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Original Article

Recovery from Respiratory Failure in Patients with Coronavirus Disease 2019

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Abstract

OBJECTIVE: Coronavirus disease 2019 (COVID-19) can cause hypoxic respiratory failure; long-term oxygen therapy (LTOT) duration is unknown.

MATERIAL AND METHODS: The aim was to investigate which patients would need LTOT after COVID-19 pneumonia. This single-center, prospective study was conducted at the Ankara University Faculty of Medicine, Department of Chest Diseases, between May 2021 and December 2021. The 70 patients hospitalized for COVID-19 pneumonia and discharged with LTOT due to hypoxemic respiratory failure were included. Patients were divided into 2 groups as group I (LTOT requirement <3 months) and group II (LTOT requirement continued ≥3 months).

RESULTS: The mean age was 64.4 ± 13.5 years, and 44 (62.9%) of them were male. The most frequently encountered comorbidities were cardiovascular disease (57.1%) and lung disease (22.9%). While PaO_2 levels increased in both groups during the follow-up period, this increment was significantly higher in group I (PaO_2: 66.6 ± 9.9 mm Hg, $P < .001$). The factors affecting the LTOT requirement were evaluated using binary logistic regression. On multivariate analyses of lymphocytes, ferritin, C-reactive protein, PaO_2, SaO_2, subpleural reticulation, and number of lobes affected (≥3 lobes), the SaO_2 level and presence of subpleural reticulation were significantly different between the 2 groups [odds ratio (OR) (95% CI): 0.853 (0.749-0.971), $P = .016$] and [OR (95% CI): 0.171 (0.042-0.733), $P = .017$], respectively.

CONCLUSION: A significant proportion of patients who develop respiratory failure due to COVID-19 recover within the first 3 months. Factors determining the LTOT requirement for more than 3 months were SaO_2 and the presence of subpleural reticulation.

KEYWORDS: COVID-19, long-term oxygen therapy, post COVID, respiratory failure
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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of coronavirus disease 2019 (COVID-19) in December 2019. It spread dramatically from China to many other countries and was declared as a pandemic by World Health Organization (WHO).[1] Pneumonia and acute respiratory distress syndrome (ARDS) are severe manifestations of COVID-19, and patients develop various degrees of respiratory failure.[2] The coronavirus disease 2019 caused one-fifth of all long-term oxygen therapy (LTOT) starts during the pandemic.[3]

Low arterial oxygenation is the fundamental problem in severely ill patients with COVID-19 pneumonia.[4] Some patients with COVID-19 pneumonia recover from respiratory failure in a short time, while others require long-term supplemental oxygen therapy. The previous studies indicate that patients ≥50 years of age and having ≥3 comorbidities are at increased risk of LTOT requirement in COVID-19 after hospital discharge.[5] While radiological, clinical, and respiratory failure data are reported in patients with COVID-19 pneumonia in the first month after discharge, follow-up data after a longer period such as 3 months are rare.[6-8] Previous studies represent that the most common risk factors are higher age and preexisting chronic respiratory disease.[9] During our follow-up, a substantial proportion were able to quit LTOT. This study aims to identify risk factors for LTOT in patients hospitalized for COVID-19 pneumonia at a 3-month follow-up after hospital discharge.

MATERIAL AND METHODS

The study was approved by the Human Research Ethics Committee of Ankara University and numbered İ1-10-21. All patients provided written informed consent at the time of enrollment.

Study Participants

This study was conducted at the Ankara University Faculty of Medicine, Department of Chest Diseases between May 2021 and December 2021. In this single-center, prospective study, we enrolled 88 patients hospitalized for COVID-19

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pneumonia and discharged with LTOT due to hypoxemic respiratory failure. Patients in need of oxygen were hospitalized. Patients with hypoxemic respiratory failure who needed invasive/noninvasive mechanical ventilation (IMV/NIMV)/high-flow nasal oxygen (HFNO) and/or patients with hemodnamic instability were followed in the intensive care unit (ICU). Patients with oxygen saturation <92% and/or PaO_2 <60 mm Hg despite 4-5 L/min nasal oxygen support were admitted to the ICU. Noninvasive mechanical ventilation is used for hypoxemia and hypercapnia. High-flow nasal oxygen was used only for hypoxemia. Indications for IMV are apnea and respiratory failure that are unlikely to be successfully managed with noninvasive approaches (simple oxygen therapy, HFNO, or noninvasive ventilation) need for airway protection in unconscious patient. Hypoxemic respiratory failure was defined as partial pressure of arterial oxygen (PaO_2) <60 mm Hg of room air and normal or low partial pressure of carbon dioxide <45 mm Hg.[10]

In our country, due to legal issues, PaO_2 has to be <55 mm Hg and SaO_2 has to be <88% in room air to prescribe LTOT. The study patients used oxygen concentrators that provided oxygen at most 5 L/min at home.

