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Original Article

A comparison study of headache characteristics and headache-associated quality-of-life of COVID-19 and non-COVID-19 patients

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Abstract

Headache is prevalent in coronavirus disease 2019 (COVID-19) patients. The main objective of this study was to compare the characteristics of COVID-19-associated headache to non-COVID-19 headache. The quality-of-life (QoL) and its associated determinants between COVID-19 and non-COVID-19 patients were also compared. A cross-sectional study was conducted in Banda Aceh, Indonesia. Headache and QoL were assessed using the International Classification of Headache Disorders, version 3 (ICHD-3), and the 36-item Short Form Health Survey (SF-36), respectively. Factors associated with poor QoL in COVID-19 and non-COVID-19 patients were examined using logistic regression. A total of 356 headache patients were included: 215 COVID-19 and 141 non-COVID-19 patients. Our data suggested that the headache in COVID-19 patients was bilateral; pain centered on one specific area with a pulsating or pressing sensation; pain intensity ranging from moderate to severe; and the frequency ranging from more than twice per week to every day. Non-COVID-19 headache was bilateral; pain centered on one side of the head resembling a migraine with pulsating or pressing sensation; mild to moderate pain intensity; and the frequency of one or two times per month. In COVID-19, low QoL was associated with unemployment status, having non-health-related jobs, having used painkillers to reduce the pain, having long duration of headache, having more frequency of attacks, and having headaches that were worsened by activities or light, and having additional symptom during a headache attach. In non-COVID-19 patients, poor QoL was associated with the use of painkillers, long duration of headache, and having conditions that aggravate the headache. To prevent long-term effects of headache associated with COVID-19, studies exploring the photobiology of headache are needed, along with the necessity of having standardised guideline on headache prevention.

Keywords: COVID-19, headache, post-COVID-19 symptom, quality-of-life, long-COVID

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Introduction

The pandemic of the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more 587 million people and resulted in over 6 million deaths as of 15 August 2022 [1]. Headache, along with shortness of

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breath and coughing are among the early symptoms of SARS-CoV-2 infection [2] and the most common neurological complaint in COVID-19 patients [3, 4]. The prevalence of headache ranges from 14 to 60% in COVID-19 patients [3-7]. The symptoms of headache vary in COVID-19 patients, including pain throughout the head and a pinching sensation to heaviness on the top of the head [3, 8, 9].

Headache is also reported in recovered COVID-19 individuals. Headache is also the most common neurological symptom in individual with long COVID-19, along with other complaints such as impaired concentration and memory [2, 10-13]. Mendelson *et al*. proposed that a headache that lasts at least six months, whether as a single clinical symptom, co-occurring with other cognitive disorders such as "brain fog" or exacerbating pre-existing migraine symptoms should be suspected of being caused by long COVID-19 [14]. Headache in long COVID-19 patients may be triggered by preexisting headache activation or by genetic predispositions to migraine [13].

A study found that headache as an acute phase symptom was more frequent in non-hospitalized patients than hospitalized patients (57.9% vs 31.1%) [15]. Another study reported no statistically significant difference in headache prevalence between severe and mild COVID-19 patients, recovered vs non-recovered patients, or between patients in intensive care units (ICU) vs non-ICU [16]. The prevalence of headache in COVID-19 patients is double when compared to individuals without COVID-19 [17, 18]; moreover, 72% of patients with COVID-19 stated that the headache experienced was different during and before infection [19].

Studies comparing the characteristics of headaches in patients with and without COVID-19 are limited. Hence, the aim of this study was to compare the characteristics of headache between COVID-19 and non-COVID-19 patients. Another goal was to compare the quality-of-life (QoL) between these groups and to explore possible determinants of poor QoL.

Methods

Study design and participants

A cross-sectional study was conducted from February to June 2022 at the Department of Neurology of Dr. Zainoel Abidin Hospital, a provincial referral hospital in Aceh Province of Indonesia. Patients were aged 18-year-old or older and came to the Department of Neurology with headache complains, both with and without a history of COVID-19 infection. COVID-19 infection was confirmed with SARS-CoV-2 polymerase chain reaction (PCR). Those who agreed to participate were interviewed. Information related to the characteristics of the headache, clinical symptoms, the history of COVID-19 and QoL were collected.

Study variables and data collection

This study collected the following information: (1) demographic data, including the history of COVID-19 vaccination; (2) headache characteristics; and (3) the assessment of QoL. Headache in COVID-19 and non-COVID-19 groups were diagnosed according to the headache characteristics by the International Classification of Headache Disorders, version 3 (ICHD-3) [20]. Headache-related questions consisted of: (1) first time of headache occurred; (2) headache characteristics, included: (a) location, (b) duration of attack, (c) frequency, (d) sensation, and (e) severity (score 0 or no pain; score 1–3 or mild pain; score 4–6 or moderate pain; score 7–9 or severe pain; score 10 or very severe pain); (3) additional symptoms during the headache attack (photophobia, phonophobia, nausea/vomiting); and (4) whether they have to take an analgesic, abortive, or prophylactic medication when the headache occurred. More details about the headache-related questions have been published elsewhere [22].

The QoL of each patient was measured using a 36-item instrument, the Short Form Health Survey (SF-36) [21]; a full description of these questions is provided elsewhere [22]. By adopting a cut-off point of 50%, levels of QoL were classified into good or poor.

