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Clinical Reflection of Pre- and Post-COVID-19 Symptoms in COVID-19 Patients

COVID-19 Hastalarında Hastalık Öncesi ve Sonrası Semptomların Klinik Yansıması

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ABSTRACT

Background: Hospitalized or non-hospitalized patients with Coronavirus disease-2019 (COVID-19) may exhibit different symptoms. Different symptoms of patients can give us an idea about the course of the disease.

Materials and Methods: A cross-sectional questionnaire study was conducted between August and October 2021. The questionnaire was sent online to patients who had COVID-19 infection with polymerase chain reaction positivity. The following categories were included in the questionnaire: Demographic characteristics, diagnosis date, initial symptoms, predominant symptoms, treatments, presence of hospitalization requirement, ongoing symptoms after the treatment, and symptom duration.

Results: Of the 596 patients, 574 (92.4%) were symptomatic at the beginning of the disease. Myalgia, fatigue, and headache were the most prominent initial symptoms. Fever and dyspnea were the most predominant symptoms that compel the patients to apply to the hospital. While dyspnea was significantly higher in hospitalized patients, fever was more common in non-hospitalized patients. Higher mean age, male gender, and comorbidity (especially chronic obstructive pulmonary disease) were found to be factors that increased hospitalization ($p<0.01$). Fever and fatigue were mostly seen among females, while myalgia was most prominent among men. Four hundred and seventy-seven patients (80%) had post-COVID symptoms and the most common symptoms were getting tired easily, fatigue, myalgia, and cough. However, post-COVID symptoms were most intense in the second month and there were cases with complaints up to one year.

Conclusion: The majority of the COVID-19 patients in our study were symptomatic. Dyspnea and fever with higher mean age were more common in patients requiring hospitalization. Post-COVID symptoms may persist for a long time, and long-term monitoring may be beneficial.

Keywords: COVID-19, hospitalization, symptom

ÖZ

Amaç: Hastaneye yatışı olan ya da ayaktan tedavi alan Koronavirüs hastalığı-2019 (COVID-19) hastaları farklı semptomlar gösterebilir. Bu semptom farklılığı, hastalığın gidişatı hakkında bilgi öngörebilir.

Gereç ve Yöntemler: Ağustos-Ekim 2021 tarihleri arasında kesitsel anket çalışması uygulandı. Polimeraz zincir reaksiyonu pozitifliği ile COVID-19 hastalığı tanısı konan hastalara, anket formu online olarak gönderildi. Ankette yer alan sorular; demografik özellikler, hastalık tanı tarihi, ilk semptom, baskın semptom, alınan tedaviler, hastane yatışı, tedavi sonrası devam eden semptomlar ve semptom süresi ile ilgili bilgileri içermekteydi.

Bulgular: Hastalığın başlangıcında, 596 hastanın 574'ünün (%92,4) semptomu mevcuttu. En sık görülen başlangıç semptomları, kas ağrısı, halsizlik ve baş ağrısıydı. Ateş ve dispne, hastanın hastaneye başvurmasına neden olan en baskın semptom olarak saptandı.

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ÖZ

Dispne hastane yatışı olan hastalarda daha sık iken, ateş ayaktan tedavi alan hastalarda daha sık saptandı. Ortalama yaşın yüksekliği, erkek cinsiyet ve komorbidite varlığı (özellikle kronik obstrüktif akciğer hastalığı) hastane yatışını artıran faktörler olarak gözlendi (p<0,01). Ateş ve halsizlik en sık kadın hastalarda görülürken, kas ağrısı erkeklerde daha sıktı. Dört yüz yetmiş yedi (%80) hastanın post-COVID semptomu mevcuttu ve en sık görülen semptomlar; çabuk yorulma, halsizlik, kas ağrısı ve öksürüktü. Post-COVID semptomlar en çok 2. ayda görülmekteydi fakat 1 yılı aşkın semptomu devam eden olgularımız da mevcuttu.

Sonuç: Çalışmamızda, COVID-19 hastalarının çoğunluğunun en az bir semptomu vardı. Hastane yatışı gereken hastalarda, ortalama yaş daha yüksek ve ateş ve dispne en sık görülen semptomlardı. Post-COVID dönemde semptomların uzun süre devam edebileceği gözlendi, bu nedenle hastaların uzun dönem takibi faydalı olabilir.

