

Evaluation of hospital admissions in the first 6 months after the COVID-19 discharge

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ABSTRACT

Aims: Although COVID-19 disease has many effects on patients after recovery, it is not known whether these effects are part of the recovery process or trigger other diseases. This study has aimed to investigate whether ferritin, which is used as an acute phase reactant to determine the severity and prognosis of the disease, has a role in determining the symptoms that occur after the disease.

Methods: The study was conducted with 300 patients who were hospitalized with PCR positive and lung involvement. Patients, hospital admissions and initial ferritin levels were recorded within 6 months of discharge. It was examined whether there was a relationship between ferritin levels and the re-admission reasons.

Results: 177 (59.0) people had no symptoms during the six-month period and 123 (41.0) patients were admitted to the hospital due to various symptoms. 6 (2.0) of the patients became ex within six months after discharge. The most common symptoms in patients were 28 (9.3) shortness of breath, 22 (7.3) myalgia, 15 (5.0) chest pain, 10 (3.3) headache and 10 (3.3) palpitations, respectively. Ferritin levels were found to be high in those with no symptoms and low in those with symptoms.

Conclusion: Determining the symptoms, re-admissions, mortality rates and predictors that will guide COVID -19 is very important for the recognition, treatment and follow-up of this disease after discharge. More studies are needed to make a prediction according to ferritin levels in the process after recovery from COVID-19.

Keywords: COVID-19, symptom, ferritin

INTRODUCTION

COVID-19 disease, which is caused by the SARS-CoV-2 virus and affects the respiratory system, is a highly contagious disease that has caused many deaths all over the world. The healing process of the disease may cover a long period. Clinical studies have shown that this disease has also many effects after recovery.^{1,2} For this reason, at the beginning of acute COVID-19 illness, management focuses on detecting and treating complications, while after the acute phase some patients require evaluation and management for persistent or new symptoms.

Many terms have been used to describe long-term symptoms following COVID-19 disease.^{3,4} "Chronic COVID-19", "post-acute sequelae of SARS-CoV-2 infection (PASC)", "post-COVID syndrome" are among these terms. It has not been determined whether these symptoms and persistent problems are a new syndrome specific to COVID-19 or they overlap with recovery from similar diseases.⁵

It has been determined that the cytokine storm is the factor affecting the course of the disease in the immunopathological mechanism of COVID-19 disease and many studies have been conducted on this issue. In these studies, markers such as serum ferritin, IL-6, D-dimer, and lactate dehydrogenase were found to be associated with poor prognosis and mortality.⁶ Hyperferritinemia caused by excessive inflammation due to infection is associated with admission to the intensive care unit (ICU) and high mortality. Also, it is an indicator of recognizing high-risk patients to guide the therapeutic intervention to control inflammation.⁷

We have not found a study that shows whether there is an association between ferritin level and symptoms appear after the disease. Therefore, in our study, we have aimed to examine the reasons for patients' re-admission to the hospital within 6 months after COVID-19 disease with pulmonary involvement and the relationship of these admissions with ferritin levels measured at the beginning of the disease.

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METHODS

The study was initiated with the approval of the Kastamonu University Clinical Researches Ethics Committee (Date: 06/05/2021, Decision No: 2020-KAEK-143-83). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In general, a positive PCR test was used to identify the disease.⁸ but in our study we included patients with both PCR-positive and lower respiratory tract involvement, where the disease was severe and the viral load was high. In our study, the records of patients who applied to the Kastamonu Training and Research Hospital COVID-19 Outpatient Clinic between April and June 2020 and were hospitalized after showing lung involvement on computed tomography were reviewed, and 300 PCR positive patients were evaluated.

According to the management of patients at the beginning of the pandemic, the hospital admission records made within 6 months after discharge of the patients, who were discharged after the results of 2 PCR negative tests and the lung findings improved, were examined. The serum ferritin levels of the patients at the time of hospitalization and the reasons for their admission after discharge were recorded.

Statistical Analysis

The data conformity to normal distribution was evaluated with histogram, q-q graphs and Shapiro-Wilk test. Mann Whitney U test was used for the comparisons between paired groups. The data analysis was made with SPSS 22 statistical software. Statistically significant level was accepted as $p < 0.05$.

RESULTS

Descriptive statistics of the 300 patients included in the study were presented in **Table 1**.

