, Feride Marim[1], Merve Akdeniz Leblebicier, Vural Kavuncu

ORCID:
Fatima Yaman: 0000-0002-6137-0166
Feride Marim: 0000-0002-5677-7842
Merve Akdeniz Leblebicier: 0000-0002-6147-300X
Vural Kavuncu: 0000-0003-2619-4977

Abstract:

BACKGROUND AND AIM: The aim of this study was to examine the functional capacity, fatigue severity, impact of fatigue, and severity of dyspnea in the first month after discharge in patients with moderate-to-critical groups of COVID-19.

METHODS: The study included 92 patients who were divided into three groups, modarate (n=31), severe (n=32), critical (n=29), based on initial dispnea severity. 6-minute walk test (6MWT), 30-second sit-to-stand test (30secSTS), the fatigue severity scale (FSS), the fatigue impact scale (FIS) and Modified Medical Research Council (mMRC) Dyspnea scale were evaluated for each patient.

RESULTS: As the disease severity increased, a significant decrease was found in the walking distance of the 6 MWT and the number of full stands of the 30secSTS (p=0.003, p<0.001, respectively). The mean scores of FIS and FSS were higher in the critical group (p<0.001). The rate of patients in mMRC grade 2 was higher in the severe and critical groups (46.9% and 58.6%, respectively).

CONCLUSIONS: The results revealed that the critical COVID-19 group had lower functional capacity and higher severity of fatigue, effect of fatigue, and severity of dyspnea.

Keywords:

Cognitive impairment, COVID-19, disease severity, dyspnea, fatigue, six-minute walk test

Department of Physical Medicine and Rehabilitation, Kütahya University of Health Sciences Faculty of Medicine, Kütahya, Türkiye, [1]Department of Chest Diseases, Kütahya Health Sciences University Faculty of Medicine, Kütahya, Türkiye

Address for correspondence:
Dr. Fatima Yaman, Department of Physical Medicine and Rehabilitation, Kütahya University of Health Sciences Faculty of Medicine, Kütahya, Türkiye.
E-mail: fatimacakir84@hotmail.com

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Introduction

Coronavirus disease 2019 (COVID-19), which is characterized by severe acute respiratory syndrome caused by Coronavirus-2, was first detected in Wuhan, China, in December 2019. According to February 2022 data, approximately 6 million people died of this disease.[1] Although the average recovery time is 2 weeks, some symptoms have been shown to last longer.[2]

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According to the recent guidelines, it is defined as acute COVID-19 if the signs and symptoms are present from the onset of COVID-19 to the fourth week, ongoing symptomatic COVID-19 if present between 4 and 12 weeks, and post-COVID-19 syndrome if present after 12 weeks.[3] It has been reported that the symptoms may be due to the pathological immune response (cytokine storm). Paul et al.[4] attributed impaired functional capacity in patients with COVID-19 and encephalomyelitis/chronic fatigue syndrome to impaired cell redox dysregulation, systemic inflammation, and mitochondrial adenosine triphosphate production. Demeco et al.[5] also reported the same etiopathogenesis to explain the reason for the decrease in functional capacity.

As a result, patients may develop various persistent symptoms such as decreased functional capacity,[5] severe fatigue, dyspnea,[6] and attention deficit disorder[7] in the post-COVID-19 follow-up period.

Understanding the short- and long-term effects of physical and mental symptoms after COVID-19 is important to assess the disability of patients. Identifying the existing symptoms and determining the severity of these symptoms, especially in patients with pneumonia and acute respiratory distress syndrome due to COVID-19, will help to evaluate the need for post-acute rehabilitation of the patients.

In this context, we aimed to examine the functional capacity, fatigue severity, impact of fatigue, and severity of dyspnea in post-acute COVID-19 patients in moderate, severe, and critical groups of COVID-19.

Materials and Methods

Study design

This observational, descriptive, and analytical study was conducted at a Training and Research Hospital of a university between January and June 2022. The study procedure is shown in Figure 1.

