Characteristics and Outcome of Headache in COVID-19 Patients in a Tertiary Care Centre of Bangladesh

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Abstract

Background: *Although the symptoms of coronavirus disease 2019 (COVID-19) are predominantly respiratory. Headache is one of the most frequent neurological symptoms. There is a wide variation in the prevalence of headaches, and little is known regarding the characteristics and outcomes of headaches in COVID-19 patients. So, this study aimed to determine the characteristics and headache outcomes among COVID-19 patients.*

Methods: *This was a hospital-based prospective cohort study conducted in Dhaka Medical College Hospital from January 2021 to December 2021. Confirmed COVID-19 patients with Reverse Transcription Polymerase Chain Reaction (RT-PCR) were enrolled in the study. The severity of the headache was assessed by the Numerical Rating Scale (NRS, 0-10). All the patients with headaches were followed up by telephonic interviews in the 2nd week and at the end of the 4th week of the onset of the headache. For patients who experienced persistent headaches after 4th week, the impact of headaches on quality of life was assessed with the Headache Disability Index (HDI).*

Results: *We included 362 patients in this study. The majority (52.5%) of the study population belonged to severe COVID-19 infection. Fever was the most common (63.81%) symptom among the study subjects. Headache was present in 19.06% of the patients. The mean (±SD) age of participants was 54(±14.7). Patients having headaches were younger 44.2±13.8 vs 56±13.8, p<0.05) than those have no headaches. Headache was more prevalent among the female (37[53.6%] vs 102[34.8%]). Tension-type headache (TTH) was the most common (60%) headache phenotype. The majority (68.12%) of the cases of headache occurred concomitantly with other COVID-19 symptoms. COVID-19-related headaches were, in most cases, bilateral, pressing, and of moderate intensity. Fever and pre-existing headaches were associated with significantly more frequency, duration, and intensity than COVID-19 headaches (p<0.05). Most patients (86.9%) recovered from headache within 4 weeks of onset. Median (IQR) recovery time was 10 (7.75) days. Nine patients (13.1%) did not recover from headaches in the 4th week of the survey. The Mean (±SD) HDI score was 24.4(±0.76) in patients who experienced headaches at the end of 4th week, which indicates mild disability.*

Conclusion: *This study revealed that headache was present in about one-fifth of the hospitalized patients with COVID-19. Younger age and female gender were significantly associated with headaches. Most of the patients recovered within four weeks of the onset of headache.*

Key words: Characrteristics, Headache, Outcome, COVID-19 patient.

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Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan City, Hubei Province, China.[1] On 30 January 2020, the World Health Organization (WHO) declared the coronavirus outbreak as a Public Health Emergency of International Concern and a pandemic on 11 March 2020.[2] In Bangladesh, the first patient was identified on 8 March 2020.

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Frequent symptoms of COVID-19 include fever, cough, shortness of breath, headache, malaise, muscle and joint pain, and loss of smell and taste.[3] Infrequent symptoms include abdominal pain, nausea, vomiting, and diarrhea.[4] The time from exposure to the onset of symptoms ranges from 5 to 14 days.[5]

The prevalence of headaches in patients with COVID-19 varies in different studies, ranging from 6% to 71%.[6,7] A possible pathophysiological mechanism of headache associated with COVID-19 is activating the trigeminovascular system.[8] At the meningeal level, its activation may be due to 1) systemic inflammation that may facilitate meningeal sensitization, leading to the local release of inflammatory peptides that stimulate trigeminal terminals 2) direct binding of SARS-CoV-2 from the blood stem on ACE2, which is expressed by the endothelium of meningeal vessels, causing endothelium and therefore inflammation. In the nasal cavities, both the specialized olfactory epithelium and the nasal epithelium are present, the latter being innervated by trigeminal nerve afferents. The olfactory neurons express ACE2, where the SARSCoV-2 may bind, causing anosmia, a symptom significantly associated with headache. At the level of nasal epithelium, the trigeminal system may be peripherally activated by the direct action of SARS-CoV-2 on the nasal epithelium or the trigeminal branches or by the indirect pathway involving the interaction between the olfactory and trigeminal innervation.[8,9] In Bangladesh prevalence of headache was 13.5% to 19.4%.[10,11] Little is known about the characteristics of these headaches.

