Persistent Headache After COVID-19: Clinical Patterns and Imaging Insights

Duygu Arslan Mehdiyev[1], Gülgün Uncu[2], Pınar Uzun Uslu[3], Zeynep Özözen Ayas[2]

1 Ankara Etlik City Hospital, Department of Neurology, Ankara, Türkiye
2 Eskişehir City Hospital, Department of Neurology, Eskişehir, Türkiye
3 Yunus Emre State Hospital, Department of Neurology, Pain Clinic, Eskişehir, Türkiye

Abstract

Aim: This study aimed to investigate the prevalence of persistent headache following coronavirus disease 2019 (COVID-19) and its association with demographic, clinical, and neuroimaging parameters.

Methods: A total of 341 patients with a confirmed diagnosis of COVID-19 by polymerase chain reaction (PCR) who presented to the neurology outpatient clinic were evaluated in this study. Patients were divided into two groups based on the presence or absence of persistent headaches. Demographic characteristics, comorbidities, accompanying neurological and systemic symptoms, and neuroimaging findings were compared between the groups.

Results: Persistent headaches were observed in 36.9% of the 341 patients. These patients were significantly younger than those without headaches (mean age 45 vs. 55 years, $p < 0.001$), and the female sex ratio was significantly higher (42.9% vs. 27.5%, $p = 0.004$) in the headache group. Insomnia ($p = 0.002$), dizziness ($p = 0.01$), and myalgia/paresthesia ($p = 0.03$) were significantly more common among patients with headache. In contrast, abnormal neuroimaging findings, including diffusion-weighted imaging (DWI) abnormalities and magnetic resonance (MR) venography pathology, were significantly more frequent in patients without headache. Patients with abnormal MR findings were older, had greater comorbidity, and had longer hospital stays. Multivariate analysis confirmed that age and female sex were independent predictors of post-COVID headache.

Conclusions: Post-COVID headache is a common condition with a distinct clinical profile characterized by specific demographic features and clinical findings. Imaging findings are not always indicative.

Keywords: *COVID-19; Post-Acute COVID-19 Syndrome; Headache; Nervous System Manifestation*

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) manifests through a variety of symptoms, with headaches being the most frequently occurring and persistent symptoms associated with coronavirus disease 2019 (COVID-19). Many studies have investigated the prevalence and clinical features of headache following COVID-19 [1-2]. These headaches often mimic primary headache syndromes, such as migraines or tension-type headaches [2]. Many patients with COVID-19 experience persistent headaches that persist even after the acute phase of infection has resolved or sometimes experience new-onset headaches after the temperature has stabilized [1]. Additionally, the severity of headaches tends to increase in the later stages of COVID-19 infection than in the acute phase [3].

The complex nature of how the virus enters the body, attacks it, and the effects it produces underscores the need for detailed research to elucidate the symptoms, characteristics, and potential neuroimaging explanations for headaches that occur after COVID-19 infection. In this type of research, a better understanding of the characteristics of headaches that are newly onset, worsen, or persist after a viral epicenter, as well as the specific emergence of COVID-19, is essential for developing treatment methods and achieving better outcomes in patients.

This study aimed to evaluate the demographic, clinical, and radiological characteristics of the patients. Despite the high prevalence of post-COVID headache, data on its neuroimaging correlates remain limited and inconsistent. In particular, it is unclear whether persistent headaches are associated with detectable structural or vascular abnormalities on routine neuroimaging or whether they primarily reflect nonstructural functional processes.

2. Materials and Methods

This cross-sectional observational study was conducted at the neurology outpatient clinic of a tertiary hospital. Adult patients (≥18 years) with a prior confirmed SARS-CoV-2 infection were evaluated after resolution of the infection. In line with the NICE guidelines, which define ongoing symptomatic COVID-19 as symptoms persisting from 4 to 12 weeks after acute infection, individuals were eligible if at least four weeks had elapsed since SARS-CoV-2 infection. For the purposes of this study, patients with neurological com-

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plaints evaluated between 4 and 24 weeks after COVID-19 were included, corresponding to the post-acute and long COVID phases. According to integrative classification frameworks, symptoms persisting beyond 24 weeks are considered persistent post-COVID symptoms and were therefore excluded [4-5]. All patients underwent a detailed history taking and neurological examination.

