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Postdischarge pain, fatigue severity and quality of life in COVID-19 survivors

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ABSTRACT

Objectives: Fatigue and pain symptoms were common complaints among post-COVID-19 patients, and these lead to impaired quality of life (QoL). We aimed to evaluate severity of pain and fatigue 3 months after disease onset in discharged COVID-19 patients.

Methods: Patients were contacted by phone at their third month following disease onset. Demographic data of the patients such as weight, height, body mass index (BMI), gender, smoking history, comorbidities, length of hospitalization, duration of stay in the intensive care unit, were recorded. The patients' pain and fatigue severities were evaluated by visual analog scale (VAS). QoL was questioned with the EuroQol Group Association five-domain, three-level questionnaire (EQ-5D-3L).

Results: A total of 392 participants enrolled into the study. At admission, 94.6% of the participants had fatigue and 73.7% of them had pain. A high proportion of them still reported fatigue (55.1%) and pain (41.3%) at third month. The mean value of pain-VAS score was 5.37 ± 3.85, and it was 7.58 ± 2.82 for fatigue-VAS at admission. VAS scores of pain and fatigue at third month were 1.44 ± 2.11 and 2.04 ± 2.40 respectively. While 66.6% of the patients reported moderate-severe pain at disease onset, the rate was 18.1% at the third month. And also almost half had severe pain at admission (48%), it was 2.8% at third month. At disease onset 89.6% of the patients reported moderate-severe fatigue (severe:48%). Aproximately one third of them had moderate-severe fatigue (27.9%) at third month (severe: 5.1%). The mean value of EQ-VAS score was 26.76 ± 20.26 at admission, and it was 78.84 ± 16.15 at third month. Statistically significant differences were recorded between the disease onset and third month in terms of pain-VAS fatigue-VAS, and EQ-VAS scores ($p < 0.001$). Female gender, ICU admission, long duration of hospitalization, older age, higher BMI scores, multiple comorbidities, fatigue and pain severity were related to the decrease in QoL scores.

Conclusions: Hospitalized COVID-19 survivors need ongoing support for pain, fatigue complaints and impaired QoL after discharge. The factors that cause poor QoL should be taken into account during post-COVID-19 follow up.

Keywords: COVID-19, pain, fatigue, visual analog scale (VAS) , quality of life, EQ-5D-3L

Coronavirus disease 2019 (COVID-19) which has become a worldwide pandemic, affects people in different ways, including asymptomatic infection, mild respiratory illness and severe pneumonia with acute respiratory failure and even death [1, 2]. Some patients do not show a rapid recovery after COVID-

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19 treatment and their symptoms may persist up months, if the symptoms persist beyond 12 weeks, it is called post-COVID-19 syndrome [3]. Highly heterogeneous clinical manifestations were found in post-COVID-19 syndrome, such as fatigue, pain, hair loss, dyspne cough, memory loss, sleep disorder, anxiety etc. [2, 4-7]. Fatigue and pain symptoms were common complaints among post covid patients [7, 8]. However, it is not known to what extent fatigue and pain intensity continue. We aimed to assess severity of pain, severity of fatigue and quality of life (QoL) of hospitalized COVID-19 patients 3 months after disease onset.

METHODS

Study Design and Participants

This was a single-center, cross-sectional study carried out in a tertiary hospital in İstanbul, Turkey during February 15, 2021 to May 15, 2021.

The study protocol was approved by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey (No. 2021/21). It was performed by the principles stated in the Declaration of Helsinki.

A total of 1921 patients hospitalized with the diagnosis of COVID-19 (positive COVID-19 PCR test, or presence of COVID-19 based on clinical and radiological criteria) between 15 November 2020 and 15 February 2021 were recruited from the hospital's database. Patients that were death, older than 65 years and younger than 18 years, prisoners and foreign nationalities were excluded. A total of 392 of the remaining 894 eligible patients were contacted at 3rd month following disease onset. Trained physicians called the patients by phone, explained the aims of the study, and asked patients to answer the questionnaire. Informed consent was given verbally over the phone and recorded by the investigators.

