Long-Term Pulmonary Evaluation of Intensive Care Unit Patients with Severe COVID-19

Ağır COVID-19 Nedeniyle Yoğun Bakımda Takip Edilen Hastaların Uzun Dönem Akciğer Değerlendirmesi

Hamide Gül Şekerbey[1], Sinem Güngör[1], Eylem Tunçay[2], Buse Nur Ertam[3],
Büşra Durak[4], Emine Aksoy[1], Özlem Yazıcıoğlu Moçin[1], Gökay Güngör[1],
Nalan Adıgüzel[1], Zuhal Karakurt[1]

[1]University of Health Sciences Türkiye, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Pulmonary Disease, İstanbul, Türkiye

[3]Defne State Hospital, Clinic of Pulmonary Disease, Hatay, Türkiye

[4]Hitit University Training and Research Hospital, Clinic of Pulmonary Disease, Çorum, Türkiye

ABSTRACT

Background: The long-term pulmonary consequences and impact on respiratory function among patients discharged from intensive care unit (ICU) after severe COVID-19 are not well known. The purpose of this study was to investigate the pulmonary sequelae and long-term respiratory function of patients with severe COVID-19 who were discharged from the ICU.

Materials and Methods: This prospective cohort study. First, 3rd, and 6th month symptoms, laboratory data, 6-minute walk test, sit-to-stand test, BORG scale, pulmonary function test, chest X-ray, and thorax computed tomographys (CTs) of patients diagnosed with COVID-19 who were treated and discharged from the ICU.

Results: Sixty (74%) of the 81 patients included in the study were male, and the median age was 49 (43-61). The most common symptoms upon admission were dyspnea (69%), cough (42%), fever (47%), and fatigue (37%). At the 6-month follow-up, 30 (45%) of the 66 patients had at least one complaint, with dyspnea, cough, and muscle pain being the most common. When the symptoms of patients upon admission were compared with those during the 1st, 3rd, and 6th months of follow-up, it was found that the symptoms of dyspnea, cough, and fatigue regressed. Furthermore, laboratory parameters such as lymphocyte and eosinophil counts, neutrophil lymphocyte ratio, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer levels were improved (p<0.01). At the 6-month follow-up, thorax CT scans showed ground glass infiltration in 7 (28%) patients, fibrosis in 4 (16%), band atelectasis in 2 (8%), and fibrotic bands in 8 (32%). 12% of patients had normal thorax CT scans.

Conclusion: There has been a growing body of knowledge regarding the long-term impacts of COVID-19. Prolonged symptoms are linked to illness convalescence and the potential development of fibrosis, emphasizing the need for regular post-discharge monitoring of patients. It is recommended that a minimum of 6 months after the onset of COVID-19 is an appropriate duration to identify the long-term effects of COVID-19.

Keywords: COVID-19, intensive care unit, convalescence, severe COVID-19, long term

ÖZ

Amaç: Ağır COVID-19 nedeniyle yoğun bakım ünitesinde (YBÜ) takip edilen olguların taburculuk sonrası akciğerlerinde nasıl sekel kaldığı, pulmoner fonksiyon ve kapasitelerinin nasıl etkilendiği net bilinmemektedir. Çalışmamızda YBÜ'de COVID-19 nedeniyle takip edildikten sonra taburcu olan olguların uzun dönem pulmoner fonksiyon ve sekel durumunu araştırmayı amaçladık.

Gereç ve Yöntemler: Prospektif çalışmada, COVID-19 tanısıyla YBÜ'de tedavi edilip taburcu olan hastaların, taburculuk sonrası 1. 3. ve 6. ay semptomları, laboratuvar verileri, 6 dakika yürüme testi, otur kalk testi, BORG skalası, solunum fonksiyon testi, akciğer grafisi ve toraks bilgisayarlı tomografileri (BT) değerlendirildi.

