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Persistent Symptoms After Discharge of COVID-19 patients

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ABSTRACT

Objective: Many observational studies have reported high morbidity and mortality associated with COVID-19 during hospitalisation. This study aimed to examine the long-term symptoms and related factors of patients hospitalised due to COVID-19.

Materials and Methods: Clinical and laboratory characteristics of 266 patients who were followed up in the hospital with the diagnosis of COVID-19 were recorded. The patients were followed for an average of 14 weeks after discharge. The discharged patients were surveyed for their symptoms by calling.

Results: On average, 14 weeks after being discharged, it was found that a least one symptom persisted in 27.4% (n =73) of 266 patients. The three most common symptoms after discharge were 38.3% (n = 28) cough, headache (36.9%, n = 27), shortness of breath (27.3%, n = 20), respectively. In multivariate analysis, it was found that symptoms persist more in patients with high CRP (C-reactive protein) and ferritin during hospitalisation (p: 0.03; p: 0.005, respectively).

Conclusion: After COVID-19, it was observed that complaints continued after discharge in a significant number of patients. During hospitalisation, high ferritin and CRP levels were found to be associated with the persistence of symptoms. It was considered that symptoms associated with COVID-19 persist more in those with a high inflammatory response.

Keywords: Covid-19, Inflammatory Response, SARS CoV-2, Post-COVID-19 syndrome, Persistent Symptoms.

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INTRODUCTION

More than a year has passed since the beginning of the COVID-19 pandemic, and we are learning more about the long-term effects of the disease. While many patients recover completely, some continue to experience fatigue, dyspnea, cough, joint pain, and chest pain for weeks or even months (1).The UK National Institute for Health and Care Excellence (NICE) defined that COVID-19 in three categories according to persistence duration of symptoms:

Acute-COVID: Persist for up to 4 weeks,

Ongoing Symptomatic COVID: 4-12 weeks,

Post-COVID: syndrome continues for more than 12 weeks and cannot be explained with an alternative diagnosis (2).

Although information about the long-term effects of COVID-19 is quite limited, it has been reported that some symptoms such as weakness, shortness of breath and body pain persist even after months (2,3). Our study aimed to examine the persistence of symptoms of patients who were followed up in the hospital with a diagnosis of COVID-19 three months after discharge and possible related factors.

MATERIALS AND METHODS

Study design and participants

The study included 266 probable and definite cases older than 18 years of age who were hospitalised with the diagnosis of COVID-19 between 01.07.2020–1.10. 2020. Case definitions were made according to the World Health Organization definitions. A positive SARS-CoV-2 "real-time" reverse transcriptase chain reaction (RT-PCR) test result in the respiratory tract sample of the patient, as a definite case; the presence of appropriate clinical complaints and the detection of findings compatible with viral pneumonia in thorax computed tomography (CT), although two SARS-CoV-2 RT-PCR tests were negative in the patient, were accepted as possible cases (4). Hydroxychloroquine or favipiravir was started in patients who were evaluated together with clinical, laboratory and radiological findings. Dexamethasone 8 mg or equivalent was started in patients with oxygen saturation (spo2) <90% at the time of admission or follow-up. Patients who developed secondary bacterial infections were evaluated in daily visits and antibiotherapy was started when necessary.

Data Collection

Demographic data of the patients, underlying diseases, laboratory and computerised thoracic tomography (CT) findings were obtained retrospectively from the hospital information system. Patients' admission date, discharge, intensive care transfer/death date, contact history, smoking, symptoms during admission, vital signs at the time of admission, as well as laboratory tests and results were recorded. The highest ferritin and CRP (C-reactive protein) levels and the lowest lymphocyte counts were also recorded during hospitalisation. Hydroxychloroquine, favipiravir, steroid and antibiotic treatments for the diagnosis of secondary infection were recorded. A telephone survey was conducted to evaluate the persistent symptoms of the patients (Supplement).

