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# Significance of Neurological Manifestations and Their Association With Clinical Outcomes in Hospitalized COVID-19 Patients in Bandar Abbas, Iran: A Cross-Sectional Study

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## ABSTRACT

**Background:** Neurological manifestations are increasingly recognized in COVID-19 patients, yet their prevalence and clinical significance remain understudied. This study aimed to determine the incidence and significance of neurological symptoms and their associations with demographic, clinical, and laboratory parameters in hospitalized COVID-19 patients.

**Method:** A cross-sectional study was conducted at Shahid Mohammadi Hospital, Bandar Abbas, Iran, from February 2020 to February 2021. A total of 540 RT-PCR-confirmed COVID-19 patients were included. Data on demographics, comorbidities, clinical symptoms, neurological manifestations (e.g., myalgia, headache, smell/taste impairment, dizziness), and laboratory findings were collected. Statistical analyses were performed using SPSS version 20.

**Results:** Myalgia was the most common neurological symptom (33.9%), followed by headache (16.7%), smell/taste impairment (10.2%), and dizziness (6.9%). A significantly higher prevalence of myalgia and smell/taste impairment was observed in patients under 50 years old ($p \leq 0.05$). Patients with myalgia also had a significantly higher prevalence of prior chronic heart disease and were more likely to experience concurrent smell/taste impairment ($p \leq 0.05$). Notably, while some inflammatory markers were elevated in both patients with and without myalgia and smell/taste impairment, the increase was significantly less pronounced in those exhibiting these neurological symptoms ($p \leq 0.05$). Additionally, patients with headache and smell/taste impairment were less frequently admitted to the ICU ($p \leq 0.05$). A statistically significant co-occurrence was also observed among the presence of headache, dizziness, and smell/taste impairment in COVID-19 patients ($p \leq 0.05$).

**Conclusion:** Neurological symptoms are prevalent in COVID-19 patients and may serve as markers of disease severity and progression. Recognizing these manifestations can aid in early diagnosis and inform tailored management strategies. Further research with larger, diverse populations and advanced diagnostic tools is needed to validate these findings and better understand the mechanisms underlying COVID-19-related neurological involvement.

**Abbreviations:** ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CNS, central nervous system; COVID-19, coronavirus disease of 2019; Cr, creatinine; CRP, C-reactive protein; EMG, electromyography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; PLT, platelet count; PNS, peripheral nervous system; SaO2, oxygen saturation; WBC, white blood cell count.

## 1 | Introduction

In December 2019, a number of acute atypic respiratory cases occurred in Wuhan, China, which quickly spread to other areas, and soon, it was discovered that a virus belonging to the Coronavirus family was the pathogen responsible. The new pathogen was named SARS-CoV-2 because of its high similarity to SARS-COV, which caused acute respiratory distress syndrome (ARDS) and increased mortality rate during the years 2002–2003 [1]. Afterward, the corresponding disease was named Coronavirus Disease 2019 (COVID-19) and was declared a world pandemic by March 2020 [2, 3].

Generally, most clinical manifestations of COVID-19 are Fever, Cough, dyspnea, myalgia, fatigue, sore throat, diarrhea, headache, and sputum production [4]. However, it didn't take too much time for healthcare providers to realize that the disease caused multiorgan damage such as central nervous system (CNS) and peripheral nervous system (PNS) disorders [5, 6]. Evidence showed that coronavirus invasion into the nervous tissue leads to various neurological manifestations and complications [7]. The neurologic symptoms that were commonly reported were headache, anosmia, ageusia, myalgia, altered level of consciousness, and mental confusion. These symptoms occurred in 8%–91% of hospitalized patients [8]. Despite neurological manifestation, the disease also results in neurological complications, including encephalitis, Guillain-Barré syndrome, acute necrotizing hemorrhagic encephalopathy, and hemophagocytic lymphohistiocytosis [9].

SARS-CoV-2 has been implicated in neurotropism, with the ability to enter the CNS through various routes. The virus can invade the CNS directly via the hematogenous route by infecting the endothelial cells of the blood-brain barrier (BBB) and the epithelial cells of the blood-cerebrospinal fluid barrier. This occurs through the binding of the virus to angiotensin-converting enzyme 2 (ACE-2) receptors [7, 10, 11]. Another route for viral invasion is through the olfactory bulb and peripheral nerves, facilitating trans-synaptic spread [11, 12].

Beyond direct viral invasion, the pathophysiology of COVID-19-related neurological complications is also influenced by secondary mechanisms, including immune-mediated processes. Cytokine storms, characterized by an excessive release of pro-inflammatory cytokines, can increase the permeability of the BBB. This allows cytokines and other pro-inflammatory markers to enter the brain, leading to neuroinflammation and neuronal damage. These processes collectively contribute to the neurological manifestations observed in COVID-19 patients [7, 12–14].

Moreover, the significant impact of SARS-CoV-2 on the structural and functional integrity of the nervous system has been highlighted in a previous systematic review. The study found various neuroimaging abnormalities, the most common being olfactory bulb and white matter abnormalities, followed by acute or subacute ischemic infarctions and encephalopathy [15].

While several studies have reported neurological manifestations and complications of COVID-19 [16–20], few have explored the association between these neurological symptoms and other prognostic factors, such as demographic, clinical, and laboratory parameters [10, 21, 22].

To date, there is a limited understanding of how neurological symptoms impact patient outcomes or how they relate to other predictive factors. This study aims to determine the incidence of neurological manifestations in COVID-19 patients and explore their association with other patient characteristics.

## 2 | Methods

This cross-sectional study was conducted at Shahid Mohammadi Hospital in Bandar Abbas, Iran, from February 2020 to February 2021 during the Delta-dominant period. The study was conducted and reported in accordance with the STROBE guidelines for observational studies [23]. Patients with a diagnosis of COVID-19 (followed by their clinical presentation) who were hospitalized were included in the study. Inclusion criteria were: a definite diagnosis of COVID-19 confirmed by reverse transcriptase PCR test (RT PCR) (sample was collected by nasopharyngeal swab) and the patient's verbal informed consent to participate in the study. Patients were excluded if they had cognitive impairment that prevented them from participating in the interview process and if they passed away before the interview could be conducted. Eventually, 540 patients were included in the study.

