



Long COVID in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

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Abstract

Background: We aimed to evaluate the Long COVID frequency, and related factors in patients followed up after hospitalization.

Methods: This retrospective cohort study included 133 inpatients with COVID-19 PCR test positivity from Nigde Province, Turkey between 01.01.2021 and 28.02.2021. The characteristics of the patients were recorded by examining the files, and the symptom questioning was made by telephone interviewing with the patients approximately four months after the date of diagnosis. The presence of at least one symptom lasting more than four weeks was described as Long COVID.

Results: The frequency of Long COVID was 64.7%. The most common Long COVID symptoms were fatigue (45.9%), respiratory distress (25.6%), and muscle / joint pain (24.8%), respectively. In comparison analysis to identify factors associated with Long COVID; Long COVID was found to be more frequent among women ($P=0.04$); patients with severe COVID-19 ($P<0.01$), patients with prolonged hospital stay ($P=0.03$), patients with the comorbid disease ($P=0.03$), and Diabetes Mellitus patients ($P=0.02$). Additionally, the frequency of Long COVID increased as the depression score stated by the person increased after COVID-19 disease ($P=0.02$).

Conclusion: The treatment of COVID-19 patients should not end when they are discharged from the hospital. On the contrary, these patients, especially high-risk patients, should be followed up in post-COVID clinics and rehabilitated physically and psychosocially with a multidisciplinary approach following the recovery period of the acute illness.

Keywords: Long COVID; COVID-19; Symptom; Hospital; Turkey

Introduction

All countries of the world have been struggling with the COVID-19 pandemic for a long time. There have been more than 125 million cases and

more than 2.5 million deaths due to COVID-19 infection (1). People need to accept the reality of living with COVID-19 disease for years or even



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decades. While the pathophysiology, transmission routes, clinical presentations, treatment options, and preventive measures of COVID-19 infection continue to be investigated, we encounter different pathophysiological changes and clinical outcomes with the genomic transformation of the virus.

It is known that not every individual infected with the SARS-CoV-2 virus develops an infection, and approximately one-third of the infected individuals have the disease asymptotically (2). A wide range of clinical presentations may occur in individuals due to factors such as genetic variations, exposed viral load, and immune response to the virus (3). Many known and unknown factors can explain clinical differences in individuals. Age, concomitant diseases (diabetes, cardiovascular diseases, chronic lung diseases, etc.), genetic variations are just some of the factors that can be explained (4,5).

There is evidence of a multisystemic response in the body following recovery from the acute phase of COVID-19 infection (6). Some patients recover entirely clinically; however, one out of three patients complain from symptoms that last for weeks, and even a small but significant part of them has symptoms that last for months (7). Although the term 'Long COVID' has not been clearly defined in the literature, the general opinion is that the presence of one or more symptoms that persist for four weeks to one year after COVID-19 infection is considered as Long COVID (8,9). In this period, the contagiousness of the virus has disappeared. The clinic is the result of the response of the body (immune system, brain, cardiovascular system, lungs, and other organs) to the virus following the first infection. Fatigue, dyspnea, chest pain, muscle/joint pain, heart palpitations, loss of smell and taste, digestive problems, hair loss, cognitive symptoms (loss of memory or attention), psychosocial problems are the most common findings in the Long COVID (6,10). Long COVID increases with age and is more common among comorbid patients. However, it should be kept in mind that it is at a substantial level among young patients and those with mild symptoms (10).

Long COVID continues to be important due to recurrent waves of the COVID-19 pandemic. The permanent effects of COVID-19 disease have negative consequences on the patients' lives. Therefore, it is essential to focus on the term of Long COVID and reveal the related factors, follow these patients closely, provide medical and psychosocial support, and minimize the burden of disease that will occur over time.

We aimed to evaluate the symptoms persisting for more than four weeks in the hospitalized patients and revealed related factors.

Methods

This retrospective cohort study included the patients with COVID-19 PCR test positivity hospitalized in Nigde Training and Research Hospital, Turkey between 01.01.2021 and 28.02.2021. Since seventeen of these patients died, two of them had hearing problems, and four people could not be reached, they were not included in the study. Information about 133 hospitalized patients included in the study was obtained from patient files. Then, the patients were contacted by the researchers via telephone between 27.04.2021 and 08.07.2021, and it was recorded which symptoms had been observed since the first PCR test positivity was detected and how long these symptoms lasted. The date of the first PCR test positivity was taken as the onset of follow-up. The follow-up period was calculated as the time between the date of interview with the patient and the date of the first PCR test positivity. The presence of symptoms more than four weeks after the first PCR test positivity was defined as 'Long COVID'.