Anahtar Kelimeler: COVID-19, hastane yatışı, semptom

Introduction

Since the first case was detected in Wuhan, China in 2019, the Coronavirus disease-2019 (COVID-19) has affected 243 million people around the World up to February 2021 (1). Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2, which is the cause of COVID-19, affects the upper and lower respiratory tract and causes a high viral load in the upper respiratory tract. The rapid human-to-human spread of SARS-CoV-2 causes a wide spectrum of clinical manifestations in patients with COVID-19 (2).

In a study involving 11 centers in the United States of America, the most common symptoms related to COVID-19 infection were fever, body aches, headache, dyspnea, weakness, nausea, diarrhea, respectively. It has been shown that symptoms such as loss of taste and smell, sore throat, and headache are more common in outpatients, while dyspnea symptoms are more common in hospitalized patients. Fever, muscle pain, cough was observed at similar rates in both groups (3). Symptoms can persist in the post-COVID period in many patients. In outpatients, symptoms persisted in 27.8% at 4 months and 34.8% at 7 months of the post-COVID period (4). In hospitalized patients, the symptoms can continue in 94.9% of the patients in the post-COVID period (5).

In our study, the aim was to represent the initial and predominant symptoms of COVID-19 patients diagnosed by polymerase chain reaction (PCR) test and to investigate the relation of symptoms on hospitalization and ongoing symptom development in the post-COVID period.

Material and Methods

This cross-sectional questionnaire study was conducted at a tertiary chest diseases hospital between August and October 2021. A questionnaire was sent online to patients who had COVID-19 before the survey date. Inclusion criteria were: (1) Being aged 18 or higher, (2) COVID-19 infection diagnosis by PCR test, (3) agreeing to participate in the study. A voluntary consent form was added to the questionnaire and those who were approved were included in the study. Eligible patients were asked to fill out a questionnaire consisting of 20 questions. The questionnaire included the following: Demographic characteristics, diagnosis date, initial symptoms at diagnosis, predominant symptoms before hospital admission, treatments, presence of hospitalization requirement, ongoing symptoms after the treatment, and symptom duration.

Ethical approval for this study was obtained from the University of Health Sciences Türkiye Hamidiye Faculty of Medicine Ethics Committee with the decision number 5/15 on 05.02. 2021.

Statistical Analysis

The analysis of the data was carried out with the SPSS 25 package program. Frequency and percentage values for qualitative variables, arithmetic mean and standard deviation values for quantitative variables are presented. The chi-square test and Fisher's Exact test were used for comparisons between the two qualitative variables. An independent sample t-test was used for comparisons between qualitative variable categories in terms of quantitative variables. In determining the factors affecting hospitalization, variables that were found significantly as a result of pairwise comparisons were evaluated by binary logistic regression analysis. The type I error rate was taken as 0.05 in the study.

Results

A total of 596 patients questionnaire were included in the study. Demographic data of the patients and their effect on hospitalization are summarized in Table 1. The hospitalization rate was 16.1% (n=96). Thirteen (2.2%) patients were treated at the intensive care unit (ICU) and eight (1.3%) patients had been intubated. Advanced age, male gender, and comorbidity were found to be factors that increased hospitalization (p<0.01). In comorbidities, patients with chronic obstructive pulmonary disease (COPD) were

hospitalized more, while patients with diabetes received more outpatient treatment (Table 1).

In the questionnaire, patients were asked about the initial symptoms they experienced due to COVID-19 infection: High fever in 70 patients (25.3%), loss of taste and smell in 47 patients (16.2%), cough in 45 patients (15.4%), fatigue in 102 patients (33.6%), myalgia in 132 patients (42.8%) and headache in 88 patients (28.8%) were detected. These are the predominant initial symptoms. Twenty-two patients (7.6%) had no symptoms at the beginning.

Another question was about the predominant symptom that compels the patient to apply to the hospital. The most common predominant symptoms, the effect of symptom status on hospitalization, and differences between genders are given in Table 2. Fever and dyspnea are the most common predominant symptoms. While dyspnea was significantly higher in hospitalized patients, fever was more common in non-hospitalized patients. Fever and fatigue were mostly seen among females, while myalgia was the most prominent among men. When the predominant symptom status and age were considered together, it was found that the hospitalization rate was statistically significantly higher in those with advanced age and fever and those with advanced age and dyspnea (p<0.001) (Table 3).

