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COVID-19 Enfeksiyonu Geçiren Hastalarda Yorgunluk Semptomunun Sıklığı ve İlişkili Faktörler

Frequency of Fatigue Symptom and Associated Factors in Patients with COVID-19 Infection

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ÖZ

Giriş: Son zamanlarda literatürde giderek artan sayıda yayın COVID-19'dan iyileştikten sonra özellikle yorgunluk dahil olmak üzere bir dizi uzun süreli nörolojik kardiyovasküler psikiyatrik ve kas-iskelet sistemi semptomları bildirmiştir. Bu çalışmada COVID-19 enfeksiyonu geçirenlerde yorgunluk semptomunun değerlendirilmesi amaçlandı.

Yöntem: Kliniğimizde takip edilen gönüllü ve ardışık 82 COVID-19 enfeksiyonu geçiren hastalara klinik ve laboratuvar parametrelerin kontrolü yanında FAS (fatigue assessment scale) yorgunluk değerlendirme anketi uygulandı.

Bulgular: Çalışmaya yaş ortalamaları 55±15 yıl olan, 45 erkek (%54,9), 37 kadın (%45,1) toplam 82 Covid-19 hastası dâhil oldu. COVID-19 hastalarının %35,4'ü ağır/kritik, %64,6'ü hafif/orta şiddette olarak değerlendirildi. Kontrol muayenesinde FAS yorgunluk skalasına göre olguların %65,9'unda (54 olgu) hafif düzeyde, %18,3'ünde (15 olgu) şiddetli düzeyde yorgunluk tespit edildi. Şiddetli yorgunluk kadınlarda erkeklerden anlamlı olarak daha sık idi. (%29,7 e karşı %8,9, p=0,015). Kontrolde yorgunluk tespit edilenlerde başvuru sırasındaki medyan hemoglobin düzeyi (13,3 d/dl), yorgunluk tespit edilmeyenlerin olguların medyan hemoglobin düzeylerinden (14,2 g/dL) anlamı olarak daha düşüktü. Tedavilerinde düşük molekül ağırlıklı heparin (DMAH) kullanılan hastalarda yorgunluk görülme sıklığı hiç DMAH tedavisi almayanlardan anlamlı olarak fazlaydı.

Sonuç: Bu çalışmada elde edilen veriler COVID-19 enfeksiyonu geçirenlerde hastalığın şiddeti ve diğer ko-morbiditelerden bağımsız olarak uzun süre devam eden yorgunluk şikâyetinin görülebileceğini göstermektedir.

Anahtar Kelimeler: COVID-19, yorgunluk, post-COVID-19

ABSTRACT

Objective: Recently, an increasing number of publications in the literature have reported a series of prolonged neurological, cardiovascular, psychiatric and musculoskeletal symptoms after recovering from COVID-19, including particularly fatigue. This study seeks to evaluate fatigue symptoms in those infected by COVID-19.

Method: 82 volunteering and consecutive patients presenting to our clinic for follow-up checks after COVID-19 infection underwent evaluations for clinical and laboratory parameters and received FAS (fatigue assessment scale).

Results: The study included a total of 82 patients who had been infected by COVID-19 of whom 45 were male (54,9%) and 37 female (45,1%). with an average age of 55±15 years (min 22- max 87 age). In 354% of the cases the disease had followed a severe/critical course and in 64,6% mild/moderate. At the follow-up check 65,9% (54 cases) were found to have mild fatigue and 18,3% (15 cases) severe fatigue according to the FAS fatigue scale. Severe fatigue was significantly more common in women than in men (29,7% vs. 8.9% p=0,015). Those who were found to have fatigue at the follow-up check had significantly lower median hemoglobin levels (13,3 d/dl) at the time of presentation compared to the median hemoglobin levels of those without fatigue (14,2 g/dL). Fatigue was significantly more common in patients who had used low-molecular-weight heparin (LMWH) for treatment than those who never received LMWH.