The patients were interviewed via telephone, and the interviews were conducted using a questionnaire developed by our research team. The questionnaire was divided into different sections. The first section focused on the patient's comorbidities, including chronic heart disease, chronic pulmonary disease, asthma, diabetes mellitus, hematologic disorders, chronic kidney disease, and a history of smoking. The second section addressed common clinical manifestations such as fever, chills, cough, dyspnea, chest pain, fatigue, abdominal pain, diarrhea, nausea, and vomiting. The final section covered neurological manifestations, including headache, myalgia, smell/taste impairment, and dizziness. The variables were assessed with dichotomous yes/no responses. Each neurological symptom was carefully explained to the patients to ensure accurate reporting of neurological manifestations. For headaches, we asked if they experienced any type of pain or discomfort in their head, scalp, or neck, which could feel like pressure, throbbing, or a dull ache. For myalgia, we inquired about any sensation of soreness, stiffness, or aching in their muscles, either localized or throughout their body. For smell/taste impairment, we asked if they noticed any changes in their ability to smell or taste, such as a loss, reduction, or alteration in these senses. For dizziness, we clarified the type of dizziness they might be experiencing: for vertigo, we asked if they felt like the room was spinning or if they were spinning, even when standing still; for lightheadedness, we asked if they felt like they might faint or lose consciousness; and for unsteadiness, we asked if they felt off-balance or as though they might fall while walking or standing. By using clear and specific descriptions, we ensured that patients could accurately describe their symptoms, allowing us to gather reliable data on their neurological manifestations.

Data, including age, sex, vital signs (such as heart rate, respiratory rate, and oxygen saturation), laboratory data (including white blood cell count [WBC], platelet count [PLT], urea, creatinine, c-reactive protein [CRP], lactate dehydrogenase [LDH], aspartate aminotransferase [AST], and alanine transaminase [ALT]), and ICU admission of the patients were obtained from their medical records in the hospital information system.

The Ethics Committee of Hormozgan University of Medical Sciences approved the study protocol (IR.HUMS.REC.1399.437), and each patient gave verbal informed consent before participating in the study.

Data were collected using standardized checklists, and statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. Numerical variables were presented as means with standard deviations (SD). Data that followed a normal distribution were compared using independent sample *t*-tests, while non-normally distributed data were analyzed using the Mann-Whitney U-test.

All statistical tests were two-sided and performed at a 95% confidence level. Statistical significance was defined as $p < 0.05$, with the significance level at $\alpha = 0.05$ for all analyses. It should be noted that no adjustments for multiple comparisons, such as Bonferroni correction, were applied in this study, as the analyses were primarily exploratory.

## 3 | Results

During the study period, 540 patients who met the inclusion criteria were included in the final analysis. Among these patients, 52.2% were under the age of 50, and 57.8% were male.

Neurological symptoms were common among the patients, with myalgia being the most frequent manifestation, reported in 33.9% of cases, followed by headache in 16.7%, smell/taste impairment in 10.2%, and dizziness in 6.9%. (Table 1). The incidence of neurological symptoms varied according to demographic factors, as symptoms were more prevalent in males and patients under 50. Notably, age showed a significant association with the occurrence of smell/taste impairment and myalgia ($p \leq 0.05$) (Tables 2–5).

The patients presented with various underlying conditions, including diabetes mellitus (22.6%), chronic heart disease (13%), history of smoking (8%), asthma (5.9%), chronic kidney disease (5.7%), hematologic disorders (2.8%), and chronic pulmonary disease (1.9%) (Table 1). While the study did not find significant correlations between most comorbidities and neurological symptoms, myalgia occurred significantly more often in patients with a history of chronic heart disease ($p \leq 0.05$) (Table 2).

In exploring the relationships between neurological symptoms (including myalgia, headache, smell/taste impairment, and dizziness), our study found that the co-occurrence of headache, dizziness, and smell/taste impairment was statistically significant ($p \leq 0.05$) (Table 3). Additionally, patients with smell/taste impairment were more likely to experience myalgia ($p \leq 0.05$) (Table 4).

Non-neurological symptoms were also prevalent, with cough (68.1%) and dyspnea (60.9%) being the most commonly reported, followed by fatigue (21.7%), fever (18.1%), nausea and vomiting (16.7%), diarrhea (16.7%), chest pain (6.3%), abdominal pain (3.9%), and chills (2.6%) (Table 1). Some of these symptoms were significantly associated with the presence of neurological manifestations. For instance, dizziness was significantly more common in patients experiencing abdominal pain, nausea, and vomiting ($p \leq 0.05$) (Table 5). Similarly, patients with smell/taste impairment had a significantly higher occurrence of fever, nausea, vomiting, and chest pain ($p \leq 0.05$) (Table 4). Moreover, Myalgia was significantly associated with a greater prevalence of fever, cough, fatigue, and diarrhea ($p \leq 0.05$) (Table 2). However, the occurrence of headache showed no significant correlation with non-neurological symptoms ($p > 0.05$) (Table 3).

Respiratory involvement was assessed through respiratory rate and (oxygen saturation) $SaO_2$ measurements, revealing that 23% of patients had elevated respiratory rates. However, no significant correlation was found between respiratory involvement and the occurrence of neurological symptoms (including myalgia, headache, smell/taste impairment, and dizziness) ($p > 0.05$).

Regarding the link between ICU admissions and the presence of neurological symptoms, we found patients with headache and smell/taste impairment were significantly less likely to require ICU admission ($p \leq 0.05$) (Table 3, Table 4). Although dizziness and myalgia were also more common in non-ICU patients, the correlation was not statistically significant ($p > 0.05$) (Table 2, Table 5).

