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Evaluation of COVID-19 patients receiving long-term oxygen support in the post-COVID period

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Abstract:

BACKGROUND AND AIM: Persistent physical and medical sequelae, including chronic hypoxemia, may be observed in patients with long-lasting post-COVID syndrome. Long-term oxygen therapy (LTOT) is commonly employed for managing chronic hypoxemia in chronic airway diseases. This study aims to assess the ongoing requirement for LTOT in Coronavirus Disease 2019 (COVID-19) patients during the post-COVID period and to ascertain the persistence of their oxygen therapy needs.

METHODS: This cross-sectional, multicentered study included 320 COVID-19 patients who were evaluated for LTOT two months post-discharge. Patient demographics, symptoms at admission, and laboratory and radiological data were retrospectively collected from hospital databases.

RESULTS: Continuous oxygen support was necessary for 22.9% of the patients, while 15% of the participants passed away during the post-COVID period. Factors significantly associated with the prolonged need for LTOT included admission to the intensive care unit (ICU), presence of anemia, high serum D-dimer levels (>1000 µg/L), and low oxygen saturation levels at hospital admission (p=0.026, p=0.011, p=0.010, and p<0.001, respectively). Multivariable regression analysis identified high D-dimer levels (p=0.012) and low oxygen saturation at admission (p<0.001) as the most significant predictors of a continued need for oxygen therapy. Furthermore, advanced age, non-use of steroids in treatment, and mechanical ventilation during hospitalization were significantly linked to mortality during the post-COVID period (p=0.003, p=0.048, and p=0.009, respectively).

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CONCLUSIONS: ICU admission and certain laboratory parameters can predict the need for LTOT during the post-COVID process. The observation that most COVID-19 patients do not require LTOT after a two-month period suggests that clinicians should adopt a more selective approach in planning LTOT.

Keywords:

COVID-19, infectious diseases, oxygen, respiratory infections

Introduction

Since January 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has escalated into a global pandemic.^[1] The clinical spectrum of Coronavirus Disease 2019 (COVID-19) varies widely, ranging from asymptomatic carriers to patients with severe manifestations. The severity of the disease primarily depends on the extent of lung involvement and resultant respiratory failure.^[2]

Several mechanisms may lead to hypoxemia in patients infected with SARS-CoV-2. Primarily, COVID-19 leads to hypoxemia due to inflammatory responses to the virus in the respiratory system, often resulting in diffusion impairment.^[2]

Hypoxemic respiratory failure is particularly prevalent among patients with severe COVID-19 infections, including those with acute respiratory distress syndrome (ARDS).^[3] Severe hypoxemia, affecting a large number of COVID-19 patients admitted to critical care, has been a major factor in the deterioration of prognosis in critically ill patients.^[4] Refractory hypoxemia has been one of the leading causes of mortality among COVID-19 patients.^[5]

Long-term oxygen therapy (LTOT) is an important component of treatment for patients with chronic hypoxemia, which may occur during exertion or even at rest in later stages, and is typically required for those with chronic airway diseases.^[6] Guidelines recommend that supplementary oxygen therapy be provided to patients experiencing resting hypoxemia or significant oxygen desaturation during exercise.^[7]

In some COVID-19 patients ready for discharge after completing inpatient treatment, hypoxemia is observed not to fully recover. The potential delayed regression of lung parenchymal damage due to severe pneumonia and the development of lung fibrosis post-COVID-19, similar to what is seen following infections like SARS and Middle East Respiratory Syndrome (MERS), may contribute to the continued hypoxemic process.^[8] There is insuffi-

cient information regarding the long-term consequences of the disease and fibrosis resulting from lung involvement, and there is no established literature or consensus on the approach to managing patients in this patient group who require long-term oxygen therapy. Oxygen saturation levels above 90% with oxygen support are indicative of a high survival probability in COVID-19 patients.^[8] Therefore, long-term oxygen support at home may be feasible for this patient group.