Conclusion: This study shows that patients with COVID-19 infection may complain of fatigue regardless of the severity of the disease and other co-morbidities.

Keywords: COVID-19, fatique, post-COVID-19

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic is an outbreak of viral infections first identified in Wuhan, the capital of China's Hubei Province on December 01, 2019 (1, 2). The rate of transmission of the virus, spreading from human to human, rose in mid-January 2020 (3). Later, several countries in Europe, America and Asia started reporting cases. It was declared a global pandemic by the World Health Organization on March 11, 2021 (4). The disease is characterized by sudden-onset high fever, malaise, joint pain, shortness of breath and cough following an incubation period of 2 to 14 days (up to 27) (5). Some patients may also experience loss of taste and smell, sore throat and runny nose. Symptoms involve multiple systems of the body and, in some people, may persist for up to 6 months after recovering from the disease (6-8). In most cases, the disease has a mild-to-moderate clinical course. Cases of COVID-19 may be mild without need for hospitalization, or may result in complications such as severe pneumonia, septic shock, acute respiratory distress syndrome, multiple organ failure and death (9).

COVID-19 has been continuing for more than two years and has so far caused 681,143,521 PCR-confirmed infections and 6,808,754 deaths worldwide by 09.03.2023 (10). Although the pandemic has been curtailed to a certain extent by various vaccines that have received emergency use authorization, it is still continuing globally in the form of wave of infections due to an inadequate and uneven distribution of vaccines worldwide, decreasing efficacy of vaccines over time and newly emerging variants (11-16).

The term “long COVID”, which was initially defined by patients on social media, later found its place in the medical literature (17-20). Many alternative definitions of delayed or long-term symptoms of cyclical or progressive character that develop during or after COVID-19 infection, attributable to COVID-19 infection have been defined as long-haul COVID, long-tail COVID, persistent post-COVID, post-acute COVID syndrome (PACS), post-acute sequelae of SARS-CoV-2, post-COVID-19 syndrome and etc. (21-27).

Fatigue is one of the most reported symptoms after COVID-19 infection. The mechanisms underlying the fatigue include abnormal release of pro-inflammatory cytokines, increased inflammatory or oxidative state, mitochondrial dysfunction, sleep alterations, autonomic nervous system abnormalities, and poor nutritional status in COVID-19 infection. Also fatigue might be due to the respiratory complication as acute respiratory distress syndrome, lung fibrotic damage (28)

Many studies have shown that there are ongoing or new-onset complaints after COVID-19. One of these complaints is fatigue (6-8) It has been shown that the causes of fatigue include gender (29-34), low hemoglobin and lymphocyte count (35, 36).

In this study, it was aimed to evaluate the frequency and severity of fatigue symptoms in patients who came to outpatient clinic control after the acute period of COVID-19 infection. In addition, it was aimed to investigate how the demographic characteristics of the patients and the clinical and laboratory parameters during the acute illness period affect the frequency and severity of fatigue symptoms encountered in the post-COVID period.

MATERIALS AND METHODS

In this study, 82 consecutive volunteer patients who were positive PCR of nasopharyngeal swab, and had COVID-19 infection in the two-month period between January and February 2021 and then applied to the Chest Diseases Outpatient Clinic of Düzce University Hospital for control were included.

The mean time for patients to come for control was 68 days. The patients who came to the control examination from both inpatients and outpatients were included in the study. Despite the typical involvement in computed tomography, PCR negative cases were not included in the study.

The patients underwent evaluation for clinical and laboratory parameters, and the FAS survey. Demographic data, clinical and laboratory parameters were extracted retrospectively from the hospital’s medical records. The study investigated the association between parameters including radiological findings, hospitalization status, drugs used in treatment, duration of treatments, and status and severity of fatigue evaluated by the FAS fatigue scale.

The study received approval from Düzce University, Ethics Committee for Non-Invasive Research (approval no: 2021/56).