The analysis of inflammatory markers showed elevated mean levels of CRP, LDH, serum creatinine, AST, ALT, and WBC counts across the patient cohort. A comparison of these markers between patients with and without myalgia, headache, smell/taste impairment, and dizziness revealed distinct patterns. Based on our obtained data, the patients with headaches had lower levels of CRP, LDH, creatinine, AST, ALT, WBC, and platelets than those without headaches, although the differences were not statistically significant ($p > 0.05$) (Table 2). On the other hand, LDH levels were elevated in patients with and without smell/taste impairment and myalgia, but the levels were significantly lower in patients experiencing these symptoms compared to those without them. ($p \leq 0.05$) (Table 4, Table 5). Similarly, serum creatinine levels were elevated in patients both with and without myalgia, but levels were significantly lower in patients with myalgia compared to those without. ($p \leq 0.05$) (Table 5).

## 4 | Discussion

Neurological manifestations are commonly observed in COVID-19 patients, ranging from mild symptoms to severe conditions [4, 13, 24–26]. SARS-CoV-2 can affect the nervous system through multiple pathways, including hematogenous spread, neuronal dissemination, and immune-mediated mechanisms. The virus may enter the nervous system via infected endothelial cells and leukocytes or through

**TABLE 1** | Demographic characteristics of COVID-19 patients.

| Variables | | | Patients ($n = 540$) |
|---|---|---|---|
| **Sex, *n* (%)** | | Males | 228 (42.2) |
| | | Females | 312 (57.8) |
| **Age, *n* (%)** | | Age < 50 | 282 (52.2) |
| | | Age > 50 | 258 (47.8) |
| **Neurological symptoms, *n* (%)** | | Headache | 90 (16.7) |
| | | Dizziness | 37 (6.9) |
| | | Smell/taste impairment | 55 (10.2) |
| | | Myalgia | 183 (33.9) |
| **comorbidities, *n* (%)** | | Chronic Heart disease | 70 (13.0) |
| | | Asthma | 32 (5.9) |
| | | Chronic pulmonary disease | 10 (1.9) |
| | | Diabetes mellitus | 122 (22.6) |
| | | Hematologic disease | 15 (2.8) |
| | | Chronic kidney disease | 31 (5.7) |
| | | Smoking | 43 (8.0) |
| **Non-neurological symptoms, *n* (%)** | | Fever | 98 (18.1) |
| | | Cough | 368 (68.1) |
| | | Dyspnea | 329 (60.9) |
| | | Chest pain | 34 (6.3) |
| | | Fatigue | 117(21.7) |
| | | Abdomen al pain | 21 (3.9) |
| | | Diarrhea | 72 (13.3) |
| | | Nausea and vomiting | 90 (16.7) |
| | | Chills | 14 (2.6) |
| **Respiratory involvement** | Sao2, *n* (%) | Normal (98%–100%) | 111 (20.6) |
| | | Insufficient (95%–97%) | 229 (42.4) |
| | | Decreased (90%–94%) | 124 (23.0) |
| | | Critical (< 90%) | 76 (14.1) |
| | Respiratory rate, *n* (%) | Normal | 416 (77.0) |
| | | Tachypnea | 124 (23.0) |
| **Lab data, mean ± SD** | | CRP (mg/L) | $35.57 \pm 21.33$ |
| | | LDH (mg/L) | $691.63 \pm 835.51$ |
| | | Creatinine (mg/L) | $1.30 \pm 1.27$ |
| | | AST (U/L) | $60.92 \pm 151.03$ |
| | | ALT (U/L) | $57.77 \pm 111.16$ |
| | | WBC (cell/mm$^2$) | $28.29 \pm 341.58*10^3$ |
| | | PLT (plt/mm$^2$) | $200.56 \pm 82.28*10^3$ |
| **ICU admission, *n* (%)** | | Yes | 82 (15.2) |
| | | No | 458 (84.8) |

retrograde axonal transport. Immune-mediated injury, triggered by cytokine storms (e.g., elevated IL-6) and binding to ACE-2 receptors, contributes to endothelial dysfunction, neuronal inflammation, and cell death [27]. Previous studies suggest that neurological symptoms may influence disease prognosis and clinical outcomes [28, 29]. Evaluating the prevalence of these manifestations and their associations with clinical parameters in COVID-19 patients can provide critical insights into the disease's impact on the nervous system and inform better management strategies.