ÖZ

Bulgular: Çalışmaya alınan 81 olgunun 60'ı (%74) erkek olup, ortanca yaş 49 (43-61) idi. Olguların yatışta en sık görülen semptomları nefes darlığı (%69), öksürük (%42), ateş (%47) ve halsizlik (%37) idi. Altıncı ay kontrolüne gelen 66 olgunun 30'unun (%45) en az bir şikâyeti vardı, en sık görülen şikâyet nefes darlığı, öksürük ve kas ağrısı idi. Hastaların yatış, 1. 3. ve 6. ay takiplerindeki semptomları karşılaştırıldığında nefes darlığı, öksürük ve halsizlik semptomlarında gerileme olduğu, laboratuvar parametrelerinden ortalama lenfosit sayısı, eozinofil sayısı, nötrofil lenfosit oranı, laktat dehidrogenaz, C-reaktif protein, ferritin ve D-dimer değerlerinde düzelme olduğu görüldü (p<0,01). Altıncı ay kontrolünde çekilen toraks BT'lerin 7'sinde (%28) buzlu cam infiltrasyonu, 4'ünde (%16) fibrozis, 2'sinde (%8) band atelektazi ve 8'inde (%32) fibrotik bant görüldü. %12 olgunun toraks BT'leri normal idi.

Sonuç: COVID-19'un uzun dönem etkileri ile ilgili bilgiler zaman içerisinde artmaktadır. Uzamış semptomlar, hastalıktan iyileşme süreci ve gelişebilecek fibrozis ile ilişkili olup hastalar taburculuk sonrası düzenli takip edilmelidir. COVID-19'a bağlı sekelleri tanımlamak için hastalık sonrası en az 6 ayın geçmesinin uygun olacağı düşünülmektedir.

Anahtar Kelimeler: COVID-19, yoğun bakım ünitesi, iyileşme dönemi, ağır COVID-19, uzun dönem

Introduction

Although the epidemiological and clinical characteristics of COVID-19 were well established since December 2019, data regarding its long-term consequences is limited. As the number of patients who recovered from the disease increased, ongoing multisystemic organ involvement, including the lungs, was observed. COVID-19-related pulmonary fibrosis, vascular diseases, and mental disorders have also been reported (1-4). Post-severe COVID-19 pulmonary diffusion disorders, muscle weakness, and radiological sequelae were identified recently (5).

Although symptoms lasting longer than a month were 10-20% of patients who recovered from COVID-19, symptoms lasting 12 weeks were reported in 2.3% of patients (6). In cases of prolonged COVID-19, symptoms like dyspnea, cough, fatigue, chest pain, joint pain, muscle pain, and anxiety were persisted, while there were limited studies regarding the sequelae left in different organ systems (6-9). Furthermore, data on the duration of COVID-19-related ongoing symptoms, radiological abnormalities, and pulmonary function alterations are limited.

This study aimed to investigate the long-term effects of severe COVID-19 on pulmonary function and sequelae of the patients who were discharged from intensive care unit (ICU).

Materials and Methods

Patients who were followed-up in the ICU between August 1, 2020, and August 31, 2021 and discharged from the hospital due to severe COVID-19 were included in the prospective cohort study. Approval was obtained from the University of Health Sciences Türkiye, Süreyyapaşa Chest Diseases and Thoracic Surgery Clinical Research Ethics Committee (approval number: 116.217.089, date: 18.06.2020), in accordance with the Helsinki Declaration.

Patients

COVID-19 patients who were followed-up in the ICU and subsequently discharged were scheduled for control appointments at the 1st, 3rd, and 6th months after the discharge date. Demographic characteristics, symptoms at diagnosis, smoking history, comorbidities, polymerase chain reaction (PCR) test results, radiological images [chest X-ray, thorax computed tomography (CT)], length of stay, blood tests (hemogram, biochemistry, coagulation, cardiac markers), APACHE II score, Charlson comorbidity index, treatments applied during hospitalization and respiratory support treatments, treatments given after discharge, and radiological images from the hospital data system and intensive care records were recorded. The study flow chart is shown in Figure 1.

Inclusion Criteria

• Severe COVID-19 patients followed up in the ICU
• Patients discharged from the ICU
• Patients undergoing 1st, 3rd, and 6th month follow-up after discharge

Exclusion Criteria

• Dieting in a palliative care unit
• Living outside the province
• Immobile
• Lost to follow-up
• Refused to participate