Fatigue Assessment Scale (FAS): The FAS is a 10-item validated and reliable scale, developed by De Vries et al. being used to assess fatigue in sarcoidosis patients. Each item is scored based on a 5-point Likert scale ranging from “never” to “always,” and the total score range is 10–50. Scores <22 indicate absence of fatigue, while scores between 22 and 34 indicate mild-to-moderate fatigue, and scores ≥ 35 indicate severe fatigue (37, 38).

Statistical Analysis: Descriptive statistics were expressed in mean, standard deviation, median, minimum and maximum values. Categorical data were compared using the Chi-square test (Fisher's exact test in 2x2 cross tabulations). Numerical data were non-normally distributed and thus compared using the Mann-Whitney U test. Statistical significance was set at $P<0.05$.

RESULTS

The study included a total of 82 patients who had been infected by COVID-19 of whom 45 were male (54.9%) and 37 female (45.1%) with an average age of 55±15 years (min 22- max 87 age). Some laboratory parameters. demographic and clinical features of the cases are summarized in Tables 1 and 2.

Table 1. Age and Some Laboratory Parameters of COVID-19 Cases			
	Mean ± SD	Median	(min-max)
Age (year)	55±15	55	(22-87)
Treatment time			
Inpatient (days)	5±8	5	(0-30)
Outpatient (days)	4±3	0	(0-15)
Ferritin (ng/mL)	137±194	71	(7-911)
D-dimer (µg/mL)	0.57±0.84	0.31	(0.2-6.46)
CRP (mg/dL)	0.46±0.52	0.20	(0.06-2.23)
SPO_2 (%)	96±1	97	(90-98)
LDH (U/L)	207±55	198	(128-481)
AST (IU/L)	20±10	17	(9-76)
ALT (U/mL)	21±17	17	(5-110)
Hemoglobin (g/dL)	13.4±1.6	13.4	(8.4-16.8)
Leukocyte (10^3/uL)	7.169±2.140	6.9	(3.50-18.50)
Lymphocyte (10^3/uL)	2.23±0.74	2.14	(0.44-6.70)
Control time (day)	68±37	69	(9-316)
FAS total score	27±6	26	(16-41)
CRP: C-reactive protein. SPO_2: Saturation of Peripheral Oxygen. LDH: Lactate Dehydrogenase. AST: Aspartate Transaminase. ALT: Alanine Transaminase			

Table 2. Demographic and Clinical Characteristics of The Cases	
	N (%)
Gender	
Male	45 (54.9)
Female	37 (45.1)
Marital Status	
Single	9 (11.0)
Married	73 (89.0)
Education Level	
Primary/Secondary school	53 (64.6)
High school/University	29 (35.4)
Comorbidities	
No	38 (46.3)
Hypertension	30 (36.6)
Diabetes mellitus	20 (24.4)
Asthma	9 (11.0)
Heart Failure	6 (7.3)
Symptoms	
Weakness / Muscle pain	69 (84.1)
Headache / Loss of sense of smell-taste	59 (72.0)
Dyspnea / Cough	55 (67.1)
Fever	25 (30.5)
Throat ache	21 (25.6)
Diarrhea / Nausea / Vomiting	19 (23.2)
Covid disease severity	
Mild/Moderate	53 (64.6)
Severe/Critical	29 (35.4)
Treatment	
Outpatient treatment (days)	35 (42.7)
Inpatient treatment (days)	47 (57.3)
Treatment features	
Oxygen support	15 (18.3)
Antibacterial	35 (42.7)
Corticosteroid	22 (26.8)
LMWH	40 (48.8)
Oxygen to the home at discharge	10 (12.2)
Corticosteroid at discharge home	15 (18.3)
LMWH at discharge home	31 (37.8)
LMWH: Low-Molecular-Weight Heparin	

In 35.4% of the cases. the disease had followed a severe/critical course. and in 64.6% mild/moderate. Patients recovering from COVID-19 were checked after an average of 68±37 days. At the follow-up check. 65.9% (54 cases) were found to have mild fatigue and 18.3% (15 cases) severe fatigue according to the FAS fatigue scale (Table 3).

