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The Relationship of Headache with Inflammatory Serum Parameters and Disease Severity in COVID-19 Patients

COVID-19 Hastalarında Başağrısının Enflamatuvar Serum Parametreleri ve Hastalık Şiddeti ile İlişkisi

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ABSTRACT

Aim: Most of the coronavirus disease 2019 (COVID-19) patients have respiratory symptoms; however, various neurological symptoms, such as headache, can be seen. The pathophysiological mechanism of headache in COVID-19 is unknown completely. In our study, we aimed to investigate the relationship between headache and inflammatory markers and disease severity in COVID-19 patients.

Material and Methods: Two hundred and three hospitalized patients with a polymerase chain reaction (PCR)-confirmed COVID-19 diagnosis between 15 March and 01 June 2020 were retrospectively investigated. A total of 62 patients with headache symptoms (n=31) and without headache symptoms (n=31), who were age and gender-matched, were included in the study. The demographic characteristics, inflammatory serum parameters, neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP)/albumin ratio (CAR), hospitalization times, and disease severity were determined.

Results: Of the 203 COVID-19 patients, 36 (17.7%) had a headache, and it was the fourth most common symptom. Headache accompanied other symptoms in all patients. Of the patients with headache, 14 (45.2%) were female, 17 (54.8%) were male, and the mean age was 37.74±16.65 years. In our COVID-19 patients, the neutrophil count, NLR, CRP, CAR were significantly higher, and hospital stay was longer in patients with headache than those without headache (p=0.023, p=0.041, p=0.034, p=0,048 and p=0.049, respectively).

Conclusion: As a result, the increased inflammatory response may play a role in the pathogenesis of headache in COVID-19 patients. Our study is the first study that evaluated the relationship between headache symptom and inflammation in COVID-19 patients. Further research is needed on this subject.

Keywords: COVID-19; headache; neutrophil-lymphocyte ratio; C-reactive protein; albumin.

ÖZ

Amaç: Koronavirüs hastalığı 2019 (coronavirüs disease 2019, COVID-19) hastalarının çoğunun solunum semptomları vardır; ancak baş ağrısı gibi çeşitli nörolojik semptomlar da görülebilir. COVID-19'daki baş ağrısının patofizyolojik mekanizması tam olarak bilinmemektedir. Çalışmamızda COVID-19 hastalarında baş ağrısının enflamatuvar belirteçler ve hastalık şiddeti ile olan ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: 15 Mart ve 01 Haziran 2020 tarihleri arasında polimeraz zincir reaksiyonu (polymerase chain reaction, (PCR) ile doğrulanmış COVID-19 tanısıyla hastaneye yatırılan 203 hasta retrospektif olarak incelendi. Baş ağrısı semptomu olan (n=31) ve baş ağrısı semptomu olmayan (n=31) yaş ve cinsiyet eşleştirilmiş toplam 62 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, enflamatuar serum parametreleri, nötrofil/lenfosit oranı (neutrophil-lymphocyte ratio, NLR), C-reaktif protein (C-reactive protein, CRP)/albümin oranı (CRP-albumin ratio, CAR), hastanede yatış süreleri ve hastalık şiddeti belirlendi.

Bulgular: İki yüz üç COVID-19 hastasının 36 (%17,7)'sında baş ağrısı semptomu vardı ve en sık dördüncü semptomdu. Baş ağrısı, hastaların tümünde diğer semptomlara eşlik ediyordu. Baş ağrısı olan hastaların 14 (%45,2)'ü kadın, 17 (%54,8)'si erkekti ve yaş ortalamaları 37,74±16,65 yıl idi. COVID-19 hastalarımızda baş ağrısı olanlarda baş ağrısı olmayanlara göre nötrofil sayısı, NLR, CRP, CAR anlamlı düzeyde yüksekti ve hastane yatış süreleri daha uzundu (sırasıyla, p=0,023; p=0,041; p=0,034; p=0,048 ve p=0,049).

Sonuç: Sonuç olarak, COVID-19 hastalarında baş ağrısı patogenezinde artmış enflamatuvar yanıtın rolü olabilir. Çalışmamız, COVID-19 hastalarında baş ağrısı semptomu ile inflamasyon arasındaki ilişkiyi değerlendiren ilk çalışmadır. Bu konuda daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: COVID-19; başağrısı; nötrofil-lenfosit oranı; C reaktif protein; albümin.