Demographic data of the patients such as weight, height, body mass index (BMI), gender, smoking history, comorbidities, length of hospitalization, duration of stay in the intensive care unit (ICU), were recorded either from their files or by phone visit. The World Health Organization (WHO) classification criteria were used for BMI classification. The patients' pain and fatigue severity and QoL at the time of the phone call and at the hospital admission were questioned. Pain and fatigue severities were evaluated by visual analog scale (VAS). QoL was questioned with the EuroQol Group Association five-domain, three-level questionnaire (EQ-5D-3L).

EQ-5D-3L

OoL was assessed using the EQ-5D-3L, which consists of two sections: the descriptive system and the VAS. The descriptive system assesses five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The participant describes the severity levels of each dimension in a categorical scale without arithmetic properties from 1 to 3, where 1 indicates no problem, 2 indicates some problem and 3 indicates extreme problem. The second part includes the VAS in which respondents evaluate their current health status between 0 (worst imaginable health) and 100 (best imaginable health) [9].

VAS

Patients score their pain or fatigue on a pain scale with 0 representing 'no pain or no fatigue' and 10 representing 'most severe pain possible or most severe fatigue possible [10].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as numbers and percentages, while continuous data were reported as means ± SD. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the normal distribution, data were normally distributed so means for continuous variables were compared using unpaired or paired t-tests. Wilcoxon test was used for categorical data. Also, Spearman's correlation was used to find the correlation between symptoms' score in acute and post COVID-19 stages. The results were evaluated bilaterally at 95% confidence interval, significance level at $p < 0.05$ and $p < 0.01$.

RESULTS

A total of 392 participants completed the survey by telephone call. Of the patients, 50% were male and 50% were female. The mean age was 51.27 ± 11.13

Table 1. Demographic and clinical charactersitics of hospitalized COVID-19 patients

	Total (n = 392)
Age (years), mean ± SD	51.27 ± 11.13
Gender, n (%)	
Male)	196 (50)
Female	196 (50)
BMI, mean ± SD	30.11 ± 5.30
Normal (BMI < 25kg/m^2), n (%)	51 (13.0)
Overweight (BMI = 25-30kg/m^2), n (%)	177 (41.8)
Obese (BMI > 30kg/m^2), n (%)	164 (37.2)
Comorbidities, n (%)	
No comorbidities	130 (33.2)
One comorbidity	106 (27.0)
> 1 comorbidity	156 (39.8)
HT	144 (36.7)
DM	134 (34.2)
Hyperlipidemi	53 (13.5)
Cardiac	60 (15.3)
Pulmoner	49 (12.5)
Renal	22 (5.6)
Malignancy	23 (5.9)
Others	21 (5.4)
Smoking status, n (%)	
Non-smoking	288 (73.5)
Current-smoking	35 (8.9)
Previous-smoking	69 (17.6)
Symptoms at hospital admission, n (%)	
Fever)	70 (17.9)
Dyspne	198 (50.5)
Cough	77 (19.6)
GIS symptom	39 (9.9)
Pain	289 (73.7)
Fatigue	371 (94.6)
Inpatient day, mean ± SD	10.36 ± 6.71
< 10 days, n (%)	213 (54.3)
≥ 10 days, n (%)	179 (45.7)
ICU day, mean ± SD	0.85 ± 3.93
Present, n (%)	25 (6.4)
No, n (%)	367 (3.6)

Data are shown as mean ± standard deviation or n (%). BMI = body mass index, HT = hypertension, DM = diabetes mellitus GIS = gastro intestinal system, ICU = intensive care unit, SD = standard deviation

years, the mean BMI was 30.11 ± 5.30 kg/m2, and most of them were overweighted (41.8%). 73.5% were non-smokers. Most of the patients had at least one comorbidy (66.8 %). There were no comorbidity in 33.2% of the patients.

Among 392 patients, 6.4% of them had required intensive care treatment at some point throughout hospital stay. The median length of hospital stay was 10.36 ± 6.71 days, although it ranged from 1 to 50 days. The characteristics of the study population are summarized in Table 1.