One Spanish study reported headaches in about 75% of patients with COVID-19, of which 24.2% have migrainous features.[12] Another study reported headaches in 22.4% of patients, half of whom showed tension-type headache (TTH) features.[13] Patients having a pre-existing primary headache disorder had significantly more frequent COVID-19-related headaches.[14]

Few studies are available regarding the outcome of headaches, and they show different outcomes. In one study, the majority of patients recovered from headaches within two weeks[15], whereas Caronna et al.[12] reported that one-third of patients had persistent headaches after six weeks. Persistent headaches may adversely affect the quality of life. The Headache Disability Index (HDI) is a validated tool to assess the impact of headaches on quality of life.[16]

The International Classification of Headache Disorders, third edition (ICHD-3) requires a confirmed diagnosis of systemic viral infection without meningitic or encephalitic involvement to diagnose headaches attributed to systemic viral infections.[17] Headache is usually diffuse and bilateral, but some cases, it may be fronto-temporal or occipital with retroocular pain. It may be associated with conjunctival injection, nausea, vomiting, photophobia, or phonophobia[18] (Marinis and Welch 1992).

Information regarding headache characteristics and outcomes may be necessary for patient management and counseling in this pandemic. This study aimed to assess the characteristics and outcomes of headaches presented by COVID-19 patients.

Methods:

This was a prospective cohort study done in the Department of Neurology from January 2021 to December 2021. Ethical approval was obtained from the Institutional Review Board (IRB) of Dhaka Medical College Hospital. We obtained informed written consent from all the study participants.

Study participants:

We use consecutive sample methods. Our estimation sample size was 384, using the formula $n = \frac{z^2 pq}{d^2}$. We enrolled confirmed COVID-19 patients of both sexes and aged more than 18 years with RT-PCR from the in-patients and triage of Dhaka Medical College Hospital. Critical and unconscious patient and those who had other previous secondary headache were excluded from the study.

Operational Definition

We defined COVID-19 and its severity in patients according to WHO and Bangladesh COVID-19 guidelines.[19,20] We defined Headaches attributed to systemic viral infection according to the third edition of the International Classification of Headache Disorders (ICHD-3[13]).

The phenotypes of headaches associated with COVID-19 headache were classified as Migraine phenotype and Tension-type headache phenotype according to the third edition of the International Classification of Headache Disorders (ICHD-3).[13] Pain was quantified by the Numerical Rating Scale (NRS).[21] Score 0 is considered no pain, 1-3 is mild pain, 4-6 is moderate pain and 7-13 is severe pain.

The headache disability index (HDI) is a 27-item questionnaire used to assess the impact of headaches on quality of life.[16] The first two questions ask the patient to identify the frequency (1 per month, more than 1 per month but less than 4 per month, more than 1 per week) and intensity (mild, moderate, and severe) of their headache.

The remaining questions evaluate the quality of life issues to determine headache disability. Using this system, if 'Yes' is checked on any given line, that answer is given 4 points; a 'Sometimes' answer is given 2 points, and a 'No' answer is given 0 points.

Using this system, a score of 10 – 28 indicates mild disability, 30 – 48 indicates moderate disability, 50 – 68 indicates severe disability, and ≥72 indicates complete disability.

The outcome of headache was considered as Recovered (patients who recovered from headache within 4 weeks) and Not recovered (patients who experienced a headache after 4 weeks)

Study procedure

A total of 400 patients were included in this study according to defined inclusion and exclusion criteria. Informed written consent was taken from all participants after describing the aim, purpose, and procedure of the study. A structured questionnaire was filled up from the answers of the participants with the help of relatives to obtain information on demographic characteristics and headache-related questions. Adequate safety measures were ensured to prevent transmission of infection during data collection. The severity of the headache was assessed by the Numerical Rating Scale (NRS, 0-10). Headache phenotype was classified according to the International Classification of Headache Disorders third edition (ICHD-3). All patients with headaches were followed up by telephonic interview at the end of the 2nd week and 4th week of onset of headache to assess the outcome. Patients without headaches at the first survey were followed up by telephonic interview after 10 days of the first survey to document any new-onset headache. If a headache was present, then two further follow-ups were given at the end of 2nd and 4th week from the onset of the headache. The impact of headaches on quality of life was assessed with the Headache Disability Index (HDI) on patients who experienced headaches after 4th week. All the above information was recorded in a data collection form consisting of the relevant questionnaire.

Data Analysis Plan

All data was registered, documented and analyzed in the statistical program- Statistical Package for Social Science (SPSS) version 26.0. Each question was coded with a number and all alternative responses for each question were registered to enable a statistical analysis. The data was systematically described**,** summarized, and presented through descriptive statistics. Shapiro-Wilk test was done to see the distribution of data. For normally distributed data, continuous variables were expressed as means ± standard deviations (SD), while categorical variables were described as frequency and percentage. Non-normally distributed data was expressed as median (Inter Quartile Range, IQR). Student's *t* test was used for the continuous variables whereas Chi-square test for categorical variables to express association. Non-parametric test was done to see association between non-normally distributed data. P value ≤0.05 was considered as level of statistical significance.