Inclusion and exclusion criteria are summarized in Table 1.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Age ≥18 years
Written informed consent
Diagnosis of SARS-CoV-2 infection by positive PCR on the nasopharyngeal swab
Presence of any radiological signs of COVID-19 pneumonia in thorax CT
Discharged with LTOT due to respiratory failure (PaO_2 <55 mm Hg)
To agree with follow-up after 3 months
Exclusion Criteria
Not eligible to follow up for 3 months
The patients with negative PCR results
Receiving LTOT before hospitalization

COVID-19, coronavirus disease 2019; CT, computed tomography; LTOT, long-term oxygen therapy; PaO_2, partial pressure of arterial oxygen; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data Collection

All patients' demographic features (age, gender, smoking history, and comorbid diseases), laboratory findings (lymphocyte, D-dimer, fibrinogen, ferritin, C-reactive protein, and neutrophil–lymphocyte ratio), arterial blood gas analysis (pH, PaO_2, $PaCO_2$, and SaO_2), thorax computed tomography (CT) findings (normal, ground-glass opacities, subpleural reticulations, fibrosis, and number of lobes affected), pharmacological therapy [corticosteroid, low-molecular-weight heparin, and acetylsalicylic acid (ASA)], and presence of ICU admission were recorded.

Patients were followed up for 3 months from discharge to evaluate the presence of LTOT need with an arterial blood gas sample at discharge and divided into 2 groups according to the duration of the LTOT requirement. Those with LTOT requirement <3 months were in group I and those with LTOT requirement continued ≥3 months were in group II. At the end of the 3-month follow-up period, these 2 groups were compared in terms of the laboratory (lymphocyte count, D-dimer, fibrinogen, ferritin, troponin, C-reactive protein, and neutrophil–lymphocyte ratio) and radiological findings, demographic features, smoking history, comorbid diseases, and medical treatment.

Main Points

- Coronavirus disease 2019 (COVID-19) can cause hypoxic respiratory failure; long-term oxygen therapy (LTOT) duration is important for follow-up.
- It is important to determine which patients would need LTOT after COVID-19 pneumonia. In this study, factors determining the LTOT requirement for more than 3 months were SaO_2 and the presence of subpleural reticulation.
- The presence of comorbidities, smoking history, and gender do not show any significant difference in terms of the LTOT requirement.

Thorax Computed Tomography Scan Examinations and Image Analysis

Patients were scanned using 4-slice CT scanner (Toshiba Asteion 4, Toshiba Medical System, Japan) and 16-slice multi detector CT scanner (GE Light Speed, GE Medical System, Milwaukee WI). The CT images were evaluated by the radiologist for the presence of the following characteristics: (1) normal; (2) ground-glass opacities; (3) subpleural reticulations; (4) fibrosis; (5) number of lobes affected by ground-glass opacities or subpleural reticulations or fibrosis. To quantify the severity of lung involvement, the number of affected lobes was recorded, and the involvement of 3 or more lobes was considered as severe.[11,12]

Primary and Secondary Endpoints

The primary endpoint of the study was improvement of respiratory failure at 3 months from hospital discharge. The secondary endpoint of the study was also assessed at 3 months from hospital discharge: alterations in laboratory values and radiological findings on thorax CT, and determining the factors that could impact the requirement for LTOT for more than 3 months.

Statistical Analysis

The data was analyzed using IBM StatisticalPackage for the Social Sciences Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA).

Based on the findings of Ogata et al,[13] we estimate that about 66% of the study population would discontinue LTOT after follow-up duration. We calculated that 70 patients are required to reach the power of 90% with an ≥alpha level of 5%. The G*POWER 3.1.9.6 program was used to calculate the sample size. Continuous variables were described using mean with SD for parametric distributed variables, or median with 25th-75th percentiles/interquartile range (IQR) for nonparametric distributed variables. Pearson's chi-square test and Fisher's exact test were used to analyze categorical data as appropriate. Median scores of 2 groups were compared with

nonparametric Mann–Whitney *U*-test. The sStudent's *t*-test for unpaired data was used to compare parametric variables.