Participant selection

Inclusion criteria: Patients who have been hospitalized in the pandemic clinic with a positive PCR test and COVID-19 diagnosis confirmed by radiological CT and in their first month after discharge, who were between the ages of 30 and 60 years, who have had COVID-19 at either moderate, severe, or critical levels, according to the WHO and Chinese Clinical Guidance, were included in the study.[8,9]

Exclusion criteria: Patients who had a psychiatric illness and cooperation disorders, vision or hearing problems, chronic heart disease, uncontrolled hypertension, chronic lung disease, two or more inactive vaccines and/or mRNA vaccines, gait disturbance due to musculoskeletal system disease, balance disorders, and neuromuscular diseases were excluded from the study.

Setting

Sampling: The sample size required for the study was calculated using the G*Power package program (3.1.9, University of Kiel, Germany). As per the post-analysis, the power of the study with 0.46 effect size, α=0.05 type I error, and β=0.05 type II error for the fatigue severity scale (FSS) parameter was calculated as 98%. A total of 93 patients with moderate (n=31), severe (n=32), and critical (n=30) levels of COVID-19 were included in the study. One patient in the critical group was excluded because the patient refused to perform the 6MWT. A total of 92 patients were evaluated.

Measures: The demographic data, comorbidities, and ongoing symptoms of patients who visited the post-COVID follow-up polyclinic 1 month after discharge were analyzed. Evaluation of the patients was carried out with the 6-minute walk test (6MWT), 30secSTS, FSS, the Fatigue Impact Scale (FIS), and Modified Medical Research Council (mMRC) Dyspnea Scale.

6MWT: It was developed by Balke in 1963 to evaluate functional exercise capacity.[10] It is used in scientific studies and follow-ups in the evaluation of functional exercise capacity in patients with COPD and other lung diseases such as interstitial lung diseases.[11] A flat and firm surface was used in a 30-m-long indoor area for this test. Patients who felt severe shortness of breath or chest pain, dizziness, or nausea during the test were told that they need to notify the researchers. The patients were informed that they should walk the longest distance they could walk in 6 min, at the fastest speed they could. It was explained that they could sit and rest during the test if they wished to, then continue the test as soon as they rested and the time spent resting would be included in the test. The distance of their walk was recorded in meters.

30-second sit to stand test: 30secSTS was used to determine the physical fitness levels of the patients. A chair