Results:

A total of 400 RT-PCR positive patients admitted into DMCH were included initially based on inclusion and exclusion criteria. Among them 362 patients who completed follow-up at the end of 2nd and 4th week were finally included for analysis.

Table I

Demographic characteristics of the study subjects (n=362).

Variable	All patients	Headache present (n=69)	Headache absent (n=293)	p value
Age group (yrs)				
18-30	29 (8.01%)	16	13	
31-40	38 (10.50%)	13	25	0.001**
41-50	84 (23.20%)	18	66	
51-60	96 (26.52%)	14	82	
61-70	80 (22.10%)	8	72	
>70	35 (9.67%)	0	35	
(Mean±SD)	54.05±14.47	44.19±13.80	55.97±13.72	0.001*
Range	18-90	19-69	18-90	
Gender				
Male	223 (62%)	32 (46.37%)	191 (65.18%)	0.006 **
Female	139 (38%)	37 (53.63)	102 (34.82%)	

*= obtained by unpaired t test, **= obtained by Chi square test

Table I shows demographic characteristics of the study subjects. It was observed that majority (26.52%) of study subjects belonged to age 51-60 years. Mean age of the study subjects was 54.05±14.47 years. Headache was more common in younger age groups (p<0.001). Majority of study subjects were male (62%). Female gender was significantly associated with presence of headache (p=0.006).

Figure 1 shows the distribution of frequency of COVID-19 symptoms. The most Common symptom was fever (63.81%) followed by shortness of breath (56.08%), cough (53.87%) and changes in taste (31.77%). Headache was present in 19.06% patients

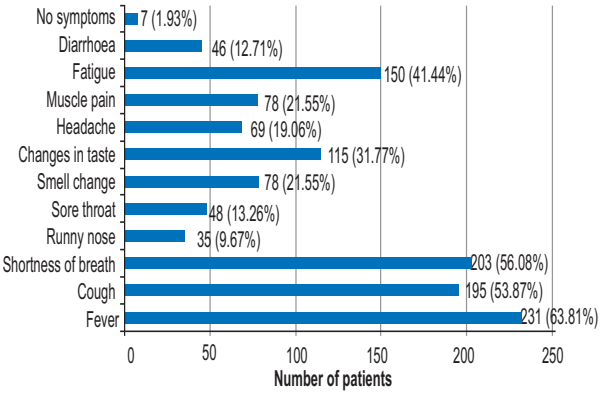

Figure 1: *Distribution of frequency of COVID-19 symptoms (n=362)*

Table II

Frequency of co-morbidities in the study subjects (n=362)

Co-morbidity	All patients (n=362)	Headache present (n=69)	Headache absent (n=293)	p value
HTN	125 (34.53%)	21 (30.43%)	104 (35.49%)	0.48*
DM	132 (36.46%)	25 (36.23%)	107 (36.51%)	0.81 *
IHD	48 (13.26%)	5 (7.2%)	43 (14.67%)	0.09 *
Asthma/COPD	35 (9.67%)	7 (10.14%)	28 (9.55%)	0.32 *
CKD	28 (7.73%)	4 (5.7%)	24 (8.1%)	0.12 *

*= Chi square test was done to see the level of significance

Table II shows the frequency of co-morbidities in the study subjects. DM was the most common (36.46%) co-morbidity followed by HTN (34.53%). Co-morbidities were not significantly associated with presence of headache (p>0.05).

Table III

Association of headache with severity of COVID-19

Severity	All patients (n=362)	Headache present (n=69)	Headache absent (n=293)	p value
Mild	83 (22.9%)	20 (28.9%)	63 (21.5%)	0.04[s*]
Moderate	89 (24.6%)	12 (17.5%)	77 (26.3%)	
Severe	190 (52.5)	37 (53.6%)	153 (52.2%)	

[s]= significant, *= Chi square test was done to see the level of significance

Table IV

Frequency and phenotypes of headache in COVID-19 patients (n=362)

	Number	Percentage (%)
Patients with headache	69	19.06
Tension type	41	59.4
Migraine type	23	33.3
Others	5	7.3
Patients without headache	293	80.94

Table III shows association of headache with severity of COVID-19. Severity of COVID-19 was significantly associated with presence of headache (p=0.04). Headache was more common in mild COVID-19 patients.