Logistic regression analysis was performed to determine the factors affecting hospitalization status. As a result of the analysis, while the result of the Hosmer and Lemeshow test was 0.630, all p-values of the model were found to be <0.001. Being male was found to be a 1.961-fold risk factor (p=0.006), having a complaint of predominant dyspnea was a 9.752-fold risk factor (p=0.012), and a 1-unit increase in age was found to be a 1.052-fold risk factor (p<0.001) (Table 4).

Four hundred and seventy-seven patients (80%) had post-COVID symptoms. Symptom duration can be seen in Figure 1. Most patients (n=176-38.5%) had symptoms between the first and second months after COVID-19 infection. The most common post-COVID symptoms and duration of symptoms were summarized in Table 5. Getting tired easily, fatigue, myalgia, and cough were the most common post-COVID symptoms. The longest-lasting symptoms were: Dyspnea, fatigue, myalgia, and getting tired easily, respectively. It was found that dyspnea and getting tired easily were found to be statistically more common in hospitalized patients compared to those without hospitalization (p<0.001).

Discussion

In our study, advanced age, male gender, and comorbidities were found to be risk factors for hospitalization of COVID-19 patients. In comorbidities, COPD was a statistically significant risk factor for hospitalization. Dyspnea was the

Table 1. Demographic characteristics of COVID-19 patients

	Total n (%)	Hospitalization No n (%)	Hospitalization Yes n (%)	p
Age (mean ± SD)	38.93±12.07	37.48±11.46	46.47±12.40	**<0.001**
Gender				
Male	234 (39.3)	182 (77.8)	52 (22.2)	**<0.001**
Female	362 (60.7)	318 (87.8)	44 (12.2)	
Comorbidities				
No	398 (66.8)	348 (87.4)	50 (12.6)	**0.001**
Yes	198 (33.2)	152 (76.8)	46 (23.2)	
Asthma	38 (6.4)	33 (86.8)	5 (13.2)	0.777
COPD	7 (1.2)	3 (42.9)	4 (57.1)	**0.014**
Coronary artery disease	13 (2.2)	10 (76.9)	3 (23.1)	0.757
Diabetes	33 (5.5)	22 (66.7)	11 (33.3)	**0.012**
Hypertension	56 (9.4)	44 (78.6)	12 (21.4)	0.344
Chronic kidney disease	2 (0.3)	1 (50)	1 (50)	0.732
Congestive heart failure	3 (0.5)	2 (66.7)	1 (33.3)	0.979
Malignancy	2 (0.3)	1 (50)	1 (50)	0.732
Rheumatologic disease	39 (6.5)	31 (79.5)	8 (20.5)	0.583
Other	70 (11.7)	52 (74.3)	18 (25.7)	**0.031**

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, COVID-19: Coronavirus disease-2019

major predominant symptom and statistically significant symptom for hospitalization. Also, the hospitalization rate was higher in those with advanced age and predominant fever. The shortness of breath, fatigue, muscle pain, and cough were the most common post-COVID symptoms and the post-COVID symptoms were mostly seen in the second month.

Over 90% of patients with COVID-19 infection are symptomatic and have at least one symptom in several studies (3,6,7). Similar to the literature, 92.4% of the cases

Table 2. Effect of predominant symptoms to hospitalization and differences between genders

Dominant symptom		Hospitalization No n (%)	Hospitalization Yes n (%)	p	Male n (%)	Female n (%)	p
Fever	No	380 (85.8)	63 (14.2)	0.045	192 (82.1)	251 (69.3)	**0.001**
	Yes	120 (78.4)	33 (21.6)		42 (17.9)	111 (30.7)	
Loss of smell, taste or both	No	498 (83.8)	96 (16.2)	1.000	232 (99.1)	362 (100)	0.300
	Yes	2 (100)	0 (0)		2 (0.9)	0 (0)	
Cough	No	500 (84)	95 (16)	0.356	233 (99.6)	362 (100)	0.826
	Yes	0 (0)	1 (100)		1 (0.4)	0 (0)	
Fatigue	No	452 (83.4)	90 (16.6)	0.394	221 (94.4)	321 (88.7)	**0.024**
	Yes	48 (88.9)	6 (11.1)		13 (5.6)	41 (11.3)	
Myalgia	No	490 (83.6)	96 (16.4)	0.325	226 (96.6)	360 (99.4)	**0.020**
	Yes	10 (100)	0 (0)		8 (3.4)	2 (0.6)	
Skin rash	No	495 (83.9)	95 (16.1)	1.000	231 (98.7)	359 (99.2)	0.903
	Yes	5 (83.3)	1 (16.7)		3 (1.3)	3 (0.8)	
Dyspnea	No	498 (84.7)	90 (15.3)	**<0.001**	231 (98.7)	357 (98.6)	1.000
	Yes	2 (25)	6 (75)		3 (1.3)	5 (1.4)	