Binary logistic regression analysis was used in the univariate and multivariate analyses. The univariate analysis was first performed to identify any potential predictor variables, and variables with $P < .25$ were included in the multivariate analysis to determine any independent predictors of LTOT requirement for more than 3 months. The statistical significance of .05 was used for all analyses.

RESULTS

Study Population

In the study period, 88 patients with COVID-19 pneumonia were discharged from the hospital with LTOT. Median follow-up time for CT and laboratory findings is 88 (82-94) days. Eighteen patients were excluded for various reasons: 13 patients lost follow-up, 2 patients were on LTOT before COVID, and 3 patients have died in the first 3 months One of these patients had died due to hematologic malignancy; 1 of them had died due to cerebrovascular event; and 1 of them had died due to myocardial infarction. The remaining 70 patients were divided into 2 groups: LTOT requirement <3 months (group I, n = 42) and LTOT requirement ≥3 months (group II, n = 28) (Figure 1).

The baseline demographic and clinical features of the study population are shown in Table 2. The mean age of the study patients was 64.4 ± 13.5 years, and 44 (62.9%) of them were male. The most frequently encountered comorbidities were cardiovascular disease (57.1%) and lung disease (22.9%). The majority of patients had a smoking history, with no differences between previous and current smokers. Eight patients in group I and 6 patients in group II quit smoking during follow-up. The majority of patients had ≤1 comorbidity (68.7 %). There was no patient with venous thromboembolism during the discharge period. But at the follow-up period, we identified 4 patients with thromboembolism. All of them were part of group I. Since these patients were included in group I, we think that it did not affect the results of our study.

Concerning the treatments received during hospitalizations for COVID-19, ASA therapy for COVID-19 was significantly lower in group I ($P = .02$). These patients have used ASA treatment for comorbidities, not for COVID pneumonia. The LMWH treatment was used during hospitalization and has been continued 1 month after discharge. Ten patients underwent IMV, 14 patients NIMV, 14 patients HFNO, and 32 patients nasal oxygen treatment. In group I: IMV, n = 2; NIMV, n = 2; HFNO, n = 6; nasal oxygen, n = 32; and in group II: IMV, n = 8; NIMV, n = 12; HFNO, n = 8; nasal oxygen, n = 0. Thirty-eight (54.3%) patients were followed in the ICU; there were no differences between the groups in terms of ICU admission.

We observed lymphopenia, increased D-dimer, fibrinogen, ferritin, troponin, C-reactive protein, and neutrophil–lymphocyte ratio during the admission of the patients. In terms of laboratory findings on admission and follow-up, the groups were not significantly different, and all parameters returned to normal levels at the end of 3 months. On arterial blood gas analyses, mean PaO_2 was low in line with respiratory failure on admission (mean ± SD, 46.7 ± 5.2 mm Hg) (Table 3). The PaO_2 level increased to 60.8 ± 11.3 mm Hg (Table 4). During the admission period, PaO_2 level was significantly lower in group I ($P = .007$). While PaO_2 level increased in both groups during the follow-up period, this increment was significantly higher in group I (PaO_2 = 66.6 ± 9.9 mm Hg, $P < .001$).

Radiological Findings

Ground-glass opacities were the most common radiological finding in thorax CT (n = 68, 97.1%). This was followed by the presence of subpleural reticulation (n = 17, 24.3%). Fibrosis was observed in only 4 patients (5.7%) on admission (Table 3). At least 3 lobes have been affected with ground-glass opacities and/or subpleural reticulations and/or fibrosis in 61 (87.1%) of patients on admission. Regarding the presence of subpleural reticulation on thorax CT on admission, we observed a statistically significant difference between the 2 groups ($P = .022$), with the highest prevalence of subpleural reticulation in the group II (Table 4).

