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Original Article

Long-Term Consequences Of Intensive Care Patients Diagnosed With COVID-19 Infection After Hospital Discharge

COVİD-19 Enfeksiyonu Tanısı Konan Yoğun Bakım Hastalarının Hastaneden Taburcu Sonrası Uzun Vadeli Sonuçları

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ABSTRACT

Aim: The COVID-19 pandemic has become a serious health problem that spreads rapidly in the world and in our country. The problems that may be encountered in the future in patients with COVID-19 infection are still unknown. This study aimed to evaluate long-term symptoms following COVID-19 infection.

Material and Methods: This study evaluated post-discharge continued symptoms of patients hospitalized in the intensive care unit with the diagnosis of COVID-19.

Results: The most common symptom that persisted after COVID-19 infection was fatigue. It was determined that as the age of the patient increases, the incidence of symptoms after COVID-19 infection increases.

Conclusion: There are persistent symptoms after COVID-19 infection. Their identification is crucial for early diagnosis and treatment.

Keywords: COVID-19, intensive care, long-term

ÖZ

Amaç: COVID-19 salgını dünyada ve ülkemizde hızla yayılım gösteren ciddi bir sağlık sorunu haline gelmiştir. COVID-19 enfeksiyonu geçirmiş hastalarda ileri ki dönemlere ait karşılaşılacak sorunlar hala bilinmemektedir. Bu çalışmada COVID-19 enfeksiyonu sonrası devam eden semptomları değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmada COVID-19 tanısı nedeni ile yoğun bakımda yatan hastaların taburculuk sonrası devam eden semptomları değerlendirilmiştir.

Bulgular: COVID-19 enfeksiyonu sonrası devam eden en sık semptomun halsizlik olduğu görüldü. Hasta yaşının artışı ile COVID-19 enfeksiyonu sonrası semptomların görülme sıklığı artmaktadır.

Sonuç: COVID-19 enfeksiyonu sonrası devam eden semptomlar mevcuttur. Bunların tanınması erken tanı ve tedavi için önemlidir.

Anahtar kelimeler: COVID-19, yoğun bakım, uzun dönem

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Introduction

SARS-CoV-2 infection (COVID-19) is a major pandemic of our century that has caused significant mortality and morbidity worldwide. By March 2022, a total of 373 million people had recovered from 441 million patients with positive COVID-19 PCR (Polymerase Chain Reaction) tests, but some of those who recovered still describe persistent symptoms and organ dysfunction. "Long COVID" was first used by Perego on social media to point out the persistence of symptoms weeks and months after infection with SARS-CoV-2. In other words, "Long COVID" is the time interval between microbiological recovery and clinical recovery (1-3).

In the guide published in March 2022 for the management of long-term effects of COVID-19, NICE (National Institute for Health and Care Excellence) defined post- COVID-19 syndrome as signs and symptoms that develop during or after an infection consistent with COVID-19, lasts more than 12 weeks, and cannot be explained by an alternative diagnosis. "Post- COVID-19 syndrome" refers to the end of the acute phase of the disease (4).

It was shown that at least one symptom was permanent even on the 60th day in 87% of patients who recovered after the COVID-19 infection and were discharged from hospitals. Fatigue (53.1%), worsening of quality of life (44.1%), shortness of breath (43.4%), joint pain (27.3%), and chest pain (27.1%) were reported as common persistent symptoms after COVID-19 infection. Cough, skin rashes, palpitations, headache, diarrhea, and pinprick feeling are other common symptoms. Patients also reported mental health problems such as anxiety, depression, post-traumatic stress disorder, and failure to perform their routine daily activities (5).

This study aimed to evaluate new onset or continued symptoms after discharge and to determine the prevalence of patients hospitalized in intensive care units due to COVID-19.

Material and Methods

Patients over the age of 18, who were hospitalized and discharged from Prof. Dr. Feriha Öz Emergency and Pandemic Hospital and Uşak University Medical Faculty Hospital COVID-19 General Intensive Care Units between February 2021 and February 2022, were included in the study. Among the patients hospitalized in the intensive care unit, those with positive COVID-19 PCR test and those whose chest computed tomography (CT) was compatible with COVID-19 were included in the study. Patients who developed mortality in the intensive care unit, who refused to participate in the study, whose COVID-19 PCR test was negative and thorax CT was not compatible with COVID-19 were excluded from the study. In this study, the criteria for defining the long-term symptoms of COVID-19 were based on the criteria published by NICE in March 2022 for the management of the long-term effects of COVID-19 (4).