Pain and Fatigue Severity

At the time of the survey (90 days post-disease onset), participants were asked to describe current pain and fatigue severity by VAS and to recall pain and fa-

Table 2. Pain, fatigue and quality of life of hospitalized covid-19 patients at hospital admission and 3 months after disease onset

	Hospital admission	3 months after COVID-19	*p value*
Pain symptom/moderate-severe pain, n (%)	282 (71.9)/261 (66.6)	162 (41.3)/71(18.1)	**< 0.001**[1]
Fatigue Symptom/moderate-severe fatigue, n (%)	371 (94.6)/351(89.6)	216 (55.1)/109 (27.9)	**< 0.001**[1]
Pain VAS, mean ± SD	5.37 ± 3.85	1.44 ± 2.11	**< 0.001**[2]
Fatigue VAS, mean ± SD	7.58 ± 2.82	2.04 ± 2.40	**< 0.001**[2]
QOL (EQ-5D-3L)			
Mobility, n (%)			**< 0.001**[1]
No problems	100 (25.6)	311 (79.3)	
Some problems	201 (51.3)	78 (19.9)	
Extreme problems	91 (23.2)	3 (0.8)	
Self-care, n (%)			**< 0.001**[1]
No problems	118 (30.1)	352 (89.8)	
Some problems	170 (43.4)	35 (8.9)	
Extreme problems	104 (26.5)	5 (1.3)	
Usual activities, n (%)			**< 0.001**[1]
No problems	93 (23.7)	342 (87.2)	
Some problems	168 (42.9)	46 (11.7)	
Extreme problems	131 (33.4)	4 (1.0)	
Pain or discomfort, n (%)			**< 0.001**[1]
No pain or discomfort	105 (26.8)	292 (74.5)	
Some pain or discomfort	125 (31.9)	94 (24.0)	
Extreme pain or discomfort	162 (41.3)	6 (1.5)	
Anxiety or depression, n (%)			**< 0.001**[1]
Not anxious or depressed	113 (28.8)	330 (84.2)	
Moderately anxious or depressed	126 (32.1)	53 (13.5)	
Extremely anxious or depressed	153 (39.0)	9 (2.3)	
EQ-VAS, mean ± SD	26.76 ± 20.26	78.84 ±16.15	**< 0.001**[2]
EQ-5D index score, mean ± SD	0.346 ± 0.318	0.86 ± 0.193	**< 0.001**[2]

Data are shown as mean ± standard deviation or n (%). QOL (EQ-5D-3L) = quality of life (EuroQol five-domain, three-level) VAS = visual analog scale, SD = standard deviation

[1]Wilcoxon, [2]Paired samples t test

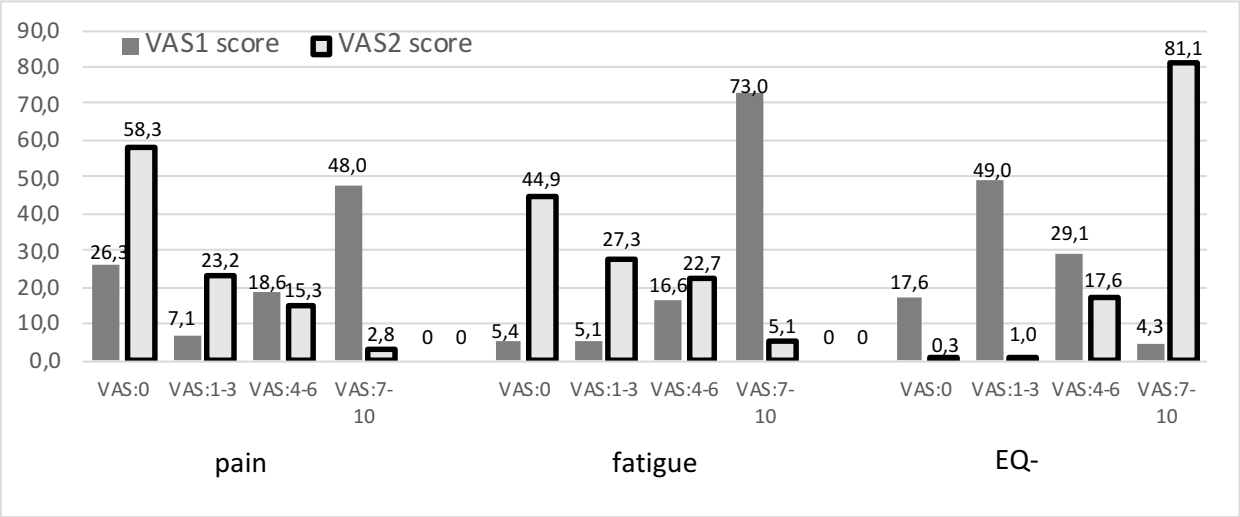

Fig. 1. VAS score frequencies of pain, fatigue and EQ of hospitalized Covid-19 patients at hospital admission and 3 months after disease onset. VAS1 = visual analog scale at hospital admission, VAS2 = visual analog scale at 3 months after disease onset, EQ-QoL = Euro Quality of Life

tigue severity at disease onset (Table 2).