Our goal was to evaluate COVID-19 patients on LTOT and assess their ongoing need for oxygen support in the post-COVID period.

Materials and Methods

This cross-sectional, multicentered study involved 320 COVID-19 patients who received LTOT at home following hospital discharge. Participants were recruited from 14 pulmonology clinics across Türkiye between December 2020 and March 2021. Eligible participants were adults over 18 years of age who tested positive for COVID-19 via real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay from oro-nasopharyngeal swab specimens or had clinical, radiological, and serological evidence of COVID-19 in the absence of a positive RT-PCR test. Data on patients' demographics, symptoms at admission, and laboratory and radiological findings were retrospectively collected from hospital databases.

Inclusion criteria

COVID-19 patients were eligible if they were recommended for and prescribed long-term oxygen therapy for at least 15 hours per day as per the American Thoracic Society Guidelines and met one of the following criteria for severe chronic hypoxemia:^[9]

- Arterial partial pressure of oxygen (PaO₂) ≤55 mmHg or oxygen saturation (SaO₂) ≤88%, or
- PaO₂ between 55–59 mmHg or SaO₂ of 89% accompanied by signs of pulmonary hypertension (“P” pulmonale), history of edema, or polycythemia (hematocrit >55%).

Exclusion criteria

Patients were excluded if they could not be contacted by phone, did not attend the scheduled control visit, or failed to obtain the prescribed oxygen device after hospital discharge.

All enrolled COVID-19 patients receiving long-term home oxygen therapy were contacted by phone and recalled to the hospital for a control visit 60 days post-discharge. During the visit, respiratory symptoms and oxygen saturation levels were documented. A questionnaire regarding the home oxygen therapy, covering the duration and regularity of oxygen use and the average daily usage time (hours per day), was administered.

Ethical approval for the study was granted by the İzmir Katip Çelebi University Hospital on December 24, 2020 (Approval number: #1114), in accordance with the Good Clinical Practices guidelines and the Helsinki Declaration. Permission was also obtained from the Ministry of Health of the Republic of Türkiye. Written informed consent was secured from all participants.

The collected data encompassed demographic information, initial symptoms, laboratory test results (including complete blood count, selected biochemistry and blood clotting tests, and arterial blood gas analysis), and clinical outcomes such as length of hospital stay and ICU admission, which were documented during hospitalization due to COVID-19.

Lymphopenia is defined as blood lymphocyte counts below $1 \times 10^9/L$. Normal hemoglobin (Hb) levels are between 14–18 g/dl for males and 12–16 g/dl for females, with levels below these ranges considered indicative of anemia.

The normal ranges for biochemical parameters are as follows: Lactate Dehydrogenase (LDH) < 220 U/L, C-Reactive Protein (CRP) < 0.5 mg/dl, and Procalcitonin (PCT) < 0.15 ng/mL. The established cutoff levels for serum ferritin and D-dimer are 500 ng/ml and 1000 µg/L, respectively, which are used as negative prognostic indicators in the National Guidelines for COVID-19.³

In the blood samples taken from the radial artery, both partial oxygen pressure (PaO₂) and oxygen saturation (SaO₂) were measured using a blood gas analyzer.

The severity of COVID-19 pneumonia was utilized as a parameter for comparing groups. Severe pneumo-

nia was defined according to the National Guidelines for COVID-19 issued by the Scientific Advisory Board on Coronavirus affiliated with the Turkish Ministry of Health, as “the presence of dyspnea, and/or respiratory frequency $\geq 30/\text{min}$, and/or blood oxygen saturation $\leq 90\%$ (PaO₂/FiO₂ ratio ≤ 300 mmHg).”^[3]

Statistical Analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 15.0 software (SPSS, Chicago, IL, USA). Baseline characteristics, including demographic data and parameters observed during hospitalization, were summarized using descriptive statistics. Continuous variables, such as oxygen saturation and partial pressure of oxygen (pO₂), were represented by means and standard deviations if normally distributed, or medians and interquartile ranges if not. Categorical data, including sex and presence of improvement in oxygenation, were expressed as numbers and percentages. The chi-square test was employed to compare categorical data, while the paired t-test was used for continuous data. The results for these parameters were analyzed both during hospitalization and at the control visit. All tests were two-tailed, and a p-value < 0.05 was considered significant.