**TABLE 2** | Anticipated risk for myalgia based on patient characteristics.

| Characteristics | | Myalgia $N = 193$ | Without myalgia $N = 357$ | $p$ value |
|---|---|---|---|---|
| **Sex, *n* (%)** | | | | |
| Female | | 86 (47.0) | 142 (39.8) | 0.11 |
| Male | | 97 (53.0) | 215 (60.2) | |
| **Age, *n* (%)** | | | | |
| Aged > 50 | | 67 (36.8) | 182 (51.0) | < **0.001*** |
| Aged < 50 | | 115 (63.2) | 175 (49.0) | |
| **Neurological symptoms, n (%)** | | | | |
| Headache | | 38 (20.8) | 52 (14.6) | 0.08 |
| Dizziness | | 14 (7.7) | 23 (6.4) | 0.59 |
| Smell/taste impairment | | 26 (14.2) | 29 (8.1) | **0.03*** |
| **Non-neurological symptoms, n (%)** | | | | |
| Fever | | 122 (66.7) | 172 (48.2) | < **0.001*** |
| Cough | | 144 (78.7) | 224 (62.7) | < **0.001*** |
| Dyspnea | | 112 (61.2) | 217 (60.8) | > 0.99 |
| Chest pain | | 15 (8.2) | 19 (5.3) | 0.19 |
| Fatigue | | 24 (13.1) | 77 (21.6) | **0.01*** |
| Abdominal pain | | 6 (3.3) | 15 (4.2) | 0.81 |
| Diarrhea | | 32 (17.5) | 40 (11.2) | **0.04*** |
| Nausea and vomiting | | 33 (18.0) | 57 (16.0) | 0.54 |
| chills | | 44 (24.0) | 54 (15.1) | **0.01*** |
| **comorbidities, *n* (%)** | | | | |
| Chronic heart disease | | 15 (8.2) | 55 (15.4) | **0.02*** |
| Chronic pulmonary disease | | 1 (0.5) | 3 (0.8) | > 0.99 |
| Asthma | | 14 (7.7) | 18 (5.0) | 0.25 |
| Diabetes mellitus | | 37 (20.2) | 85 (23.8) | 0.34 |
| Hematologic disease | | 4 (2.2) | 11 (3.1) | 0.78 |
| Chronic kidney disease | | 7 (3.8) | 24 (6.7) | 0.24 |
| Smoking | | 15 (8.2) | 28 (7.8) | 0.86 |
| **Respiratory involvement** | | | | |
| SaO2, *n* (%) | Normal (98%–100%) | 41(22.4) | 70 (19.6) | 0.73 |
| | Insufficient (95%–97%) | 78 (42.6) | 151 (42.3) | |
| | Decreased (90%–94%) | 42 (23.0) | 82 (23.0) | |
| | Critical (< 90%) | 22 (12.0) | 54 (15.1) | |
| Respiratory rate, *n* (%) | Normal (12–20) | 134 (73.2) | 282 (79.0) | 0.16 |
| | Tachypnea (> 20) | 49 (26.8) | 75 (21.0) | |
| **ICU admission, *n* (%)** | | | | |
| ICU admission | | 21(11.5) | 61(17.1) | 0.10 |
| **Lab data, mean ± SD** | | | | |
| CRP (mg/L) | | 29.60 ± 18.83 | 39.18 ± 22.14 | 0.54 |
| LDH (mg/L) | | 616.03 ± 328.34 | 728.15 ± 990.23 | **0.04*** |
| Creatinine (mg/L) | | 1.18 ± 1.24 | 1.35 ± 1.28 | **0.01*** |
| AST (U/L) | | 48.34 ± 28.53 | 67.26 ± 183.86 | 0.64 |

(Continues)

**TABLE 2** | (Continued)

| Characteristics | Myalgia $N = 193$ | Without myalgia $N = 357$ | $p$ value |
|---|---|---|---|
| ALT (U/L) | 49.04 ± 28.19 | 62.21 ± 134.90 | 0.84 |
| WBC (cell/mm$^2$) | 6.88 ± 6.14 | 7.70 ± 6.80 | 0.15 |
| Plt (cell/mm$^2$) | 206.02 ± 78.17 | 197.75 ± 84.30 | 0.21 |

The present study investigated neurological symptoms in 540 hospitalized COVID-19 patients across different stages of disease severity. The most frequent neurological symptom was myalgia, followed by headache, smell/taste impairment, and dizziness. These findings align with two previous systematic reviews and meta-analyses, identifying myalgia as the most common neurological manifestation [20]. However, other studies have reported different results, with Amanat et al. highlighting smell/taste impairment and Fogang et al. identifying headache as the most prevalent symptom [30, 31]. These discrepancies may stem from variations in sample sizes, methodologies, and assessment criteria across studies.

## 5 | Myalgia

The underlying mechanisms of myalgia in COVID-19 patients may include direct viral invasion of muscle tissue or an infection-mediated immune response [32].

Regarding the association of myalgia with demographic data, a Bulgarian study reported that myalgia was significantly more prevalent in patients over 60, which contrasts with our findings. This discrepancy may be explained by the younger mean age of our study population, as well as the larger and more diverse sample size, which included a broader age range. However, the same study found no significant sex-related differences in myalgia prevalence, aligning with our results [33].

Furthermore, Kavaz et al. reported that patients with smell/taste impairment had a significantly higher prevalence of myalgia, which is consistent with our findings [34]. This correlation may be attributed to shared underlying mechanisms, including viral neurotropism (through binding of the virus to ACE-2 receptors) and inflammatory response (due to increased pro-inflammatory cytokines) [34–37].

The relationship between myalgia and comorbidities is also noteworthy. The significant correlation between chronic heart disease and myalgia observed in our study may be partially mediated by the role of anxiety, which has been associated with both cardiovascular disease and the severity of myalgia in COVID-19 patients [33, 38, 39].

Özlü et al. investigated the prevalence of respiratory involvement and other symptoms (including cough, sore throat, headache, nausea, diarrhea, smell/taste loss, nasal congestion, dyspnea, and weakness) in COVID-19 patients with myalgia and found no significant correlation between myalgia and these factors. Their findings regarding respiratory involvement were consistent with ours; however, they differed in the correlation between myalgia and other symptoms. A possible explanation for this difference is the methodological approach used in their study, where all neurological and non-neurological symptoms in patients with myalgia were grouped and analyzed collectively. In contrast, our study categorized non-neurological symptoms separately and assessed the correlation of each symptom with myalgia, leading to different results. This approach revealed a significantly higher prevalence of fever, cough, fatigue, and abdominal pain in patients with myalgia in our study [40].

In terms of myalgia as a predictive indicator for ICU admission, an Iranian study stated that myalgia was significantly more prevalent in patients with ICU admission which differs from our findings [41]. An explanation for this discrepancy may stem from the higher rate of ICU admission in the mentioned study (more than half of the patients), suggesting a poorer overall prognosis compared to our study population. The lower ICU admission rate in our study may reflect differences in disease severity or patient characteristics.

Comparing the inflammatory parameters of COVID-19 patients with and without myalgia, we found no significant differences in the levels of CRP, WBC, AST, ALT, and platelets between the two groups, which was consistent with prior studies [37, 38, 42]. However, a notable finding was that while both LDH and creatinine levels were elevated in both the myalgia and non-myalgia groups, the extent of the increase was significantly lower in the myalgia group compared to the non-myalgia group. This observation could suggest differences in the underlying mechanisms of tissue damage or metabolic dysfunction in COVID-19 patients with myalgia. More studies are needed to explore these patterns further, particularly to see if lower LDH and creatinine levels are linked to faster recovery or less severe tissue damage. Long-term studies could also help understand if these trends change as the disease progresses.