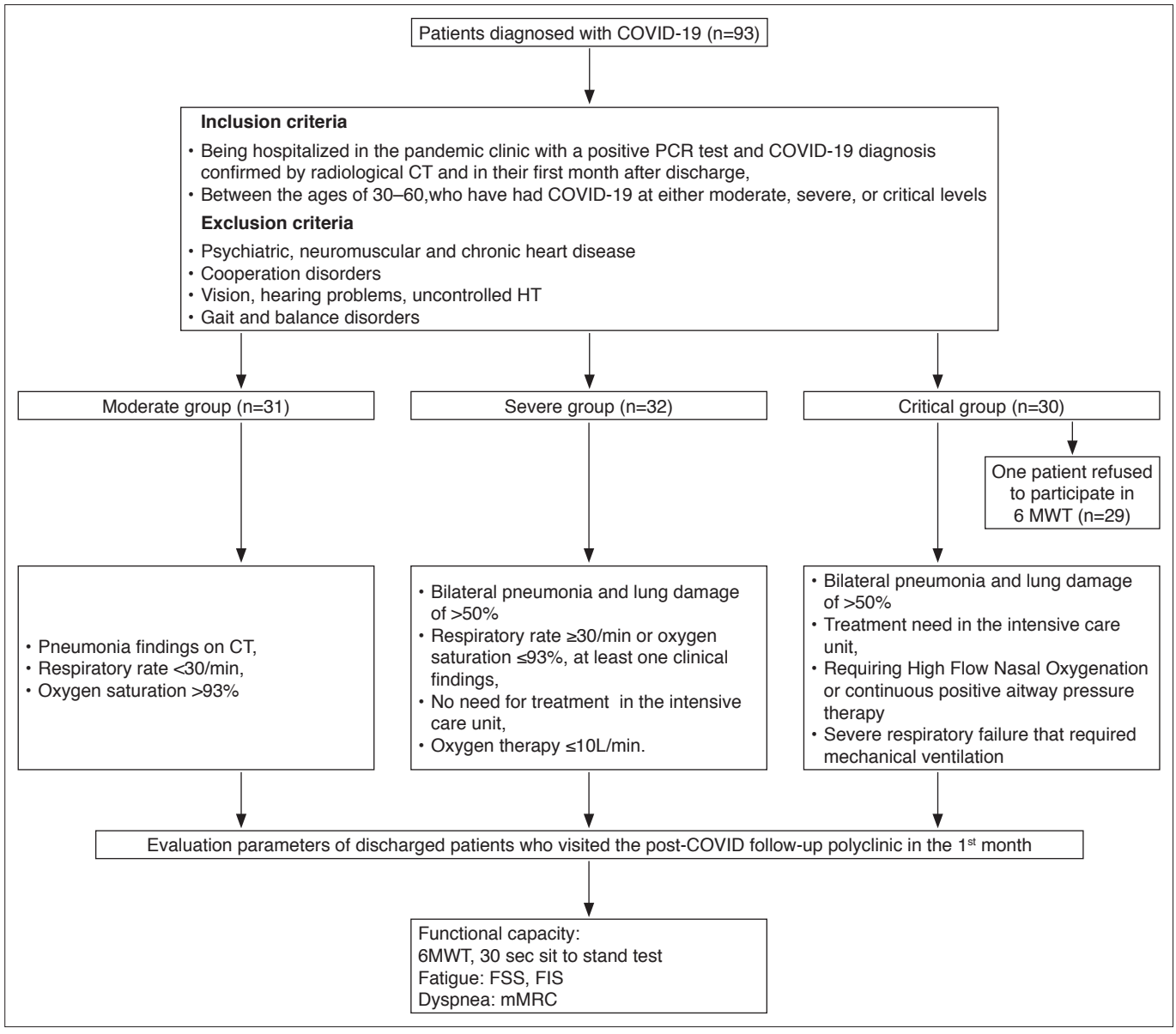

Figure 1: Study procedure

CT: Computed tomographic, HT: Hypertension, MWT: Minute walk test, FSS: Fatigue Severity Scale, FIS: Fatigue Impact Scale, mMRC: Dyspnea Scale: Modified Medical Research Council Dyspnea Scale

with a sitting height of 43.0 cm with an upright back without armrests was used. It was ensured that the patients sit in the middle of the chair with their back straight, feet on the floor, and arms crossed in front of their chest. The test was started with the start command while the patient was in this position, and the number of full stands made during 30 s formed the patient's score. A score of less than 10 indicates poor muscle endurance.[12]

Fatigue severity scale (FSS): Turkish validity and reliability studies for the scale were carried out by Armutlu et al. in 2007.[13] Each item in the scale, which consists of nine items that patients can apply on their own, is scored between 1 and 7 (1=I strongly disagree, 7=I completely agree) and questions the state of fatigue in the last week. The scale score is the mean value of the items. If the mean score is 5 or above, it refers to the "presence of fatigue". An increase in the scale score indicates an increase in the level of fatigue.

Fatigue impact scale (FIS): The validity and reliability studies of the scale in Turkish were performed by Armutlu et al.[14] in 2007. The 40-item scale evaluates patients' cognitive, physical, and psychological status. Each item is ranked from 0 (no problem) to 4 (extreme

problem). The scale determines the fatigue status of people within the last month. The impact of fatigue is interpreted as none (0–32)/slightly (33–64)/moderately (65–96)/significantly (97–128)/very significantly (129–160).

Modified Medical Research Council (mMRC) Dyspnea Scale: The mMRC Dyspnea Scale is a 5-point scale based on various physical activities that cause a sense of dyspnea. Grade 0: no dyspnea except in vigorous exercise; Grade 1: presence of dyspnea when walking in a hurry on a level road or climbing a slight slope; Grade 2: walks slower than people of the same age on the level because of dyspnea or has to stop for breath when walking on a level road at his/her own pace; Grade 3: stops for breath after walking about 100 m or after a few minutes of the walk; Grade 4: unable to go out of the house due to dyspnea or having dyspnea when dressing and undressing.

Intervention

All intervention steps are shown in Figure 1. Patients who agreed to participate in the study and signed the informed consent form were included in the sample. The COVID-19 disease severity classification of the patients at the time of hospitalization was carried out by the same researcher (FM).