INTRODUCTION

In December 2019, many cases of pneumonia that were later found to be caused by a new type of coronavirus (CoV) were seen in Wuhan, China, and it quickly spread to different parts of China (1). The new CoV was reported to show symptoms like severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, and both act using the angiotensin-converting enzyme 2 (ACE2) receptor (2). Therefore, the World Health Organization (WHO) named the disease caused by the virus called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy, as coronavirus disease 2019 (COVID-19) in February 2020. On March 11, 2020, the COVID-19 outbreak was proclaimed as a pandemic. As of July 12, 2020, the total number of cases of COVID-19 is 12.7 million in the world the number of deaths due to the disease is more than 560 000 in the world, and the disease continues to spread rapidly (3,4).

SARS and COVID-19's "spike proteins" use ACE2 to bind to cells (2,5). The ACE2 receptor in the body is usually found in the lungs, mouth and nasal mucosa, and in many areas such as the skin, heart, arteries, kidneys, reproductive system and brain (6). Coronavirus infections defined in humans are mostly in the form of respiratory infections and can cause deadly pneumonia, described typical clinical symptoms such as fever, cough, shortness of breath, diarrhea, and fatigue in COVID-19 (7). COVID-19 also has typical laboratory findings and lung computed tomography (CT) abnormalities (8). In COVID-19 patients, not only respiratory symptoms but also neurological symptoms such as dizziness, headache, myalgia, inability to taste and smell, polyneuropathy, myositis, cerebrovascular diseases, and rarely encephalitis have been reported (9). Headache is a common symptom of COVID-19 at rates ranging from 10.0-40.0% in patients (10,11). The exact mechanisms of headache have not yet been fully studied in COVID-19 patients. In our study, whether the headache symptom was associated with inflammatory serum parameters, disease severity, and length of hospital stay in COVID-19 patients were investigated. This study focused on the presence of headache in COVID-19 infection, and it was aimed to examine the relationship between headache symptom and inflammation and disease severity.

MATERIAL AND METHODS

Prior to the study, approval was obtained from the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine of (01.10.2020, 37). Two hundred and three patients who were hospitalized with a poliymerase chain reaction (PCR)-confirmed diagnosis of COVID-19 between 15 March and 01 June 2020 were retrospectively investigated. Five patients (3 with tension headache, and 2 with migraine) with previous recurrent headaches among 36 patients aged 18 years and over with headache were excluded from the study. A total of 62 patients with headache symptoms (n=31) and without headache symptoms (n=31), who were age and gender-matched, were included in the study. Patient data were analyzed retrospectively by screening files, and their demographic characteristics were recorded. In the patients included in our study, complete blood count (neutrophil, lymphocyte, platelet, hemoglobin), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, ferritin, procalcitonin, D-dimer levels, neutrophil/lymphocyte ratio (NLR), CRP/albumin ratio (CAR), and hospitalization times were compared. The relationship between headache and disease severity was investigated. The disease severity in COVID-19 was classified as mild (no pneumonia, slightly symptomatic), as moderate (there are signs of COVID-19 compatible pneumonia in CT, no need for respiratory support) and severe (patient with severe pneumonia findings in CT, in need of invasive or non-invasive mechanical ventilation (MV) according to clinical and lung CT abnormalities).

Statistical Analysis

Data were analyzed with SPSS v.22.0 program. The distribution of numerical variables was investigated by Shapiro-Wilk normality test. Categorical variables were expressed as numbers and percentages, and the numerical variables with normal distribution were expressed as mean and standard deviation, and those that were not normally distributed were expressed as median, interquartile range (IQR) and minimum-maximum. Normally distributed data were analyzed with Student's t-test, and Mann-Whitney U test was used for data without normal distribution. Chi-square and Fisher's exact tests were used for the analysis of categorical variables. The significance level was set at $p<0.05$.