Table 3. Effect of predominant symptom and age together to hospitalization

Dominant symptom	Hospitalization No $\bar{x}$ ± SD	Hospitalization Yes $\bar{x}$ ± SD	t	p
Fever	36.52±11.14	46.11±11.91	-8.928	**<0.001**
Fatigue	38.92±12.18	39.09±10.95	-0.101	0.919
Myalgia	38.98±12.09	36.4±11.1	0.669	0.504
Skin rash	38.94±12.1	38.33±9	0.122	0.903
Dyspnea	38.7±11.9	56.13±12.5	-4.111	**<0.001**

SD: Standard deviation

Table 4. Results of logistic regression analysis to determine the factors affecting hospitalization status

	B	S.E.	Wald	p	OR (95% CI)
Gender (ref: Female)	-0.673	0.247	7.459	**0.006**	1.961 (0.209-3.179)
COPD	0.739	0.907	0.664	0.415	2.094 (0.354-12.39)
Diabetes	0.497	0.476	1.089	0.297	1.643 (0.646-4.176)
Other comorbidities	0.606	0.324	3.5	0.061	1.833 (0.972-3.457)
Fever	0.007	0.319	0.001	0.982	1.007 (0.539-1.882)
Dyspnea	2.277	0.909	6.278	**0.012**	9.752 (1.642-57.911)
Age	0.051	0.012	19.491	**<0.001**	1.052 (1.029-1.076)
Constant	-1.865	0.954	3.821	0.051	0.155

COPD: Chronic obstructive pulmonary disease, OR: Odds ratio, CI: Confidence interval

had an initial symptom in our study. Previous studies reported that, the most common symptoms were: Fever, myalgia, weakness, dyspnea, loss of taste and smell, and headache, respectively. Although gastrointestinal symptoms such as diarrhea were observed at rates ranging from 5% to 30% in studies, diarrhea and GIS symptoms were not observed in our study (3,8,9).

Fever and fatigue were mostly seen in females, myalgia was mostly seen in men. There are different results in the studies about gender and symptoms. In the study of Tandan et al. (10), while malaise/body soreness, cough, anorexia, and headache were more common in men, sorethroat and rhinorrhea was more common in women. Fever was seen equally in both genders. In another study, while loss of smell, headache, nasal obstruction, throat pain, and fatigue were mostly seen in females, males more from cough and fever. Differences between the genders have been attributed to factors related to different immune systems, steroid hormones, and sex hormones. Immune regulatory genes on the X-chromosome have been shown to cause lower viral load and less inflammation than men (11).

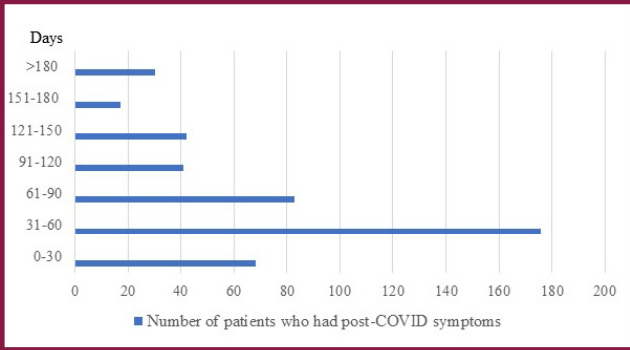

Figure 1. Number of patients who had post-COVID symptoms according to post-COVID days
COVID-19: Coronavirus disease-2019