## 6 | Headache

In our study, headache emerged as the second most common neurological symptom. Previous review has indicated that headaches occur more frequently in COVID-19 patients than in the general population [43]. Consistent with our findings, Poncet et al. and Garcia et al. found no significant association between headache occurrence and age or sex [44, 45]. However, some studies have reported that headaches were significantly more common in younger patients, which may be attributed to the older mean age of their study populations [46–49]. Additionally, Caronna et al. and Trigo et al. found that female COVID-19 patients experienced headaches significantly more

**TABLE 3** | Anticipated risk for headache based on patient characteristics.

| Characteristics | | Headache $N = 90$ | Without headache $N = 450$ | $p$ value |
|---|---|---|---|---|
| **Sex, *n* (%)** | | | | |
| Female | | 37 (41.1) | 191 (42.4) | 0.90 |
| Male | | 53 (58.9) | 259 (57.6) | |
| **Age, *n* (%)** | | | | |
| Aged > 50 | | 36 (40.0) | 213 (47.4) | 0.20 |
| Aged < 50 | | 54 (60.0) | 236 (52.6) | |
| **Neurological symptoms, *n* (%)** | | | | |
| Dizziness | | 11 (12.2) | 26 (5.8) | **0.03*** |
| Smell/taste impairment | | 15 (16.7) | 40 (8.9) | **0.03*** |
| Myalgia | | 38 (42.2) | 145 (32.2) | 0.08 |
| **Non-neurological symptoms, *n* (%)** | | | | |
| Fever | | 56 (62.2) | 238 (52.9) | 0.13 |
| Cough | | 56 (62.2) | 312 (69.3) | 0.21 |
| Dyspnea | | 52 (57.8) | 277 (61.6) | 0.55 |
| Chest pain | | 8 (8.9) | 26 (5.8) | 0.33 |
| Fatigue | | 18 (20) | 83 (18.4) | 0.76 |
| Abdominal pain | | 3 (3.3) | 18 (4.0) | > 0.99 |
| Diarrhea | | 16 (17.8) | 56 (12.4) | 0.176 |
| Nausea and vomiting | | 20 (22.2) | 70 (15.6) | 0.12 |
| chills | | 20 (22.2) | 78 (17.3) | 0.29 |
| **Comorbidities, *n* (%)** | | | | |
| Chronic Heart disease | | 9 (10.0) | 61 (13.6) | 0.49 |
| Chronic pulmonary disease | | 2 (2.2) | 2 (0.4) | 0.13 |
| Asthma | | 3 (3.3) | 29 (6.4) | 0.33 |
| Diabetes mellitus | | 16 (17.8) | 106 (23.6) | 0.23 |
| Hematologic disease | | 3 (3.3) | 12 (2.7) | 0.72 |
| Chronic kidney disease | | 2 (2.2) | 29 (6.4) | 0.14 |
| Smoking | | 7 (7.8) | 36 (8.0) | > 0.99 |
| **Respiratory involvement, *n* (%)** | | | | |
| SaO2, *n* (%) | Normal (98%–100%) | 18 (20.0) | 93 (20.7) | 0.82 |
| | Insufficient (95%–97%) | 40 (44.4) | 189 (42.0) | |
| | Decreased (90%–94%) | 22 (24.4) | 102 (22.7) | |
| | Critical (< 90%) | 10 (11.1) | 66 (14.7) | |
| Respiratory rate, *n* (%) | Normal (12–20) | 76 (84.4) | 340 (75.6) | 0.07 |
| | Tachypnea (> 20) | 14 (15.6) | 110 (24.4) | |
| **ICU admission, *n* (%)** | | | | |
| ICU admission | | 7 (7.8) | 75 (16.7) | **0.03*** |
| **Lab data, mean ± SD** | | | | |
| CRP (mg/L) | | 28.18 ± 17.18 | 36.68 ± 21.79 | 0.26 |
| LDH (mg/L) | | 680.44 ± 340.85 | 693.93 ± 904.63 | 0.33 |
| Creatinine (mg/L) | | 1.21 ± 0.87 | 1.31 ± 1.33 | 0.73 |
| AST (U/L) | | 50.94 ± 29.36 | 62.98 ± 165.29 | 0.65 |

(Continues)

**TABLE 3** | (Continued)

| Characteristics | Headache $N = 90$ | Without headache $N = 450$ | $p$ value |
|---|---|---|---|
| ALT (U/L) | $48.85 \pm 27.03$ | $59.58 \pm 121.25$ | 0.91 |
| WBC (cell/mm$^2$) | $6.47 \pm 3.53*10^3$ | $7.61 \pm 7.04*10^3$ | 0.44 |
| Plt (cell/mm$^2$) | $188.73 \pm 72.40*10^3$ | $203.04 \pm 84.07*10^3$ | 0.32 |

often than males [48, 49]. This disparity could be explained by the lower proportion of women in their study groups compared to ours. In agreement with our results, Carrona et al. and Trigo et al. stated that the presence of dizziness and smell/taste impairment were strong indicators of headaches in COVID-19 patients [48, 49]. Following exposure to the SARS-CoV virus through inhalation, the virus can spread to the olfactory bulb and further disseminate to the piriform cortex, brainstem, and spinal cord. The presence of the virus in the brainstem, where respiratory rhythm is regulated, may impact respiratory effort [50]. Given these shared pathways of viral spread and the fact that hypoxemia induced by respiratory distress can contribute to symptoms such as headache [51] and dizziness [52], our findings on the significant correlation of headache with dizziness and smell/taste impairment may be explained.

Supporting our findings on the correlation between prognostic factors and headache, Gonzalez et al. reported that oxygen saturation (SatO2) and respiratory rate were not significantly affected by the presence of headache [46]. Similarly, Membrilla et al, observed that patients experiencing headaches were significantly less likely to require ICU admission during hospitalization [47]. Together, these findings suggest that the presence of headaches may be linked to a more favorable prognosis in COVID-19 patients.