RESULTS

In this study, the data of 203 PCR-confirmed COVID-19 patients were investigated retrospectively. Headache symptom was present in 36 (17.7%) patients and was the fourth most common symptom followed by cough in 78 (38.4%), fever in 57 (28.1%), weakness-fatigue in 41 (20.2%) patients. Neurological symptoms were present in 61 (30.0%) of the patients and headache was the most common among neurological symptoms such as loss of sense of taste and smell, myalgia, dizziness (Table 1).

The data of the patients with headache (n=31) and without headache (n=31) were compared. Of the patients with headache, 14 (45.2%) were female and 17 (54.8%) were male, and the mean age was 37.74±16.65 years. Headache accompanied other symptoms in all patients, and it was most commonly together with cough and fever. There were no patients presenting with isolated headache (Table 2).

Table 1. Demographic data of COVID-19 patients (n=203)

Age (years), mean±SD	46.98±19.71
Gender, n (%)	
Female	93 (45.8)
Male	110 (54.2)
Frequent symptoms*, n (%)	
Cough	78 (38.4)
Fever	57 (28.1)
Fatigue	41 (20.2)
Headache	36 (17.7)
Neurological symptoms, n (%)	
Total	61 (30.0)
Headache	36 (59.0)
Myalgia	15 (24.6)
Loss of taste and smell	7 (11.5)
Dizziness	3 (4.9)

COVID-19: coronavirus disease 2019, SD: standard deviation, *: There were total 212 symptoms

The comorbid symptoms and comorbidities, smoking status, disease severity of the COVID-19 patients with and without headache were compared. The most common symptoms accompanied by headache were fever and cough, and at the same time, these symptoms were the most common. There was no significant difference between patients with and without headache in terms of accompanying symptoms. Complaints of smell or taste loss were present only in patients who did not have a headache (Table 2).

While 5 (16.1%) of the patients with headache had concomitant disease, 4 (12.9%) of the patients without headache had concomitant disease, and there was no statistical difference between the groups (p=1.000). These diseases accompanying headache were hypertension (HT) in 2 (6.4%) patients, chronic obstructive pulmonary disease (COPD) in 1 (3.2%) patient, chronic kidney disease (CKD) in 1 (3.2%) patient, and hypothyroidism in 1 (3.2%) patient, in patients with headache. In patients without headache, each of the comorbid diseases of HT, COPD, CKD and coronary artery disease (CAD) were seen in 1 (3.7%) patient. Overall 6 (9.7%) of the patients had a history of smoking, and this ratio was equal in patients with and without headache (Table 2).

When the COVID-19 patients with headache were evaluated in terms of disease severity, 8 (25.8%) patients had a mild clinical condition without pneumonia, while 19 (61.3%) patients were moderate and 4 (12.9%) patients were severe. Non-invasive MV was performed in patients who were severe in our study and none of them were intubated. There were no patients with exitus. There was no statistically significant difference between the patients with and without headache in terms of disease severity. In one of the patients with headache symptom, a brain MRI was taken due to the development of respiratory distress and lethargy during follow-up and the results were normal. The patient was discharged after non-invasive MV treatment. The median duration of hospitalization was statistically significantly longer in patients with headache than those without headache (median 11 vs. 8 days, p=0.049, Table 2).

In patients with COVID-19, the neutrophil count was significantly higher in the group with headache than the group without headache (median 3.80 vs. 2.70 $x10^3/\mu L$, p=0.023). NLR was significantly higher in the patient group with headache than in the group without headache (p=0.041, Table 3).

No significant difference was found between white blood cell, lymphocyte, and platelet counts, hemoglobin, D-dimer, procalcitonin levels between the groups (p=0.071, p=0.602, p=0.502, p=0.794, p=0.612, p=0.873, respectively).

The ESR in patients with headache was higher than it was in patients without headache, but this difference was not statistically significant (median 15 vs. 10, p=0.345, Table 3). In patients with COVID-19, the CRP in the group with headache was significantly higher than it was in the group without headache (median 12.1 vs. 4 mg/dL, p=0.034). The albumin values in the group with headache were lower than those in the group without headache, but this difference was not statistically significant (median 3.76 vs. 3.9 g/dL, p=0.438). The CAR value was significantly higher in patients with headache compared to the group without headache (median 3.16 vs. 1.01, p=0.048, Table 3).