Statistical analysis

Frequency tables and descriptive statistics were used to interpret the findings. Whether the variables had a normal distribution was examined by visual (histogram and probability graphs) and analytical (Shapiro–Wilk test) methods. The Chi-squared test was used to compare the two qualitative values, and the Mann–Whitney U test was used for the post hoc analysis. The one-way ANOVA test was used to compare the mean values of more than two groups, and the Bonferroni test was used for the post hoc analysis. The significance value in all statistics was accepted as $p<0.05$. The IBM SPSS Statistics 24.0 package program was used for the statistical analysis (IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

Ethical aspects

Ethics committee approval of the study (022-02/08) was obtained from the Clinical Research Ethics Committee of the University on January 25, 2022. It was also carried out in accordance with the principles of the Helsinki Declaration and with the approval of the Ministry of Health of the country. Patients who agreed to participate in the study signed the informed consent form.

Results

Gender, occupation, age distribution, presence of comorbidity, length of stay (days), BMI (kg/cm^2), and age of the patients participating in the study are given in Table 1. A total of 58.7% of patients had comorbidity. The presence of comorbidity was lowest in the moderate group and highest in patients in the critical group, and this was statistically significant ($p=0.021$) (Table 1). The length of stay in the hospital was 11.96±3.45, 21.12±7.72, and 27.89±6.93 days for the moderate, severe, and critical groups, respectively, and there was a significant difference between the groups ($p<0.001$) (Table 1).

According to the presence of post-acute COVID-19 symptoms, there was no difference between the groups ($p=0.134$) (Table 2). Dyspnea (94.6%) and fatigue (91.3%) were the most common symptoms. There was a significant difference in dyspnea ($p=0.006$), sputum ($p=0.013$), myalgia ($p=0.003$), arthralgia ($p=0.018$), fatigue ($p=0.035$), and cognitive ($p=0.012$) symptoms between the groups (Table 2).

As the severity of the disease increased, the 6MWT walking distances of the patients decreased, and this was found to be statistically significant ($p=0.003$). In the 30secSTS, the number of full stands was determined to decrease gradually with an increase in the disease severity ($p<0.001$). The mean scores of FSS were higher in the critical group, and there was a significant difference between the groups ($p<0.001$). As the severity of the disease increased, the total score of the FIS test, social, physical, and cognitive subdimensions increased ($p<0.001$). The rate of patients in mMRC grade 1 (19%) was found to be higher in the moderate group, and the rate of patients in mMRC grade 2 was higher in the severe and critical groups (46.9% and 58.6%, respectively). There was a significant difference between the groups ($p<0.001$) (Table 3). The post hoc analysis of the parameters according to disease severity is shown in Table 4. This study was planned to examine the functional capacity, fatigue severity, the impact of fatigue, and the severity of dyspnea in post-acute COVID-19 patients in moderate, severe, and critical groups of COVID-19.

Discussion

The duration of symptoms increases after the treatment of COVID-19 infection in patients who are hospitalized and/or in the intensive care unit due to COVID-19. Especially in these patients, it is necessary to evaluate the

Table 1: Demographic data and clinical characteristics according to the severity of the disease

Parameter	Total (n=92)		Moderate (n=31)		Severe (n=32)		Critical (n=29)		$\chi^{2,f}$	p
	n	%	n	%	n	%	n	%		
Gender										
Female	47	51.1	17	54.8	16	50	14	48.3	0.281	0.869
Male	45	48.9	14	45.2	16	50	15	51.7		
Employment status										
Yes	26	28.3	10	32.3	10	31.3	6	20.7	1.205	0.547
No	66	71.7	21	67.7	22	68.8	23	79.3		
Age distribution (years)										
18–30	1	1.1	0	0	1	3.1	0	0	4.387	0.624
31–40	3	3.3	1	3.2	2	6.3	0	0		
41–50	31	33.6	12	38.7	10	31.3	9	31		
51–60	57	62	18	58.1	19	59.3	20	69		
Comorbidity										
Yes	54	58.7	12	38.7	22	68.8	20	69	7.703	0.021
No	38	41.3	19	61.3	10	31.3	9	31		
Hypertension										
Yes	33	35.9	7	22.6	16	50	10	34.5	5.182	0.075
No	59	64.1	24	77.4	16	50	19	65.5		
Diabetes mellitus										
Yes	34	37	7	22.6	13	40.6	14	48.3	4.529	0.104
No	58	63	24	77.4	19	59.4	15	51.7		
Hyperlipidemia										
Yes	4	4.3	1	3.2	1	3.1	2	6.9	0.662	0.718
No	88	95.7	30	96.8	31	96.9	27	93.1		
Other diseases										
Yes	5	5.4	1	3.2	3	9.4	1	3.4	1.484	0.476
No	87	94.6	30	96.8	29	90.6	28	96.6		
	X±SD		X±SD		X±SD		X±SD			
Duration of hospital stay (days)	20.17±9.01		11.96±3.45		21.12±7.72		27.89±6.93		48.141	<0.001
BMI (kg/m^2)	28.62±4.22		28.02±3.64		28.48±4.52		29.42±4.48		0.845	0.433
Age (years)	51.84±6.99		50.70±6.20		51.18±8.27		53.79±6.01		1.699	0.189