Table 3. Fatigue Status of The Cases According to The FAS Score

Fatigue by FAS score	N (%)
No	13 (15.9)
Yes	69 (84.1)
No	13 (15.9)
Mild	54 (65.9)
Severe	15 (18.3)
No and *Mild*	67 (81.7)
Severe	15 (18.3)

There was no statistically significant correlation between age and disease severity and fatigue. Severe fatigue was significantly more common in women than in men (29.7% vs. 8.9%. p=0.015). There was no statistically significant correlation between marital status. educational level and the prevalence of fatigue. Although fatigue was more common in those with comorbidities. there was no statistically significant difference. The presence of comorbidities such as hypertension. diabetes. asthma and heart failure did not affect the prevalence of fatigue at a statistically significant level. (Table 4).

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Patients who had dyspnea/cough and malaise/muscle pain at the time of first presentation were significantly more likely to have fatigue at the follow-up check (p=0.025 and p=0.029. respectively). There was no significant correlation between the severity of the disease and the prevalence of persistent fatigue (Table 5).

Fatigue was significantly more common in patients who had used low molecular weight heparin (LMWH) for treatment than those who never received LMWH. Other drugs used in treatment and oxygen therapy did not have a significant effect on the prevalence of fatigue in the long term (Table 6).

Time to follow-up check was significantly longer in those with severe fatigue. Those who were found to have fatigue at the follow-up check had significantly lower median hemoglobin levels (13.3 d/dl) at the time of presentation compared to the median hemoglobin levels of those without fatigue (14.2 g/dL) (p=0.044). Median lymphocyte count was significantly lower in those with severe fatigue (1880) compared to lymphocyte counts of those without fatigue or with mild fatigue (2230) (p=0.022). There was no significant correlation between other laboratory parameters and fatigue (Table 7).

Table 4. Evaluation of The Frequency of Fatigue According to Gender, Marital Status, Education Level and Comorbidities						
	Fatigue by FAS score			Fatigue by FAS score		
	No	Yes	p	No/Light	Severe	p
	n (%)	n (%)		n (%)	n (%)	
Gender						
Male	9 (20.0)	36 (80.0)	0.257	41 (91.1)	4 (89)	0.015
Female	4 (10.8)	33 (89.2)		26 (70.3)	11 (29.7)	
Marital Status						
Single	3(33.3)	6(66.7)	0.149	8(88.9)	1(11.1)	1.000
Married	10(13.7)	63(86.3		59(80.8)	14(19.2)	
Education level						
Primary/ Secondary School	5 (9.4)	48 (90.6)	0.055	42 (79.2)	11 (20.8)	0.436
High School/ University	8 (27.6)	21 (72.4)		25 (86.2)	4 (13.8)	
Comorbidities						
No	9 (23.7)	29 (76.3)	0.071	34 (89.5)	4 (10.5)	0.091
Yes	4 (9.1)	40 (90.9)		33 (75.0)	11 (25.0)	
HT						
No	10(19.2)	42(80.8)	0.357	43(82.7	9(17.3)	0.761
Yes	3(10.0)	27(90.0)		24(80)	6(20)	
DM						
No	11(17.7)	51(82.3	0.410	52(83.9)	10(16.1)	0.372
Yes	2(10)	18(90)		15(75)	5(25)	
CHF						
No	13(17.1)	63(82.9)	0.583	62(81.6)	14(18.4)	1.000
Yes	0(0)	6(100)		5(83.3)	1(16.7)	
Asthma						
No	12 (16.4)	61 (83.6)	0.680	64 (87.7)	9 (12.3)	0.201
Yes	1 (11.1)	8 (88.9)		3 (33.3)	6 (66.7)	

HT: Hypertension; DM: Diabetes Mellitus; CHF: Congestive Heart Failure;