WHO classification method was used to classify acute disease (11).

1. Asymptomatic: no clinical signs OR symptoms
2. Mild: Mild signs of upper respiratory tract infection and lower respiratory tract infection AND no signs of hypoxia or viral pneumonia
3. Moderate: signs of pneumonia are present AND SpO₂ 90 or more in room air

4. Severe: signs of pneumonia are present AND with severe respiratory distress or SpO₂ 90 or less in room air

5. Critical: Clinical presentation with accompanying acute respiratory distress syndrome.

Ethical approval from Nigde University Ethics Committee (Decision Number: 2021/08-01) and institutional permission from Nigde Training and Research Hospital were obtained.

For statistical analysis, mean, standard deviation, median, minimum, maximum values, frequency, and percentages were used in the presentation of

descriptive data. The distribution of continuous data was evaluated with the Kolmogorov Smirnov Test. Chi-square Test and Fisher's Exact Test for the comparison of categorical variables; Mann Whitney U Test for analysis of continuous variables was used. Logistic Regression analysis 'Enter' method was used in multivariate analysis.

Results

Characteristics of patients are seen in Table 1.

Table 1: Characteristics of patients and related variables

<i>Variable</i>	<i>Mean (sd)</i>	<i>Median</i>	<i>Min.</i>	<i>Max.</i>
Age (yr)	65.7 (13.1)	68	29	93
Follow-up period (days)	126.5 (19.8)	123	96	211
Hospitalization period (days)	7.8 (5.9)	6	1	39
	n		%	
Female	64		48.1	
Male	69		51.9	
Acute Disease Severity				
Mild	18		13.5	
Moderate	72		54.1	
Severe	29		21.8	
Critical	14		10.5	
ICU Treatment	2		1.5	
Comorbidity				
Diabetes Mellitus	51		38.3	
Coronary Artery Disease	29		21.8	
Hipertension	73		54.9	
COPD	37		27.8	
Asthma	12		9.0	
Cancer	9		6.8	
Autoimmune Disease	7		5.3	
Psychiatric Illness	9		6.8	
Musculoskeletal Disease	2		1.5	
Renal Disease	6		4.5	
Liver Disease	2		1.5	
Number of Comorbid Disease				
0	17		12.8	
1	42		31.6	
2 or more	74		55.6	

Table 2 shows the frequencies and durations of Long COVID symptoms.

Table 2: Long COVID Symptoms of Patients

<i>Long COVID</i>	<i>n</i>	<i>%</i>	<i>%</i>
	86		64.7
Long COVID Symptoms	n	%	median (min-max) (days)
Fatigue / Weakness	61	45.9	75 (30-150)
Respiratory Distress	34	25.6	90 (30-150)
Muscle-Joint Pain	33	24.8	100 (30-150)
Memory Loss	21	15.7	120 (30-150)
Cough	18	13.5	50 (30-150)
Hair loss	18	13.5	30 (30-60)
Insomnia	17	12.8	120 (30-150)
Loss of Smell/Taste	15	11.3	45 (30-120)
Headache	12	9.0	50 (30-150)
Chest Pain	9	6.8	100 (30-150)
Attention Deficit	8	6.0	90 (30-150)
Nausea/Vomiting	6	4.5	30 (30-60)
Heart Palpitation	6	4.5	42.5 (30-150)
Fever	5	3.8	30 (30-30)
Diarrhea	3	2.3	30 (30-150)
Flu-Like Symptoms	1	0.8	100

Long COVID was more frequently seen in women patients ($P=0.04$). In addition, participants were asked to rate their depression and anxiety levels between 0 and 100 points before and after the COVID-19 disease. Accordingly, the depression score after the COVID-19 disease increased,

the frequency of Long COVID increased ($P=0.02$) (Table 3). No significant difference was found between the blood parameters (lymphocyte count, D-dimer, CRP, ferritin) in the first hospitalizations of patients and the presence of Long COVID.