The presence, characteristics, duration, frequency, severity, and nature of the headache were recorded. Headache severity was assessed using a 0-100 Visual Analog Scale (VAS).

Myalgia or paresthesia, sleep disturbances, and cogni-tive impairment were also investigated. Clinical information was obtained from the patients, and their history, particularly regarding memory or concentration problems, was supplemented by anamnesis obtained from family members. Demographic characteristics, comorbidities, body mass index (BMI), smoking history, previous headache disorders, medication use, and hospitalization during acute COVID-19 were also recorded.

Neuroimaging was performed according to clinical indications and included conventional brain magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), and magnetic resonance venography (MRV). MRI sequences (T1, T2, FLAIR, and SWI) were reviewed and classified as normal or pathological. Pathological MRI findings were defined as ischemic lesions, age-inconsistent white matter hyperintensities, microhemorrhages, structural abnormalities, and clinically significant changes in the brain. DWI was used to assess restricted diffusion, indicating acute or subacute ischemia or other focal abnormalities. MR venography was used to assess clinically relevant venous abnormalities, including venous sinus thrombosis and significant flow alterations. The imaging findings were categorized into three groups: normal, pathological, and no image.

Data collection included demographic and clinical variables, laboratory parameters (glucose, ferritin, vitamin B12, folate, and complete blood count), subjective cognitive complaints, and the time between COVID-19 diagnosis and neurological assessment.

Statistical analyses were performed using the IBM SPSS Statistics software (version 26.0). The Shapiro-Wilk test was used to assess the normality of continuous variables. Intergroup comparisons were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Imaging methods were analyzed separately using appropriate nonparametric methods. Variables with a p-value <0.10 in univariate analyses were included in a multivariate logistic regression model to identify the independent determinants of post-COVID headache. Variables with a p-value < 0.10 in univariate analyses were entered into the multivariate model to avoid excluding potentially relevant predictors and to reduce the risk of type II error. Probability ratios (OR) and 95% confidence intervals (CI) were calculated for the analyses. The statistical significance level was set at $P < 0.05$.

This study was evaluated by the Eskişehir City Hospital Scientific Research Ethics Committee and found to be ethically appropriate with the decision dated 11.09.2025, ESH/BAEK 2025/216.

3. Results

Of the 341 patients included in the study, 126 (36.9%) reported persistent headaches after COVID-19 infection. Headache was significantly more common in women than in men. Patients with headache were significantly younger than those without headache (Table 1). No statistically significant association was found between headache and body mass index (BMI), smoking status, or comorbidities. The median time from COVID-19 diagnosis to neurological evaluation did not differ significantly between patients with and without headache (P = 0.060).

The presence of headache was significantly associated with various concomitant symptoms. Individuals experiencing headaches had a higher incidence of dizziness, myalgia or paresthesia, and sleep disturbance. However, no statistically significant association was found between headache and cognitive complaints (Table 2).

Neuroimaging analysis revealed significant differences between patients with and without headache. Pathological DWI findings were more frequent in patients without headaches than in those with headaches (37.2% vs. 15.1%), whereas normal DWI findings were more common in patients with headaches (31.7% vs. 16.7%; $p < 0.001$). A similar distribution was observed on MR venography. Pathological venous findings were significantly more frequent in patients without headaches than in those with headaches (62.3% vs. 19.8%), whereas normal venography results predominated among patients with headaches (45.2% vs. 14.9%; $p < 0.001$). In contrast, the conventional brain MRI findings did not differ significantly between the two groups ($p = 0.097$).