Table 5. Evaluation of Long-Term Fatigue Prevalence According to Symptoms and Disease Severity						
	Fatigue by FAS Score			Fatigue by FAS Score		
	No	Yes	p	No/Light	Severe	p
	n (%)	n (%)		n (%)	n (%)	
Fever						
No	11(19.3)	46(80.7)	0.325	46(80.7)	11(19.3)	1.000
Yes	2(8)	23(92)		21(84)	4(16)	
Dyspnea or Cough						
No	8 (29.6)	19 (70.4)	0.025	25 (92.6)	2 (7.4)	0.126
Yes	5 (9.1)	50 (90.9)		42 (76.4)	13 (23.6)	
Weakness or Muscle Pain						
No	5 (38.5	8 (61.5)	0.029	13 (100)	0 (-)	0.112
Yes	8 (11.6)	61 (88.4)		54 (78.3)	15 (21.7)	
GIS Symptoms						
No	10(15.9)	53(84.1)	0.993	54(85.7)	9(14.3)	0.087
Yes	3(15.8)	16(84.2)		13(68.4)	6(31.6)	
Neurological Symptoms						
No	2(8.7)	21(91.3)	0.268	20(87.0)	3(13)	0.443
Yes	11(18.6)	48(81.4)		47(79.7)	12(20.3)	
Throat Ache						
No	10(16.4)	51(83.6)	0.820	51(83.6)	10(16.4)	0.448
Yes	3(14.3)	18(85.7)		16(76.2)	5(23.8)	
Disease Severity						
Mild/Medium	10 (18.9)	43 (81.1)	0.364	46 (86.8	7 (13.2)	0.138
Severe/Critical	3 (10.3)	26 (89.7)		21 (72.4)	8 (27.6)	
GIS: Gastro-Intestinal System (diarrhea, abdominal pain etc.)						

Table 6. Evaluation of The Frequency of Fatigue in The Long Term According to The Oxygen and Other Drugs Used in The Treatment

	Fatigue by FAS Score			Fatigue by FAS Score		
	No	Yes	p	No/Light	Severe	p
	n (%)	n (%)		n (%)	n (%)	
O_2 Therapy						
No	12(17.9)	55(87.1)	0.281	57(85.1)	10(14.9)	0.136
Yes	1(6.7)	14(93.3)		10(66.7)	5(33.3)	
Antibacterial						
No	10(21.3)	37(78.7)	0.119	40(85.1)	7(14.9)	0.356
Yes	3(8.6)	32(91.4)		27(77.1)	8(22.9)	
Corticosteroid						
No	10(16.7)	50(83.3)	1.000	50(83.3	10(16.7)	0.532
Yes	3(13.6)	19(86.4)		17(77.3)	5(22.7)	
LMWH Treatment						
No	10 (23.8)	32 (76.2)	0.043	35 (83.3)	7 (16.7)	0.696
Yes	3 (7.5)	37 (92.5)		32 (80.0)	8 (20.0)	
O2 therapy at home						
No	13(18.1)	54(81.9)	0.351	60(83.3)	12(16.7)	0.380
Yes	0(0)	10(100)		7(70)	3(30)	
CS Therapy at Home						
No	13(19.4)	54(80.6)	0.112	56(83.6)	11(16.4)	0.459
Yes	0(0)	15(100)		11(73.3)	4(26.7)	
LMWH at Home						
No	12 (23.5)	39 (76.5)	0.014	43 (84.3)	8 (15.7)	0.557
Yes	1 (3.2)	30 (96.8)		24 (77.4)	7 (22.6)	

Abbreviations; O_2: Oxygen; AB: Antibiotic; CS: Corticosteroid; LMWH: Low Molecular Weight Heparin