## 7 | Smell/Taste Impairment

Regarding the novel presence of smell/taste impairment in COVID-19 patients, Previous systematic reviews have reported that at least one in three COVID-19 patients experiences either smell impairment, taste impairment, or both, identifying these symptoms as early indicators of the disease [49]. Several hypotheses were proposed related to the underlying pathophysiology of these impairments including direct damage to olfactory and gustatory receptors by SARS-CoV-2, the binding of the virus to ACE2 receptors present in the oral and olfactory mucosa, and inflammatory responses by releasing cytokines like IL-6 [53].

In assessing the correlation between patient characteristics (age and sex) and the presence of smell/taste impairment, we found that such impairments occurred significantly more frequently in younger patients. This finding aligns with the results reported by Lee et al. However, unlike Lee et al., our study did not find a significant correlation between smell/taste impairment and the patient's sex [54].

The significant correlation between smell/taste impairment, headache, and myalgia in COVID-19 patients can be explained by shared anatomical and physiological pathways, particularly involving the trigeminal nerve and vascular dysfunction. The trigeminal nerve (comprising V1, V2, and V3 branches) plays a central role in transmitting sensory and nociceptive signals from the face, nasal cavity, and oral mucosa to the Trigeminocervical complex (TCC), which processes pain. In COVID-19, inflammatory activation of this pathway can lead to headaches by sensitizing pain pathways and disrupting autonomic functions. Additionally, since the V1 and V2 branches of the trigeminal nerve innervate the nasal cavity, their involvement in inflammation can impair smell and taste by disrupting sensory transmission and altering autonomic signaling [55]. Moreover, SARS-CoV-2 infection can lead to vascular dysfunction, which may impair blood flow to sensory organs and muscle tissues, resulting in sensory impairments and myalgia. The virus can lead to damage the endothelial cells (endothelitis), micro thrombosis, and capillary congestion, which disturbs the normal flow of blood and oxygen delivery to the tissues. These microvascular changes can lead to symptoms such as muscle weakness and pain [56]. Consistent with our findings, a study by Demiryurek et al. also reported a significant correlation between headache and hyposmia/anosmia in COVID-19 patients. They attributed these results to pathophysiological mechanisms involving the trigeminal and olfactory nerves, linked to ACE-2 expression in nasal epithelial cells, and the shared mechanism of viral invasion affecting these cells [57].

The evidence from our study highlights several key findings regarding the impact of mild to moderate COVID-19 on the sense of smell or taste. Patients with mild COVID-19 who experience smell/taste impairment are less likely to have coexisting conditions such as chronic heart disease, chronic pulmonary disease, asthma, diabetes, or a history of smoking. This aligns with findings from studies by Kavaz et al. and Johnson et al., [34, 58] suggesting that these sensory impairments are more common in individuals without significant underlying health issues. Furthermore, patients with smell/taste impairment tend to have lower levels of certain biomarkers, including C-reactive protein (CRP), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), along with a significantly greater decrease in lactate dehydrogenase (LDH) levels compared to those without these sensory deficits. This may indicate a less severe inflammatory response or distinct pathophysiological mechanisms in these patients. Lastly, patients experiencing smell/taste impairment are significantly less likely to require ICU admission, suggesting that these sensory deficits are associated with a milder course of COVID-19. Together, these findings support the idea that smell/taste impairment is more common in less severe cases of COVID-19 and may serve as a marker for a milder disease trajectory.

**TABLE 4** | Anticipated risk for smell/taste impairment based on patient characteristics.

| Characteristics | | Smell/taste impairment $N = 55$ | Without Smell/taste impairment $N = 485$ | $p$ value |
|---|---|---|---|---|
| **Sex, *n* (%)** | | | | |
| Female | | 22 (40) | 206 (42.5) | 0.77 |
| Male | | 33 (60) | 279 (57.5) | |
| **Age, *n* (%)** | | | | |
| Aged > 50 | | 17 (30.9) | 232 (47.9) | **0.02*** |
| Aged < 50 | | 38 (69.1) | 252 (52.1) | |
| **Neurological symptoms, *n* (%)** | | | | |
| Headache | | 15 (27.3) | 75 (15.5) | **0.03*** |
| Dizziness | | 4 (7.3) | 33 (6.8) | 0.78 |
| Myalgia | | 26 (47.3) | 157 (32.4) | **0.03*** |
| **Non-neurological symptoms, *n* (%)** | | | | |
| Fever | | 37 (67.3) | 257 (53.0) | **0.04*** |
| Cough | | 40 (72.7) | 328 (67.6) | 0.54 |
| Dyspnea | | 37 (67.3) | 292 (60.2) | 0.38 |
| Chest pain | | 8 (14.5) | 26 (5.4) | **0.01*** |
| Fatigue | | 7 (12.7) | 94 (19.4) | 0.27 |
| Abdominal pain | | 2 (3.6) | 19 (3.9) | > 0.99 |
| Diarrhea | | 12 (21.8) | 60 (12.4) | 0.06 |
| Nausea and vomiting | | 16 (29.1) | 74 (15.3) | **0.01*** |
| Chills | | 12 (21.8) | 86 (17.7) | 0.46 |
| **Comorbidities, *n* (%)** | | | | |
| Chronic Heart disease | | 5 (9.1) | 65 (13.4) | 0.52 |
| Chronic pulmonary disease | | 1 (1.8) | 3 (0.6) | 0.35 |
| Asthma | | 2 (3.6) | 30 (6.2) | 0.76 |
| Diabetes mellitus | | 13 (23.6) | 109 (22.5) | 0.84 |
| Hematologic disease | | 1 (1.8) | 14 (2.9) | > 0.99 |
| Chronic kidney disease | | 3 (5.5) | 28 (5.8) | > 0.99 |
| smoking | | 5 (9.1) | 38 (7.8) | 0.79 |
| **Respiratory involvement** | | | | |
| SaO2, *n* (%) | Normal (98%–100%) | 13 (23.6) | 98 (20.2) | 0.09 |
| | Insufficient (95%–97%) | 30 (54.5) | 199 (41.0) | |
| | Decreased (90%–94%) | 8 (14.5) | 116 (23.9) | |
| | Critical (< 90%) | 4 (7.3) | 72 (14.8) | |
| Respiratory rate, *n* (%) | Normal (12–20) | 41 (74.5) | 375 (77.3) | 0.61 |
| | Tachypnea (> 20) | 14 (25.5) | 110 (22.7) | |
| **ICU admission, *n* (%)** | | | | |
| ICU admission | | 2(3.6) | 80(16.5) | **< 0.001*** |
| **Lab data, mean ± SD** | | | | |
| CRP (mg/L) | | 29.25 ± 20.09 | 35.96 ± 21.49 | 0.54 |
| LDH (mg/L) | | 536.23 ± 208.97 | 708.75 ± 876.09 | **0.01*** |
| Creatinine (mg/L) | | 1.05 ± 0.25 | 1.32 ± 1.33 | 0.24 |