At admission, 94.6% of the participants had fatigue and 73.7% of them had pain. A high proportion of individuals still reported fatigue (55.1%) and pain (41.3%) at the time of the questionnaire. The mean value of pain VAS score was 5.37 ± 3.85 for pain, and 7.58 ± 2.,82 for fatigue VAS at admission. 3 months after COVID-19 onset the VAS scores of pain and fatigue was 1.44 ± 2.11, 2.04 ± 2.40 respectively. A statistically significant decrease was found both in pain and fatigue VAS scores at 3rd month of COVID-19 according to disase onset ($p < 0.001$). VAS scores of pain and fatigue of the patients at hospital admission and 3 months after disease onset were shown in Fig. 1.

Quality of Life

The mean value of EQ-VAS score was 26.76 ± 20.26 at admission, and it was 78.84 ±16.15 3 months after COVID-19 onset. The EQ-5D index score was 0.346 ± 0.318 at admission, and it was 0.86 ± 0.193 at 3rd month. A statistically significant improvement was found both in EQ-VAS and EQ-5D index scores at 3rd month of COVID-19 according to disase onset ($p < 0.001$). Although the QOL of the patients according to EQ-5D-3L were better at third month, 25.5% had still pain and discomfort complaints and 15.8 % felt anxious and depressed, 21.7% had problems with mobility (Table 2).

Demographic and clinical variables can affect pain, fatigue and QoL. So we examined the relation between the parameters. A statistically significant relationship was found between female gender and 3rd month pain VAS ($p = 0.033$), fatigue VAS ($p = 0.018$), EQ-VAS ($p = 0.002$). ICU admission and longer inpatient day affected 3rd month VAS pain, VAS fatigue, EQ-VAS scores negatively ($p < 0.05$) (Table 3). According to the correlation analysis, a statistically significant relationship was found between EQ-VAS at 3rd month and female gender, older age, higher BMI scores, having multiple comorbidities, ICU admission, and length of hospital stay, fatigue VAS and pain VAS (Table 3). Fatigue-VAS had a correlation with female gender, older age, higher BMI, having multiple comorbidities, length of ICU stay, and length of hospital stay. Pain-VAS had a correlation with female gender, ICU admission, and length of hospital stay

DISCUSSION

Post-COVID-19 syndrome is a debilitating problem for those who recovered from COVID-19. Highly heterogeneous clinical manifestations were found in post-COVID-19 syndrome [2, 4-7]. Aproximately 64% - 76% of the patients reported persistence of at least 1 symptom for > 12 weeks [2, 11]. At post acute period (> 4 weeks) the rate of persistant symptomps was 87%

Table 3. Relationship between the parameters of hospitalized covid-19 patients 3 months after disease onset

	Inpatient day	ICU day	Pain-VAS2	Fatigue-VAS2	EQ-VAS2
Age					
r	.140**	0.038	0.094	.119*	-.176**
p value[2]	**0.006**	0.455	0.063	**0.019**	**< 0.001**
Female	10.40 ± 7.42	0.96 ± 4.36	1.66 ± 2.18	2.32 ± 2.45	76.33 ± 16.60
Male	10.32 ± 5.92	0.73 ± 3.46	1.21 ± 2.01	1.75 ± 2.31	81.35 ± 15.32
p value[1]	0.904	0.564	**0.033**	**0.018**	**0.002**
BMI					
r	0.085	.122*	0.060	.115*	-.134**
p value[2]	0.091	**0.015**	0.237	**0.023**	**0.008**
Non-smoking	10.48 ± 7.08	0.79 ± 3.92	1.52 ± 2.15	2.10 ± 2.44	78.68 ± 15.56
Current/previous smoking	10.02 ± 5.57	1.01 ± 3.97	1.20 ± 1.96	1.87 ± 2.31	79.28 ± 17.74
p value[1]	0.549	0.629	0.168	0.399	0.747
Number of comorbidities					
r	.141**	.147**	0.093	.237**	-.271**
p value[2]	**0.005**	**0.004**	0.067	**< 0.001**	**< 0.001**
Inpatient day					
r	1	.644**	.158**	.141**	-.178**
p value[2]		**< 0.001**	**0.002**	**0.005**	**< 0.001**
ICU admision					
yes	25.32 ± 10.76	1	2.32 ± 2.15	1.96 ± 2.39	70.00 ± 15.20
No	9.34 ± 4.91		1.38 ± 2.09	3.16 ± 2.17	79.44 ± 16.05
p value[1]	**0.001**		**0.030**	**0.015**	**0.005**
Pain-VAS2					
r	.158**	. 125*	1	.597**	-.439**
p value[2]	**0.002**	**0.013**		**< 0.001**	**< 0.001**
Fatigue-VAS2					
r	.141**	. 130**	.597**	1	-.567**
p value[2]	**0.005**	**0.010**	**< 0.001**		**< 0.001**