Table 5. Post-COVID symptoms

Post-COVID symptoms	n (%)	Symptom duration-day (Median/min-max)
Fever	1 (0.2)	-
Loss of weight	70 (11.7)	51 (4-239)
Anorexia	14 (2.3)	58 (31-153)
Diarrhea	4 (0.7)	-
Cough	71 (11.9)	43 (4-135)
Fatigue	152 (25.5)	55 (9-354)
Myalgia	114 (19.1)	66 (10-354)
Headache	56 (9.4)	67 (9-274)
Skin rash	11 (1.8)	43 (24-267)
Dyspnea	65 (10.9)	71 (19-354)
Getting tired easily	197 (33.1)	55 (9-290)
Other	56 (9.4)	51 (11-273)
No symptom	119 (20)	59 (6-358)

COVID: Coronavirus

In studies examining the relationship between symptoms and hospitalization, it was found that dyspnea was more common in patients who required hospitalization. Fever was generally found at similar rates in the two groups (3,6,7). In our study, predominant dyspnea was the most common symptom in hospitalized patients, while predominant fever was more common in non-hospitalized patients. However, when associated with age, it was found that hospitalization was more common in those with both dyspnea and fever symptoms in advanced age.

As summarized in the review of Gallo Marin et al. (12), advanced age, male gender, and comorbidities such as diabetes, hypertension, respiratory diseases (especially COPD) are related to hospital and intensive care stays in COVID-19 disease, and the disease progresses more seriously in these patients. In our study, hospitalization was higher in patients with advanced age and male gender. Considering the comorbidities, COPD was associated with a statistically significant level of hospitalization. Unlike the data in the literature, diabetes was observed more frequently in patients without hospitalization. This may be due to the fewer number of hospitalized patients in our study.

Iqbal et al. (5) showed that 94.9% of patients experienced at least one post-COVID symptom after COVID infection and the most commonly observed symptom was fatigue. In a different study, the most common post-COVID symptoms in non-hospitalized patients were: Shortness of breath, anosmia, ageusia, and fatigue, respectively (4). In our study, 80% of patients had post-COVID symptoms and the most common post-COVID symptoms were getting tired easily and fatigue, similar to the literature. In a study in which SARS cases were followed for around 4 years, it was observed that 40.3% of patients had chronic fatigue complaints (13). The other most common post-COVID symptom seen in these studies was dyspnea/shortness of breath, which was still observed in the sixth month of studies (5,14). In our study, although the duration of symptoms was most intense in the second month of post-COVID, there were cases with complaints of up to one year.

In a study conducted in China, post-COVID-19 patients who received and did not receive pulmonary rehabilitation were evaluated and after 6 months of pulmonary rehabilitation, a significant increase was found in the 6-minute walking test in the group receiving pulmonary rehabilitation (15). Close follow-up and, if necessary, rehabilitation may be helpful

against fatigue and dyspnea symptoms after COVID-19 infection.

Study Limitations

Our study has some limitations. Firstly, it was a single-center study. The population of the study was not randomized and consisted mostly of non-hospitalized patients. Since our study was a questionary study, the results were based on the answers given by the patients, and data such as radiological or pulmonary function tests could not be used to confirm these results. We also do not have the data for COVID-19 variants.

Conclusion

Dyspnea is the most common symptom with hospitalized COVID-19 patients. Advanced age, male gender, and COPD in comorbidities were found to be risk factors for hospitalization. In the post-COVID period, fatigue, and dyspnea can be seen in many patients and can last for a long time.

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Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Türkiye Hamidiye Faculty of Medicine Ethics Committee with the decision number 5/15 on 05.02. 2021.

Informed Consent: A voluntary consent form was added to the questionnaire and those who were approved were included in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D., Ş.G., M.Ç., A.S.K., U.İ., E.Ç., Concept: B.D., Ş.G., M.Ç., U.İ., K.N.B., E.Ç., Design: B.D., Ş.G., M.Ç., A.S.K., U.İ., K.N.B., E.Ç., Data Collection or Processing: B.D., M.Ç., U.İ., K.N.B., Analysis or Interpretation: B.D., Ş.G., M.Ç., A.S.K., K.N.B., E.Ç., Literature Search: B.D., Ş.G., A.S.K., K.N.B., Writing: B.D., Ş.G., M.Ç., E.Ç.

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