Table 3: Related Factors with Long COVID

<i>Variables</i>		<i>Long COVID n (%)</i>	<i>P value *</i>
Sex	Female	47 (73.4)	0.04
	Male	39 (56.5)	
Acute Disease Severity	Mild	9 (50.0)	<0.01
	Moderate	41 (56.9)	
	Severe	26 (89.7)	
	Critical	10 (71.4)	
Diabetes Mellitus	Yes	39 (76.5)	0.025
	No	47 (54.7)	
Coronary Artery Disease	Yes	20 (69.0)	>0.05
	No	66 (63.5)	
Hypertension	Yes	52 (71.2)	>0.05
	No	34 (56.7)	
COPD	Yes	23 (62.2)	>0.05
	No	63 (65.6)	
Asthma	Yes	7 (58.3)	>0.05
	No	79 (65.3)	
Cancer	Yes	6 (66.7)	>0.05
	No	80 (93.0)	
Autoimmune Disease	Yes	5 (71.4)	>0.05

Psychiatric illness	No	81 (64.3)	>0.05
	Yes	6 (66.7)	
Musculoskeletal Disease	No	80 (93.0)	>0.05
	Yes	2 (100.0)	
Renal Disease	No	84 (64.1)	>0.05
	Yes	5 (83.3)	
Liver Disease	No	81 (63.8)	>0.05
	Yes	2 (100.0)	
Comorbidity	No	84 (64.1)	0.03
	Yes	79 (68.1)	
Number of Comorbid Disease	0	7 (41.2)	>0.05
	1	28 (66.7)	
	2 or more	51 (68.9)	
ICU Treatment	Yes	2 (100.0)	>0.05
	No	84 (64.1)	
		Std test sta.**	P value***
Age (yr)		0.5	>0.05
Hospitalization period (days)		2.1	0.03
Number of Symptoms in the Acute Period of COVID-19 Disease		-0.2	>0.05
Depression Score	Before COVID-19	1.0	>0.05
	After COVID-19	2.3	0.02
Anxiety Score	Before COVID-19	0.7	>0.05
	After COVID-19	1.1	>0.05

*Chi-square and Fischer's Exact Tests **Standardized test statistics ***Mann Whitney-U Test

Multivariate analysis was used to identify predictors of Long COVID with variables that were related with Long COVID statistically significant level or border level in univariate analysis. Ac-

cording to the logistic regression analysis, Long COVID was present 12.29 times more in those who have had a 'severe' COVID-19 disease ($P<0.01$) (Table 4).

Table 4: Logistic regression analysis of factors associated with prolonged COVID

Variable	OR	% 95 CI	P value
Sex			
Female	2.05	0.88-4.80	0.09
Male (ref)			
Acute Disease Severity			
Mild (ref)			
Moderate	1.40	0.44-4.44	0.42
Severe	12.29	2.25-67.08	<0.01
Critical	3.46	0.60-19.96	0.16
Diabetes Mellitus	1.98	0.80-4.86	0.13
Hypertension	1.22	0.49-3.05	0.65
Comorbidity	1.47	0.39-5.50	0.56
Hospitalization period (days)	1.01	0.93-1.09	0.74
Depression Score (Post COVID-19)	1.01	1.00-1.03	0.05

Logistic Regression analysis 'Enter' method (variables included in the model; sex. acute disease severity. diabetes mellitus. hypertension. presence of comorbidity. hospitalization duration. and depression score)

Discussion

In the present study, the frequency of Long COVID was 64.7%. The most common Long COVID symptom is fatigue/weakness. Long COVID was more frequent in women, patients with severe acute COVID-19 disease, with a comorbid disease, with diabetes mellitus and, patients with a high depression score.

Long COVID is seen approximately twice frequently in hospitalized patients compared to outpatients in a previous study than in our study (12). In a study evaluating sick leave, which can be a health determinant after COVID-19 disease, the risk of having sick leave for more than one month was found to be 1.8 times higher in hospitalized COVID-19 patients compared to non-hospitalized patients (13). In Italy, 87% of patients had at least one Long COVID symptom. The most common symptoms were reported as fatigue (53%), dyspnea (43%), and arthralgia (27%) (6). In a meta-analysis, one or more Long COVID symptoms were observed in 80% of the patients, and the most common findings in the present study were fatigue (58%), headache (44%), and attention deficit (27%) (14). Prolonged fatigue, in which chronic oxidative stress and inflammatory responses play a role in the pathophysiology, can also be seen after other viral infections.