BMI = body mass index, ICU = intensive care unit, EQ-5D = Euro Quality of Life five-domain, VAS2 = visual analog scale at 3 months after disease onset,

[1]Chi square, [2]Pearson, **Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed).

[7, 8, 11].

Musculoskeletal pain was one of the most reported complaint in acute infection (70% - 89.5%) [7, 8, 12, 13]. As a persistant symptom post covid pain was found in a range of 27-61% [5-8, 14, 15]. We found 41.3% pain symptom at the time of the questionnaire, while it was 73.7% at disease onset. We also measured the severity of pain with the VAS scale both at acute period and at the 3rd month. While 66.6% of the patients reported moderate to severe pain at disease onset, the rate was 18.1% at the third month. And also almost half had severe pain at the onset of the disease

(48%), it was 2.8% at third month.

In a study using only the initial VAS scores it was found that 68% of patients had severe myalgia complaints at disease onset [12]. Murat *et al*. [12] found that 96.2% of the patients had moderate pain symptom according to VAS during acute period.

Since there was no pain severity measurement at third month, we investigated EQ-5D results. Pain/discomfort problems were reported in a range of 39.5-81.1%, with 4.5-12.4% of severe problems at third month [11, 16]. At sixth month after COVID-19 33-48.4% of the patients had still pain/discomfort problems (8.8% with severe problems) [17, 18].

We also assesed the corelation of pain with demographic and clinical parameters. According to our results female gender presented higher frequencies of pain in agreement with previous studies [5]. In addition to this we found that ICU requirement, and longer length of hospital stay caused more pain complaints. According to ED-5Q results Halpin *et al*. found worsened pain/discomfort ratio 14.7% among wards patient, 28.1% among ICU patients [196]. On the other hand an association was found between higher BMI and myalgia [5]. However we couldn't confirm this association.

Post-COVID fatigue has been found to be the most frequent symptom either at acute or post-COVID period [2, 4-8, 12-15, 20] and also our prevalence of fatigue in the acute period was 94.6%. In previous studies initial fatigue symptom range was 80 - 85% [7, 8, 12, 13] and as a persistant symptom the range was 55-85% [2, 4-6, 14, 15, 20].

Tuzun *et al*. [13] evaluated fatigue with Chalder Fatigue Score CFS at the acute period and found 85.3% of the patients had severe mean fatigue VAS scores, but they didn't have postcovid period results. Townsend *et al*. [21] also examined the prevalence of fatigue with CFS at 10 weeks after initial COVID-19 symptoms. Half of the patients met the criteria for fatigue with half of them reporting severe fatigue, but they didn't have acute period results. Sykes *et al*. [5] found extreme fatigue 39.6% at forth month after post-discharge.

We didn't use a specific fatigue scale but according to VAS scores 55% of our patients reported fatigue at 3rd month. Aproximately one third of them had moderate-severe fatigue (27.9% including severe of 5.1%). At disease onset 89.6% of the patients reported moderate-severe fatigue (severe: 48%).

We examined corelation of fatigue with demographic and clinical parameters. According to our results fatigue-VAS had an assosiation with female gender, older age, higher BMI, having multiple comorbidities, ICU recuirement, and longer length of hospital stay. Unlike our results Townsend *et al*. [21] didn't find a relation with fatigue and ICU or ward admission. On the other hand Halpin *et al*. [19] investigated hospitalized patients and found that ICU group were more likely to report fatigue than wards group (72% vs 60.3%). Similar to our results Sykes *et al*. [5] also found that female gender and higher BMI was associated with fatigue.