Results

The study included 189 men (59.1%) and 131 women (40.9%) with a mean age of 70.6 ± 12.6 years. A total of 242 (84.8%) patients had at least one comorbid disease, with hypertension being the most common (58.2%).

Of the participants, 244 (76.3%) were diagnosed with COVID-19 via a positive RT-PCR nasopharyngeal swab, while 76 patients (23.7%) were diagnosed based on clinical and radiological findings.

The most common symptoms were dyspnea (87.4%) and cough (70%), followed by fatigue (67.2%), and fever (31.3%). Less common symptoms included myalgia (30.3%) and gastrointestinal symptoms (15.2%), such as nausea and diarrhea. These characteristics among patients with COVID-19 are seen in Table 1.

Thorax computed tomography (CT) scans revealed COVID-19 pneumonia in 96.5% of the participants, with 79.2% categorized as severe. The predominant abnor-

Table 1: Characteristics of study patients

Characteristics	n	%
Age (years) (mean±SD)	70.6±12.6	
Gender		
Male	189	59.1
Female	131	40.9
Comorbidities		
Present	242	80.7
Not	78	19.3
Diagnosis based on positive PCR	244	76.3
Clinical&radiological findings	76	23.7
Symptoms		
Fever	100	31.3
Dyspnea	280	87.4
Cough	224	70
Fatigue	215	67.2
Myalgia	97	30.3
Gastrointestinal symptoms	49	15.2

SD: Standard deviation, PCR: Polymerase chain reaction

mality observed in patients with COVID-19 pneumonia was peripherally located ground-glass opacities, identified in 78.1% of cases.

Among laboratory findings, elevated levels of LDH (90.7%) and CRP (84.3%), along with lymphopenia (62.9%), were the most frequently detected abnormalities.

On hospital admission, the mean oxygen saturation was 82.6%±9.4, and the mean pO₂ was 50.6±12.9 mmHg. Prior to hospital discharge, arterial blood gas analysis showed an average oxygen saturation of 85.2%±13.1 and a mean pO₂ of 53.1±16.4 mmHg.

The average length of hospital stay was 19.6 days ±8.1. A total of 117 patients (36.7%) required admission to the intensive care unit during hospitalization. The use of non-invasive ventilation (NIV) was necessary for 20.2% of patients, and the intubation rate stood at 17.1%.

All patients received favipiravir and low molecular weight heparin during their stay. Corticosteroid therapy

was administered to 83.8% of patients, with 68% receiving methylprednisolone and 32% receiving dexamethasone. Intravenous pulse corticosteroid therapy was utilized in 13.4% of cases.

The average daily use of oxygen support was 10.2±7.2 hours. Regular daily oxygen therapy was maintained by 77% of patients. The requirement for oxygen support continued post-discharge in 22.9% of patients. At the control visit, mean oxygen saturation was 94.7% ±3.2 with oxygen support, and 89.7% ±5.8 without it. Table 2 displays a comparison of oxygen parameters during hospitalization and at the control visit.

ICU admission, the presence of anemia, and high serum D-dimer levels (>1000 µg/L) were significant risk factors for the ongoing need for home oxygen therapy (p=0.026 and p=0.010, respectively) (Table 3). It was determined that patients requiring continued oxygen therapy had significantly lower oxygen saturation levels at hospital admission (p<0.001). Multivariable regression analysis revealed that significant predictors of the continued need for oxygen therapy were a high D-dimer level (p=0.012) and a lower oxygen saturation level at admission (p<0.001) (Table 4).