Table IV shows Frequency and phenotypes of headache in COVID-19 patients. Headache was present in 19.06% of study subjects and tension type headache was most common (59.4%).

Table V shows the characteristics of COVID-19 related headache. In most (68.12%) cases headache was concomitant with other COVID symptoms. Most cases headache was bilateral (60.87%), pressing (44.93%) and of moderate intensity in 56.52% cases. In 18.8% cases of COVID related headache had pre-existing primary headache.

Table V

Characteristics of COVID-19 related headache (n=69).

		Frequency	Percentage (%)
Onset	Before other COVID symptoms	14	20.29
	With other COVID symptoms	47	68.12
	After other COVID symptoms	8	11.59
Location	Unilateral	9	13.04
	Bilateral	42	60.87
	Diffuse	18	26.09
Characteristics of pain	Throbbing	23	33.33
	Pressing	31	44.93
	Dull	15	21.74
Headache intensity (NRS)	Mild (NRS 1-3)	13	18.84
	Moderate (NRS 4-6)	39	56.52
	Severe (NRS 7-10)	17	24.64
Duration of headache attack (hours/day)Median (IQR)		8 (7)	
Frequency of headache (attacks/week)Median (IQR)		5 (3)	
Pre-existing primary headache			
Present		13	18.8
Migraine		8	61.5
TTH		3	23.1
Others		2	15.4
Absent		56	81.2

Table VI shows the association of presence of fever with duration, frequency and intensity of headache in COVID-19 patients. Fever was significantly associated with increase in the duration, frequency and intensity of COVID-19 headache ($p<0.05$).

Table VII shows association of pre-existing primary headache with duration, frequency and intensity of COVID-19 headache. Duration, frequency and intensity of headache was significantly higher in patients with pre-existing headache ($p <0.05$).

Table VI

Association of presence of fever with duration, frequency and intensity of headache (n=69)

Characteristics	Headache with fever (n=59)	Headache without fever (n=10)	p value
Frequency/weekMedian (IQR)	7 (4)	3 (5)	0.004*
Duration (hours) Median (IQR)	11 (10)	6 (14)	0.001*
Intensity (NRS)Median (IQR)	7 (2)	6 (4)	0.03*

*= p value obtained by Mann Whitney U test

Table VII

Association of pre-existing primary headache with duration, frequency and intensity of COVID-19 headache (n=69)

Characteristics	Pre-existing primary headache present (n=13)	Pre-existing primary headache absent (n=56)	p value
Duration (hours) Median (IQR)	11 (10)	5 (9)	0.001*
Frequency/weekMedian (IQR)	7 (4)	3 (5)	0.001*
Intensity (NRS)Median (IQR)	7 (3)	5 (3)	0.012*

*=Mann Whitney U test was done to see the level of significance.

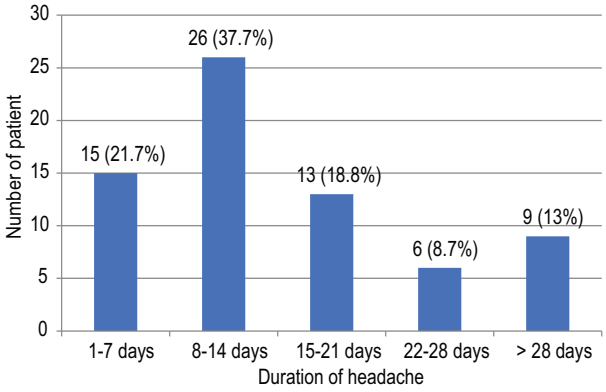

Figure 2: *Recovery time for patients with headache (9 patients did not recover after 4th week) (n=69).*

Figure 2 shows the recovery time for patients with headache. Maximum patients (37.7%) recovered between 8-14 days.

Table VIII

Recovery of headache (cumulative) at different survey period and median recovery time (n=69)

	At end of 2nd week		At end of 4th week	
	No.	%	No.	%
Recovered	41	59.42	60	86.9
Median recovery time Median (IQR) day	10 (7.75)			

Table VIII shows the recovery of headache at different survey period and median recovery time. Majority (86.9%) of the patient recovered within 4 week of onset of headache. Median (IQR) recovery time was 10 (7.75) days.

Table IX

Recovery time based on presence of pre-existing primary headache and severity of COVID-19 (n=60)*

	Number	Recovery time Median (IQR) days	p value
Pre-existing headache			
Present	9	18 (12.5)	0.032**
Absent	51	10 (8)	
Severity of COVID-19			
Mild	17	10 (11.5)	0.022***
Moderate	10	9 (5.5)	
Severe	33	14 (10)	

*= 9 patients who did not recover after 4 weeks are not included

**= Mann-Whitny U test was done to see the level of significance

***= Kruskal-Wallis test was done to see the level of significance

Table IX shows recovery time based on presence of pre-existing headache and severity of COVID-19. Recovery time was significantly higher in patients with pre-existing primary headache and severe COVID-19 patients ($p<0.05$).