Table 1. Descriptive statistics and demographic characteristics	
Variables	Descriptive statistics (n=300)
Age	68.0 (58.0-77.0)
Re-hospitalization	
No	279 (93.0)
Yes	21 (7.0)
Gender	
Woman	132 (44.0)
Man	168 (56.0)
Ferritin level (ng/mL)	210.1 (100.4-364.6)
Presence of symptoms	
No	177 (59.0)
Yes	123 (41.0)
Ex Status	
Alive	294 (98.0)
Ex	6 (2.0)
Shortness of breath	
No	272 (90.7)
Yes	28 (9.3)
Myalgia	
No	278 (92.7)
Yes	22 (7.3)
Chest pain	
No	285 (95.0)
Yes	15 (5.0)
Headache	
No	290 (96.7)
Yes	10 (3.3)
Palpitation	
No	290 (96.7)
Yes	10 (3.3)

The data were presented as n(%) and median (25th percentile – 75th percentile).

The average age of the patients was 68.0 (58.0-77.0) years. The gender distribution was 132 (44.0) females and 168 (56.0) males. The ferritin level was calculated as 210.1 (100.4-364.6). During the six-month period after the disease, no symptom had seen in 177 (59.0) patients and 123 (41.0) patients were admitted to the hospital due to various symptoms. The most common symptoms in patients were 28 (9.3) shortness of breath, 22 (7.3) myalgia, 15 (5.0) chest pain, 10 (3.3) headache and 10 (3.3) palpitations, respectively. Less common symptoms such as weakness, dizziness, loss of taste and smell were presented in **Table 2**.

Table 2. Less common symptoms	
Fatigue	8 (2.6)
Dizziness	7 (2.3)
Dermatitis	7 (2.3)
Cerebrovascular disease	6 (2.0)
Gastrointestinal symptoms	6 (2.0)
Dementia	5 (1.6)
Urinary tract infection	4 (1.3)
Numbness of extremities	4 (1.3)
Hearing loss	3 (1.0)
Hemoptysis	2 (0.6)
Menstrual irregularities	2 (0.6)
Nausea and vomiting	2 (0.6)
Facial paralysis	1 (0.3)
Loss of taste	1 (0.3)
Loss of smell	1 (0.3)

21 patients were hospitalized again. 6 patients were hospitalized due to cerebrovascular accident, 7 patients due to cardiac disease, 7 patients due to covid pneumonia and 1 patient due to spontaneous pneumothorax. 6 of the patients were ex; 5 were caused by pneumonia, and 1 was caused by acute coronary syndrome.

Table 3. Comparison of ferritin levels between groups		
Groups	Ferritin Level	p
Presence of symptoms		0.026
No	229.8 (111-375.7)	
Yes	170 (85.7-313.1)	
Re-hospitalization		0.918
No	210.1 (100.2-364.4)	
Yes	199.0 (118.5-440.6)	
Ex Status		0.700
Ex	213.15 (100.4-364.4)	
Alive	175.05 (135.6-655.4)	
Shortness of breath		0.272
No	218.4 (102.35-364.55)	
Yes	161.3 (86.2-278.15)	
Myalgia		0.730
No	210.1 (100.4-364.4)	
Yes	199.2 (108.8-340.7)	
Chest pain		0.161
No	218.1 (103.4-364.9)	
Yes	151.4 (65.1-275)	
Headache		0.223
No	217.15 (101.3-364.7)	
Yes	123.65 (96.8-278.1)	
Palpitation		0.693
No	210 (100.4-355.2)	
Yes	295.15 (65.1-466.4)	

The data were presented as n(%) and median (25th percentile – 75th percentile)

In **Table 3**, the ferritin level was compared according to the state of symptoms, being ex and occurrence of various symptoms. Accordingly, a statistically significant relationship was found between the presence of symptoms and the level of ferritin ($p < 0.05$). This significance is due to the fact that the level of ferritin was high in those who had no symptoms, and the level of ferritin was low in those who had symptoms. There was no statistically significant relationship between the status of re-hospitalization, ex status, shortness of breath, myalgia, chest pain, headache, palpitations and ferritin level ($p > 0.05$).

DISCUSSION

Although there are no widely accepted definitions for the recovery process of COVID-19 disease, the process is divided into categories by the Centers for Disease Control and Prevention (CDC).⁹ The symptoms from the onset of the disease up to the first 4 weeks have been defined as "Acute COVID-19"; the physical and mental symptoms that cannot be explained by an alternative diagnosis have been defined as "Post-Covid Conditions." The physical symptoms seen after acute COVID-19 have been examined in some studies and the most common symptoms have been determined as fatigue, shortness of breath, chest pain and cough. Anosmia, joint pain, headache, rhinitis, taste disturbances, loss of appetite, dizziness, myalgia, insomnia, alopecia, sweating, and diarrhea are less common symptoms.^{1,5,10}

In the mentioned studies, the data were obtained through questionnaires applied to patients by phone or e-mail. Our study was designed to investigate the symptoms that disturb people at a level that caused them to admit to the hospital. That is why we examined only the admissions of the emergency department and the polyclinic. In our study, in accordance with other studies, it was found that the most common causes of admission were shortness of breath, myalgia and chest pain.