n: Number of participants, %: Percentage, kg: Kilogram; m^2: Square meter, X: Average, SD: Standard deviation, χ^2: Chi-squared test, f: One-way ANOVA, p<0.05; BMI: Body mass index

severity of fatigue, the decrease in exercise capacity, and shortness of breath, which are common in the post-acute COVID-19 period for rehabilitation management. The results of our study showed that the functional capacity, severity of fatigue, and severity of dyspnea were more impaired in the critical group.

In a study evaluating 143 post-acute COVID-19 patients, the symptoms were found to persist in 87.5% of the patients. Similar to our study, fatigue and dyspnea were found to be the most common symptoms.[15] It was emphasized in a similar study that the symptoms of dyspnea and fatigue after hospitalization can often be accompanied by cognitive disorders.[16] Nalbandian et al.[7] reported that accompanying symptoms were more common in post-acute COVID-19 patients in severe and critical groups. The symptom data in our study results are similar to the literature. We think that the length of hospital stay and comorbidities play a role in increasing the symptoms in the critical group.

Functional capacity is an important parameter used in clinical evaluation, prognostic classification, and exercise prescription, especially in cardiopulmonary diseases. 6MWT and 30secSTS tests are used in functional capacity assessment, especially in geriatric, neurological, intensive care, and cardiopulmonary patients.[17] It has been shown in the literature that they have also been used in COVID-19 patients.[18,19] Strumiliene et al.[20] found that the 6MWT distance of patients in the critical group in the

Table 2: Post-acute COVID-19 symptoms according to disease severity

Parameter	Total (n=92)		Moderate (n=31)		Severe (n=32)		Critical (n=29)		χ^2	p
	n	%	n	%	n	%	n	%		
Post-COVID-19 symptoms										
Yes	90	97.8	29	93.5	32	100	29	100	4.023	0.134
No	2	2.2	2	6.5	0	0	0	0		
Dyspnea										
Yes	87	94.6	26	83.9	32	100	29	100	10.404	0.006
No	5	5.4	5	16.1	0	0	0	0		
Cough										
Yes	24	26.1	6	19.4	10	31.3	8	27.6	1.205	0.547
No	68	73.9	25	80.6	22	68.8	21	72.4		
Loss of taste and/or smell										
Yes	17	18.5	4	12.9	7	21.9	6	20.7	0.979	0.613
No	75	81.5	27	87.1	25	78.1	23	79.3		
Dizziness										
Yes	18	19.6	7	22.6	4	12.5	7	24.1	1.579	0.454
No	74	80.4	24	77.4	28	87.5	22	75.9		
Sputum										
Yes	22	23.9	2	6.5	7	28.1	11	37.9	8.639	0.013
No	70	76.1	28	93.5	23	71.9	18	62.1		
Myalgia										
Yes	40	43.5	6	19.4	16	50.0	18	62.1	11.973	0.003
No	52	56.5	25	80.6	16	50.0	11	37.9		
Arthralgia										
Yes	25	27.2	3	9.7	10	31.3	12	41.4	8.021	0.018
No	67	72.8	28	90.3	22	68.8	17	58.6		
Fatigue										
Yes	84	91.3	25	80.6	31	96.9	28	96.6	6.693	0.035
No	8	8.7	6	19.4	1	3.1	1	3.4		
Cognitive impairments										
Yes	54	58.7	12	38.7	20	62.5	22	75.9	8.824	0.012
No	38	41.3	19	61.3	12	37.5	7	24.1		