At the third-month follow-up visit, 3 (4.3%) patients in group I had normal thorax CT images. While the prevalence of ground-glass opacities decreased, distribution of subpleural

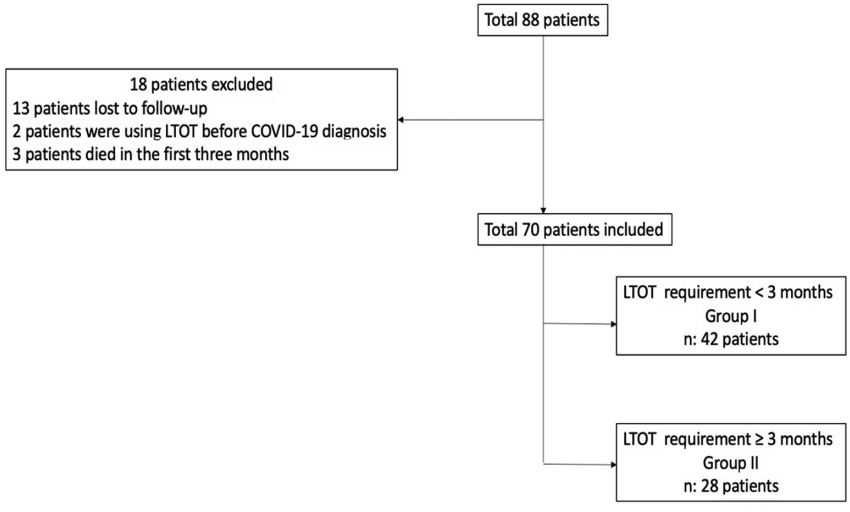

Figure 1. Flowchart of study patients. COVID-19, coronavirus disease 2019; LTOT, long-term oxygen therapy.

Table 2. Characteristics of Study Patients and Comparison of Parameters Between Groups I and II

	All Patients (n = 70)	Group I (n = 42)	Group II (n = 28)	*P*
Age (years) (mean ± SD)	64.4 ± 13.5	65.5 ± 13.4	64.8 ± 13.7	.414
Gender				
Male, n (%)	44 (62.9)	23 (54.8)	21 (75.0)	.086
Female, n (%)	26 (37.1)	19 (45.2)	7 (25.0)	.086
Smoking history (previous and current), n (%)	37 (52.9)	20 (47.6)	17 (60.7)	.509
Comorbid Diseases, n (%)				
Lung disease*	16 (22.9)	12 (28.6)	4 (14.3)	.163
Cardiovascular disease**	40 (57.1)	25 (59.59	15 (53.6)	.622
Malignancy#	5 (7.1)	4 (9.5)	1 (3.6)	.641
Immunosuppression##	7 (11.0)	5 (11.9)	2 (7.2)	1.000
Pharmacological Therapy				
Corticosteroid, n (%)	68 (97.1)	41 (97.6)	27 (96.4)	1.000
LMWH, n (%)	67 (95.7)	42 (100.0)	25 (89.3)	.060
Acetylsalicylic acid, n (%)	26 (37.1)	11 (26.2)	15 (53.6)	.020
ICU admission, n (%)	38 (54.3)	21 (50.0)	17 (60.7)	.378

ICU, intensive care unit; LMWH, low-molecular-weight heparin.
*Asthma, chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea syndrome.
**Heart failure, coronary artery disease, hypertension.
#Lung cancer, leukemia, metastatic cancer.
##Solid-organ transplantation, bone marrow transplantation, chemotherapy.

Table 3. Laboratory and Radiological Findings on Admission and 3 Months After Discharge of All Patients

	Admission (n = 70)	Follow-Up (n = 70)
Laboratory parameters, median [IQR]		
Lymphocytes, × 10^3/μL	810.0 [597.5-958.7]	2070.0 [1637.5-2692.5]
D-dimer, ng/mL	698.5 [337.5-1972.0]	194.0 [123.0-412.7]
Fibrinogen, g/L	5.7 [4.8-6.7]	3.4 [2.9-3.9]
Ferritin, ng/mL	429.0 [217.1-1158.5]	141.0 [51.4-343.5]
Troponin, pg/mL	15.3 [8.3-29.1]	11.5 [5.9-28.0]
C-reactive protein, mg/L	118.7 [73.3-172.7]	5.0 [2.9-9.7]
Neutrophil–lymphocyte ratio	7.5 [4.9-11.0]	2.1 [1.6-2.9]
Arterial blood gas analysis		
pH	7.43 ± 0.05	7.43 ± 0.04
PaO_2, mm Hg (mean ± SD)	46.7 ± 5.2	60.8 ± 11.3
$PaCO_2$, mm Hg (mean ± SD)	36.9 ± 6.8	37.3 ± 6.3
SaO_2, % (mean ± SD)	82.0 ± 6.9	90.3 ±5.4
Thorax computed tomography findings		
Normal, n (%)	0	3 (4.3)
Ground-glass opacities, n (%)	68 (97.1)	50 (71.4)
Subpleural reticulation, n (%)	17 (24.3)	60 (85.7)
Fibrosis, n (%)	4 (5.7)	23 (32.9)
Number of lobes affected ≥3, n (%)	61 (87.1)	52 (74.3)

Cutoff points: Lymphocyte, 1500-4000 × 10^3/μL; D-dimer, 0-243 ng/mL; fibrinogen, 2-3.93 g/L; ferritin, 30-400 ng/mL; troponin, 0-14 pg/mL; C-reactive protein: 0-5 mg/L.
IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation.