Evaluation/Patient Follow-Ups

In the first month of follow-up of the patients participating in the study, questions regarding symptoms and oxygen support, saturation measurement, BORG scale, chest X-ray, biochemistry tests [glucose, urea, creatinine, aspartat transferaz, alanin aminotransferaz, alkaline phosphatase, gamma-glutamyl transferase, ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH)], coagulation tests (D-dimer, prothrombin time, international normalized ratio), and hemogram tests were performed. In the 3rd month
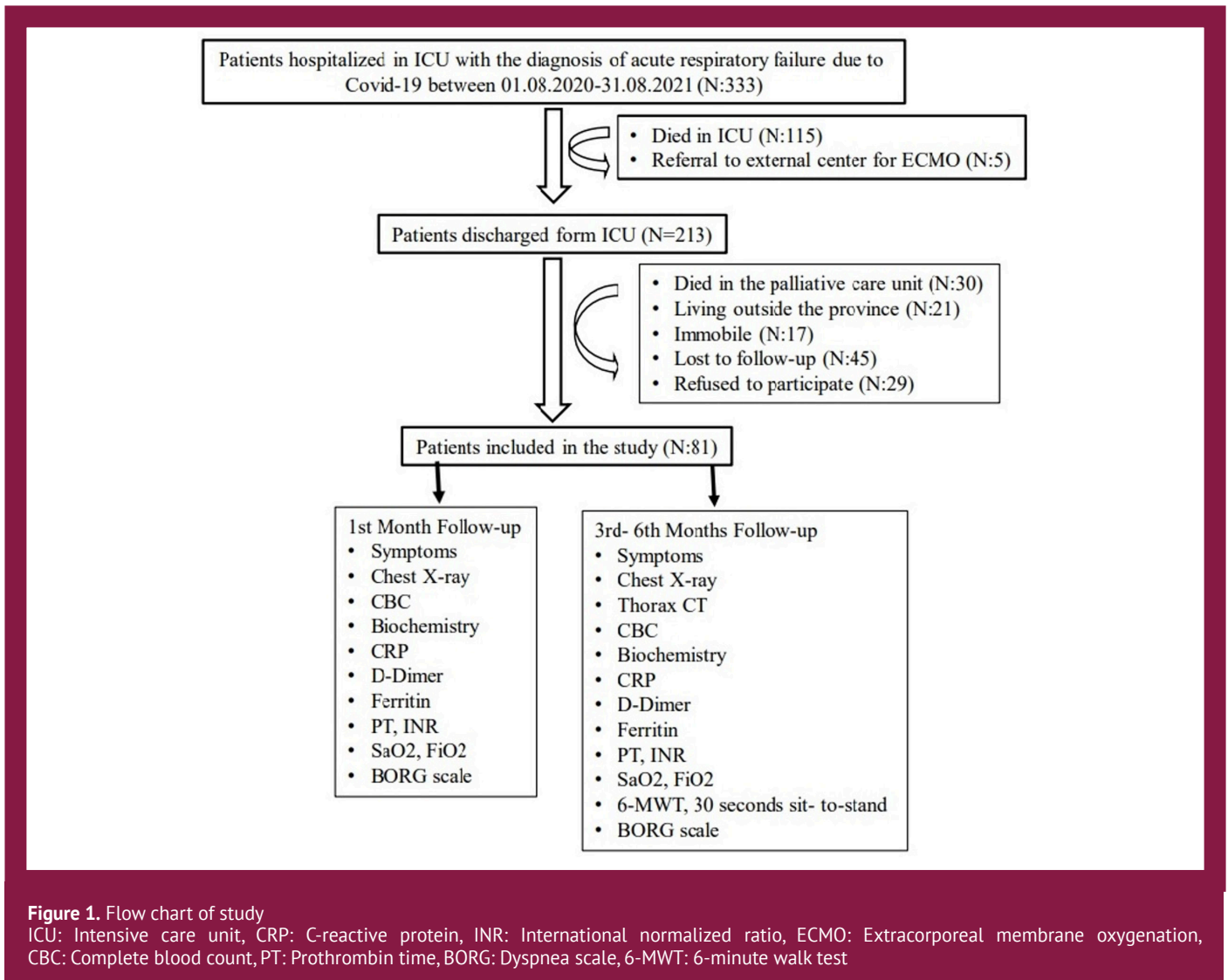
Figure 1. Flow chart of study
ICU: Intensive care unit, CRP: C-reactive protein, INR: International normalized ratio, ECMO: Extracorporeal membrane oxygenation, CBC: Complete blood count, PT: Prothrombin time, BORG: Dyspnea scale, 6-MWT: 6-minute walk test

follow-up, in addition to the 1st month outpatient clinic control, 6-minute walk test (6-MWT) and sit-stand tests, pulmonary function tests (PFTs) were performed, and thorax CT was requested. In the 6th month follow-up, in addition to the 3rd month outpatient clinic follow-up, thorax CT was performed if there was a sequel on X-ray. Lung function was evaluated using the PFT, BORG dyspnea scale, 6-min walk test, and sit-to- stand test.