n: Number of participants; %: Percentage; χ^2: Chi-squared test; $p<0.05$

second month after discharge was lower than the moderate and severe groups, and this was associated with the severity of the disease. In the study of Pérez et al.,[21] a significant decrease in 6MWT was shown in patients with critical COVID-19 disease who could not complete more than 75% of their physical and functional recovery 6–8 weeks after discharge, compared to patients in the fully recovered group. In the same study, the group that could not complete more than 75% of their physical and functional recovery was found to have less number of full stands in the 30secSTS although it was not statistically significant. Núñez-Cortés et al.[22] emphasized that the 30secSTS was not only associated with the functional capacity of post-COVID-19 patients but also negatively correlated with the length of hospital stay. Although we did not evaluate the relationship between functional capacity and disease severity in our study, functional capacity was shown to decrease in the critical group, in line with the literature. Therefore, individual exercise programs need to be organized to increase functional capacity according to the severity of the disease in post-COVID-19 follow-up outpatient clinics.

It is important to determine the severity of fatigue and its associated impacts for planning rehabilitation programs and evaluating the outcomes of treatment.[23] In a meta-analysis investigating accompanying symptoms and health-related quality of life in post-acute COVID-19, fatigue and dyspnea were noted to be the most common symptoms. The mean FSS score was found to be 5.6, and 78% of the patients had a score of 4 and above on the FSS.[24] Our results are in line with the literature, and the comparison of the severity and impact of fatigue according to the severity of the disease is the strength of our study.

Table 3: Evaluation parameters according to disease severity

	Total (n=92)		Moderate (n=31)		Severe (n=32)		Critical (n=29)		f	p
	X±SD		X±SD		X±SD		X±SD			
6MWT	482.26±92.14		519.25±89.24		484.34±78.35		440.41±94.49		6.116	0.003
FSS	4.93±1.80		4.04±1.96		4.85±1.72		5.97±1.08		10.347	<0.001
Total FIS	83.52±28.64		67.12±23.30		82.03±26.54		102.68±24.98		15.246	<0.001
Social FIS	38.27±13.01		31.77±10.92		38.15±12.75		45.34±12		9.7	<0.001
Physical FIS	22.66±9.11		18.83±8.24		20.87±8.26		28.72±7.95		12.158	<0.001
Cognitive FIS	22.69±10.01		16.51±7.28		23.00±10.34		28.96±11.65		11.887	<0.001
30secSTS	9.95±2.12		11.06±1.93		10.03±1.92		8.68±1.89		11.536	<0.001
	n	%	n	%	n	%	n	%	χ^2	p
mMRC Dyspnea Scale										
0	4	4.30	4	12.90	0	0.00	0	0.00	37.696	<0.001
1	28	30.40	19	61.30	7	21.90	2	6.90		
2	40	43.50	8	25.80	15	46.90	17	58.60		
3	20	21.70	0	0.00	10	31.30	10	34.50		

f: One-way ANOVA, p<0.05, X: Average, SD: Standard deviation, χ^2: Chi-squared test, 6MWT: 6-Minute walk test, FSS: Fatigue Severity Scale, FIS: Fatigue Impact Scale, 30secSTS: 30-Second sit-to-stand test, mMRC Dyspnea Scale: Modified Medical Research Council Dyspnea Scale, n: Number of participants, %: Percentage.

Table 4: Post hoc analysis of the parameters according to disease severity

Variables	Moderate–severe		Moderate–critical		Severe–critical	
	Mean difference	p	Mean difference	p	Mean difference	p
6MWT	34.914	0.349	78.844	0.002	–43.930	0.159
FSS	–0.813	0.159	–1.929	<0.001	–0.813	0.029
Total FIS	–14.902	0.061	–35.560	<0.001	20.658	0.005
Social FIS	–6.382	0.110	–13.571	<0.001	7.189	0.063
Physical FIS	–2.036	0.975	–9.885	<0.001	7.849	0.001
Cognitive FIS	–6.484	0.033	–12.449	<0.001	5.966	0.063
30secSTS	1.033	0.106	2.375	<0.001	–1.342	0.023
mMRC Dyspnea Scale	–4.602	<0.001	–5.464	<0.001	0.950	0.342

6MWT: 6-Minute walk test, FSS: Fatigue Severity Scale, FIS: Fatigue Impact Scale, 30secSTS: 30-Second sit-to-stand test, mMRC Dyspnea Scale: Modified Medical Research Council Dyspnea Scale