Table 4. Comparison of Parameters on Admission and Follow-Up between Groups I and II

	Admission			Follow-Up		
	Group I	**Group II**	***P****	**Group I**	**Group II**	***P****
Laboratory parameters, median [IQR]						
Lymphocyte, × 10^3/μL	775.0 [590.0-930]	845.0 [610.0-1117.5]	.335[#]	2140.0 [1740.0-2662.5]	1920.0 [1440.0-2837.5]	.385[#]
D-dimer, ng/mL	579.0 [314.2-1757.7]	899.5 [410.0-2614.5]	.491[#]	207.0 [114.5-459.7]	194.0 [129.2-406.0]	.719[#]
Fibrinogen, g/L	5.9 [5.0-7.0]	5.4 [4.3-6.6]	.162[#]	3.3 [2.9-3.8]	3.4 [2.7-4.7]	.415[#]
Ferritin, ng/mL	449.5 [232.4-1308.6]	429.0 [176.1-1067.0]	.378[#]	92.5 [37.2-291.8]	207.5 [91.5-347.7]	.051[#]
Troponin, pg/mL	15.3 [7.8-28.8]	16.3 [8.7-31.9]	.640[#]	10.9 [5.6-28.4]	11.9 [6.1-29.2]	.933[#]
C-reactive protein, mg/L	123.5 [86.8-175.3]	112.5 [46.7-171.7]	.350[#]	4.5 [2.9-9.4]	6.0 [2.9-18.3]	.319[#]
Neutrophil–lymphocyte ratio	7.7 [5.4-10.5]	7.3 [3.6-11.3]	.510[#]	2.3 [1.6-2.6]	1.9 [1.1-3.2]	.606[#]
Artery blood gas analysis						
pH (mean ± SD)	7.43 ± 0.05	7.43 ± 0.5	.957[δ]	7.43 ± 0.4	7.43 ± 0.3	.501[δ]
PaO_2, mm Hg (mean ± SD)	48.0 ± 5.2	44.7 ± 4.6	.009[δ]	66.6 ± 9.9	51.9 ± 6.7	<.001[δ]
$PaCO_2$, mm Hg, (mean ± SD)	35.5 ± 6.6	38.9 ± 6	.040[δ]	36.4 ± 5.9	38.6 ± 6.2	.148[δ]
SaO_2, % (mean ± SD)	84.0 ± 6.4	79.1 ± 6.6	.003[δ]	93.2 ± 2.3	86.1 ± 6.1	<.001[δ]
Thorax computed tomography findings						
Normal, n (%)	0	0		3 (7.1)	0	.270[γ]
Ground-glass opacities, n (%)	41 (97.6)	27 (96.4)	.643[γ]	27 (64.3)	23 (82.1)	.105[γ]
Subpleural reticulation, n (%)	7 (16.7)	10 (35.7)	.022[γ]	33 (78.6)	27 (96.4)	.036[γ]
Fibrosis, n (%)	0	4 (14.3)	.069[γ]	10 (23.8)	13 (46.4)	.048[γ]
Number of lobes affected ≥3, n (%)	35 (83.3)	26 (92.9)	.244[γ]	25 (59.5)	27 (96.4)	<.001[γ]

IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; SaO_2, oxygen saturation.
*Comparison of admission parameters between groups I and II.
**Comparison of follow-up parameters between groups I and II.
[δ]Student *t*-test was used for the comparison of parametric values between groups I and II.
[#]Mann–Whitney *U*-test was used for the comparison of nonparametric values between groups I and II.
[γ]Chi-square was used for the comparison of categorical values between groups I and II.

reticulations and fibrosis rose on follow-up in both study groups, 60 (85.7%) and 23 (32.9%), respectively (Table 3). In terms of the presence of ground-glass opacities on admission, while there was no difference at admission, there was a statistically significant difference in terms of the presence of subpleural reticulation and fibrosis between the groups at follow-up, and it is shown in Table 4 (Figure 2 and 3).