Table 1

Age and Sex Distribution by Headache Status

Variable		No Headache	Headache	Test statistic	p-value
Age (years)		51.99 ± 14.16; median 55 (17–84)	46.02 ± 12.69; median 45 (17–74)	U = 9862.5	<0.001*
Sex	Male	95 (72.5%)	36 (27.5%)	χ^2 = 8.187	0.004*
	Female	120 (57.1%)	90 (42.9%)		

Table 2

Relationship Between Headache and Other Post-COVID Symptoms

Symptom	No Headache n (%)	Headache n (%)	Test Statistic	p-value
Dizziness	24 (11.2%)	25 (19.8%)	χ^2 = 4.183	0.041*
Subjective cognitive complaints	74 (34.4%)	50 (39.7%)	χ^2 = 0.951	0.329
Myalgia / Paresthesia	53 (24.7%)	49 (38.9%)	χ^2 = 7.682	0.006*
Sleep disturbance	43 (20.0%)	37 (29.4%)	χ^2 = 3.880	0.049*

Further exploratory analyses were conducted to evaluate the laboratory and clinical correlates of cognitive symptoms. Patients reporting forgetfulness exhibited significantly higher folate levels (mean: 8.04 vs. 6.33 ng/mL, $p = 0.002$) and higher fasting blood glucose levels (median: 103.5 vs. 97 mg/dL, $p = 0.017$) than those without forgetfulness. No other significant associations were found between forgetfulness and hematological parameters.

Headache severity, assessed using a visual analog scale (VAS), was significantly higher in patients with a prior history of headache than in those without (median VAS score: 63 vs. 55; $p < 0.001$). In addition, headache severity differed according to MR venography status ($p = 0.039$), with higher median VAS scores observed in pa-

tients with abnormal or unavailable venography compared with those with normal findings.

In the multivariate logistic regression analysis, younger age and female sex were independently associated with post-COVID headache. Specifically, while increasing age emerged as a protective factor, female participants were almost twice as likely to experience headaches as male participants.

Among the accompanying symptoms, myalgia or numbness remained significantly associated with headache, even after adjusting for other variables. In contrast, although more common in the headache group in univariate analyses, dizziness and sleep disorders did not show statistical significance in the multivariate model (Table 3).

Table 3
Multivariate Logistic Regression Results for Post-COVID Headache

Variable	Odds Ratio	95% CI	p-value
Age	0.97	0.95 – 0.98	< 0.001*
Female sex	1.85	1.13 – 3.04	0.015*
Dizziness	1.57	0.81 – 3.03	0.181
Myalgia / paresthesia	1.83	1.11 – 3.01	0.017*
Sleep disturbance	1.54	0.90 – 2.62	0.116

4. Discussion

In this study, we evaluated the clinical features, accompanying symptoms, and neuroimaging findings related to persistent headaches after COVID-19. Persistent headache was observed in 36.9% of patients and was particularly more common in young women; this demographic pattern is consistent with previous reports on post-infection and post-COVID headache syndromes [1-3]. Although headache after viral illness is not a new clinical phenomenon, the COVID-19 pandemic has significantly expanded our understanding of long-term neurological sequelae following viral infection [6-7]. Our findings confirm the known epidemiological trends and provide new evidence of associated symptoms and imaging correlations.

A key observation of this study was the strong association between headache and accompanying symptoms such as dizziness, myalgia/paresthesia, and sleep disturbances. These symptom clusters reflect previously identified dysautonomic and neuroinflammatory patterns in patients with long-term COVID and chronic fatigue-related disorders [8-9]. Their consistent co-occurrence supports the hypothesis that post-COVID headache is part of a broader neuroimmune or central sensitization process rather than a purely nociceptive or peripheral mechanism [10]. These findings suggest that both demographic factors and specific neurological symptoms may contribute to the pathophysiology and perception of post-COVID headache.

Contrary to conventional assumptions, patients experiencing headaches had fewer abnormal findings on DWI and MR venography than those without headaches. Although conventional MR results did not differ between the groups, pathologies such as diffusion restriction or venous abnormalities were significantly more common in the group without headache. This was an unexpected finding, which has clinical significance and suggests that post-COVID headaches do not correspond to structural brain changes detectable by routine imaging but may reflect functional, metabolic, or connectivity-based changes [11-13]. This interpretation is consistent with studies showing microcirculatory disturbances, autonomic imbalance, and altered functional connectivity with more advanced imaging methods in long-term COVID patients without visible lesions on routine imaging [14-15]. Individuals with pre-existing headache disorders reported significantly higher VAS scores, indicating an underlying sensitivity. Notably, the highest pain scores were observed in patients who did not undergo venography, which may indicate a subgroup whose symptoms are driven by functional rather than structural mechanisms [2, 16]. Traditional systemic risk factors, including BMI, smoking, and comorbidities, were not statistically associated with headache, highlights that post-COVID headache is driven by neurobiological rather than systemic factors.

