Severe acute respiratory syndrome coronavirus 2 infection altered the factors associated with headache: evidence from a multicenter community-based case–control study

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Abstract
Introduction: Headache is one of the significant global public health concerns. Furthermore, it is a standard feature of patients with acute and postacute COVID-19.

Objectives: This study aimed to estimate and compare the prevalence of headaches among postacute COVID and non-COVID individuals and identify and contrast the risk factors between both groups.

Methods: This was a multicenter case–control study. Individuals who had recovered from acute SARS-CoV-2 infection were considered “case”, and those who never tested positive for COVID-19 were considered “control.” Headaches were measured using the musculoskeletal subscale of the subjective health complaints scale. Multiple logistic regression analysis was used to identify the predictors of headaches.

Results: A total of 878 individuals (439 cases) aged 38.30 ± 12.77 years (mean ± standard deviation) participated in this study. The prevalence of headaches was 26.2% among COVID-19 survivors; however, only 10.7% of unaffected participants reported headaches at the same time. Regression analyses suggested that the recovery duration from acute COVID-19 ≥ 90 days (adjusted odds ratio [AOR] = 2.03, CI = 1.13–3.65) was the only predictor of headache among postacute COVID-19 survivors. However, the female gender (AOR = 3.09, 95% CI = 1.51–6.32), members of a joint family (AOR = 1.99, 95% CI = 1.02–3.90), and city dwellers (AOR = 2.43, 95% CI = 0.94–6.25) were the predictor of headache among non-COVID participants.

Conclusion: This study found a higher prevalence of headaches among COVID-19 survivors. In addition, predictors of headache among cases and controls were unmatched, indicating heterogenous impact of COVID-19 on human health. The health care providers should be informed of the study’s results when discussing better practices to mitigate the burden of headaches.

Keywords: Coronavirus infection, Case–control study, Global burden of diseases, Headache, Long-COVID, Pandemic

1. Introduction

The Global Burden of Disease Study 2019 recognized headaches as a significant global public health concern. More than half of the world’s population suffers from active headache disorder; however, the 1-day prevalence of headaches was estimated at 15.8%. The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already affected 0.60 billion people since it started in 2019. The broader and heterogeneous manifestation of COVID-19 clinical features in the acute phase mainly includes fever, cough, body ache, tiredness, odor, and tastelessness, and headache. A systemic review and meta-analysis found that the prevalence of headaches was 2-fold higher among patients with COVID-19 than that of non-COVID individuals. Furthermore, a previous study suggested that clinical features such as headaches found in acute illness could significantly predict the same feature as a long-term post-COVID sequel. Therefore, the high prevalence of headaches as a clinical
feature of acute illness indicates that this problem may remain the same among patients with post-acute COVID-19. Female sex, family history, geographical location, climate, and mental health symptoms are generally significantly associated with headaches. Nonetheless, SARS-CoV-2 infection tremendously alters the neuropsychiatry of the survivors regardless of the biological sex and age. Furthermore, having a novel, the life-threatening disease produces heterogeneous psychological stress among sufferers. In addition, pandemic-induced multidimensional uncertainties are also responsible for many mental health and neurological disorders such as headaches. Therefore, the cumulative impact of COVID-19 on headaches might be unprecedentedly diversified.

Previous studies measured the overall prevalence of headaches among the general population and mainly hospital-discharged postacute COVID-19 survivors during the pandemic. However, a significant portion of the patients with COVID-19 experienced mild symptoms and did not require hospital admission. The data regarding the association between SARS-CoV-2 infection and headache among general community dwellers are scarce. Furthermore, to the best of our knowledge, no study compares the prevalence of headaches in patients with postacute COVID-19 with their age and gender-matched healthy controls at the same point in time. In addition, the prevalence distribution of headaches among the subgroup of patients with postacute COVID-19 living in the community is mainly unknown. This study aimed to estimate and compare the prevalence of headaches among postacute COVID and non-COVID community dwellers and identify and contrast the risk factors between both groups.

2. Methods

2.1 Study design and definition of case and control

A multicenter case–control study was conducted in Bangladesh. This study included participants who lived at the community level. Individuals who had recovered from acute SARS-CoV-2 infection were considered “case”, and those who never tested positive for COVID-19 were considered “control” for this study.

2.2 Definition of the patient with postacute COVID-19

Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Postacute COVID-19 is defined as persistent symptoms and delayed or long-term complications beyond 4 weeks from the onset of symptoms. For the case group, we collected data from the individuals who tested positive at least 6 weeks ago. Therefore, the patients were considered postacute COVID survivors after 6 weeks of acute symptoms.