(Continues)

**TABLE 4** | (Continued)

| Characteristics | Smell/taste impairment $N = 55$ | Without Smell/taste impairment $N = 485$ | $p$ value |
|---|---|---|---|
| AST (U/L) | 44.12 ± 19.93 | 62.91 ± 159.46 | 0.35 |
| ALT (U/L) | 48.60 ± 23.77 | 58.88 ± 117.37 | 0.70 |
| WBC (cell/mm$^2$) | 5.50 ± 2.06 | 7.64 ± 6.89 | 0.10 |
| Plt (cell/mm$^2$) | 209.48 ± 90.55 | 48.60 ± 23.77 | 0.65 |

## 8 | Dizziness

Dizziness is a common neurological symptom among those diagnosed with COVID-19, which can be categorized into various types, such as vertigo, presyncope, disequilibrium, and lightheadedness, based on the patient's description [59, 60]. Dizziness can occur due to the virus directly affecting the vestibular system or as a secondary effect of conditions like respiratory distress, hypoxia, hypotonia, dehydration, and sepsis-induced fever [52]. Another explanation for the common occurrence of dizziness could be related to the pandemic effect, as stated by a Brazilian study that lack of social communication could aggravate depression, anxiety, sleep quality, and dietary habits resulting in different types of dizziness even if the vestibular system is not affected by the virus [61]. To the best of our knowledge, few studies assessed predicted factors of dizziness in COVID-19 patients specifically compared to other neurological symptoms [59, 62].

In light of the association between a patient's demographic data (sex and age) and the occurrence of dizziness, some studies have reported a significantly higher incidence of dizziness among females, while age differences were not statistically significant [59, 63, 64]. Our findings are consistent with these studies regarding age, as we observed no significant difference between patients with and without dizziness. However, unlike previous research, we did not find a significant association between the female sex and dizziness. This discrepancy may stem from variations in study populations, sample sizes, or methodological approaches, underscoring the need for further research to clarify the influence of sex on dizziness prevalence.

In evaluating the prevalence of underlying diseases in COVID-19 patients with dizziness, Korkmaz et al. found no significant differences in the occurrence of coronary or cardiac diseases, hypertension, or other underlying conditions such as diabetes, renal failure, asthma, and chronic respiratory disease, which aligns with our findings [64]. Moreover, the study conducted in Italy that assessed different types of dizziness in COVID-19 patients found that a previous history of smoking was associated with a higher probability of dizziness, which contrasts with our findings [59]. This discrepancy may be attributed to the larger study population in the Italian study, which could have provided greater statistical power to detect such associations. Differences in demographic characteristics, regional variations, or methodological approaches between the studies may also have contributed to these contrasting results. The mentioned Italian study, along with two other studies, also assessed different nonspecific neurological symptoms as predictors for dizziness in which headache had a positive correlation with dizziness aligns with our study [52, 59, 65]. The co-occurrence of dizziness and headache in COVID-19 patients can be explained by interconnected mechanisms related to the disease's pathophysiology, including the direct invasion of SARS-CoV-2 into the central nervous system or the hyperinflammatory state (cytokine storm) observed in affected individuals [47, 48, 52].

According to Obeidant et al. [63], respiratory symptoms during the acute phase of COVID-19 were significantly correlated with dizziness. On the contrary, the study determined no discernible difference in gastrointestinal symptoms between the groups with and without dizziness. This goes against our findings, which revealed that dizziness was associated with a higher probability of abdominal pain, nausea, and vomiting. These discrepancies may be because Obeidant et al. assessed dizziness in patients with long COVID-19 after the acute phase of the disease. Lastly, as our findings demonstrated no significant difference in ICU admissions and raised inflammatory markers between patients with and without dizziness, we can relate our results to the previous studies that stated dizziness had no significant correlation with the severity and the mortality rate of the COVID-19 disease [64, 66, 67].

This study has some limitations. The first was associated with its cross-sectional design, which limits the ability to establish causal relationships or assess long-term outcomes. Second, the sample size utilized for this study may not indicate the overall population of hospitalized COVID-19 patients, particularly given the regional focus on Bandar Abbas, Iran, during the Delta-dominant period. This introduces potential regional biases and limits generalizability to other geographic areas or COVID-19 variants. Third, the single-center design and retrospective data collection may have introduced selection bias and timing bias, respectively, affecting the accuracy and interpretation of the results. Fourth, the study did not account for potential confounding factors, such as vaccination status, pre-existing neurological conditions, or variations in healthcare access, which could influence the prevalence of neurological symptoms. Additionally, infection control precautions restricted the use of diagnostic procedures such as magnetic resonance imaging (MRI) and electromyography (EMG), meaning that the neurological symptoms in our study were mostly subjective descriptions provided by the patients. Finally, the absence of a regression model also represents a limitation in this study, and we plan to incorporate it in future research to better examine the predictive links between the variables involved.