Statistical Analysis

The minimum sample size required to achieve 80% study power was calculated to be 62. Statistical analysis was performed using SPSS 20 (IBM Corporation, Armonk, NY, USA) software to evaluate the study findings. Numerical values, such as age and hospital stay, were presented as mean and standard deviation (SD) if normally distributed and as median and 25%-75% if not normally distributed.

Dichotomous values, such as sex and comorbidities, were presented as numbers and percentages. The patients' data from their intensive care hospitalization, 1st, 3rd, and 6th month follow-ups were evaluated. The data were compared by mean (SD) deviation and the Student t-test was performed if the numerical values were normally distributed. In addition to the numerical values that were not normally distributed, they were compared by the median (25%-75%) and the Mann-Whitney U test was performed. Cochran's analysis was used to evaluate the follow-up symptom data at the 1st, 3rd, and 6th months after admission to the ICU, and descriptive analysis was performed for radiological data.

Results

A total of 81 volunteers were included in the study out of the 333 patients who were hospitalized in the ICU

due to severe COVID-19. Among the included patients, 60 (74%) were male, with a median age of 49 (43-61). At least one comorbid disease was present in 52 (64%) cases, most frequently accompanied by hypertension, diabetes mellitus, and asthma. The most common symptoms during hospitalization were dyspnea (69%), cough (42%), fever (47%), and fatigue (37%). Table 1 summarizes the demographic characteristics.

Upon evaluation of the intensive care hospitalization data, the mean APACHE II score was 13, and the median Charlson comorbidity index was 2. PCR tests were positive in 89% of the 81 patients admitted to the ICU. Acute Respiratory Distress Syndrome was observed in 32% of the patients, whereas 33% had sepsis. Most cases had bilateral infiltration on chest X-ray and typical findings on thorax CT upon admission to the ICU. While 74 patients were followed up with nasal cannula oxygen therapy, 6 were followed up with invasive mechanical ventilation. The median length of stay in the ICU was 9 days. A summary of intensive care data and treatments is presented in Table 1.

On the day of discharge from the ICU, the mean SaO_2 was 95±2, and the median FiO_2 was 28% (21-40). Long-term oxygen therapy was administered on the day of discharge for 40% (n=32) patients. Methylprednisolone was administered to 36 patients, and dexamethasone was administered to 28 patients after discharge.

Table 2 summarizes the complaints, laboratory data, thorax CT scan, and pulmonary status evaluation of the patients at the 1st, 3rd, and 6th months after discharge. Among the 81 patients who attended the 1-month follow-up, 67% (n=54) reported complaints. Among the 80 patients who attended the 3rd-month follow-up, 56% (n=45) had complaints. At the 6-month follow-up, 45% (n=30) of the 66 patients had complaints, with dyspnea, cough, and myalgia being the most common. During the 6-month follow-up, 7 (28%) patients had ground glass infiltration, 4 (16%) had fibrosis, 2 (8%) had band atelectasis, and 8 (32%) had fibrotic bands. Normal thorax CTs were observed in 12% of the patients.

Comparison of admission symptoms with the 1st, 3rd, and 6th-month follow-ups showed a reduction in dyspnea, cough, and fatigue, and laboratory parameters such as lymphocyte and eosinophil counts, neutrophil lymphocyte ratio, laktat dehidrogenaz, CRP, ferritin, and D-dimer levels showed improvement (p<0.01) (Table 3).

Discussion

In the present prospective study, the 6-month follow-up of patients hospitalized in the ICU due to acute respiratory failure caused by COVID-19 was investigated. It has been shown that more than half of the patients still had at least