All patients' contact information was obtained from the Hospital Information Management System of both hospitals. The link https://www.surveymonkey.com/r/6Q98B28 was created for the questionnaire consisting of nine questions. At the beginning of the survey, the participants were informed about the purpose of the research and that participation was on a voluntary basis, and consent was requested from those who volunteered to participate. No questions revealing the identities of the patients were included in the questionnaire form. Patient privacy was protected, and data was used by anonymizing. An information message stating that we were conducting a survey and asking for their permission to be included in the study was sent to the patients via phone. After obtaining consent to participate in the study, patients were asked to answer the questions in the link sent. In addition, patients who applied to the hospital for control or any reason were given a written questionnaire via e-mail, and the patients who gave their consent were asked to fill out the questionnaire. Ethical approval was obtained from the Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (E-46059653-020).

Statistical Analysis

Statistical analysis was performed using the SPSS-15 (SPSS, Inc., Chicago, IL) software package. Normally distributed variables were expressed as mean and standard deviation, and non-normally distributed variables were expressed as median and interquartile range. The symptoms and findings of the patients who met the inclusion criteria were summarized with descriptive statistics. Persisting and newly observed symptoms and findings in patients after discharge from the intensive care unit were evaluated and given as a percentage. The groups were compared for differences in frequencies using chi-square or Fisher tests, whichever is suitable. P value less than 0.05 was considered to be statistically significant.

Results

A total of 1018 patients from both research centers were evaluated in the study. Of these patients, 130 could not be reached, 20 were excluded due to negative PCR test results despite thorax CT compatible with COVID-19 infection, 219 patients refused to participate in the study, and 50 patients were excluded because of the time elapsed after discharge was less than 12 weeks. Mortality developed in 16 patients after discharge, and a total of 583 patients were evaluated in this study. The median age of the patients was 62 (IQR, 40-73) years, and the proportion of male patients was 68%. In the study group, 28% of patients were between the ages of 18-30, 30% were between the ages of 30-50, and 42% were over the

age of 50. One or more symptoms persisted in 8% of the 18-30 age group, 17% of the 30-50 age group, and 72% of the 50+ age group. A comparison of the groups by age revealed that the incidence of Long COVID-19 symptoms increased statistically significantly as age increased. Long COVID-19 symptoms were not different between male and female patients (P=0.09). Comorbidities in COVID-19 patients are shown in Table 1. The frequency of long-term symptoms (56%) was higher in patients with two or more comorbidities (28%). This frequency was 46% in patients with no or only one comorbidity, and the difference between the two groups was statistically significant (P=0.03). During the intensive care hospitalization, 15% of the patients were intubated and 76.4% were followed up with a reservoir mask, high-flow oxygen therapy or noninvasive ventilation. The mean hospital stay in the intensive care unit was 8.4 days (2-56 days). The median APACHE II of patients was 17 (IQR, 11-26). The symptoms and incidence in patients after COVID-19 infection are presented in Table 2. Fatigue was the most frequently persisting symptom with 64%. The second most common symptom was exertional dyspnea (52%). These were followed by forgetfulness 28%, joint pain 21%, cough 12%, muscle pain 8%, loss of appetite 5%, taste-smell loss 4%, and headache 1%, respectively. The incidence of fatigue and exertional dyspnea after COVID-19 infection was significantly higher in APACHE II≥10 patients than in APACHE II<10 patients (p<0.001). However, no statistically significant difference was found in other symptoms.

Table 1. Demographic data and comorbidities of the patients

Gender	Male (68%)	
Age	Year	%
	18-30	28
	30-50	30
	≥50	42
Length of ICU-Stay(day)	8,4	
Entubation rate (%)	15	
APACHE II (median)	17	
Reservoir mask, High-flow oxygen therapy, Noninvasive ventilation (%)	76.4	
Comorbidity		
COPD, Asthma(%)	35	
HT(%)	33	
DM(%)	28	
Chronic kidney disease(%)	5	
Other (dementia, Alzheimer's disease, malignancy, hyperthyroidism, cirrhosis, etc.)(%)	1	

ICU: intensive care unit, COPD: chronic obstructive pulmonary disease; HT: hypertension;
DM: Diabetes Mellitus

Table 2. Manifestations of Long-COVID-19

Symptoms of patients'	(%)
Fatigue	64%
Dyspnea	52%
Cognitive impairment, brain fog	28%
Joint pain	21%
Cough	12%
Muscle pain	8%
Loss of appetite	5%
Loss of taste and smell	4%
Headache	1%

Discussion

COVID-19 is a significant cause of mortality and morbidity worldwide. While 80% of the affected individuals survived the disease mildly and moderately, 5% needed intensive care (2). In this study, all patients had a history of intensive care hospitalization. The most prominent symptoms that persisted after COVID-19 were fatigue and exertional dyspnea.