Statistical analysis

In our study, the 21.0 version of the SPSS (Statistical Package for the Social Sciences) program (IBM, Armonk, NY, USA) was used to analyse the data. Descriptive statistics are as mean ± standard deviation or median (minimum-maximum) for discrete and continuous numerical variables; categorical variables were expressed as the number of cases and percentage (%). Cross-table statistics were used to compare categorical variables (Chi-square, Fisher). Normally distributed parametric data were compared with Student t-test and ANOVA, and non-parametric data that did not suitable to normal distribution were compared with Mann Whitney U and Kruskal Wallis tests. Comparisons between multiple groups were made with Post Hoc Tukey analysis. Multivariate logistic regression analysis was used to evaluate the relationship of clinical and labo-

HIGHLIGHTS

- After COVID-19, it was observed that complaints continued after discharge in a significant number of patients.
- The three most common symptoms after discharge were cough, headache, shortness of breath.
- Higher CRP levels at admission and higher ferritin values in their follow-up suggested that symptoms continued at a higher rate after COVID-19 in those who showed high inflammatory activity.
- During hospitalization, high ferritin and CRP levels were found to be associated with persistence of symptoms.

Table 1. Clinical characteristics of the patients with COVID-19.

	Clinical Variables	n	%
Gender	Male	129	48.5
	Female	137	51.5
Age	< 65 year	176	66.2
	> 65 year	90	33.8
PCR[1]	Negative	73	27.4
	Positive	193	72.6
ICU[2]	No	255	95.9
	Yes	11	4.1
Tobacco usage	Absent	236	88.7
	Present	30	11.3
HT[3]	Absent	156	58.6
	Present	110	41.4
DM[4]	Absent	193	72.2
	Present	73	27.4
COPD/Asthma[5]	Absent	217	81.6
	Present	48	18.0
Coronary artery disease	Absent	233	87.6
	Present	33	12.4
Congestive heart failure	Absent	255	95.9
	Present	11	4.1
Malignancy	Absent	264	99.2
	Present	2	0.8
Acute renal failure*	Absent	263	98.9
	Present	3	1.1
Any Comorbidity	Absent	112	42.1
	Present	154	57.9

1. PCR: Polymerase Chain Reaction **2.** ICU: İntensive Care Unit **3. HT:** Hypertension **4. DM:** Diabetes mellitus **5. COPD:** Chronic Obstructive Pulmonary Disease *during the hospitalisation

ratory parameters with persistent symptoms. The statistical significance was set as $p < 0.05$.

RESULTS

Totally 266 patients, 137 women (51.5%), were included in the study who were called by phone after an average of 99.80 ± 26.16 days after discharge. While 9.8% of the patients were defined as Ongoing-Symptomatic COVID-19, 90.2% were defined as Post-COVID-19 syndrome. The mean age of the patients was 56.96 ± 16.62 (range = 14-92), while 33.8% (n = 90) were 65 years and older. There was at least one comorbidity in 57.9% (n = 157/266) of the patients. Among the accompanying comorbidities, hypertension (HT) was the most common (n = 110) with a rate of 41.4%; followed by diabetes (n = 73) with 27.4% and COPD (Chronic Obstructive Pulmonary Disease) / Asthma with 18.0% (n = 48). The need for intensive care admission developed in 4.1% of the patients (n = 11). In the treatment of the cases, 50.4% (n = 134) hydroxychloroquine and 65.8% (n = 175) favipiravir were used (Table 1). The symptoms of the patients during hospitalisation are summarized in Table 2.

While at least one symptom was observed in 19.9% of the patients (n=53) after discharge, it was observed that ≥3 symptoms persisted in 7.5% (n = 20). While the most common ongoing symptom was cough (38.3%, n = 28); headache (36.9%, n = 27), dyspnea (27.3%, n = 20), anorexia (23.2%, n = 17), weakness (17.8%, n = 13), myalgia (16.4%, n = 12), followed respectively (Table 2).

Persistent symptoms were observed with a rate of 57.9% in cases with comorbidity; the most common symptom was reported in patients were hypertension (HT) with a rate of 41.1%. This was followed by patients who previously diagnosed with DM (Diabetes mellitus) at 26.4% and COPD/Asthma at 15.3%, respectively. No significant relationship was found between the presence of persistent symptoms and comorbidities, CT involvement severity, advanced age, gender, smoking, PCR positivity, ICU admission need, and treatments (Table 3).