Cognitive complaints, frequently reported in long-term COVID, were not associated with headache in this cohort, consistent with previous studies showing that cognitive dysfunction and headache generally follow separate trajectories [16]. However, the observed differences in folate and glucose levels in patients with cognitive complaints highlight the complexity of post-COVID cognitive symptoms and warrant further investigations. Overall, the findings of this study reinforce the idea that post-COVID headache may constitute a distinct clinical phenotype. Although the acute phase of the pandemic is diminishing, long-term neurological complaints, including persistent headaches, continue to pose significant clinical challenge [17-19]. Longitudinal cohort studies using functional imaging techniques and inflammatory or immunological biomarkers are crucial for elucidating the underlying mechanisms of persistent headaches and identifying effective treatment strategies. Clinicians should be aware that standard structural neuroimaging may not capture the underlying dysfunction in these patients, and more detailed imaging studies may be required to identify these cases.

Some methodological limitations of this study should be considered. Neuroimaging examinations were performed based on clinical indications and not within a standard screening protocol. This carries a risk of selection bias, particularly because patients with more severe, persistent, or atypical neurological symptoms are more likely to be referred for DWI or MR venography. Therefore, the absence or presence of imaging findings may not be representative of the entire post-COVID-19 headache population. Furthermore, the time between COVID-19 diagnosis and neuroimaging was not systematically recorded in this retrospective dataset; therefore, the median imaging time could not be determined. The fact that imaging was performed at different time points than infection may have contributed to the failure to capture functional or microvascular changes, particularly those occurring late with conventional imaging. These limitations should be considered in the interpretation of the findings and addressed in future prospective studies with standardized imaging time. Another limitation of this study is its cross-sectional design, which does not allow for causal or dynamic inferences about the course, persistence, or spontaneous resolution tendencies of headaches over time. Patients were evaluated at a single time point, and longitudinal headache follow-up, symptom progression, and treatment response were not included in this dataset. This may limit the interpretation of the findings, particularly regarding the natural course and phenotypic transformation of post-COVID headache. Future prospective and longitudinal studies will elucidate the evolution of headaches over time, determinants of persistence, and underlying mechanisms.

5. Conclusions

This study contributes to the understanding of post-COVID-19 headache by identifying its characteristic demographic and clinical profiles and examining neuroimaging abnormalities. The absence of structural correlations in routine MRI, DWI, and MR venography suggests a predominantly functional or neuroimmune mechanism rather than an anatomical mechanism. By synthesizing clinical features, associated symptom clusters, and imaging data from a large real-world cohort, this study highlights critical gaps in current diagnostic approaches and underscores the need for multidisciplinary management strategies for long-term COVID-related neurological symptoms. This information can contribute to a broader understanding of post-COVID headache syndrome and improve the clinical interpretation of post-COVID headaches.

Statement of ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Eskişehir City Hospital Scientific Research Ethics Committee on 11 September 2025 (Approval No: ESH/BAEK 2025/216).

The protocol titled *"Persistent Post-COVID Headache: Clinical Features and Neuroimaging Findings"* was reviewed and approved without any ethical or scientific objection.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The data and materials of this study are available upon reasonable request.

Author contributions

DAM: Conceptualization, methodology, investigation, data acquisition, formal analysis, writing – original draft, writing – review and editing.

GU: Data acquisition, clinical evaluation, writing – review and editing.

PUU: Data acquisition, resources, writing – review and editing.

ZÖA: Data acquisition, resources, writing, review and editing.

All authors read and approved the final version of the manuscript.

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No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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