A study conducted in England categorized the symptoms in the acute phase of COVID-19 into 3 groups: Group 1 respiratory symptoms (cough, sputum, shortness of breath, fever); Group 2 musculoskeletal symptoms (myalgia, joint pain, headache, fatigue and malaise); Group 3 enteric symptoms (abdominal pain, vomiting and diarrhea). These symptoms were found to persist in some patients even if they have survived COVID-19 (6). Watson and Yong defined these patients with continuing symptoms as "long haulers" (1, 3).

A study conducted in Italy reported that 87% of patients who recovered from COVID-19 and were discharged had symptoms that persisted even 60 days after discharge. It was stated that 1 or 2 COVID-19 symptoms persisted in 32% of these patients, and 3 or 4 COVID-19 symptoms persisted in 55%. Commonly reported symptoms were fatigue (53.1%), worsening of quality of life (44.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%) (5). In this study, we reached similar findings among COVID-19 patients treated in the intensive care unit. The most common post- COVID-19 symptom was fatigue (64% of patients), followed by exertional dyspnea (52% of patients).

In another study supporting our findings, it was reported that complaints such as shortness of breath and fatigue persisted even 3 months after discharge in patients treated for COVID-19 infection (7). A meta-analysis by Lopez-Leon et al. determined the most common long-term covid symptoms as fatigue (58%), headache (44%), concentration impairment (27%), hair loss

(25%), and dyspnea (24%). (8). Consistent with the literature, the most common post- COVID-19 symptom in this study was fatigue. However, fatigue is a nonspecific symptom and can often be seen in respiratory, cardiac or endocrinological disorders and diseases such as anemia. For this reason, it would be appropriate to investigate the patients with persisting fatigue symptoms after COVID-19 in more detail. In addition, these results have created awareness that patients may need to be called for intermittent control even if the COVID-19 PCR test becomes negative until achieving clinical improvement.

Telford et al. (9) reported that long-term COVID-19 symptoms were more common in the elderly patient group. They found that long-term symptoms persisted in 26% of patients aged 18-34, 32% of patients aged 35-49, and 47% of patients over the age of 50. In the same study, they reported that long-term COVID-19 symptoms persisted in 28% of patients with one comorbidity, 46% in patients with two comorbidities, and 57% in patients with three or more comorbidities.

Women are twice as likely to develop long-term symptoms of COVID-19 than men. Again, even if the disease has been mild, advanced age, the presence of 5 or more symptoms in the acute disease period, and the presence of comorbidity arise as other risk factors (10). Another study showed that severe fatigue and weakness persisted in 50% of patients at a 10-week post-COVID-19 follow-up. In the same study, severe fatigue was found to be higher in women and those with pre-existing depression and anxiety disorders (11). In the present study, the rate of patients with two or more comorbidities was 28%, and Long COVID-19 symptoms were found to be statistically significant and higher than patients with no or single comorbidity. Again, in our study, it was determined that the incidence of long-term COVID-19 symptoms increased with increasing age. However, unlike the findings in the literature, our study found no gender-dependent difference in long-term COVID-19 symptoms. Our patient group consisted of intensive care patients. Besides, 68% of our patients were male. This may explain the inconsistency of our results with the literature in terms of gender.

Various pulmonary problems such as chronic cough, pulmonary vascular disease, bronchiectasis and fibrotic lung disease are encountered after COVID-19 infection, and it is stated that these may lead to persistent dyspnea (12). Of the patients in our study, 15% were followed up as intubated, and the remaining patients required additional oxygen (nasal oxygen, reservoir mask, high-flow oxygen support, noninvasive mechanical ventilation support). Dyspnea was found to be a long-term symptom of COVID-19 in 52% of our patients. In addition, respiratory complaints came to the fore in patients who were admitted to the intensive care unit due to COVID-19 infection. Dyspnea was the second most common Long COVID-19 symptom. For this reason, we think that continuing respiratory physiotherapy to increase the lung capacity of COVID-19 patients after discharge and keeping the patient under the control of a chest disease specialist would be the right approach to improve the patient's quality of life.

COVID-19 has also been detected in the cerebrospinal fluid. This supports the neuro-invasive properties of the virus. Neurological symptoms such as headache, tremor, concentration disorder, cognitive blunting ("brain fog"), anxiety, depression, and post-traumatic stress disorder may emerge as long-term COVID-19 symptoms in patients recovering from COVID-19 infection (13,14). Among the long-term symptoms of COVID-19, concentration impairment and forgetfulness were also found in 28% of the patients in this study.

Inflammatory arthralgias have been reported after post-COVID-19 infection, and musculoskeletal or joint pain was suggested as long-term symptoms (15). Consistent with these data, we found joint pain in 21% of patients and muscle pain in 8% of patients as post- COVID-19 symptoms. Intensive care neuromyopathy is a condition that we frequently encounter in patients hospitalized in intensive care units for reasons other than COVID-19, and especially in patients with prolonged hospital stays. This can be prevented by early mobilization, weaning from the mechanical ventilator as soon as possible, initiating physiotherapy early, and developing effective nutritional strategies. We believe that the same strategies will be beneficial in preventing musculoskeletal and joint pain seen in COVID-19 patients in the long term.