Also, in the meta-analysis in which Huang et al.[25] evaluated 1733 post-COVID patients, they noted that the group who received oxygen therapy with a high-flow nasal cannula, noninvasive ventilation, or invasive mechanical ventilation had more fatigue than those who did not. In another study with 128 post-COVID patients, more than half of the patients were found to have persistent fatigue symptoms. They noted that the fatigue symptoms continued for a mean of 10 weeks during the follow-up period, and the severity of fatigue was high. Fatigue was emphasized as not to be associated with the initial severity of the disease. Furthermore, depression or anxiety was reported more in patients with fatigue symptoms.[17] However, we did not include patients diagnosed with psychiatric illness and complaints before or after COVID-19. Therefore, we believe that our study will add unique contributions to the literature in evaluating the severity and impact of post-COVID-19 fatigue symptoms.

Although the negative impact of fatigue on rehabilitation programs and treatment outcomes is known, there has been no study found in the literature that used the FIS in post-acute COVID-19. Even though the groups were not evaluated according to the severity of the disease, the Chalder Fatigue Scale was used in a study investigating the persistence of fatigue in post-COVID-19 patients. Physical fatigue, mental fatigue, and total fatigue scores were found to be higher in severe fatigue.[17] In our study, both the total FIS and all of the subdimension parameters (social, physical, and cognitive) were negatively affected

in the critical group. Our study is the first, to the best of our knowledge, to show the impact of fatigue according to the severity of the disease in the early post-acute period.

About half of the patients recovering from COVID-19 report symptoms of chronic dyspnea even 2–3 months after infection.[15,26] Dyspnea is an independent predictor of morbidity and mortality in the general population.[27] It is important to evaluate this multidimensional symptom, which is associated with physical capacity and quality of life, in post-COVID-19 patients. Garrigues et al.[26] called 120 patients by phone at least 100 days after their discharge, who had been hospitalized in the intensive care unit and ward, and evaluated them for symptoms. Similar to our study, they noted that those with a history of ICU stay had mMRC grade 2 or a higher percentage of dyspnea severity. In contrast, van den Borst et al.[28] found a higher median value of mMRC (grade 2.0) 3 months after the recovery from acute COVID-19 in the mild group than in the critical (grade 1.0) and moderate group (grade 1.0). They also stated in their study that dyspnea, regardless of the initial COVID-19 clinical severity, might be a common and persistent symptom. These different findings in the literature can be attributed to the different evaluation durations, as well as the fact that the dyspnea perception of the patients has many components such as psychological, social, and environmental, not only pathophysiological.

According to our post-COVID-19 follow-up outpatient clinic experience, many patients report not being able to return to their preinfection activity and functional levels. Therefore, we believe that identifying the symptoms of dyspnea and fatigue, which are common in the post-acute COVID-19 period, with scales according to disease severity and evaluation of functional capacity will provide guidance on the possible need for cardiopulmonary rehabilitation.

This study has some limitations. First, the fact that the study sample consisted of patients who were not fully vaccinated may have affected the frequency of symptoms. 6MWT, which is a submaximal test, was applied to our patients. Cardiopulmonary exercise testing was not considered appropriate to be used in this study as many patients had a leading symptom of diffuse muscle weakness/fatigue within 30 days of their discharge, as noted in the study by Huang et al.[29] However, our limitation was that the lung capacity had not been evaluated with objective tests such as pulmonary function tests or imaging methods although we used the accepted evaluation parameter to determine the severity of dyspnea in patients.

In conclusion, our study showed that the functional capacity was lower, the severity and impact of fatigue and the severity of dyspnea were higher in the critical group in COVID-19 patients in the first month after discharge. We believe that identifying the severity of the ongoing symptoms in the early period after COVID-19 will provide guidance on the need for rehabilitation and outcomes. We also think that our results will provide guidance for the rehabilitation evaluation of leading symptoms in all three post-COVID-19 groups. Furthermore, we think that a longer period of follow-up is required in patients with a history of hospitalization to determine the ongoing symptoms and consequences of COVID-19.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Kütahya University of Health Sciences Clinical Research Ethics Committee (No: 022-02/08, Date: 25/01/2022).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

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