We present clinical parameters and laboratory findings of patients at the time of admission to the hospital in Table 4.

Table 2. Prevalence of symptoms during the infection and at follow-up after 12 weeks patients with COVID-19.

During Hospitalisation	n	%	Follow-Up	n	%
Fatigue	177	66.5	Cough	28	38.3
Cough	158	59.4	Headache	27	36.9
Shortness of breath	134	50.4	Shortness of breath	20	27.3
Fever	94	35.3	Chest pain	17	23.2
Headache	51	19.2	Fatigue	13	17.8
Nausea	35	13.2	Anorexia	17	23.2
Diarrhea	16	6.0	Myalgia	12	16.4

In the univariate analysis, the highest ferritin values during hospitalisation were found to be significantly higher in patients with persistent symptoms (p: 0.04). However, in patients with persistent symptoms, the mean ferritin values are higher, and the lowest mean lymphocyte values are lower, and the statistics tend to be significant. In the multivariate analysis, a statistically significant relationship was found between the high CRP level detected at the time of admission and the presence of persistent symptoms with the height of ferritin detected in the patient's follow-up (p-value = 0.03 and 0.005, respectively) (Table 5).

DISCUSSION

It has long been known that some symptoms persist for a long time after viral infections. In a study conducted by Magnus et al. In Norway during the influenza A (H1N1) pandemic in 2009, the incidence rate of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) was found to be 2.08 per 100,000 people/months. It was found that this rate was higher in patients younger than 30 years old, and researchers thought that the development of ME/CFS was associated with the immune response to influenza (5). It has been reported that patients with SARS (Severe acute respiratory syndrome) continue to have symptoms such as chronic fatigue, myalgia, dysfunction or depression in the long term. It has been reported that these ongoing symptoms are similar to chronic fatigue syndrome and fibromyalgia (6). In a study in which 1733 patients were evaluated, patients who do not need oxygen, those who need intense oxygen and those who need mechanical ventilation were evaluated separately, and it was determined that 76% of the patients showed at least one symptom at the end of six months. Fatigue or muscle weakness (63%), difficulty sleeping (26%), and hair loss (22%) come first among these symptoms (7). In another study evaluating persistent symptoms after COVID-19, symptom severity was classified as mild, moderate, or severe. The most common persistent symptoms are reported as myalgia (60.0%), arthralgia (57.2%), restriction of daily activities (57.0%), sleeping troubles (50.9%), followed by anorexia (42.6%), chest pain (32.6%), gastritis (32.3%) %), cough (29.3%) and dyspnea (29.1%) (8). In this study, we observed that the symptoms of COVID-19 continued even after an average of three months after hospitalisation in a significant portion of the patients, coherent with previous studies. The most common persistent symptoms of COVID-19 were cough, headache, shortness of breath and loss of appetite and fatigue. Although the retrospective design, the survey method, being a single centre study, and the low number of patients are important limitations of our study, our findings were consistent with previous studies.

Table 3. Comparison of persistent symptom frequency in cases according to clinical variables.

	Clinical Variable	Persistent Symptoms	
		Non-Existent n (%)	Exists n (%)
Age	< 65 year > 65 year	126 (71.6) 67 (74.4)	50 (28.4) 23 (25.6)
Gender	Male Female	88 (68.2) 105 (76.6)	41 (31.8) 32 (23.4)
Smoking	Absent Present	170 (72) 23 (76.7)	66 (28) 7 (23.3)
PCR	Negative Positive	49 (67.1) 144 (74.6)	24 (32.9) 49 (25.4)
Comorbidity	Absent Present	79 (70.5) 114(74)	33 (29.5) 40 (26)
HT[1]	Absent Present	113 (72.4) 80 (72.7)	43 (27.6) 30 (27.3)
DM[2]	Absent Present	139 (72.4) 54 (74)	53 (27.6) 19 (26)
COPD/Asthma[3]	Absent Present	156 (71.9) 37 (77.1)	61 (28.1) 11 (22.9)
Coronary artery disease	Absent Present	171 (73.4) 22 (66.7)	62 (26.6) 11 (33.3)
Congestive heart failure	Absent Present	186 (72.9) 7 (72.6)	69 (27.1) 4 (27.4)
Malignancy	Absent Present	191 (72.3) 2 (100)	73 (27.7) 0 (0.0)
Acute renal failure	Absent Present	191 (72.6) 2 (66.7)	72 (27.4) 1 (33.3)
CT[4]	Mild Severe	148 (74.4) 43 (67.2)	51 (26.6) 21 (32)
ICU[5]	No Yes	185 (72.5) 8 (72.7)	70 (27.5) 3 (27.3)