2.3 Sample size determination

This study had 1.9 million laboratory-tested COVID-19–positive individuals in Bangladesh. A formula that allows a confidence level of 95%, a response distribution of 50%, and a margin of 5% error was used that estimated a minimum sample size of 385 participants for case data. To calculate the total sample, a 1:1 case–control ratio allowed 878 participants.

2.4 Inclusion and exclusion criteria

For the case data, this study included patients with postacute COVID-19 aged 18 years and older living in Bangladesh. Control data were collected from the individuals matched with the age and gender of the cases. For both the groups, we excluded individuals who were patients with acute COVID-19 and unreliable, ie, participants diagnosed with a severe psychological disorder. Furthermore, bedridden, pregnant women and patients with severe chronic health conditions such as rheumatoid arthritis, stroke, or cancer were excluded from this study.

2.5 Data source and data collection

Particulars of 600 laboratory-tested postacute COVID-19–positive individuals were collected from conveniently selected government-affiliated 10 COVID-19 testing centres in Bangladesh. Primarily, selected participants were contacted over the telephone to check eligibility criteria. After considering inclusion and exclusion criteria, an interview was scheduled with 450 participants. The study aims were explained, and informed consent was taken from all the expected participants to participate, collect, and analyze their data. Finally, participants were interviewed face to face using a paper-based semistructured questionnaire at their homes or workplaces. This study found 439 data eligible for the “case” group. Data from 439 non-COVID participants were subsequently taken. “Control” participants were chosen from the case’s eligible family members, neighbourhoods, or office colleagues. Therefore, 878 data were collected between February 24 and April 7, 2022. Six previously trained expert researchers were engaged with data collection processes.

Optimal confidentiality was maintained throughout the data collection process. Data were collected anonymously and stored in a password-encrypted computer unidentifiable way. All the identifiable particulars of each participant were destroyed immediately after data collection.

2.6 Questionnaire

The first part of the questionnaire recorded various sociodemographic information: gender, age, marital status, education, employment status, monthly household income in Bangladeshi taka, and present address. The second part has gathered information regarding participants’ chronic disease diagnosis (eg, hypertension, diabetes, kidney disease, and asthma), tobacco use history, and regular physical exercise habit. These questions were answered using dichotomous options (yes/no). In the third part (only for case data), participants were asked to provide information about their COVID-19 illness. Information about the severity of the symptoms (mild, moderate, severe, and very severe) and the treatment facility they had taken (home, hospital’s general ward, or hospital’s intensive care unit) was recorded. The severity of the symptoms of COVID-19 was recorded from patients’ perceptions. In addition, the duration of being tested negative for COVID-19 was also recorded for postacute COVID-19 subjects.

The final part of the questionnaire measured headaches using the musculoskeletal subscale of subjective health complaints produced by Eriksen et al. that estimated headaches experienced in the past 30 days. Participants were asked to rate the occurrence of headaches with 4 answering categories. The severity of headache is rated on a 4-point scale (0 = none, 1 = some, 2 = much, and 3 = severe). This complaint is also scored for the duration (number of days) during the last 30 days. Severity X duration was used to obtain a total score (0–90), indicating the degree of complaint. In this study, participants who complained
of at least some pain for 3 days (1 × 3 = 3) in the past month and scored ≥3 were considered to have headaches.

2.7 Ethics

Ethical clearance was obtained from the Ethical Review Committee of Uttara Adhunik Medical College and Hospital. Furthermore, prospective registration for the case–control study was obtained from the WHO-endorsed Clinical Trial Registry – India: CTRI/2022/02/040449 [Registered on February 2, 2022]. The STROBE guideline for the case–control study was strictly followed throughout the study. All the invited participants had provided formal informed consent for participation, collection, and analysis of their data.

2.8 Statistics

Statistical Package for the Social Science software (version 22.0; IBM Corp) was used to perform all data analyses for this study. To compute the prevalence, the 4 responses to the headaches question were dichotomized as either having the problem (yes) or does not have the problem (no). Chi-squared tests were used to compare categorical variables with and without headaches. Multiple logistic regression analyses were applied to compute adjusted odds ratios (AOR) with a 95% confidence interval (CI) with headache as a dependent variable and sociodemographic characteristics and clinical and COVID-19 illness-related factors as predictor variables for headache. The statistically significant variables in the 2 descriptive analyses were included in the appropriate regression models. The Hosmer–Lemeshow goodness-of-fit test ensured that the models adequately fit the data. $P$-values <0.05 were considered statistically significant.

3. Results

3.1 Participants’ characteristics

Overall, data of 878 individuals aged 38.3 ± 12.8 years (mean ± standard deviation) were analyzed for this study. Postacute COVID-19 cohort (cases) included 439 individuals (49.2% women) aged 38.3 ± 12.5 years, and the control group consisted of 51.7% of women, and the age of the participants was 38.3 ± 13.0 years.