There are different results according to hospitalization or evaluation time after disease onset. There had been still persistant pain and fatigue complaints with higher rates than ours 4 months after disease onset [2, 5, 14] persistent symptoms such as pain and fatigue often lead to impaired quality of life [7, 14, 15].

The EQ-5D data showed that patients had worse QoL at disease onset and the impaired QoL lasts on months after discharge [11, 15, 16]. Restriction of daily activities was found at 84.9% of patients at disease onset [7]. Among our patients 76.3% of them reported problems with usual activities and 69.9% with self care at disease onset.

Studies showed that 23.2-67% of the patients reported poorer QoL at post covid period [6, 8, 17, 18]. Restriction of daily activities (57%) was the most frequently seen [7]. Shah *et al*. [11] found that 79.5% of patients had problems with usual activities at third month (severe: 26.3%). Among our patients 12.7% of them reported problems with usual activities and 10.2% with self care at third month.

Todt *et al*. [16] found pain/discomfort and anxiety/depression as the most affected domains at third month after discharge. According to our results pain-discomfort domain was the most affected (25.5% of the patients had problems). Unlike their results we found that 21.7% of the patients had mobility problems. Perhaps it was because of ongoing dyspne complaints, it would be better if we had asked persistant dyspne symptom.

In our study 15.8 % of the patients felt anxious and depressed at third month. But the rates in previous studies were higher than ours (24-53%) [2, 7, 19]. Six

months after symptom onset, Anxiety or depression was reported among one forth of patients [2]. In addition to these psychological distress was also higher in ICU discharged patients. (46.9% in ICU group and 23.5% in ward group) [19].

Similar to our results Garrigues *et al*. [4] found that post-discharge mean EQ-VAS was 70.3% and mean EQ-5D index was 0.86, there were no difference between ICU and ward patients. Female gender, being hospitalized, ICU requirement, longer length of hospital stay and comorbidity presence were associated with decreased QoL scores in agreement with previous studies [11, 16, 22]. In addition to these findings we also found that older age, higher BMI scores, fatigue and pain severities caused decrease in QoL scores. Unlike our results Tabooda found male sex was associated with poor QoL [18].

Sixth months after disease EQ-5D scores worse than ours was also detected. The results according to EQ-5D questionaire were as follows: 33-56% of the patients had problems with mobility, 35-37% with usual activities, 13-17% with self-care, 33-48% with pain/discomfort and 26-46% with anxiety/depression [17, 18]. Perhaps it was because of older patients or ICU discharged patients that included into these studies.

Limitations

A limitation of the present study is that it was a phone survey because of pandemic conditions. Another limitation is that it included only hospitalized patients and the number of ICU patients that we had reached was very low. Our results were based on patients' self-reported data. Also we could assess anxiety/depression and sleep with a disease spesific questionaire since these exacerbate fatigue and impact QoL negatively. Regardless, our results show either pain or fatigue lasts long periods of time altough the treatment is over.

CONCLUSION

Post-COVID-19 syndrome is a debilitating problem. Pain and fatigue were the most common post-COVID-19 syndromes. Our findings are in agreement with other previous studies, different from others we evaluated the severity of pain and fatigue. Half of the patients had severe fatigue and pain symptoms at COVID-19 onset. Despite the end of the treatment, it was determined that moderate-to-severe pain and fatigue complaints continued at 3rd month in some patients, and these worsened QoL. Patients which were female, older or overweighted, who had multiple comorbidities, who required ICU or stayed at hospital for a long time had higher fatigue severity and poor QoL. These findings may be important for planning the ongoing support for these patients. The factors that cause poor QoL should be taken into account during post-COVID-19 follow up.

Authors' Contribution

Study Conception: ED, SA, GE, İO, ÖK; Study Design: ED, SA, GE, İO, ÖK; Supervision: ED, SA, GE, İO, ÖK; Funding: ED, SA, GE, İO, ÖK; Materials: ED, SA, GE, İO, ÖK; Data Collection and/or Processing: ED, SA, GE, İO, ÖK; Statistical Analysis and/or Data Interpretation: ED, SA, GE, İO, ÖK; Literature Review: ED, SA, GE, İO, ÖK; Manuscript Preparation: ED, SA, GE, İO, ÖK and Critical Review: ED, SA, GE, İO, ÖK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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