GalvanCasas, and Dasguptave suggested dividing patients with long-term COVID-19 symptoms into 3 categories as post- COVID-19 cardio-respiratory syndrome, post- COVID-19 fatigue-burnout syndrome, and post- COVID-19 neuro-psychiatric syndrome. They stated that the classification of symptoms according to the organ system involved would be a guide in elucidating the etiology. They also noted that anemia, hyperglycemia, electrolyte imbalance, and hypothyroidism should be considered in the differential diagnosis in patients with severe fatigue. In addition, they emphasized that the heart and lung involvement of patients with ongoing dyspnea should also be evaluated. They also suggested that new-onset symptoms in COVID-19 patients may be useful in detecting emergencies

such as coronary artery disease, stroke, pulmonary embolism, and pneumothorax (16, 17). The pathophysiology of COVID-19 has not been fully elucidated. This study also revealed that some symptoms persist after COVID-19 infection. We believe that clinical recovery is more important than microbiological recovery in COVID-19 infections. Therefore, when investigating long-term symptoms in patients with COVID-19 infection, we recommend intermittent check-ups until clinical improvement is achieved to make sure not to miss any underlying or new-onset comorbidity.

Evaluation of only intensive care patients and including patients with positive COVID-19 PCR test results are the limitations of our study. In addition, underlying comorbidities such as asthma, COPD, and heart failure could not be distinguished when evaluating the long-term COVID-19 symptoms.

Conclusion

Uncovering the long-term symptoms of COVID-19 will be beneficial for better understanding and clarification of the pathophysiology of the disease. It will contribute to the early diagnosis and treatment of the disease and the prevention of long-term complications. However, there is a need for multicenter and more comprehensive studies on the subject. We think that it is crucial to continue clinical controls, gradual exercise, and physical therapy protocols in patients diagnosed with COVID-19. It is also essential to detect changes with intermittent controls after determining the patient's basal respiratory, cardiac, neurological and mobility status.

References

1. Perego E. Twitter 20 May 2020. https://twitter.com/elisaperego78/status/1263172084055838721
2. Edwards E. COVID-19 "long-haulers" report nearly 100 symptoms for more than 100 days. NBC News. Available at: https://www.nbcnews. com/health/health-news/covid-19-long-haulers-report-nearly-100-symptoms-more-100-n1235217. Accessed Feb 16, 2022
3. Yong E. COVID-19 can last for several months. The Atlantic. Available at: https://www.theatlantic.com/health/archive/2020/06/covid-19-coronavirus-longterm-symptoms-months/612679/. Accessed Feb 11, 2022
4. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021;372 doi:10.1136/bmj.n136
5. Carfì A, Bernabei R, Landi F. Persistent symptoms in patient safter acute COVID-19. JAMA 2020;324(6):603-5. doi: 10.1001/jama.2020.12603.
6. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985
7. Arnold DT, Hamilton FW, Milne A, et al Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax. 2021;76(4):399-401. doi: 10.1136/thoraxjnl-2020-216086.
8. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv 2021;30;2021.01.27.21250617. doi: 10.1101/2021.01.27.21250617. Preprint
9. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with covıd-19 in a multistate health care systems network - united states, march-june 2020. MMWR Morb Mortal Wkly Rep. 2020;69(30):993-8. doi: 10.15585/mmwr.mm6930e1.
10. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of Long-COVID. Nat Med. 2021;27(4):626-31. doi: 10.1038/s41591-021-01292-y.
11. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020;15(11):e0240784. doi: 10.1371/journal.pone.0240784
12. Fraser E. Long term respiratory complications of covid-19. BMJ 2020;370:m300. doi: 10.1136/bmj.m3001
13. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55e8.doi: 10.1016j.ijid.2020.03.062
14. Lu Y, Li X, Geng D, et al. Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3- monthfollow-upstudy. EClinicalMedicine. 2020; 25: 100484. doi: 10.1016/j.eclinm.2020.100484.
15. Chandrashekara S, Jaladhar P, Paramshetti S, Ramachandran V, Nizar SF, Kori D. Post COVID inflammation syndrome: different manifestations caused by the virus. J Assoc Phys India 2020;68(12):33e4.
16. Dasgupta A, Kalhan A, Kalra S. Long term complications and rehabilitation of COVID-19 patients. J Pakistan MedAssoc 2020;70: (5):131-5. doi:10.5455/JPMA.32.
17. Casas CG, Catala A, Hernandez GC, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nation wide consensus study in Spain with 375 cases. Br J Dermatol 2020;183(1):71-7. doi: 10.1111/bjd.19163.