While the number of affected lobes decreased in both groups in the follow-up, a statistically significant difference was found between the groups during the follow-up ($P < .001$) (Table 4).

The admission parameters were evaluated for the factors affecting the LTOT requirement using binary logistic regression. On univariate analysis, PaO_2 and SaO_2 levels on follow-up were significantly different between 2 groups [odds ratio (OR) (95% CI): 0.876 (0.789-0.972), $P = .013$] and [OR (95% CI): 1.892 (0.822-0.968), $P = .006$], respectively. On multivariate analysis of lymphocyte, ferritin, C-reactive protein (CRP), SaO_2, subpleural reticulation, and number of lobes affected (≥3 lobes); SaO_2 level and presence of subpleural reticulation were significantly assoociated with the requirement of LTOT [OR (95% CI): 0.843 (0.759-0.936), $P = .001$] and [OR (95% CI): 5.084 (1.306-19.788), $P = .019$], respectively (Table 5).

DISCUSSION

In this study, we report the prevalence and severity of respiratory failure and factors, which affect the LTOT requirement after 3 months of hospital discharge in COVID-19 patients. We observed a considerable improvement in respiratory failure at 3 months from hospital discharge.

In this study, males (44, 62.9%) were affected more than females (26, 37.1%), with an M : F ratio of 1.6 : 1. This male gender dominance has also been observed in previous studies for various coronavirus infections.[5,14] In a study by Martin et al,[15] the vast majority of patients with respiratory failure who were admitted to the ICU due to COVID-19 pneumonia were male and they had at least 1 comorbidity.

Female sex hormones are thought to be responsible for a better immune response to respiratory virus infections such as SARS-CoV-2 infection.[16] In our study, most of the female patients had continued LTOT requirements less than 3 months after discharge, compared to males; however, this was not statistically significant.

Age is an important host factor in the host response to infections; elderly have a poor prognosis.[17] In a study evaluating the relationship between the course of COVID-19 and age, laboratory findings revealed that disease severity and inflammation were directly related to increased ferritin levels in all age groups and increased CRP in the elderly.[18] In the same study, the ground-glass opacities on chest CT were more frequent among the elderly.[18] In our study, we observed that age has no effect on the requirements for LTOT, according to multivariate logistic regression analysis.

The association between smoking status and severe COVID-19 remains controversial. Smoking has been associated with

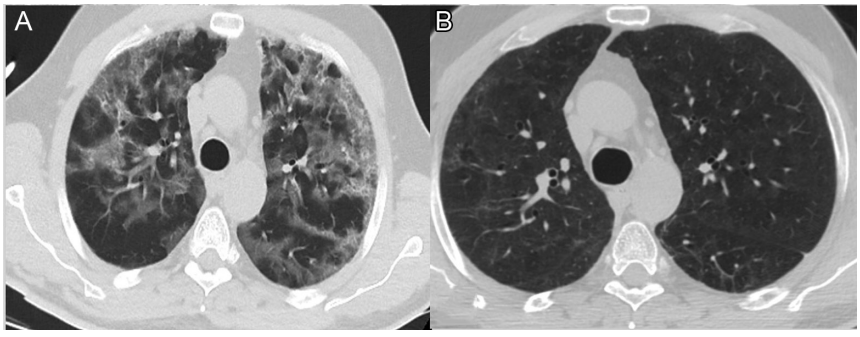

Figure 2. Fifty-eight-year-old male patient with coronavirus disease 2019 pneumonia in Group I has no smoking history and no comorbidities. (A) Thorax computed tomography (CT) scan at admission includes bilateral ground-glass opacities. (B) Thorax CT scan at follow-up period includes decreasing range of ground-glass opacities.

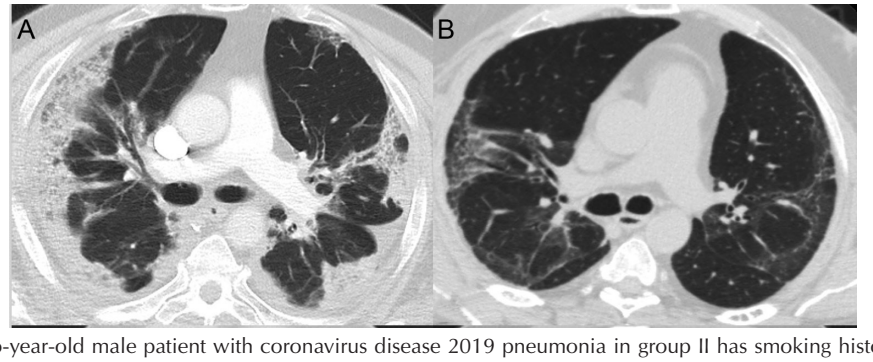

Figure 3. Seventy-two-year-old male patient with coronavirus disease 2019 pneumonia in group II has smoking history and comorbidities such as hypertension and diabetes mellitus. (A) Thorax computed tomography (CT) scan at admission includes bilateral ground-glass opacities, consolidations, and subpleural reticulations. (B) Thorax CT scan at follow-up period showed decreasing range of ground-glass opacities and consolidations, increasing subpleural reticulations.

