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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Investigation of the Effect of Laboratory Values of ICU Patients Diagnosed with COVID-19 During Hospitalization on Their Symptoms After Discharge

COVID-19 Tanılı Yoğun Bakım Hastalarının Yatış Sürecindeki Laboratuar Değerlerinin Taburculuk Sonrası Semptomları Üzerine Etkisinin İncelenmesi

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ABSTRACT *Objective:* It is known that coronavirus infectious disease 2019 (COVID-19), patients continue to have symptoms, respiratory system insufficiency and loss of functional status in the post-COVID period after dischargefrom the hospital.
Materials and Methods: A total of 101 patients who werehospitalized in the intensive care unit and who could be questioned for their post-COVID symptoms at the1st and 3rd months after discharge from the hospital were included in this study.
Results: The most frequent symptom observed at the time of discharge was dyspnea (n=89), which has been found to be related to comorbidity, hypoxiaand hypertension. Moreover, it was observed thatat least 1 symptom persisted in 50 patients at the 3rd month of discharge, and the most frequentsymptom was fatigue and forgetfulness.
Conclusion: Taking into account the patients' risk factors, comorbidities and conditions during the hospitalization process, the process of transition to normal life after discharge can be accelerated with early discharge and more effective rehabilitation according to their functional status. Thus, labor loss can be prevented and costs can be reduced.
Keywords: Prolonged COVID-19, dyspnea, intensive care

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) hastalarının taburculuk sonrası post COVID dönemde de semptomlarının devam ettiği, solunum sistemi yetersizliklerinin ve fonksiyonel durum kaybının olduğu bilinmektedir.
Gereç ve Yöntem: Yoğun bakım servisinde yatmış ve taburculuk sonrası 1. ay ve 3. ay post COVID semptom sorgulaması yapılabilen 101 hasta çalışmaya dahil edilmiştir.
Bulgular: Taburculuk esnasında en sık semptomdispne (n=89) olmuştur. Bu semptom komorbidite, hipoksi ve hipertansiyon ile ilgili bulunmuştur. Üçüncü ayda 50 hastada en az 1 semptomun devam ettiği ve en sık devam eden semptomun ise halsizlik ve unutkanlık olduğu görülmüştür.
Sonuç: Hastaların risk faktörleri, komorbiditeleri ve yatış sürecindeki durumları göz önüne alınarak erken taburculuk ve fonksiyonel durumlarına göre de daha etkin rehabilitasyon ile taburculuk sonrası normal hayata geçiş süreci hızlandırılabilir. Böylece iş gücü kaybı önlenerek, maliyet azaltılabilir.
Anahtar Kelimeler: Uzamış COVID-19, dispne, yoğun bakım

Introduction

Coronavirus infectious disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first detected in December 2019 in the city of Wuhan in China. The World Health Organization declared COVID-19 as a pandemic on March 11, 2020, when the first case was reported in Turkey (1). Although COVID-19 can be asymptomatic, it may lead to the development of extremely different clinical conditions, such as severe respiratory symptoms and extrapulmonary findings in addition to clinical conditions that may lead to death (2).

The term "prolonged COVID-19"was first used by Elisa Perego from Lombardy in Italy, to sum up the disease experience (3). It was described as the symptoms or signs that could be unexplained by an alternative diagnosis and which lasted for >12 weeks according to the National Institute for Health and Care Excellence guideline. In addition to this description, the prolonged COVID-19 term was later used to include both the continuing (Subacute 4-12 weeks) and post-COVID-19 (>12 weeks) period (4). Currently, the term "prolonged COVID-19" is used to refer to the disease in people not only whose effects of the infection continue despite having recovered but also whose symptoms continued to show for longer than the expected period (5).

According to the study by the King's College London, the risk factors for prolonged COVID-19 include advanced age, female gender, obesity and asthma (6). However, without an officially accepted definition of this post-COVID-19 state, there is no clear data on how long this state lasts, who is at risk, what factors lead to this condition, its pathophysiology, and how it can be treated and prevented through early diagnosis.