Table 1. Demographic characteristics, intensive care and laboratory data, radiological characteristics, and treatments of patients hospitalized in the ICU due to COVID-19 between 01.08-2020-31.08.2021 (n=81)	
Age (years), median (Q1-Q3)	49 (43-61)
Sex, male, n (%)	60 (74)
BMI, (kg/m²), mean ± SD	27±4
Cigarettes, n (%)	
• Non-smoker	47 (58)
• Smoker	12 (15)
• Ex-smoker	22 (27)
Co-morbidity, *n (%)	52 (64)
• Hypertension	30 (37)
• Diabetes mellitus	24 (30)
• Asthma	11 (14)
• Coronary artery disease	6 (7)
• COPD	3 (4)
• Cancer	2 (3)
Hospitalization symptoms, n (%)	
• Dyspnea	56 (69)
• Cough	42 (52)
• Fever	38 (47)
• Fatigue	30 (37)
• Myalgia	8 (10)
• Nausea	5 (6)
• Chest pain	4 (5)
APACHE II, mean ± SD	13±4
Charlson comorbidity index, median (Q1-Q3)	2 (1-3)
Admission RT-PCR-positive, n (%)	72 (89)
ARDS, n (%)	26 (32)
Sepsis, n (%)	27 (33)
Laboratory data	
• Lymphocyte count, 10⁹/L, median (Q1-Q3)	0.77 (0.43-1.04)
• NLR, median (Q1-Q3)	10.5 (6.6-16.6)
• Eosinophil count, 10⁹/L, median (Q1-Q3)	0 (0-0)
• LDH, U/L, median (Q1-Q3)	399 (312-547)
• CRP level, mg/dL, median (Q1-Q3)	85 (45-181)
• Ferritin level, ng/mL, median (Q1-Q3)	742 (386-1402)
• D-dimer, mg/L; median (Q1-Q3)	0.81 (0.52-1.47)
Chest X-ray infiltration rate, n (%)	
• Unilateral	6 (7)
• Bilateral	75 (93)
Thorax CT classification, **n (%)	
• Normal	3 (4)
• Typical	54 (68)
• Likely	7 (9)
• Atypical	4 (5)
ICU treatment, n (%)	
• IMV	6 (7)
• NIV	10 (12)
• HFNC	6 (7)
• Reservoir mask oxygen	37 (45)
• Mask oxygen	24 (30)
• Nasal cannula	74 (91)

Table 1. Continued

Medical treatment, n (%)	
• Antibiotic	80 (99)
• Anticoagulant	77 (95)
• Favipiravir	76 (94)
• Methylprednisolone	73 (90)
• Tocilizumab	17 (21)
• Apharesis immune plasma	16 (20)
• Anakinra	7 (9)
Length of ICU stay, days, median (Q1-Q3)	9 (5-14)

*There was a case with more than one comorbid disease, **According to the American College of Radiology and The Radiological Society of North America.
Q1-Q3: 1st and 3rd quartile values, BMI: Body mass index, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, APACHE: Acute physiology and chronic health evaluation, RT-PCR: Reverse transcription-polymerase chain reaction, ARDS: Acute Respiratory Distress Syndrome, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIV: Non-invasive mechanical ventilation, HFNC: High-flow nasal cannula, NLR: Neutrophil lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CT: Computed tomography

one complaint in the first month after discharge, but the symptoms significantly regressed after 6 months. Dyspnea, cough, and muscle pain were the most common symptoms at 6-month follow-up. Although most cases initially had bilateral infiltration, approximately 80% of the cases had normal radiological findings during follow-up. Although approximately half of the patients required oxygen therapy upon discharge from the ICU, the need for oxygen decreased during follow-up. PFTs were within normal limits, and no dyspnea was detected on the BORG dyspnea scale, which was used to assess the perception of dyspnea from the first month. There were no significant sequelae in terms of radiological and respiratory function after discharge in patients who were followed-up in the ICU due to severe COVID-19.

At the beginning of the pandemic, it was not known how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease would progress and what kind of sequelae would occur in patients who recovered. However, post-viral syndromes have been well defined in previous outbreaks of COVID-19, such as SARS and Middle East respiratory syndrome (MERS). Patients who recovered from SARS were reported to have sequelae, such as pulmonary function deterioration, chronic muscle pain, and mental status deterioration. Similarly, pulmonary fibrosis-related changes have been described radiologically after MERS (10-12). As more people recovered over time, data emerged that symptoms associated with COVID-19 persisted after the acute stage of the disease (7,8). Symptoms lasting longer than 12 weeks that cannot be explained by an alternative diagnosis are defined as "long COVID" (7-9). It has been reported that 10-20% of patients who recover from COVID-19 have symptoms lasting longer than one month, whereas symptoms last for more than 12 weeks in 2.3% of patients (6). Common symptoms associated with prolonged COVID; dyspnea, cough, fatigue, chest pain, joint pain, muscle pain, and mood changes (6-8,13). In approximately half of our cases, there were symptoms that persisted at the 12th week after discharge. In the multicenter study of Baris et al. (4), which included a 1-year follow-up period after COVID-19 and evaluated 504 cases; presence of comorbidity (especially COPD), initial pneumonia, persistence of symptoms after treatment, and post-treatment emergency admission were defined as independent risk factors for prolonged COVID symptoms.