Table X

HDI score for patients who did not recover after 4 weeks of onset of headache (n=9)

HDI score	Number	Percent
Mild disability (10-28)	7	77.77
Moderate disability (30-48)	2	22.23
Severe disability (50-68)	0	0
Mean HDI score (Mean±SD)	24.44±10.76	
Range	14-36	

Table X shows the HDI score for patients who did not recovered after 4 weeks of onset of headache. Maximum patient (77.77%) had mild disability. Mean HDI score was 24.44±10.76 SD

Discussion:

In the study, most of the patients had severe COVID-19 infection. Among them about one-fifth of patients presented with Headaches. Patients having headaches were younger than those have no headaches. Headache was more prevalent among the female. Tension-type headache (TTH) was the most common (60%) headache phenotype. COVID-19-related headaches were, in most cases, bilateral, pressing, and of moderate intensity. Fever and pre-existing headaches were associated with significantly more frequency, duration, and intensity than COVID-19 headaches. Most patients recover from headaches within 4 weeks of the onset. Headache is the most common neurological manifestation of COVID-19 infection. Previous studies show variable information regarding headaches' frequency, characteristics, and outcome.

Most (52.5%) of the study population belonged to severe COVID-19 infection because it was a hospital-based study and the maximum number of patients admitted to hospitals were in serious condition. Headache frequency is relatively low in this study. The frequency varies from 35-58%[22] in overall COVID-19 patients. Headache is more prevalent among the mild COVID patients.[23] This variation may be explained by the use of different methodologies in different studies and the genetic background of study populations, which may influence the prevalence of this neurologic symptom and the appearance of new SARS-CoV2 strains.[24,25] The mean age of the patient with headache was significantly lower in patients with headache than patients without headache ($p<0.05$). Membrilla et al.[26] and Caronna et al.[12] showed similar findings, but the mean age in patients with and without headaches was higher in a

later study. Like other studies, headache is common among females in our study.[12,27] Estrogen plays an important role in the neuroexcitability.[28]

TTH was the most common (60%) headache phenotype. Magdy et al. (2020) found TTH was present in 40.7% of cases.[29] Another study conducted by Rocha-Filho et al. (2020) showed that the majority of headaches (51%) were migraine-type.[30] This may differ in different populations based on the prevalence of pre-existing migraine headaches. In most cases, the headache was bilateral, pressing, and of moderate intensity. A study conducted by Magdy et al. (2020) showed almost similar findings, except the headache was severe in intensity.[29]

Pre-existing headaches were present in 18.8% of the cases of COVID-19 headaches, which were associated with significantly more frequency, duration, and intensity of headache. A similar finding was found in the study by Caronna et al.[12] This may be explained by derangement of the pain modulatory pathway, decreased pain threshold, and for migraine, cortical spreading depression may add to hyper-excitability of the trigeminovascular neurons.[31,32]

Most patients (86.9%) recovered from headaches within 4 weeks of their onset. A study conducted by Kacem et al.[33] reported complete recovery in 83.2% of patients after 1 month. Another study reported 62.2% recovery at 6 weeks of follow-up.[12] The median (IQR) recovery time was 10 (7.75) days. Patients with pre-existing headaches and severe COVID-19 had significantly longer recovery time.

Nine patients (13.1%) did not recover from headaches in the 4th week of the survey. Poncet-Megemont et al. (2020) reported that 3.6 % of patients had persistent headaches one month after fever and dyspnea remission. A post-COVID-19 condition may be responsible for such a condition.[34]

Neuroimaging, cerebrospinal ûuid tests, and ophthalmoscopy were not performed to rule out other causes of secondary headaches, such as meningitis, encephalitis, and cerebrovascular diseases, which may be complications of COVID-19. However, these patients had no meningeal or focal signs, confusional states, or impaired level of consciousness, which makes these complications less likely.

This study was conducted in a single center and involved only inpatients. This decreases the ability to generalize the study, and therefore, extrapolating the results to patients with mild forms of the disease who do not require hospitalization should be undertaken with caution.

Conclusion:

This study revealed that headache was present in about one-fifth of the hospitalized patients with COVID-19. Younger age and female gender were significantly associated with headaches. Most of the patients recovered within four weeks of the onset of headache.

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