The most frequently reported symptoms of prolonged COVID are fatigue, shortness of breath, coughing, joint pain, and chest pain. The rare symptoms include difficulty in concentrating, depression, myalgia, headache, intermittent fever and palpitations (7). Although the time of regression of symptoms varies, it seems that the time until the complete disappearance of symptoms depends on both the severity of the acute illness and the spectrum of the symptoms experienced by the patient in addition to the pre-disease risk factors (8). In a study conducted in Switzerland, 669 patients (mainly outpatients) tested positive for COVID-19 and 32% of these patients continued to manifest at least one symptom on an average of 43 days after their discharge (9).

Routine biochemical, hematological, and immunochemical laboratory tests are important for the assessment of the severity of this disease, determining the appropriate treatment options, and pursuing the treatment response (10). Nevertheless, no specific parameter for the post-COVID period has been obtained so far and the number of relevant studies conducted on this subject is insufficient.

This study aimed to analyze the demographic data of patients with COVID-19 who were followed in the intensive care unit (ICU) and whose vital signs and laboratory values were recorded during the hospitalization stay so as to determine their effect on the clinical symptoms that continue after discharge, including respiratory failure and the degree of functional status. In addition, contributions to the literature studies on early discharge, mobilization, and rehabilitation were assessed with reference to the continuing symptoms and respiratory failure at home after discharge.

Material and Methods

Inour study, patients aged >18 years and whose diagnosis was confirmed by reverse transcriptase-polymerase chain reaction and who received inpatient treatment at the ICU between March 2020-2021at the Eskişehir Osmangazi University and the Eskişehir Yunus Emre State hospital were examined with due approval from the ethics committee (decision number: 04) of the Eskişehir Osmangazi University (dated: 13/07/2021).

101 of these patients who were discharged with an oxygen concentrator, whose data during the intensive care process could be accessed, and who could be questioned about their symptoms either directly or through relatives after discharge from the hospital were includedin this study.

The data used in the study were obtained from the hospital information system records and patient files. The demographic data of patients, comorbidities, hospitalization vital signs, APACHE 2 scores at the time of admission to the ICU, hemogram, and biochemical parameters were used in the determination of the length of hospital stay and follow-up, and laboratory data such as the values of C-reactive protein, ferritin, and d-dimer were also evaluated. The values that showed the greatest deviation from the physiological values at the time of admission to the ICU were specifically recorded. Macrophage activation syndrome criteria, as recommended by the Ministry of Health, used in the ICUs and the treatments applied were also examined.

Patients discharged from the hospitals were contacted via phone to question about symptoms related to respiratory failure and dyspnea after discharge, the use duration of oxygen concentrator, headache persisting for 1 month and 3 months, fatigue, weakness, breath shortness, loss of taste and smell, chronic cough, whole-body muscle pain, forgetfulness, distraction, sleep disorder symptoms, functional status scale (score 1-7) and the functional status (11).

The functional status was graded as follows:

- Totally dependent
- Needs a high level of help
- Need a moderate level of help
- Need low-level of help
- Can perform their routine jobs with supervision
- Semi-independent
- Fully independent

Statistical Analysis

SPSS version 25.0 (IBM, Armonk, NY, USA) software was applied to conduct all statistical analyses, and the statistical significance threshold was set to p=0.05. The normality of distributions in quantitative variable groups was analyzed with the Shapiro-Wilk test, and the variants were assessed

Table 1. Comparison of patients according tothe stage of dyspnea at discharge

		Dyspnea on discharge		
		No (n=12)	**Yes (n=89)**	**p-value**
Age		61.6±16.4	67.9±12.6	0.227
Gender	Man	9 (75%)	52 (58.4%)	0.431
	Woman	3 (25%)	37 (41.6%)	
Comorbidity	None	6 (50%)	13 (14.6%)	0.011
	There is	6 (50%)	76 (85.4%)	
MAS	None	10 (83.3%)	70 (78.7%)	1.000
	There is	2 (16.7%)	19 (21.3%)	
Pulse		103.33±18.01	95.73±17.21	0.111
Systolic BP		105±14.46	122.03±22.15	0.007
Diastolic BP		58.33±9.37	72.18±13.37	0.001
APACHE 2		18.75±9	18.03±6.72	0.812
Hospital lasting period		12.17±5.36	19.11±19.53	0.034
D-dimer		3033.33±1049.98	4541.8±3856.18	0.089
Ferritin		961.17±652.13	1047.18±604.57	0.570
Lymphocyte		678.33±369	802.36±529.03	0.475
Leukocyte		15050±9773.39	7648.99±4272.09	0.005
Thrombocyte		242666.67±70250.63	218988.76±140088.32	0.111
LDH		487.67±213.62	388.67±135.22	0.062
PaO_2		69.17±14.49	55.74±10.91	0.002
SaO_2		90.67±5.77	85.62±8.07	0.049
CRP		42.25±80.34	146.06±71.22	0.093