Hemoglobin breakdown and iron accumulation boost ferritin levels in patients with severe COVID-19, as indicated by a meta-analysis. Ferritin, CRP, and erythrocyte sedimentation rate are markers of inflammatory burden and are associated with disease severity (14). Sirayder et al. (3) conducted a study on 26 post-COVID cases and 26 healthy controls who were followed up for 6 months after being discharged from the ICU. No changes in leukocyte, neutrophil, lymphocyte, and platelet values were detected during the follow-up period, whereas creatinine, lactate dehydrogenase, D-dimer, ferritin, and CRP levels were decreased. Inflammatory markers returned to normal levels by the 3rd month (3). Similarly, Darcis et al. (5) evaluated 199 severe COVID-19 cases, 80% of whom received oxygen therapy after discharge; hemoglobin, lymphocyte values increased in the 1st and 3rd months after discharge, D-dimer, and CRP values decreased compared with discharge values. In our study, inflammatory marker levels were decreased in the 1st, 3rd, and 6th month controls, which is consistent with the literature. This may be due to the reduction of the inflammatory process activated by SARS-CoV-2 over time.

Chest graphy in the early phases of COVID-19 plays an important role in disease detection. Consolidation in bilateral subareas and peripheral and diffuse opacities are radiological manifestations of COVID-19 (15). In our cases, bilateral involvement was present in the chest X-ray in approximately all cases at the beginning of the study period and in ¾ of them at 1 month after discharge. At the 6-month follow-up, chest X-ray was found to be normal in approximately 75% of the patients. Among the studies evaluating the post-COVID period, chest radiography was mostly normal during follow-up (4,16). The typical tomographic features of COVID-19 were bilateral, peripheral ground glass appearance, consolidation, multifocal ground glass, focal edema, and organizing pneumonia (17).

During the recovery period from COVID-19 pneumonia, time is required for tomographic findings to improve. When

Table 2. Complaints, laboratory data, thorax CT, and pulmonary status evaluation of patients followed-up in the ICU due to COVID-19 at the 1st, 3rd, and 6th months after discharge

	1st month (n=81)	3rd month (n=80)	6th month (n=66)
Complaint, n (%)	54 (67)	45 (56)	30 (45)
Dyspnea	17 (21)	19 (23)	10 (15)
Cough	9 (11)	5 (6)	3 (5)
Chest pain	8 (10)	3 (4)	4 (6)
Fatigue/weakness	16 (20)	12 (15)	6 (9)
Myalgia	5 (6)	3 (4)	9 (13)
Hair loss	2 (2)	4 (5)	2 (3)
Drowsiness	5 (6)	6 (7)	2 (3)
Palpitation	3 (4)	1 (1)	1 (1)
Dizziness	2 (3)	1 (1)	0 (0)
Sweating	3 (4)	3 (4)	1 (1)
Laboratory data			
Lymphocyte count, 10^9/L, median (Q1-Q3)	2.10 (1.70-2.89)	2.33 (1.95-2.86)	2.41 (1.88-2.89)
NLR, median (Q1-Q3)	1.80 (1.38-2.78)	1.59 (1.17-2.07)	1.64 (1.16-2.21)
Eosinophil count, 10^9/L, median (Q1-Q3)	1.10 (0.60-1.80)	1.30 (0.8-19.5)	1.50 (0.9-2.40)
LDH, U/L, median (Q1-Q3)	232 (208-286)	191 (174-212)	187 (168-209)
CRP level, mg/dL, median (Q1-Q3)	3.8 (3.0-8.5)	3.0 (1.7-4.9)	3.1 (1.8-5.7)
Ferritin level, ng/mL, median (Q1-Q3)	188 (83-382)	59 (27-123)	69 (38-119)
D-Dimer, mg/L; median (Q1-Q3)	0.42 (0.25-0.70)	0.28 (0.19-0.48)	0.25 (0.19-0.42)
Chest X-ray infiltration rate, n (%)			
Normal	21 (26)	44 (55)	51 (76)
Unilateral	16 (19)	15 (19)	11 (16)
Bilateral	44 (55)	21 (36)	4 (8)
Thorax CT findings, n (%)	**n=6**	**n=5**	**n=26**
Ground glass	4 (68)	2 (40)	7 (28)
Fibrosis	1 (17)	0	4 (16)
Band atelectasis	1 (17)	3 (60)	2 (8)
Mosaic pattern	0	0	1 (4)
Fibrotic band	0	0	8 (32)
Normal	0	0	3 (12)
Pulmonary status evaluation results	**1st month (n=81)***	**3rd month (n=80)**	**6th month (n=66)**
SaO_2 %, mean ± SD	97±2	98±1	98±1
FiO_2, mean ± SD	22±4	21±2	21±2
LTOT, n (%)	28 (35)	10 (12)	5 (8)
PFT, n (%)	-	47 (59)	32 (50)
FEV_1 mL, median (Q1-Q3)	-	2850 (2250-3420)	2780 (2180-3440)
FEV_1 %, median (Q1-Q3)	-	93 (75-102)	93 (81-103)
FVC mL, median (Q1-Q3)	-	3180 (2480-3740)	3100 (2535-3680)
FVC %, median (Q1-Q3)	-	84 (72-94)	88 (71-98)
FEV_1/FVC, mean ± SD	-	92±11	88±9
6-MWT, n (%)	-	n=44 (55)	n=26 (39)