Tables 1 and 2 show that the study data included a higher number of married participants (case = 85.6% and control = 81.5%), participants with bachelor’s degree (case = 33.9% and control = 34.2%), and service holder (case = 34.4% and control = 33%). Furthermore, a higher number of the participants had household income > $ 45000 (case = 45.1% and control = 39.9%), were from a nuclear family (case = 67.9% and control = 65.4%), were from the city area (case = 68.6% and control = 54.4%), had no morbidity (case = 51.7% and control = 64.5%), and were not a tobacco user (case = 55.1% and control = 67.2%).

Table 2 also displays that most of the participants (36.7%) from the case group recovered from acute COVID more than 180 days ago; however, 49.9% of patients with postacute COVID-19 had mild symptoms, and 65.1% of participants had taken treatment at home.

3.2 Results of descriptive analysis

Overall, 26.2% of COVID-19 survivors reported headaches. The higher headache incidence rate was found in married (28.5%; $P = 0.008$) and homemakers (38.5%; $P = 0.004$). Furthermore, a higher prevalence of headaches was also found among the participants who recovered from COVID-19 recently (35.6%; $P = 0.001$), experienced moderate symptoms (40.4%; $P = 0.001$), and took treatment at the hospital’s general ward (38.8%; $P = 0.023$) (Table 1).

However, the prevalence of headaches among the control group was 10.7%. The incidence of headaches was significantly higher among women (15.4%; $P = 0.001$), aged participants (26.7%; $P = 0.002$), participants from a joint family (16.4%; $P = 0.005$), and semicrylic dwellers (13.8%; $P = 0.05$) (Table 2).

3.3 Results of multiple logistic regression analysis

Two separate regression models were used to determine the predictors of headaches among control and case groups.

Model 1 reported that significantly higher odds of headache had been found only among the participants who recovered from acute COVID-19 recently (≥90 days) (AOR = 2.03, 95% CI = 1.13–3.65) (Table 3).

Regression model 2 (Table 4) suggested that in controls, significantly higher risk of headaches was found among female gender (AOR = 3.09, 95% CI = 1.51–6.32), member of a joint family (AOR = 1.99, 95% CI = 1.02–3.90), and city dwellers (AOR = 2.43, 95% CI = 0.94–6.25).

4. Discussion

This community-based comprehensive case–control study found a significantly higher prevalence of headaches among postacute COVID-19 survivors than the unaffected controls. Traditionally associated factors for headaches such as biological sex, age, and geographical location have been found significant among the control group; nonetheless, these factors were not associated with headaches in the postacute COVID-19 cohort. The findings indicated that the heterogeneous impact of COVID-19 on most organs, including the victim’s nervous system and blood vessels, could also explain the masking of other factors to be significantly associated with headaches.

A systematic review and meta-analysis concluded that headache prevalence ranged from 8% to 15%, depending on the days passed from the onset during the first 6 months after acute SARS-CoV-2 infections. Another 2 systematic review and meta-analyses by Lopez- Leon et al. and Iqbal et al. reported a prevalence of post-COVID headache at 44% and 12%, respectively. However, most of the studies reviewed in these 3 analyses were from high-income settings, Europe and America, and mainly included hospital-discharged patients with post-acute COVID-19. Little was known about the prevalence of headaches among the general population and the population of low-resourced countries during the COVID-19 pandemic. This study estimated the prevalence of headaches among COVID-19 survivors (26.2%) and age and gender-matched healthy individuals (10.7%) living at the community level in Bangladesh. Therefore, this study added pieces of evidence regarding COVID-19–related headaches from both the community people and a low-resourced subcontinental country.

The mechanism of headaches among patients with acute and postacute COVID-19 is largely unknown. Some pathophysiological mechanisms can explain the postacute COVID-19 neurological manifestation, for example, (1) direct neuroinvasion of SARS-CoV-2 that damage the neuronal pathway and (2) passive impacts produced by the virus in the central nervous system.
through hypoxia, hypertension, coagulopathy, and cytokine storm. Primary evidence also indicated that the SARSCoV-2 is permeable to trigeminal nerve terminals and consequently enters the central nervous system through transsynaptic pathways. In addition, SARS-CoV-2 invades meningeal endothelial cells and produces high angiotensin-converting enzyme 2 receptors in the brain, known as the infection’s generator. All these factors undermine preexisting brain conditions or produce novel disorders in the nervous system that may result in headaches or alter the associated factors.
The nature of the exclusive impact of mediating factors in acute, subacute, or long-COVID-19 is unclear; however, in agreement with the other research, our study identified the recovery duration from acute COVID-19 was the only predictor of headache among postacute COVID-19 survivors. Additional investigation is warranted to understand the time course of COVID-19 impact on headaches.