MAS: Macrophage activation syndrome, BP: blood pressure, LDH: lactate dehydrogenase, CRP: C-reactive protein

Table 2. Logistic regression analysis of the patient data

	B	**S.E.**	**Wald**	**df**	**p-value**	**Exp(B)**	**95% CI for Exp(B)**	
Leukocyte	–0.001	0	4.819	1	0.028	0.999	0.998	0.999
PaO_2	–0.214	0.091	5.553	1	0.018	0.807	0.676	0.965
Systolic BP	0.197	0.091	4.714	1	0.030	1.217	1.019	1.454

BP: Blood pressure, df: degree of freedom, CI: confidence interval

with the Levene test. Quantitative data were defined as the mean ± standard deviation values irrespective of the parametric/non-parametric status. Nonetheless, depending on whether the parametric assumptions were met (Student's t-test or Mann-Whitney U test); validation was made with comparison tests. Chi-square tests (continuity correction or Fisher's sharpness) were performed to match the distributions of the nominal or ordinal variables between the groups. Multiple regression analysis was performed for the independent variables, and the statistical significance threshold was set to p=0.1.

Results

The average age of the 101 (61 men, 40 women) study patients evaluated was 67 years. Of these, 18 patients did not have any comorbid disease, 83 had common comorbid diseases of diabetes mellitus (n=33), hypertension (n=27), coronary artery disease (n=18), chronic obstructive pulmonary disease and asthma (n=13), congestive heart failure, cancer, atrial fibrillation, component resolved diagnosis, and circumventricular organs. The mean APACHE 2 score calculated for these patients during the intensive care hospitalization was 18, and the mean hospitalization period was 18 days. Respiratory support provided to the patients during hospitalization was in the form of nasal cannula (n=4), simple mask (n=3), mask with reservoir (n=13), high flow nasal oxygen (n=45), non-invasive mechanical ventilation (NIMV) (n=29) and intermittent mandatory ventilation (IMV) (n=7).

All patients included in the study were discharged with an oxygen concentrator support and assigned to two groups based on the presence (n=89) or absence (n=12) of dyspnea at the time of discharge. These two groups were analyzed and compared individually based on age, gender, presence of comorbid diseases, vital signs (such as pulse and blood pressure), APACHE 2 score, laboratory parameters, and the length of stay. In this comparison (shown in Table1), although the mean age and the number of men were higher in the dyspnea group, the differences were not statistically significant.

The comorbidity rate in the dyspnea group was 85.4% and14.6% of the patients did not have any comorbidities (p=0.011). Moreover, the length of hospital stay was19.11±19.53 days in the dyspnea group and 12.17±5.36 days in the non-dyspnea group, indicating that this difference was statistically significant (p=0.034). On the other hand, the levels of d-dimer, ferritin, and C-reactive protein were higher in the dyspnea group, albeit the difference was not statistically significant.

In the data supported by multivariate logistic regression analysis in the independent variables (Table2), the low values of PaO_2 (55.74±10.91) and SaO_2 (85.62±8.07) (p=0.002 and p=0.049) and the high values of systolic and diastolic blood pressure (122.03±22.15 and 72.18±13.37; p=0.007 and p=0.001) in the dyspnea group were found to be significant. In addition, dyspnea symptoms were present at the time of discharge in 6 of the 7 patients who received IMV support, in 26 of the 29 patients who received NIMV support, and in 42 of the 45 patients who received high-frequency oscillation support. Meanwhile, 85 of the 101 patients did not need an oxygen concentrator at the end of the 3rd month and their dyspnea symptoms decreased from 89% to 18%.