The mortality rate during the post-COVID phase was found to be 15.1%. Factors significantly associated with increased mortality included advanced age, non-use of steroids in treatment, and the need for mechanical ventilation during hospitalization (p=0.003, p=0.048, and p=0.009, respectively). Table 4 displays the characteristics of COVID-19 patients with respect to survival and the requirement for oxygen therapy in the post-COVID period.

Discussion

Our study revealed that less than a quarter of participants still required oxygen support in the post-COVID phase. Being in the intensive care unit, the presence of anemia, and elevated serum D-dimer levels were significant risk

Table 2: Evaluation of oxygen parameters during hospitalization and at follow-up visits

Parameters	Hospital admission (initial)*	Before Hospital discharge*	p**	Control visit*	p***
Mean oxygen saturation (%)	82.6±9.4	85.2±13.1	0.775	89.7±5.8	0.129
Mean PaO ₂ (mmHg)	50.6±12.9	53.1±16.4	0.271		

*: Without oxygen support, **: Comparison of means at hospital admission and before hospital discharge, ***: Comparison of means at hospital admission and control visit. PaO₂: Partial pressure of oxygen

Table 3: Characteristics of COVID-19 patients based on survival status and oxygen therapy needs in the post-COVID period

Feature	Survivors (n=272)		Non-survivors (n=48)		p	Patients with O ₂ need (n=73)		Patients without O ₂ need (n=247)		p
	n	%	n	%		n	%	n	%	
Gender										
Male	158	58.1	33	69.6	0.097	44	60	147	59	0.886
Female	114	41.9	15	30.4		29	40	100	41	
Age (years) (mean)	69.5±11.2		75.4±13.4		0.003*	70.7±11.6		69.1±12.7		0.399
Comorbidities										
Present	227	83.5	42	87	0.552	63	82.2	209	84.6	0.660
Not present	45	16.5	6	13		13	17.8	38	15.4	
Active smoking										
Yes	108	39.5	24	50	0.184	25	34.5	114	46	0.134
No	164	60.5	24	50		48	65.5	133	54	
Pneumonia										
Yes	262	96.5	47	97.9	0.534	68	93	242	98	0.054
No	10	3.5	1	2.1		5	7	6	2	
Severe pneumonia										
Yes	216	79.3	35	73	0.413	63	86	188	76	0.243
No	56	20.7	13	27		10	14	59	24	
Lymphopenia										
Present	160	58.7	28	58.7	0.366	47	64.8	141	51.8	0.396
Not Present	112	41.3	20	41.3		26	35.2	106	48.2	
Anemia										
Present	85	31.2	22	45.7	0.057	31	42.6	76	30.8	0.011*
Not Present	187	68.8	26	54.3		42	57.4	171	69.2	
High CRP level										
Present	236	86.8	39	81.2	0.089	44	87.3	226	91.5	0.591
Not Present	36	13.2	9	18.8		29	12.7	21	8.5	
High PRC level										
Present	92	34	17	35	0.962	24	32.6	85	34.4	0.674
Not Present	180	66	31	65		49	67.4	162	65.6	
High serum LDH level										
Present	246	90.5	45	94	0.429	69	94.5	222	89.9	0.223
Not Present	26	9.5	3	6		4	5.5	25	10.1	
Serum ferritin level (>500 ng/mL)										
Present	145	53.3	19	38.9	0.119	39	53.7	125	50.6	0.848
Not Present	127	47.2	29	61.1		34	46.3	122	49.4	
Serum D-dimer level (>1000 µg/L)										
Present	139	63	26	54.3	0.326	57	78.2	108	43.7	0.010*
Not Present	133	37	22	45.7		16	21.8	139	56.3	
Mean oxygen saturation at Hospital admission (%)	82.5±9.6		82.3±9.5		0.897	76.9±13.3		84.3±7.4		<0.001*
Length of hospital stay	23.5±15.2		18.9±11.2		0.232	21.3±13.3		17.7±10.4		0.067
Usage of NIMV										
Yes	48	17.6	16	33.5	0.009*	9	12.4	55	22.3	0.271
No	224	82.4	32	66.5		64	87.6	192	77.7	
Corticosteroid usage										
Yes	231	85	35	73.2	0.048*	63	86.5	203	82.2	0.402
No	41	15	13	26.8		10	13.5	44	17.8	
Admission to the ICU										
Yes	99	36.4	19	39.5	0.727	32	44	86	34.8	0.026*
No	173	63.6	29	60.5		41	56	161	65.2	