Table 5. Binary Logistic Regression Analysis of Coronavirus Disease 2019 Patients Who Had Long-Term Oxygen Therapy Requirement for More Than 3 Months

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	***P***	**Odds Ratio (95% CI)**	***P***
Age, years	1.015 (0.980-1.052)	.408		
Gender, male	2.478 (0.868-7.077)	.090		
Smoking	1.700 (0.644-4.487)	.284		
Lymphocytes	1.001 (1.000-1.002)	.111	1.001 (1.000-1.002)	.094
D-dimer	1.000 (1.000-1.000)	.463		
Fibrinogen	0.829 (0.601-1.143)	.253		
Ferritin	1.000 (0.999-1.000)	.202	0.999 (0.998-1.000)	.143
C-reactive protein	0.996 (0.990-1.009)	.280	0.999 (0.990-1.007)	.737
PaO_2	0.876 (0.789-0.972)	.013		
SaO_2	1.892 (0.822-0.968)	.006	0.843 (0.759-0.936)	.001
Ground-glass opacities	1.519 (0.091-25.325)	.771		
Subpleural reticulation	2.778 (0.906-8.520)	.074	5.084 (1.306-19.788)	.019
Number of lobes affected ≥3	0.385 (0.074-2.005)	.257	0.297 (0.039-2.249)	.240

PaO_2, partial pressure of arterial oxygen; SaO_2, oxygen saturation.

an increased risk of infection and poor outcomes for bacterial and viral pathogens.[19] However, some studies reported a low prevalence of current smokers among people hospitalized due to COVID-19.[20,21] In a meta-analysis comparing non-smokers with current smokers, former smokers appear to be at increased risk of hospitalization, severe disease, and mortality, while current smokers appear to be at reduced risk of SARS-CoV-2 infection.[22] In our study, smoking history did not differ between the groups and was not a factor affecting the requirement for LTOT.

The presence of comorbidities is an important risk factor for severe COVID-19 and possesses a greater risk of mortality due to COVID-19.[19] The most common comorbidities associated with severe COVID-19 are coronary artery disease, congestive heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, diabetes mellitus, cancer, chronic kidney disease, and obesity.[21,23,24] In previous studies, it has been reported that recovery is delayed in patients with comorbidities and aged >50 years.[5,25] In our study, lung disease, cardiovascular disease, malignancy, and immunosuppression were evaluated in the groups. Cardiovascular and lung diseases were the most common comorbidities but in contrast to previous studies did not affect the course of the disease after discharge.

In a study, abnormal CRP results and lymphocyte count have been observed as prognostic factors in COVID-19 patients.[15] In another study, admission oxygen saturation of <88%, troponin level >1 pg/mL, C-reactive protein level >200 mg/L, and D-dimer level >2500 ng/mL were strongly associated with critical illness than age or comorbidities.[26] In terms of laboratory findings, there were no significant differences between the groups at the admission and follow-up periods in our study. In a study, researchers have explored relationships between the severity of acute respiratory failure, and they considered that patients recovering from ARDS from any cause may have persistent functional impairment 1 year after hospital discharge; therefore, these findings might not be COVID-19-specific.[27] In another study, decreased P/F ratio (PaO_2 divided by the inspired oxygen concentration) during the early discharge period was associated with severe COVID-19 pneumonia and fibrosis.[28] In our study, we observed that PaO_2 and SpO_2 levels significantly affected the need for LTOT for at least 3 months.