Gender influence on headaches is acknowledged. Generally, a significantly high number of women suffer from headaches. Our study also suggested that in the control group, headaches were 3-fold higher among women than men. Nonetheless, the gender disparity was not observed in the postacute COVID-19 cohort. It is well known that SARS-CoV-2 infection impact differently in men and women, and the prognosis of the illness is also unmatched. A previous survey. This may be due to the use of different scales and scoring for headaches in various studies.

4.1. Limitations

This study had several limitations. First, this study did not measure the participants’ preexisting, chronic, or family history of headaches and the history of headaches during the acute phase of COVID-19. Second, the type of headaches also was not differentiated in this study. Third, only the information on headaches occurrence in the past month had taken; thus, these data cannot measure the chronicity of acute, subacute, or chronic headaches. Fourth, the study found a slightly lower prevalence of headaches among the healthy population compared with the general people’s headaches prevalence found in the previous survey. This may be due to the use of different scales and scoring for headaches in various studies.

Furthermore, the measurement of participants’ BMI would provide more precious results. Finally, the face-to-face interview format may have led to social desirability bias, so more anonymous methods should be used in further studies to tackle the problem. Despite these limitations, this study provides strong evidence of the heterogeneous and harmful impact of SARS-CoV-2 infection on headaches.

5. Conclusion

This study reported a significantly higher prevalence of headaches among postacute COVID-19 survivors than controls. The common predictors of headaches were found to be significant among control data; however, the high prevalence of headaches was equally distributed among the participants included in the case group regardless of their biological sex, age, and living location. Therefore, physicians and public health experts should stress exclusive post-COVID headache management when discussing prevention and treatment strategies for a sizable number of long-COVID patients.

| Variables                  | Adjusted OR | 95% CI      | P     |
|----------------------------|-------------|-------------|-------|
| Biological sex             |             |             |       |
| Female                     | 3.087       | 1.509       | 6.318 | 0.002 |
| Male                       | Reference   |             |       |
| Age group (y)              |             |             |       |
| 18–30                      | Reference   |             |       |
| 31–40                      | 0.456       | 0.142       | 1.425 | 0.175 |
| 41–50                      | 1.768       | 0.733       | 4.265 | 0.205 |
| 51–60                      | 1.899       | 0.705       | 5.118 | 0.205 |
| >60                        | 2.701       | 0.991       | 7.361 | 0.050 |
| Family type                |             |             |       |
| Nuclear family             | Reference   |             |       |
| Joint family               | 1.992       | 1.017       | 3.901 | 0.045 |
| Living location            |             |             |       |
| Village                    | Reference   |             |       |
| City                       | 2.426       | 0.943       | 6.245 | 0.050 |
| Semicity                   | 2.263       | 0.758       | 6.757 | 0.143 |

Table 4

Multiple logistic regression analysis of control data: predictor(s) of headache.

| Variables                  | Adjusted OR | 95% CI      | P     |
|----------------------------|-------------|-------------|-------|
| Variables Adjusted OR 95% CI | P           |             |       |
| Marital status             |             |             |       |
| Single                     | Reference   |             |       |
| Married                    | 1.786       | 0.736       | 4.332 | 0.199 |
| Occupation                 |             |             |       |
| Service                    | 0.721       | 0.344       | 1.510 | 0.386 |
| Business                   | 0.603       | 0.242       | 1.503 | 0.278 |
| Unemployed                 | 0.464       | 0.142       | 1.513 | 0.203 |
| Student                    | 0.286       | 0.032       | 2.564 | 0.264 |
| Home maker                 | 1.705       | 0.743       | 3.913 | 0.208 |
| Health care                | Reference   |             |       |

Table 3

Multiple logistic regression analysis of case data: predictor(s) of headache.

| Variables                  | Adjusted OR | 95% CI      | P     |
|----------------------------|-------------|-------------|-------|
| Days past after recovery from acute COVID-19 |             |             |       |
| ≤90 d                      | 2.030       | 1.130       | 3.645 | 0.018 |
| 91–180 d                   | 1.677       | 0.896       | 3.140 | 0.106 |
| >180 d                     | Reference   |             |       |
| COVID-19 symptom           |             |             |       |
| Mild                       | 0.432       | 0.095       | 1.955 | 0.276 |
| Moderate                   | 1.085       | 0.262       | 4.487 | 0.910 |
| Severe                     | 1.516       | 0.507       | 4.530 | 0.457 |
| Very severe                | Reference   |             |       |
| COVID-19 treatment facility |             |             |       |
| Home                       | 1.850       | 0.448       | 7.631 | 0.395 |
| General ward               | 1.977       | 0.578       | 6.761 | 0.278 |

Bold faces represent significance at a 5% significance level.
Disclosures
The author has no conflicts of interest to declare.

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M. Ali: conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools, or data; and wrote the paper.

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