In the 1st and 3rd months after discharge, the symptom inquiries were made using the information obtained from the patients who were in a good general condition and from the relatives of the patients who were in a poor health state. The most common symptoms in the 1st month were weakness, fatigue (99%), shortness of breath (89%), headache (37%), forgetfulness (35%), sleep disturbance (33%), cough (24%), muscle pain (22%), and the loss of taste and smell (8%). The frequency of symptoms decreased significantly in the 3rd month, and the most common symptoms that continued were fatigue (28%), forgetfulness (27%), and breath shortness (18%). No such symptoms continued or remained in 50 patients.

Another parameter questioned during the study was the functional status scoring, and the patients were scored in the range of 1-7. While the dependent group (n=75) was scored between 1 and 4 on the functional status scale, the independent group was scored between 5 and 7 (n=28). Although there was no significant difference in age, gender, laboratory parameters, the length of stay, and treatment received between the dependent and independent groups (based on the functional status scale at the 1st month), the significance of male gender and comorbidity was higher in the dependent group. Although the APACHE 2 score was 19.03±6.75 in the functionally dependent group, it was 15.5±7.1 in the independent group. The high APACHE 2 score (p=0.038) detected in the addicted group was found to be statistically significant. In addition, the functional status of oxygen support administered during the ICU admission

was found to be significantly higher in the dependent group (p=0.019). All patients who received the IMV support and 24 of the 29 patients who received the NIMV support at the time of discharge were found to be dependent. In conclusion, according to the functional status scale of 101 patients, 75 of them were dependent and 26 were independent in the 1st month and 20 patients became dependent and 81 patients became independent by the end of the 3rd month. Furthermore, 62 patients in the independent group returned to their fully independent working life mode (Table 3).

Discussion

According to the Centers for Disease Control and Prevention (CDC) data, the incidence of symptoms during the post-COVID period was 5-80%. According to this study, the risk factors were found to be age >50 years, presence of hypertension, female gender, asthma, and obesity (12). In our study, the average age of the patient was 67 years, which was consistent with these data. Moreover, comorbidity and the length of hospital stay were found to be significant in terms of the incidence of dyspnea at the time of discharge in patients followed up at the ICU with the diagnosis of COVID-19. Diagnoses of diabetes mellitus and hypertension were found to be the most common ones among the comorbid diseases. Low PaO_2 and SaO_2 values and the hypertensive course of the patients were also determined as risk factors for the continuation of dyspnea. The length of the dyspnea period in hypertensive patients is believed to be related to the renin–angiotensin

Table 3. Comparison of dependent and independent patients

		Dependant (n=75) FDS=1-4	**Independent (n=26) FDS=5-7**	**p-value**
Age		67.4±12.9	66.7±14.2	0.867
Gender	Man	44 (58.7%)	17 (65.4%)	0.711
	Woman	31 (41.3%)	9 (34.6%)	
Comorbidity	None	13 (17.3%)	6 (23.1%)	0.565
	There is	62 (82.7%)	20 (76.9%)	
MAS	None	60 (80%)	20 (76.9%)	0.958
	There is	15 (20%)	6 (23.1%)	
CRP		148.19±75.71	124.31±61.42	0.161
D-dimer		4402.67±3665.05	4246.92±3921.14	0.532
Ferritin		1002.61±623.41	1136.04±559.2	0.296
Lymphocyte		717.6±394.49	989.62±730.6	0.085
Leukocyte		8351.73±5977.09	9037.69±4829.92	0.253
PaO_2		55.65±10.7	62.19±14.69	0.094
SaO_2		85.51±8.04	88.27±7.61	0.139
Systolic BP		120.65±23.35	118.15±17.97	0.805
Diastolic BP		69.75±14.11	72.81±12.37	0.207
APACHE 2		19.03±6.75	15.5±7.1	**0.038**
Hospital period		18.97±20.72	16.31±9.98	0.354
Oxygen support	Nasal O_2	1 (1.3%)	3 (11.5%)	**0.019**
	Mask	3 (4%)	0 (0%)	
	Mask with reservoir	9 (12%)	4 (15.4%)	
	High flow O_2	31 (41.3%)	14 (53.8%)	
	NIMV	24 (32%)	5 (19.2%)	
	IMV	7 (9.3%)	0 (0%)	