In an observational study conducted on 1600 patients with acute COVID-19 in the USA, 60 days after discharge, 33% of patients reported persistent symptoms, while 19% reported new or worsening symptoms.¹¹ The most common symptoms were dyspnea along with climbing stairs (%24), shortness of breath/chest tightness (%17), cough (%15) and loss of taste and smell (%13). In our study, shortness of breath was found to be 9.3%, chest pain 5%, and loss of taste and smell of 1.5% at lower rates. The results of our study suggested that these symptoms might be more common after COVID-19 disease, but the rate of patients with complaints at such an disturbing level that would cause them to apply to the hospital was less.

In another study conducted in Italy, only % 13 of the 143 patients hospitalized with COVID-19 were found to be completely symptom-free within 60 days of the onset of the disease.¹ In our study, 177 patients (59%) did not admitted to the hospital within 6 months with any symptoms. Although the data obtained directly from the patients appear to be higher, these patients may not have shown any disturbing clinical symptoms enough to be admit to the hospital.

Although most of the patients hospitalized with COVID-19 are successfully discharged, about 10 to 20 percent need rehospitalization within 30 to 60 days.¹² In a retrospective study of more than 100,000 patients admitted to hospitals with COVID-19 in the USA, 9% of discharged patients were re-hospitalized to the same hospital within two months.¹³ In our study, 21 (7%) patients were re-hospitalized within six months.

In a study conducted with about 50,000 patients discharged after COVID-19 in the United Kingdom, %30 of patients were re-hospitalized and %10 died after discharge.¹⁴ In this study, patients with an average age of 65 were followed up for 140 days. In our study, the average age of the patients was 68 and they were followed up 180 days. The mortality rate was 2%. Despite the higher average age, the mortality rate was found to be lower in our study.

The demographic and serological characteristics of COVID-19 disease were tried to be determined to be a guide in determining the severity and prognosis. Advanced age, male gender and certain inflammatory markers were associated with COVID-19 prognosis.¹⁵ In addition, higher levels of ferritin were identified in patients with a more severe course and resulting in death.¹⁶

There are evidences that cytokine storm and release of inflammatory mediators, which are thought to affect the tue in the course of COVID-19 disease, are caused by abnormal activation of immune and coagulation systems.¹⁷ It is estimated that the increase in ferritin associated with cytokine storm may also be included in the hyperferritinemic syndrome spectrum of severe COVID-19 disease.¹⁶ Therefore, it is predicted that the ferritin level may be useful in estimating the severity of the disease and the size of the cytokine storm. In some studies, hyperferritinemia resulting from excessive inflammation was found to be associated with admission to intensive care unit and high mortality rate. It was stated that it would be a guide for identifying patients at risk.^{7,18,19} In a study conducted in Italy, ferritin was found to be associated with the severity of the disease; it was determined that it was not related to the outcome of the disease such as discharge, admission to the intensive care unit, or death.²⁰

In our study, we investigated whether ferritin was associated with symptoms that occurred again after discharge and were permanent. Accordingly, ferritin levels were found to be lower in patients admitted to the hospital with any symptoms compared to those who did not apply. There was no statistically significant relationship between the rehospitalization, ex-condition, shortness of breath, myalgia, chest pain, headache, palpitations and ferritin level. In general, we did not found a physiopathological basis to explain the low level of ferritin in those who did not have symptoms. In the studies conducted on the relationship of ferritin levels with the outcome of the disease, complete clarity was also not been achieved.

Study Limitations

In our study, a comparison has been made with the ferritin levels of the patients before receiving treatment, and in future studies, the ferritin levels measured at the time of discharge may be more significant in terms of prognosis. More comprehensive studies at the molecular and physiopathological level are needed to make a prediction according to ferritin levels in the process after recovery from COVID-19. In addition, a much larger number of patients is needed to reach definitive decisions in the prognosis estimation of COVID-19, which affects the whole world and is described as a pandemic, and this is one of the limitations of our study. The findings need to be supported by multicenter studies.

CONCLUSION

Determining the symptoms after COVID-19 disease, hospitalizations, mortality rates and other predictors that will guide this issue is very important for the recognition, treatment and follow-up of this disease after discharge.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Kastamonu University Clinical Researches Ethics Committee (Date: 06/05/2021, Decision No: 2020-KAEK-143-83).

Informed Consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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