**TABLE 5** | Anticipated risk for dizziness based on patient characteristics.

| Characteristics | | Dizziness $N = 37$ | Without dizziness $N = 503$ | $p$ value |
|---|---|---|---|---|
| **Sex, *n* (%)** | | | | |
| Female | | 16 (43.2) | 212 (42.1) | > 0.99 |
| Male | | 21 (56.8) | 291 (57.9) | |
| **Age, *n* (%)** | | | | |
| Aged > 50 | | 18 (48.6) | 231 (46.0) | 0.86 |
| Aged < 50 | | 19 (51.4) | 271 (54.0) | |
| **Neurological symptoms, *n* (%)** | | | | |
| Headache | | 11 (29.7) | 79 (15.7) | **0.03*** |
| Smell/taste impairment | | 4 (10.8) | 51 (10.1) | 0.78 |
| Myalgia | | 14 (37.8) | 169 (33.6) | 0.59 |
| **Non-neurological symptoms, *n* (%)** | | | | |
| Fever | | 20 (54.1) | 274 (54.5) | > 0.99 |
| Cough | | 25 (67.6) | 343 (68.2) | > 0.99 |
| Dyspnea | | 23 (62.2) | 306 (60.8) | > 0.99 |
| Chest pain | | 3 (8.1) | 31 (6.2) | 0.50 |
| Fatigue | | 6 (16.2) | 95 (18.9) | 0.82 |
| Abdominal pain | | 4 (10.8) | 17 (3.4) | **0.04*** |
| Diarrhea | | 6 (16.2) | 66 (13.1) | 0.61 |
| Nausea and vomiting | | 13 (35.1) | 77 (15.3) | < **0.001*** |
| Chills | | 7 (18.9) | 91 (18.1) | 0.82 |
| **Comorbidities, *n* (%)** | | | | |
| Chronic heart disease | | 3 (8.1) | 67 (13.3) | 0.45 |
| Chronic pulmonary disease | | 1 (2.7) | 3 (0.6) | 0.24 |
| Asthma | | 2 (5.4) | 30 (6.0) | > 0.99 |
| Diabetes mellitus | | 8 (21.6) | 114 (22.7) | 0.88 |
| Hematologic disease | | 1 (2.7) | 14 (2.8) | > 0.99 |
| Chronic kidney disease | | 3 (8.1) | 28 (5.6) | 0.46 |
| Smoking | | 1 (2.7) | 42 (8.3) | 0.34 |
| **Respiratory involvement, *n* (%)** | | | | |
| SaO2, *n* (%) | Normal (98%–100%) | 12 (32.4) | 99 (19.7) | 0.08 |
| | Insufficient (95%–97%) | 9 (24.3) | 220 (43.7) | |
| | Decreased (90%–94%) | 11 (29.7) | 113 (22.5) | |
| | Critical (< 90%) | 5 (0.9) | 71 (13.1) | |
| Respiratory rate, *n* (%) | Normal (12–20) | 29 (78.4) | 387 (76.9) | > 0.99 |
| | Tachypnea (> 20) | 8 (21.6) | 116 (23.1) | |
| **ICU admission, *n* (%)** | | | | |
| ICU admission | | 6 (16.2) | 76 (15.1) | 0.81 |
| **Lab data, mean ± SD** | | | | |
| CRP (mg/L) | | 33.67 ± 20.18 | 35.72 ± 21.56 | 0.83 |
| LDH (mg/L) | | 693.68 ± 239.61 | 691.49 ± 861.32 | 0.09 |
| Creatinine (mg/L) | | 1.31 ± 0.92 | 1.29 ± 1.29 | 0.50 |
| AST (U/L) | | 52.33 ± 26.18 | 61.61 ± 156.79 | 0.22 |

(Continues)

**TABLE 5** | (Continued)

| Characteristics | Dizziness $N = 37$ | Without dizziness $N = 503$ | $p$ value |
|---|---|---|---|
| ALT (U/L) | $51.66 \pm 28.22$ | $58.26 \pm 115.25$ | 0.53 |
| WBC (cell/mm$^2$) | $6.54 \pm 4.05$ | $7.48 \pm 6.73$ | 0.27 |
| Plt (cell/mm$^2$) | $195.45 \pm 103.20$ | $200.96 \pm 80.55$ | 0.65 |

## 9 | Conclusion

This study highlights the significant burden of neurological manifestations, including myalgia, headache, smell/taste impairment, and dizziness, with myalgia being the most frequent symptom. These findings underscore the multifaceted impact of SARS-CoV-2 on the nervous system, potentially mediated by direct viral neurotropism, inflammatory responses, or vascular dysfunction. Key associations emerged, such as the correlation of smell/taste impairment and myalgia with younger age and milder disease severity, and the co-occurrence of headache, dizziness, and smell/taste impairment, suggesting shared pathophysiological pathways. Notably, patients with smell/taste impairment or myalgia exhibited less severe inflammatory markers (e.g., lower creatinine and LDH), and reduced ICU admission rates were observed in patients with headache and smell/taste impairment, indicating these symptoms may serve as markers for a milder disease trajectory.

Our results emphasize the critical importance of recognizing and monitoring neurological symptoms in COVID-19 patients, as they offer valuable insights into disease progression, severity, and potential outcomes. By identifying patterns such as the association of some COVID-19 symptoms with milder disease trajectories, healthcare providers may better tailor management strategies and allocate resources effectively. However, future studies should involve larger, more diverse populations and incorporate advanced diagnostic methods, such as neuroimaging and electrophysiological testing, to validate and expand upon these observations. Such efforts will enhance our understanding of the neurological impact of COVID-19 and improve patient care in both acute and long-term settings.

### Author Contributions

**Ahmadagha Negahi:** visualization, investigation, writing – review and editing, supervision. **Parivash Davoodian:** conceptualization, visualization, supervision, methodology, writing – review and editing. **Omid Esmaeili:** writing – original draft, writing – review and editing, methodology, supervision. **Reza Nabavi:** investigation, writing – original draft, methodology, visualization, resources. **Niloufar Khatibzade-Nasari:** writing – review and editing, writing – original draft, project administration, formal analysis. **Mobina Imeri:** writing – original draft, writing – review and editing.

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The authors have nothing to report.

### Ethics Statement

The Ethics Committee of Hormozgan University of Medical Sciences approved the study protocol (IR.HUMS.REC.1399.437), and each patient gave verbal informed consent before participating in the study.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

### Transparency Statement

The lead author Niloufar Khatibzade-Nasari affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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