Table 2. Continued

	1st month (n=81)	3rd month (n=80)	6th month (n=66)
6- MWT, m, mean ± SD	-	475±95	496±71
6- MWT, expected walking %, mean ± SD	-	82±13	87±11
Thirty seconds sit-stand test, n (%)	-	n=45 (56)	n=27 (40)
Sit-to-stand time of 30 s/unit, mean ± SD	-	11±2	11±3
BORG scale, median (Q1-Q3)	1 (0-2)	0 (0-1)	0 (0-1)

*PFT, 6-MWT, sit-stand test were not performed during the 1-month follow-up. SD: Standard deviation, Q1-Q3: 1st and 3rd quartile values, NLR: Neutrophil lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CT: Computed tomography, FEV$_1$: Forced expiratory volume in 1 s, FVC: Forced vital capacity, 6-MWT: 6-minute walk test, SaO$_2$: Oxygen saturation, FiO$_2$: Fractionated oxygen, LTOT: Long-term oxygen therapy, PFT: Pulmonary function test, BORG: Dyspnea scale

Table 3. Comparison of admission, 1st, 3rd and 6th months symptom and laboratory parameters of cases followed in the ICU due to COVID-19 disease (n=67)

	Admission to the ICU	1st month	3rd month	6st month	p-value
Symptoms					
• Dyspnea	46 (68)	14 (21)	13 (19)	10 (14)	**<0.001***
• Cough	36 (54)	8 (12)	4 (1)	3 (1)	**<0.001***
• Myalgia	6 (1)	4 (1)	3 (1)	9 (2)	0.198*
• Fatigue	23 (34)	13 (19)	8 (12)	6 (1)	**<0.001***
• Chest pain	4 (1)	5 (1)	3 (1)	4 (1)	0.909*
Laboratory					
• Lymphocyte, 10⁹/L	0.77 (0.43-1.04)	2.18 (1.77-3.12)	2.33 (1.88-2.87)	2.43 (1.89-2.90)	**<0.001β**
• NLR	10.5 (6.6-16.6)	1.63 (1.32-2.78)	1.58 (1.15-2.07)	1.64 (1.17-2.24)	**<0.001β**
• Eosinophil, 10⁹/L	0 (0-0)	1.10 (0.55-1.75)	1.20 (0.80-1.90)	1.50 (0.85-2.50)	**<0.001β**
• LDH, U/L	399 (312-547)	232 (210-294)	192 (177-214)	187 (168-210)	**<0.001β**
• CRP, mg/dL	85 (45-181)	4.3 (3.0-9.5)	2.7 (1.6-4.5)	3.1 (1.8-5.6)	**<0.001β**
• Ferritin, ng/mL	742 (386-1402)	200 (90-399)	59 (27-118)	69 (35-119)	**<0.001β**
• D-dimer, mg/L	0.81 (0.52-1.47)	0.40 (0.26-0.70)	0.28 (0.20-0.49)	0.25 (0.19-0.42)	**<0.001β**

*Theochran Q test was used, βFriedman analysis test was used. Data were expressed as number (%) or median interquartile range (25th-75th percentile). Q1-Q3: 1st and 3rd quartile values, NLR: Neutrophil lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ICU: Intensive care unit