Table 2. Demographic and clinical features of COVID-19 patients with and without headache

	Total (n=62)	**With Headache (n=31)**	**Without Headache (n=31)**	**p**
Age (years), mean±SD	37.85±16.64	37.74±16.65	37.97±16.91	0.958
Gender, n (%)				
Female	28 (45.2)	14 (45.2)	14 (45.2)	1.000
Male	34 (54.8)	17 (54.8)	17 (54.8)	
Frequent symptoms that accompany headache				
Cough	28 (45.2)	17 (54.8)	11 (35.5)	0.126
Fever	23 (37.1)	14 (45.2)	9 (29.0)	0.189
Sore throat	14 (22.6)	6 (19.4)	8 (25.8)	0.544
Fatigue	13 (21.0)	5 (16.1)	8 (25.8)	0.349
Shortness of breath	6 (9.7)	4 (12.9)	2 (6.5)	0.671
Myalgia	7 (11.3)	3 (9.7)	4 (12.9)	1.000
Abdominal pain, diarrhea	7 (11.3)	4 (12.9)	3 (9.7)	1.000
Loss of taste and smell	5 (8.1)	-	5 (16.1)	0.053
Nausea	6 (9.7)	4 (12.9)	2 (6.5)	0.671
Comorbid diseases, n (%) (HT, CAD, CKD, COPD, Hypothyroidi)	9 (14.5)	5 (16.1)	4 (12.9)	1.000
Smoking, n (%)	6 (9.7)	3 (9.7)	3 (9.7)	1.000
Disease severity, n (%)				
Mild	19 (30.6)	8 (25.8)	11 (35.5)	
Moderate	37 (59.7)	19 (61.3)	18 (58.1)	0.556
Severe	6 (9.7)	4 (12.9)	2 (6.5)	
Hospital stay (days), median (IQR) [min-max]	10 (6) [3-28]	11 (8) [3-28]	8 (5) [4-16]	**0.049**

COVID-19: coronavirus disease 2019, SD: standard deviation, IQR: interquartile range, min-max: minimum-maximum, HT: hypertension, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease

Table 3. Comparison of serum parameters of COVID-19 patients with and without headache

	Total (n=62)	With Headache (n=31)	Without Headache (n=31)	p
White Blood Cell ($x10^3/\mu L$)	5.30 (2.42) [2.50-20.70]	6.10 (2.40) [2.50-20.70]	4.80 (2.36) [3.30-12.10]	0.071
Neutrophil ($x10^3/\mu L$)	3.17 (2.42) [1.20-17.90]	3.80 (2.40) [1.30-17.90]	2.70 (1.91) [1.20-9.20]	**0.023**
Lymphocyte ($x10^3/\mu L$)	1.42 (0.94) [0.44-4.00]	1.45 (0.99) [0.44-2.43]	1.40 (1.00) [0.75-4.00]	0.602
Platelet ($x10^3/\mu L$)	222.79±50.34	227.12±54.15	218.45±46.71	0.502
Hemoglobin (g/dL)	14.56±1.78	14.50±1.60	14.62±1.96	0.794
NLR	2.32 (2.73) [0.74-19.27]	2.81 (3.78) [0.74-19.27]	1.82 (2.11) [0.75-7.07]	**0.041**
D-dimer (mg/L)	431 (438) [56-4600]	414 (373) [56-4600]	450 (635) [105-3860]	0.612
ESR (mm/h)	14 (19) [2-91]	15 (29) [2-91]	10 (14) [5-85]	0.345
CRP (mg/L)	7.2 (15.3) [3-138]	12.1 (40.7) [3-138]	4.0 (7.4) [3.0-101]	**0.034**
Albumin (g/dL)	3.82 (0.53) [2.30-4.78]	3.76 (0.50) [2.30-4.40]	3.90 (0.65) [2.45-4.78)	0.438
CAR	1.76 (4.22) [0.63-69.80]	3.16 (9.74) [0.68-60]	1.01 (1.85) [0.63-69.8]	**0.048**
Ferritin (ng/mL)	83.5 (165.5) [5.2-2734]	94.8 (188) [7.2-2734]	75 (100.5) [5.2-1148]	0.564
Procalcitonin (ng/mL)	0.04 (0.04) [0.01-0.33]	0.04 (0.04) [0.01-0.33]	0.04 (0.02) [0.01-0.20]	0.873