Table 7. Long-Term Fatigue in COVID-19 Cases and Comparison of Age and Laboratory Parameters According to The Severity of Fatigue						
	Fatigue by FAS Score			Fatigue by FAS Score		
	No	Yes		No/Light	Severe	
	median	median	p	median	median	p
	(min-max)	(min-max)		(min-max)	(min-max)	
Age (years)	49	56	0.139	55	54	0.692
	(24-70)	(22-87)		(22-87)	(34-80)	
Ferritin (ng/mL)	75	70	0.995	74	32	0.103
	(15-763)	(7-911)		(7-911)	(19-545)	
D-dimer (µg/mL)	0.24	0.32	0.466	0.28	0.34	0.253
	(0.2-1.26)	(0.2-6.46)		(0.2-6.44)	(0.2-3.03)	
CRP (mg/dL)	0.33	0.20	0.374	0.22	0.16	0.834
	(0.06-1.91)	(0.06-2.23)		(0.06-2.23)	(0.06-1.69)	
SpO_2 (%)	98	97	0.185	97	98	0.431
	(94-98)	(90-98)		(90-98)	(93-98)	
LDH (U/L)	194	201	0.233	198	190	0.792
	(135-225)	(128-481)		(135-481)	(128-308)	
AST (IU/L)	17	17	0.652	17	17	0.417
	(10-39)	(9-76)		(9-76)	(9-27)	
ALT (U/mL)	17	17	0.571	18	15	0.397
	(5-39)	(7-110)		(5-110)	(9-56)	
Hgb (g/dL)	14.2	13.3	0.044	13.6	13.2	0.212
	(11.8-16.7)	(8.4-16.8)		(8.4-16.8)	(11.1-15.4)	
Leukocyte (10^3/uL)	6.8	6.9	0.727	7.0	6.3	0.070
	(3.5-18.5)	(4.2-9.6)		(3.5-14.3)	(4.2-18.5)	
Lymphocyte (10^3/uL)	1950	2190	0.477	2230	1880	0.022
	(950-3250)	(440-6700)		(950-6700)	(440-4200)	
Follow up duration (day)	62	70	0.546	65	83	0.046
	(5-103)	(9-316)		(9-316)	(27-103)	
Outpatient treatment (days)	4±2	4±3	0.578	4±3	3±3	0.649
	(0-10)	(0-15)		(0-15)	(0-10)	
Inpatient treatment (days)	4±8	5±7	0.275	5±8	5±7	0.286
	(0-22)	(0-30)		(0-30)	(0-24)	

Abbreviations; CRP: C-reactive protein. SPO_2: Saturation of Peripheral Oxygen. LDH: Lactate Dehydrogenase. AST: Aspartate Transaminase. ALT: Alanine Transaminase. Hgb: hemoglobin

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DISCUSSION

This study examined factors associated with persistent fatigue after infection with COVID-19. Fatigue was found to be more common in those with low hemoglobin and lymphocyte levels, in those who used anticoagulants during disease, and in female patients with severe infection. Time to follow-up check was significantly longer in those with severe fatigue.

There are numerous studies that have examined the association between COVID-19 infection and fatigue symptoms. The prevalence of the fatigue after COVID-19 infection range between %44 and %71 (6, 7, 18, 39). A study by Bakılan et al. with 280 patients who recovered from COVID-19 evaluated the patients in the post-acute period and found the prevalence of fatigue symptoms to be 71.8% (n:201). Our study, on the other hand, found this rate to be higher at 84.1% (n:69) (6). Likewise, a study by Lopez-Leon et al. estimated that 80% of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms. The most common symptom was fatigue (58%) (7).

A study by Munbilit et al. with 4755 patients reported that the most common symptom was chronic fatigue (25%) (8), a rate lower than that reported in other studies. This may be because their study sample was much larger than in our study. Their study also found the rate of fatigue to be higher in women, in line with our study.

In our study, while severe fatigue was 29% in women, it was 8% in men. Severe fatigue was significantly greater than in women. A study by Pela et al. investigated the association between gender and prolonged symptoms after COVID-19 infection; multivariate logistic regression analysis in their study found that women were statistically significantly more likely to experience persistent symptoms such as shortness of breath, fatigue, chest pain and palpitations (29).