1. HT: Hypertension **2. DM:** Diabetes mellitus **3. COPD:** Chronic Obstructive Pulmonary Disease **4. CT:** Computed Tomography **5. ICU:** Intensive Care Unit
*Fisher's exact test (2-sided)

In inflammatory diseases, ferritin increase is an important marker in terms of macrophage activation and hyperinflammatory response as well as being an acute phase reactant (9,10). However, the increase in ferritin in influenza has been associated with a poor prognosis (11). In a meta-analysis in which 5350 patients with COVID-19 were included; along with acute phase reactants such as procalcitonin and CRP, increased ferritin has been shown to be associated with poor prognosis (12). In our study, the mean CRP and maximum ferritin levels during hospitalisation were found to be higher in patients with persistent symptoms. This indicates that the symptoms continue at a higher rate in patients with a more inflammatory response. Cytokine storm observed in COVID-19 is an important component of severe symptoms and mortality, similar in SARS, MERS (Middle East respiratory syndrome), and influenza (13). In cases with high CRP and ferritin values, a higher cytokine response may have caused the symptoms to persist longer. The elevation of CRP and ferritin in the disease course may be considered as a predictor of persistent symptom development. There are conflicting results in the literature showing the relationship between the presence of comorbidity and persistent symptoms. Patients diagnosed with COVID-19 with underlying health problems or comorbidities tend to progress rapidly and severely. For example, patients with HT or DM were found to have higher intensive care transfer and mortality rates (14). In a study in which 150 non-critical COVID-19 patients with pneumonia but did not need oxygen support were evaluated, it was found that symptoms persist on the 30th and 60th days in two-thirds of the patients, the most common symptoms were anosmia/ageusia 55 (64.0%), fatigue/weakness (40% 52/130), dyspnea 30% (39/130) respectively. Symptoms were seen more frequently between the ages of 40-60, but as in our study, no relationship was found with comorbidity (15). In another study evaluating persistent symptoms, more persistent symptoms were found in patients with comorbidities (8). In our study, no relationship was found between the presence of comorbidity and persistent symptoms.

Table 4. Comparison of persistent symptom frequency in cases according to laboratory findings patients with COVID-19.

	Admission	Persistent symptoms	
		Non-Existent	Exists
Body Temperature (°C)	36.80±0.70	36.83±0.69	36.72±0.63
Oxygen saturation (SpO2)	89.30±5.89	89.53±5.71	88.68±6.35
Systolic BP[1] (mmHg)	118.4±14.41	119.1±14.63	116.6±13.76
Diastolic BP[1] (mmHg)	72.19±10.09	72.78±10.11	70.69±9.94
Hemoglobin (g/L)	13.69±1.87	13.72±1.66	13.62±2.34
WBC[2] (10^6/uL)	7.256±1.003	7.398±1.162	6.879±3.191
Neutrophile (x10^9/L)	4.939±2.797	4.852±2.701	5.170±3.043
Lymphocyte (x10^9/L)	1.422±0.763	1.454±0.744	1.337±0.811
Neutrophil/Lymphocyte Ratio	4.67±4.93	4.41±4.34	5.36±6.22
BUN[3] (mg/dL)	42.85±32.86	41.91±32.55	45.35±33.75
Creatinine (mg/dL)	1.05±0.68	1.04±0.65	1.08±0.77
Glucose (mg/dL)	133.4±61.07	130.6±56.88	141.0±70.91
AST[4] (U/L)	33.48±17.87	32.94±16.57	34.91±20.97
ALT[5] (U/L)	28.27±18.12	27.52±17.14	30.24±20.48
GGT[6] (IU/L)	48.32±56.94	47.16±53.99	51.34±64.31
LDH[7] (mg/dL)	297.0±126.1	287.7±113.8	321.3±152.0
CRP (mg/dl)	55.49±93.11	50.41±46.85	57.42±105.56
Ferritin (ng/mL)	290.8±293.4	270.2±277.4	344.7±327.7
D-dimer (µg/mL)	0.63±1.20	0.55±1.04	0.83±1.51
Troponin (ng/l)	7.38±22.01	5.96±10.56	11.13±38.23
Highest Ferritin	389.0±362.2	361.2±342.5	462.3±402.9
Highest CRP[8]	68.15±50.55	66.72±50.75	71.93±50.17
Lowest Lymphocyte	1.220±0.655	1.271±0.695	1.085±0.518