COVID-19 can adversely affect mental health in the long term. This can be considered as a multifactorial process. Physical effects of viral infection in the body, immunological response, drugs use, social isolation, stigma are some of the affecting factors. Canadian researchers have shown that 33% of the infected patients in the SARS epidemic had mental health problems in a one-year period (15). In a study, in which hospitalized patients were followed up for six months, depression was a common problem after COVID-19 disease (16). In the present study, patients were asked to score their depression status before and after COVID-19 disease, and the depression score after COVID-19 disease was significantly higher in patients with Long COVID. Psycholog-

ical health deteriorates with prolonged illness but, it is difficult to establish a causal relationship and determine the direction of the relationship.

Although COVID-19 can be seen in all age groups, hospitalization is more common in the older age group, and this group is more affected by the prolonged effects of COVID-19. Sudre et al reported the prevalence of Long COVID, which was 10% in the 18-49 age group, as 22% over the age of 70 (17). In the present study, no relationship was found between age and Long COVID. However, hospitalized patients were included in the present study, and the average age was 66 yr. The less number of the young age group in the present study was thought to limit the evaluation of the effect of the age variable on Long COVID.

The risk of Long COVID is approximately twice as high in women as in men (17,18). Especially in recent studies evaluating hospitalized patients, women were at risk in terms of Long COVID (16,19,20). There are also studies in which men were at least as affected by Long COVID as women (21-23). In this study, the frequency of Long COVID in women was 73%, while it was 57% in men.

Concomitant diseases may delay the recovery of COVID-19 symptoms (17). In the USA, the presence of comorbidity increased the risk of Long COVID-19 12 times (24). According to another study, 35% of the patients could not return to their works 14-21 days after the COVID-19 test positivity, this frequency was higher in those with a comorbid disease, and the frequency increased as the number of comorbidities increased (25). The most common comorbid diseases in the present study were hypertension and diabetes mellitus. Long COVID incidence was higher in those with the comorbid disease.

Lung fibrosis in CT scans in COVID-19 patients was associated with prolonged hospital or intensive care stay (26). The presence of fibrotic changes in the lung may cause many symptoms with decreased respiratory capacity and impaired

oxygenation of the body. In the present study, the long hospitalization period was found to be associated with the Long COVID.

Although it is known that Long COVID can be seen in people with mild COVID-19 disease, there are a few studies showing that those with severe disease are more prone to Long COVID (20,27,28). Hospitalization is prolonged in patients with severe disease, and associated consequences such as fatigue, anemia, and neuropsychiatric disorders are observed (29). In a study, three subgroups were determined according to the severity of the COVID-19 disease. At the end of the follow-up period, which was six months on average, in the group with the most severe disease, the incidence of at least one symptom was 2.42 times higher than in the group with the less severe disease (16). In the present study, the frequency of Long COVID was 12.29 times higher in patients with severe acute disease than the patients with mild disease.

There were some limitations in this study. Due to the data was collected retrospectively; there may have been recall bias during data collection. The effect of some variables on Long COVID may not have been revealed due to the small sample size of the study. Since the present study included only hospitalized patients from only one center, it does not provide information about the Long COVID findings in the whole community, and the results cannot be generalized to the community. Therefore, population-based, controlled, prospective, long-term surveys are needed. In the literature review, no study was found that evaluated the Long COVID frequency and associated risk factors in Turkey. In our country, which has been severely affected by the COVID-19 pandemic, like other countries in the world and has about 6 million confirmed COVID-19 cases (1). Long COVID emerges as a serious cause of morbidity. Therefore, our study was valuable in terms of presenting data from Turkey.

Conclusion

Two out of three hospitalized COVID-19 patients had Long COVID symptoms. Fatigue was

the most common Long COVID symptom. Female gender, the severity of acute disease, presence of comorbidity, and length of hospital stay were associated with Long COVID. The treatment of COVID-19 patients should not end with the discharge from the hospital, on the contrary, these patients, especially high-risk patients, should be followed up in post-COVID clinics with a multidisciplinary approach, and they should be physically and psychosocially rehabilitated following the recovery period of the acute disease.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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