COVID-19: coronavirus disease 2019, NLR: neutrophil/lymphocyte ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CAR: CRP/albumin ratio, data were presented as mean±standard deviation or median (interquartile range) [minimum-maximum]

DISCUSSION

In our study, the headache symptom was the fourth most common symptom with 17.7% of the patients with COVID-19, after cough, fever, weakness-fatigue symptoms. When the serum parameters of the patients were compared, the neutrophil count, NLR, CRP, CAR rates were significantly higher in the patients with headache compared to the group without headache. As far as we know, our study is the first study to show the relationship of headache symptoms with inflammation in COVID-19 patients.

Neurological involvement has been reported in 36.4-67.0% of COVID-19 patients (12,13). In our study, 30.0% of the patients had neurological involvement. Neurological symptoms of SARS-CoV-2 include headache, dizziness, cerebrovascular disease, seizure, altered consciousness, lack of taste and smell, visual disruption, neuropathic pain, Guillain-Barre Syndrome and muscle damage (13). In the study in Wuhan, the most common neurological symptoms of COVID-19 patients were dizziness 16.8% and headache 13.1% (13-17), while in the studies conducted, headache symptoms have been reported at the rates of %8.0, 11.0%, 14.0%, and 34.0% (18-21). In our study, headache was in the fourth place with 17.7% of all symptoms, and the first among neurological symptoms in 203 COVID-19 patients. Our findings have similar features to the literature.

Respiratory viruses can cause neurological symptoms in general and headache is among the most common symptoms, as in our study (18). Headache due to systemic viral infection is included as a separate title in the International Classification of Headache Disorders (ICHD)-III. Accordingly, it is defined as a headache that occurs with other symptoms and/or clinical signs of a systemic viral infection in the absence of meningitis or encephalitis (19). In our study, the patients with chronic headaches were excluded. Headache was one of the initial symptoms of COVID-19 and accompanied other symptoms. There were no patients presenting with isolated headache. In a patient with headache symptom, a brain MRI, which was taken due to the development of lethargy during follow-up, was normal. Our patients with and without headache symptoms did not have meningitis, encephalitis, stroke, or cerebral venous thrombosis (CVT) that may indicate a secondary headache. When all of the COVID-19 patients were discharged, the headache had passed, that is, the headache improved with the healing of the disease. In addition, the increase in NLR, CRP, and CAR in patients with headaches showed that the pain was associated with inflammation. With these features, headache in COVID-19 disease was compatible with the headache attributed to systemic viral infection.

The exact mechanisms of systemic infection headache are not still exactly known. Likely reasons include fever and activation of various immuno-inflammatory mediators such as endogenous or exogenous pyrogens, cytokines, and direct effects of microorganisms themselves (19).

Neutrophils are the most important cells that cause an inflammatory response during acute phase reactions. Lymphocytes are the main constituents of both humoral and cellular responses (20,21). The stress response of circulating lymphocytes results in an increase in neutrophil count and a decrease in lymphocyte count. Therefore, the ratio of these two white blood cell subgroups, NLR, is used as an inflammatory marker. In various studies, NLR was found to be higher in migraine patients than in the control group (22). NLR level has been previously shown to be a marker of a more severe infection in COVID-19 patients; however, there is no study in the literature showing the relationship between NLR and headache (23). In our study, the COVID-19 patients with headaches had a significantly higher neutrophil count and NLR than those without headaches.

CRP is an acute-phase protein synthesized in hepatocytes in reply to pro-inflammatory cytokines during inflammatory and infectious states (24). There are studies reporting increased serum CRP levels during migraine attack periods (25). Albumin is a negative acute-phase protein whose serum levels decrease in inflammatory conditions. Recently, CAR, which is a marker for systemic

inflammation, has been investigated as an independent prognostic marker in patients with infectious and other diseases (26). Similar to NLR, CAR has previously been shown to be high in migraine patients and it has been emphasized that peripheral inflammation may play a role in migraine pathogenesis (27). Similarly in our study, CRP and CAR were significantly higher in the COVID-19 patients with headache than those without headache, and according to our results, inflammation may play a role in the pathogenesis of headache in COVID-19.