1. BP: Blood pressure **2. WBC:** White Blood Cell **3. BUN:** Blood Urea Nitrogen
4. AST: Aspartate aminotransferase **ALT:** Alanine aminotransferase
6. GGT: Gamma-Glutamyl Transpeptidase **7.LDH:** Lactate Dehydrogenase
8. CRP (C-Reactive Protein)
* $p<0.05$ statistically significant. ** Mann-Whitney U =Alive-Exitus

Although it is known that the disease has a severe course in patients with comorbidities and that the presence of comorbidity is associated with a poor prognosis (14, 16), this patient group may not have persistent symptoms because of the absence of a strong immune response.

Although COVID-19 disease has a high mortality, there is little data on the long-term course of patients who recover. In our study, we observed that some complaints continued (after 12 weeks) in a significant portion of the patients hospitalised for COVID-19. Higher CRP levels at admission and higher ferritin values in their follow-up suggested that symptoms continued at a higher rate after COVID-19 in those who showed high inflammatory activity. Therefore, it is important to plan long-term follow-up of patients diagnosed with COVID-19 with a multidisciplinary approach.

Table 5. Table 5. Multivariate analysis for the persistence of symptoms patients with COVID-19.

	Odds ratio	Confidence interval	P value
Age	1.239	0.56-1.24	0.563
Smoking	2.185	0.16-2.18	0.163
ICU admission	0.404	0.34-0.40	0.345
Favipiravir Treatment	0.634	0.29-0.63	0.293
Congestive Heart Failure	3.994	0.10-3.994	0.100
Hypertension	1.034	0.92-1.03	0.926
Acute renal failure	0.317	0.20-5.28	0.317
Highest Ferritin Level	1.002	1.001-1.002	**0.005***
CRP	0.99	0.98-0.99	**0.029***
D-Dimer	0.093	0.09-1.26	0.093

Ethical Approval: Ağrı Training and Research Hospital Ethics Committee approved the study with the decision number of 30 (11.12.2020).

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SUPLEMENT: POST COVID SYNDROME QUESTIONNAIRE

(For patients with ongoing symptoms following Coronavirus)

- This questionnaire was prepared to evaluate the patients' symptoms of COVID-19 that continued 12 weeks after discharge.
- What was your health like before you had Covid-19?

A. I did not have any restrictions on my life

B. I had some complaints:

Cough	Yes ☐	No ☐
Headache	Yes ☐	No ☐
Shortness of breath	Yes ☐	No ☐
Chest pain	Yes ☐	No ☐
Fatigue	Yes ☐	No ☐
Anorexia	Yes ☐	No ☐
MyalgiaYes	Yes ☐	No ☐

- Please tick the description in each column how the patient currently feels following conversation with Clinician

Yes ☐ No ☐

1. Do you still have a cough after being discharged?

Yes ☐ No ☐

2. Do you still having headache after being discharged?

Yes ☐ No ☐

3. Do you still having shortness of breath after being discharged?

Yes ☐ No ☐

4. Do you still having chest pain after being discharged?

Yes ☐ No ☐

5. Do you still have fatigue after being discharged?

Yes ☐ No ☐

6. Do you still having anorexia after being discharged?

Yes ☐ No ☐

7. Do you still have myalgia after being discharged?

Yes ☐ No ☐