*: Statistically significant (Tests applied: Chi-squared test or Fisher's exact test when n<5). The mortality rate during the post-COVID phase was found to be 15.1%. Factors significantly associated with increased mortality included advanced age, non-use of steroids in treatment, and the need for mechanical ventilation during hospitalization (p=0.003, p=0.048, and p=0.009, respectively). COVID-19: Coronavirus Disease 2019, CRP: C-reactive protein, PRC: Procalcitonin, LDH: Lactate dehydrogenase, NIMV: Non-invasive mechanical ventilation, ICU: Intensive care unit

Table 4: Multivariate logistic regression analysis on the continued requirement for oxygen therapy

Variable	β	SE	Wald	Sig.	Exp (β)	95.0% CI for Exp (β)	
						Lower	Upper
Oxygen saturation at hospital admission	-0.068	0.017	15.477	<0.001	0.934	0.903	0.967
High D-dimer Level	0.817	0.327	6.265	0.012	2.264	1.194	4.294

The variables included in the model are anemia, admission to the intensive care unit, high D-dimer levels (>1000 $\mu\text{g/L}$), the presence of C-reactive protein (CRP) elevation, and mean oxygen saturation at hospital admission. SE: Standard error, CI: Confidence interval

factors for the continued need for home oxygen therapy. The lower the initial oxygen levels, the longer the duration of LTOT required by COVID-19 patients. This multicenter, cross-sectional study exploring the characteristics of COVID-19 patients on long-term oxygen therapy appears to be the first of its kind in the literature on this topic.

Hypoxemia was found to be independently associated with in-hospital mortality among COVID-19 patients.^[10] Voshaar et al.^[11] reported that the majority of surviving COVID-19 patients could be discharged without the need for oxygen support. However, persistent post-COVID syndrome may involve ongoing physical and medical sequelae following COVID-19, potentially leading to a continued requirement for oxygen support in these patients, even after hospital discharge.^[12] The need for supplemental oxygen due to persistent hypoxemia was reported in 6.6% of patients at a 60-day follow-up in a post-acute COVID-19 study.^[13] Despite the minority of COVID-19 patients being scheduled for home oxygen support, many cases exhibit prolonged hospitalization because they cannot be weaned off oxygen, as observed in our daily practice. This is evidenced by the 320 patients in our study who required LTOT at home.

In our study, patients admitted to the hospital for COVID-19 who required oxygen therapy had statistically significantly low oxygen saturation levels. Dillon et al.^[14] suggested that the lowest recorded oxygen saturation value on hospital admission could be an independent predictor of poor prognosis and mortality in COVID-19 patients, more so than other factors. Dense acute inflammation in the respiratory system, which can cause significant pulmonary damage and severe hypoxemia, may be responsible for persistent hypoxemia during the recovery process.^[10]

Our results indicate that admission to the intensive care unit, the presence of anemia, and elevated serum D-dimer levels during hospitalization were significant risk

factors for the continued need for home oxygen therapy in the post-COVID period. Few studies have focused on prolonged oxygen therapy in COVID-19 patients, particularly those who were inpatients and not discharged.^[13,15] Hypoxemic and refractory respiratory failure has been one of the most common complications, occurring in 60–70% of COVID-19 patients admitted to the intensive care unit.^[16] Although anemia is not a common laboratory finding in COVID-19 patients, there appears to be a correlation between severe COVID-19 pneumonia and reduced hemoglobin levels.^[17] A low hemoglobin level can induce hypoxia by depriving various organs of oxygen. Persistent hypoxemia that requires prolonged oxygen support is associated with a marked increase in inflammatory markers, including elevated D-dimer levels.^[18]