Persisting abnormalities in radiology at discharge may be continued despite the absence of symptoms in patients with COVID-19 pneumonia. To assess enduring CT findings, it is advisable to conduct CT scans at both three and six months to determine the frequency of radiological abnormalities. In a previous study, 3 months after hospital discharge, pulmonary structural abnormalities and functional impairment were observed to be highly prevalent in patients with ARDS secondary to COVID-19 who required an ICU stay.[1] In our study, while the most frequent finding was ground-glass opacities on admission CT, subpleural reticulation was observed as the most common finding at 3-month CT, followed by ground-glass opacities and fibrosis. The CT features of lung fibrosis were seen in 32.8% of all study patients and in 46.4% of the patients in group II. Fibrosis and subpleural reticulation were more common among Group II patients (Table 4). Although fibrosis occurs in such a large proportion of subjects in patients with COVID-19 pneumonia, most of those "fibrotic-like" changes, such as subpleural reticulations, are reversible.[5]

In RECOVERY Collaborative Group's randomized controlled study, 14892 patients were evaluated for ASA usage in COVID-19 pneumonia.[29] In this study, 1222 (17%) of 7351 patients allocated to aspirin and 1299 (17%) of 7541 patients

allocated to usual care died within 28 days. Patients allocated to aspirin had a slightly shorter duration of hospitalization (median 8 days, IQR 5 to >28 vs. 9 days, IQR 5 to >28), and a higher proportion were discharged from hospital alive within 28 days (75% vs. 74%; rate ratio 1.06, 95% CI: 1.02-1.10; *P* = .0062). Among patients not on IMV at baseline, there was no significant difference in the proportion meeting the composite endpoint of IMV or death (21% vs. 22%; risk ratio 0.96, 95% CI: 0·90-1·03; *P* = .23). In patients hospitalized with COVID-19, ASA was not associated with reductions in 28-day mortality or in the risk of progressing to IMV or death, but was associated with a small increase in the rate of being discharged alive within 28 days. In our study, ASA use was higher in patients who required LTOT for 3 months, and this was statistically significant. It was observed that the use of ASA did not contribute to the early termination of oxygen therapy. When compared to the RECOVERY study, it can be said that the patients using ASA in our study had similar discharge results.

In the light of the data obtained from our study, it is not possible to determine at the beginning which group of patients would need LTOT after 3 months. It may be recommended that patients be followed up at regular intervals after COVID-19 pneumonia. In this regard, it is crucial to establish follow-up criteria to assess the clinical and radiological sequelae that may arise in patients after experiencing COVID-19 pneumonia.

In a study, patients were divided into 2 groups: as early recovery and refractory groups, in terms of respiratory support time. In the refractory group, it was determined that oxygen support could not be stopped within 6 months after the COVID-19 diagnosis.[13] Similarly, in our study, patients who required LTOT were more likely to be hospitalized in the ICU, and their radiological pathological findings continued in the follow-ups.

As seen in previous studies, it is thought that the radiological findings of patients will regress in longer follow-ups.

We think that subpleural reticulation, which persists for a long time, is a radiological finding similar to fibrosis and may transform into fibrosis in the future. Therefore, patients with continued subpleural reticulations should be followed. However, it is not yet clear whether there will be a decrease in oxygen demand as the radiological findings regress. We think that it is important for future studies to investigate the presence of COVID-19-related underlying vascular pathologies in patient groups who require oxygen therapy for more than 3 months and whose radiological findings regress, and to investigate whether there is an underlying interstitial lung disease in patients whose radiological findings last longer than 3 months.

Our study had some limitations. It was a single-center study with a small sample size. Study observation was limited to the follow-up period, lacking longer follow-up. In terms of the requirement of LTOT, long-term follow-up of patients with COVID-19 pneumonia would be more reliable to estimate the development of chronic respiratory failure.

In conclusion, our findings reveal that a significant proportion of patients who develop acute respiratory failure due to COVID-19 recover within the first 3 months. Since chronic respiratory failure after COVID-19 recovery is an emerging threat to global health, advances in post-COVID-19 management are important. Since patients whose radiological findings continue after COVID-19 pneumonia may require LTOT, we recommend planning thoracic CT controls in appropriate cases to follow-up the formation of fibrosis. Whether subpleural reticulation will regress or turn into fibrosis can be determined by longer follow-ups. Another important finding of the study is that the number of involved lobes at follow-up is associated with respiratory failure. Although it is not possible to say which patients need oxygen therapy for a long time, it can be said that patients whose radiological findings continue in the follow-ups need oxygen support for a longer period of time. More studies are needed to determine the necessity of LTOT in the diagnosis and to identify treatment options that will enable the discontinuation of oxygen therapy in the early period.

Ethics Committee Approval: This study was approved by Ethics Committee of Ankara University (Approval No: İ1-10-21).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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