A study by Huang et al. with 2469 COVID-19 patients found that women experienced symptoms of fatigue more during the post-COVID period, which was associated with women having higher levels of stress, depression and anxiety (30). Our study also found fatigue to be more common in the post-COVID period in female patients. As our study Townsend et al. have shown that post-COVID fatigue was more common in women (31). Another study by Fernández et al. achieved results similar to our study, and reported that biological differences on the expression of angiotensin-converting enzyme-2 and transmembrane protease serine 2 receptors between males and females, and immunological differences, e.g., lower production of pro-inflammatory interleukin-6 after viral infection in females, could explain the higher development of post-COVID symptoms (33). Similar to our study, many studies have shown that post-COVID fatigue and post-COVID dispne was more common in women. (31, 32, 34, 40).

Some other studies have found no association between female gender and post-COVID fatigue (41-43). These contradictory results may be due to race, conditions in respective countries and socio-economic status. Moreover, women may be experiencing fatigue more in the post-COVID period due to higher sensitivity to their body in general and to conditions associated with their body.

In our study, it is seen that patients with symptoms such as fatigue, weakness, shortness of breath, and cough during the period of COVID-19 infection are more likely to have more fatigue/weakness in the post Covid-19 controls they come after an average of 68 days. Carfi et al. reported that patients who had symptoms such as fatigue and dyspnea at the time of initial presentation had persistent fatigue symptoms in the post-COVID period after an average of 60.3 days (44). A meta-analysis by Fernandez et al. involving 15,244 hospitalized and 9,011 non-hospitalized patients found that more than 60% of COVID-19 survivors continued to have at least one symptom post-COVID-19 for over 30 days following onset of disease or hospitalization. Fatigue was found to be one of the most common symptoms after COVID-19 at follow-up checks at 60 and ≥90 days in patients who had symptoms such as fatigue, dyspnea and cough at the initial presentation. These results are in line with our study (45).

Studies reported that as hemoglobin and lymphocyte levels decrease, and the severity of disease increases (35, 36). Symptoms of prolonged fatigue may be more common in those who had a more severe form of COVID-19. The results of our study seem to confirm this; those with low hemoglobin and lymphocyte counts were found to have a higher rate of fatigue symptoms. No correlation was found with other laboratory parameters.

A study from China that investigated the adverse effect of LMWH on hemoglobin fall in COVID-19 treatment showed significant differences in onset symptoms fatigue between the 2 groups (81 in the LMWH group and 98 in the control group). Fatigue symptom was significantly less present in the heparin group (46). Similarly, fatigue was significantly more common in patients who had used LMWH for treatment in our study. Heparin therapy was used to patients requiring hospitalization, outpatients but with non-COVID-19 thrombotic risk factors such as previous surgery, trauma history, immobilization and active cancer, and these patients may have had a more severe disease and may have felt more tired due to their comorbidities.

Comorbidities that are defined as having a significant association with increased the risk of mortality in patients with COVID-19 pneumonia are cardiovascular disease, chronic renal disease, malignancy in a study (47). Although comorbidities were associated with death, no association with post COVİD-19 fatigue was found. Although fatigue was more common in those with comorbidities, there was no statistically significant difference. The presence of comorbidities such as hypertension, diabetes, asthma and heart failure did not affect the prevalence of fatigue at a statistically significant level.

The limitations of our study were that it was a a single center with a limited number of patients. Our study needs to be supported by large number of prospective studies.

The results of this study show that those recovering from COVID-19 infection may experience persistent fatigue regardless of the severity of the disease and other co-morbidities. More extensive studies conducted over a longer period of time are needed to clarify the physiopathology of prolonged symptoms such as fatigue and to identify longer-term outcomes after COVID-19 infection.

Ethics Committee Approval: Ethics committee approval dated 01.03.2021 and numbered 2021/56 was obtained from Düzce University Faculty of Medicine Ethics Committee for this study.

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