MAS: Macrophage activation syndrome, BP: blood pressure, CRP: C-reactive protein, NIMV: non-invasive mechanical ventilation, IMV: intermittent mandatory ventilation

system. Kreutz et al. (13) indicated the relationship between immune and inflammatory dysregulation and hypertension in patients diagnosed with COVID-19 in their study. Detailed information about lung damage and pathophysiology caused by angiotensin-converting enzyme 2 down regulation and the proinflammatory and profibrotic effects of the renin-angiotensin system on angiotensin type-1 receptors have also been discussed (13). In our study, both the presence of hypertension as comorbidity and the hypertensive follow-up of the patients were found to be risk factors indicative of possible lung damage and the continuation of dyspnea symptoms. Despite this, 85 of the 101 patients did not require an oxygen concentrator at the end of the 3rd month and the dyspnea symptom reduced from 89 to 18% by the end of the 3rd month.

The most common symptoms noted in the 1st month of the prolonged COVID-19 period were weakness, fatigue, and shortness of breath, although these symptoms were completely resolved in 50% of the patients and at least 1 symptom continued in 50% of the patients by the end of the 3rd month. The most common ongoing symptoms were determined to be fatigue and forgetfulness. In a study conducted in Italy, 83% of the 143 patients hospitalized due to COVID-19 continued to show at least 1symptom even after 60 days of discharge on an average (14). Our results were found to be consistent with these past data. In fact, similar results were reported in the study conducted by Mark et al. (15) who examined different age groups of patients with COVID-19, the duration of symptoms, the time to return to a healthy life after discharge, and the relevant risk factors. The presence of post-COVID-19 symptoms was not found to be associated with any laboratory data in CDC data. In addition, there are insufficient studies and data in the literature on this subject. Based on our findings and as per the literature, there are no laboratory parameters yet established to determine the post-COVID symptoms.

Although the usability of the functional status scale has been demonstrated in patients with prolonged COVID symptoms by Felipe et al. (16), it is imperative that the scales used in the ICUs should be able to be easily integrated into clinical follow-up without the need for physical function and additional equipment (11).Therefore, we used a similar scale, as demonstrated in a Brazilian study, to evaluate patients for their functional status. The patients were compared as either dependent or independent. Our results showed that 75 out of 101 patients were still dependent in the 1st month, whereas 81 gained independence by the 3rd month and 62 returned to their work post-COVID. The high APACHE 2 score between the two groups was indicative of statistical significance in the dependent group. The APACHE 2 scoring system provides an assessment by taking into consideration several physiological variables of the body systems, the patient's age, and the chronic health status. An APACHE 2 score >15 signifies that the disease is severe (17). In our study, the APACHE 2 score in the addicted group was found to be 19.03±6.75, which is consistent with past reports. Hence, the oxygen requirement and the mechanical ventilation support provided during the ICU hospitalization were found to be significantly higher in the dependent group relative to that in the independent group. Immobilization, physical reconditioning, and the loss of strength were common in patients receiving MV due to the diagnosis of acute respiratory failure. Long-term mechanical ventilation application can reduce the muscle strength in patients hospitalized in the ICU (18).

Conclusion

The study findings indicated that the most important risk factors for dyspnea during the prolonged COVID-19 period were comorbidity and hypertension. No determinant laboratory parameters were recorded during this period. An inverse correlation was noted between the improvement of prolonged COVID-19 symptoms and the functional status after discharge and between the severity of the disease during the intensive care hospitalization and the oxygen support provided.

Considering the risk factors, comorbidities, and the hospitalization process of the patients, the transition to normal life after discharge can be accelerated with early discharge and more effective rehabilitation in accordance with their functional status. This approach can prevent labor loss and reduce the healthcare expenditure.

Ethics

Ethics Committee Aproval: Eskişehir Osmangazi University (Dated: 13/07/2021,decision number: 04).

Informed Consent: The data used in the study were obtained from the hospital information system records and patient files.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.V.K., İ.K.G., B.Y.Y., Concept: İ.V.K., İ.K.G., B.Y.Y., Design: İ.V.K., İ.K.G., B.Y.Y., Data Collection and Process: İ.V.K., İ.K.G., B.Y.Y., Analysis or Interpretation: İ.V.K., İ.K.G., B.Y.Y., Literature Search: İ.V.K., İ.K.G., B.Y.Y., Writing: İ.V.K., İ.K.G., B.Y.Y.

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