The cytokine release syndrome seen in various viral diseases such as SARS, MERS, influenza, is another significant consideration for the headache mechanism (28). High pro-inflammatory cytokine concentrations in plasma were measured in patients with serious SARS-CoV-2 (14). These cytokines are known to cause direct tissue damage and another inflammatory cascade various immuno-inflammatory mediators (13). Neuroinflammation and various inflammatory mediators are well known to play a part in trigeminovascular activation (29). The headache in COVID-19 infection may have been caused by the release of proinflammatory mediators and cytokines triggering the perivascular trigeminal nerve endings (30). In our study, the increase in inflammatory parameters such as neutrophil count, NLR, CRP, and CAR, suggests that headache in COVID-19 disease may be associated with an increase in proinflammatory cytokines.

As is known, ACE2 has been identified as the main receptor for SARS-CoV-2 entry (31). It has been suggested that direct invasion of trigeminal nerve endings in the nasal cavity by SARS-CoV-2 may be another possibility for the headache mechanism associated with COVID-19 (30). However, ambiguity remains in this issue since ACE2 expression has not yet been demonstrated in the peripheral trigeminal nerve endings (32). In our study, headache was not an accompanying symptom in any of our five patients who had complaints of lack of taste and smell.

Headache can occur as a result of neurological damage caused by the virus directly infecting the central nervous system (CNS). Neurotropism of SARS-CoV-2 has been demonstrated in autopsy samples of COVID-19 patients (13,14). As previously shown in other coronaviruses (33,34), SARS-CoV-2 can enter the brain through systemic circulation or retrograde neuronal dissemination (35,36). SARS-CoV-2 in the systemic circulation can enter the brain through ACE2 receptors in capillary endothelium and cause neuronal damage (35). Similar to SARS-CoV, SARS-CoV-2 can also enter into the brain through the olfactory tract (37). The presence of anosmia in COVID-19 patients suggests an olfactory nerve invasion (38). Although there are opinions that it can directly invade the CNS through the olfactory nerve, this is not fully clarified (28,39). In our study, the patients with olfactory disorders were in the group without headache. In COVID-19 patients, the headache symptom may be associated with meningitis, encephalitis, or encephalopathy. Although the frequency of headache due to viral meningitis remains uncertain, a limited number of encephalitis cases in COVID-19 (40). Encephalopathy is likely to develop in patients with severe infection and comorbidities in COVID-19 (41). In our study, none of our patients had meningitis, encephalitis, or encephalopathy.

Increased D-dimer is common in COVID-19 patients (42). Elevations in the D-dimer can lead to headache-causing neurological complications such as CVT and stroke (43). Previously, stroke in COVID-19 patients (3%) and CVT (0.5%) have been reported (44,54). In our study, there was no statistically significant difference in D-dimer levels between patients with headache and patients without headache. No stroke or CVT was detected in our COVID-19 patients with and without headache symptoms.

In a recent study, headache was 17% in serious cases and 10% in milder cases, and it was emphasized that inflammation and hypoxia associated with disease seriousness may have a role in headache (13,16). In our study, there was no significant difference between patients with headache (25.8% mild, 61.3% moderate, and 12.9% severe) and without headache (35.5% mild, 58.1% moderate, and 6.5% severe) in disease severity. However, non-invasive MV was performed in patients with severity in our study, none of them were intubated and there were no patients with exitus. Therefore, there is a need for larger studies involving patients with more severe clinics on this subject. In addition, the duration of hospital stay of patients with headaches was higher in our study than those without headaches. It can be said that the recovery process of patients with headache takes longer.

As a result, there was a significant increase in neutrophil count, NLR, CRP, and CAR levels in COVID-19 patients with headache symptoms compared to those without headache. According to our study, the increased inflammatory response may play a role in the pathogenesis of headaches in COVID-19 patients. As far as we know, our study is the first to show the relationship of headache with inflammation in COVID-19 patients. In this regard, more comprehensive studies are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of Atatürk University Faculty of Medicine (01.10.2020, 37).

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