CT scans at the time of hospitalization due to COVID-19 and at the 3rd month after the disease were compared, it was observed that the persistent main pattern was ground glass (5). In the study of Wu et al. (1), 83 COVID-19 cases discharged from the hospital were evaluated, and 78% of the cases showed regression in CT findings at the 3rd month after discharge; however, ground glass (78%), interlobular septal thickening (34%), reticular opacities (33%) were most common, and subpleural diffuse opacities (11%) were persisted In the present study, although the number of patients who underwent CT at 1st and 3rd months was low, ground glass and band atelectasis were often present. In a meta-analysis evaluating 30 studies that included 6- to 12-month follow-up after COVID-19, it was determined that while ground glass opacity continued in 34% of cases at 6th month, this rate decreased to 24% at the 12th month. During the follow-up period, no abnormal CT scan was detected in

43% of the patients (65% at 6 months, 36% at 12 months) (18). Although ground glass infiltration was observed in approximately 1/3 of our patients who underwent CT at 6 months, controls showed fibrotic bands at a similar rate. Thorax CT was normal in 12% of the cases. In a meta-analysis including 2018 cases in which 13 studies were evaluated, it was determined that 45% of the patients recovered with pulmonary fibrosis after COVID-19, and the most important risk factor for the development of fibrosis was disease severity. It was reported that hospitalization in intensive care increased the development of fibrosis 5.6 times, noninvasive ventilator support 8 times, and corticosteroid treatment 3.3 times among factors associated with disease severity (19). According to various studies mentioned, the time required for radiological improvement would be 6-12 months.

During the pandemic, severe COVID-19 patients receiving oxygen therapy in the ICU were discharged from

the hospital with long-term oxygen therapy. In the present study, nearly 50% of patients required long-term oxygen therapy at discharge, but the requirement for oxygen therapy significantly decreased during follow-up. In a study, patients who required high levels of oxygen during hospitalization no longer required oxygen therapy during the 6-month follow-up, which was similar to our study (2).

Severe COVID-19 can lead to various complications, such as lung injury, polyneuropathy, myopathy, weakness, and depression, all of which can result in decreased pulmonary function. Sirayder et al. (3) discovered that patients who recovered from COVID-19 had significantly lower FEV1, forced vital capacity (FVC), peak expiratory flow, and FEF25-75 values than the control group. Accordingly, the severity of the disease and the length of ICU stay were associated with a decrease in respiratory function, and it was concluded that COVID-19 could cause permanent lung damage, reducing respiratory function, functional capacity, and quality of life (3). Among the patients who recovered from COVID-19, 8% had decreased FVC and 14% had decreased total lung capacity. Furthermore, impaired diffusion capacity was found to be more common than restrictive patterns (1,3,18). Decreased diffusion capacity has been associated with the influence of COVID-19 on the interstitium or vascular bed (1). However, in our study, pulmonary function values remained within normal limits during follow-up. Consequently, restrictive dysfunction, which may emerge because of lung parenchymal degradation, might heal with time.

While dyspnea persisted in our study, it showed a decreasing trend during follow-ups, and the 6-MWT, sit-stand test, and BORG scale were within normal limits in the 3rd and 6th month controls. In a study that compared COVID-19 cases discharged from the ICU and a healthy control group, the 6-MWT of the COVID-19 group was lower than that of the healthy group (561 m and 652 m, respectively). It was shown that the COVID-19 group also had lower SaO_2 levels during the test and more weakness and dyspnea after the test (3). Damanti et al. (2) reported a positive association between high BORG scores and low PaO_2/FiO_2 during follow-up after severe COVID-19 and stated that this condition was associated with a longer hospital stay. Muscle weakness caused by severe illness and prolonged hospital stay might have contributed to the shorter-than-expected 6-MWT results.

Study Limitation

Our study has several limitations, including its single-center design, which may limit its generalizability to other populations. However, following the same protocol may provide valuable insights for similar patient groups.

Furthermore, the pulmonary function values and radiological findings of the patients were unknown before the study, but it is likely that these parameters were within the normal ranges given the low prevalence of chronic pulmonary diseases.

CONCLUSION

The knowledge on COVID-19's long-term impacts is growing over time. Prolonged symptoms are associated with disease recovery and potential fibrosis; therefore, patients should be followed up regularly after discharge. It is believed that defining permanent sequelae due to COVID-19 might require at least 6 months post-disease.

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