Our findings show that 22.9% of patients continued to require oxygen therapy. This indicates that more than three-quarters of COVID-19 patients initially scheduled for LTOT no longer needed it. Data on the follow-up and ongoing oxygen needs of COVID-19 patients receiving long-term oxygen support are limited in the literature. Öz et al.^[19] revealed that a significant proportion of patients who developed acute respiratory failure due to COVID-19 recovered within the first three months. The findings that most COVID-19 patients no longer required oxygen support suggests that clinicians should be more selective when planning home oxygen therapy for those with chronic hypoxemia. For these patients, temporary solutions such as oxygen tanks may be preferable over more costly, continuous-use devices like oxygen concentrators.

According to our study data, 15% of patients died during the post-COVID period after hospital discharge. Factors significantly associated with increased mortality included advanced age, absence of steroid treatment, and the need for mechanical ventilation during hospitalization. A related study reported a 13.4% post-discharge mortality within 28 days among COVID-19 patients.^[20] Donnelly et al.^[21] found that 27% of COVID-19

survivors were readmitted or died within 60 days of discharge, and these patients were significantly older than those who were not readmitted and survived. Systemic corticosteroid therapy was associated with lower 28-day all-cause mortality in critically ill COVID-19 patients.^[22] Those requiring mechanical ventilation in the hospital often suffer from severe COVID-19 pneumonia, and their lungs are severely affected. This may explain the increased mortality observed in this patient group during the post-COVID period. Our findings regarding risk factors associated with mortality in the post-COVID process are consistent with the literature.

Most LTOT experience relates to patients with Chronic Obstructive Pulmonary Disease (COPD). Specifically, for COPD patients who start LTOT during an exacerbation, the need for LTOT may diminish as their condition improves.^[23] The criteria for initiating LTOT include a re-evaluation after 3–4 weeks of stability.^[24] As there is limited experience with LTOT in COVID-19 patients, the data from our study is particularly valuable.

Our study has several limitations. First, evaluating COVID-19 patients after a consistent and specific period post-discharge can provide insights into the duration of their oxygen support needs in the post-COVID period. Secondly, the causes of mortality in COVID-19 patients who used LTOT are unknown. Knowing whether oxygen support is used regularly could inform the effectiveness of LTOT. Thirdly, including patients who show strong clinical features of COVID-19 (including radiological and serological findings), despite negative PCR test results, may increase the risk of misdiagnosis.

Conclusion

As long-term complications like chronic hypoxemia are common, home oxygen support can also be applied to COVID-19 patients. Admission to the ICU and the presence of certain laboratory parameters may predict the long-term need for home oxygen support during the post-COVID process in hospitalized COVID-19 patients. Since most COVID-19 patients were found to no longer need oxygen support, clinicians should be more selective when planning home oxygen therapy for those with chronic hypoxemia. For this patient group, devices that can be used temporarily, such as oxygen tanks, may be preferable over more costly, continuous-use devices like oxygen concentrators.

Ethics Committee Approval

The study was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Hospital Ethics Committee (No: 1114, Date: 24/12/2020).

Authorship Contributions

Concept – M.O.T.; Design – M.O.T.; Supervision – M.O.T.; Funding – M.O.T.; Materials – M.O.T.; Data collection &/ or processing – M.O.T., F.B., Ö.B., A.A., P.A.K., E.A., Y.S., A.A.G., A.Ç., S.A., P.A.T., A.Ş., H.B., Y.A., O.Y., P.Y.G., Ş.T.G., J.Ç.E., A.M.; Analysis and/or interpretation – M.O.T.; Literature search – M.O.T.; Writing – M.O.T.; Critical review – M.O.T.

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There are no conflicts of interest.

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