Statistical analysis

All analyses were conducted in SPSS v.22 (IBM, Armonk, New York, US). The Shapiro-Wilk test was used to determine the normality of data, which was described as mean and standard deviation (SD). Frequency (n) and percentage (%) were used to describe the sample. The Student t-test was used to compare variables between the two study groups (COVID-19 vs non-COVID-19 patients). To compare the demographic and headache characteristics between COVID-19 and non-COVID-19 patients, the Chi-square test or Fisher's exact test were used. Logistic regression analysis was performed to assess the predictors of headaches. A p value of ≤0.05 was considered to be statistically significant in the analyses.

Results

Sociodemographic characteristics

In the final analysis, we included 356 headache patients (215 COVID-19 and 141 non-COVID-19). The demographic characteristics of the patients from both groups are presented in **Table 1**. More than half of patients in both categories had been vaccinated, with 1st and 2nd dose, against COVID-19; the frequency of non-COVID-19 patients was slightly higher when compared to COVID-19 patients (83.7% vs 62.8% and 78.7% vs 60.9% for the 1st and 2nd dose, respectively).

In both COVID-19 and non-COVID-19 patients, more than half have not received a booster dose of vaccination. The COVID-19 group was mostly aged between 30–39, while non-COVID-19 patients were predominantly aged 20–29-year-old (**Table 1**). Women outnumbered men in both categories (69.8% and 60.3%, respectively). Approximately 21% and 35% of COVID-19 and non-COVID-19 groups earned less than 3 million Indonesian Rupiah (IDR) per month (equal to 190 $US as per November 2022 currency rate) (**Table 1**).

Table 1. Patients' characteristics (n=356)

Questions	COVID-19		Non-COVID-19	
	n	%	n	%
Have received the 1st dose of COVID-19 vaccine				
No	80	37.2	23	16.3
Yes	135	62.8	118	83.7
Have received the 2nd dose of COVID-19 vaccine				
No	84	39.1	30	21.3
Yes	131	60.9	111	78.7
Have received a booster dose of COVID-19 vaccine				
No	177	82.3	77	54.6
Yes	38	17.7	64	45.5
Age group (year)				
20–29	55	25.6	70	49.6
30–39	98	45.6	48	34.0
40–49	41	19.1	11	7.8
>50	21	9.8	12	8.5
Gender				
Male	65	30.2	56	39.7
Female	150	69.8	85	60.3
Employment status				
Unemployed	47	21.9	47	33.3
Employed	168	78.1	94	66.7
Health-related workers				
No	76	35.3	64	45.4
Yes	139	64.7	77	54.6
Monthly income (Indonesian Rupiah)				
<3 million	46	21.4	50	35.5
3-5 million	112	52.1	46	32.6
5-10 million	45	20.9	34	24.1
>10 million	12	5.6	11	7.8

Comparison of headache characteristics between COVID-19 and non-COVID-19 groups

Over 71% of COVID-19 patients required pain killers to relieve their headaches, whereas more than half of non-COVID-19 patients did not (**Table 2**). The most reported location of headaches by both groups was throughout the head (47.4% vs 39.0%); approximately 20% was unable to describe where the pain was located. The headache of both groups was in the different locations. The percentage of patients who complained of headache only occurring at one point or area was different between COVID-19 and non-COVID-19 groups (16.7% vs 2.1%).

Table 2. Headache characteristics between COVID-19 vs non-COVID-19 patients (n=356)

Characteristics	COVID-19		Non-COVID-19		*p*-value
	n	%	n	%	
Had taken painkillers for the headache					<0.001**
No	61	28.4	80	56.7	
Yes	154	71.6	61	43.3	
Location					0.001**
Only in one point/area	36	16.7	3	2.1	
Right side	20	9.3	25	17.7	
Left side	11	5.1	25	17.7	
Whole head	102	47.4	55	39.0	
Cannot be described	46	21.4	33	23.4	
Duration (hour)					0.096
Less than 1	134	62.3	86	61.0	
1-6	68	31.6	40	28.4	
7-12	4	1.9	10	7.1	
More than 12	9	4.2	5	3.5	
Frequency					<0.001**
1-2 times/month	96	44.7	98	69.5	
1-2 times/week	32	14.9	31	22.0	
>2 times or more/week	87	40.5	12	8.5	
Characteristic					<0.001**
Pulsating	132	61.4	44	31.2	
Pressing	45	20.9	51	36.2	
Fiery	4	1.9	29	20.6	
Stabbing	11	5.1	1	0.7	
Combination of 2 characteristics	20	9.3	10	7.1	
Combination of 3 or 4 characteristics	3	1.4	6	4.3	
Severity (on a pain scale of 0–10, where 0 is no pain and 10 is very painful)					0.002**
0	3	1.4	5	3.5	
1–3	88	40.9	80	56.7	
4–6	100	46.5	50	35.5	
7–9	22	10.2	4	2.8	
10	2	0.9	2	1.4	
What makes the headache worse					0.012*
None	56	26.0	23	16.3	
Activity	97	45.1	76	53.9	
Light	10	4.7	13	9.2	
Noise	15	7.0	7	5.0	
Activity and light	4	1.9	5	3.5	
Activity and noise	20	9.3	3	2.1	
Light and noise	4	1.9	3	2.1	
All three (activity, light and noise)	9	4.2	11	7.8	
What makes the headache better					<0.001**
None	24	11.2	10	7.1	
Rest	76	35.3	82	58.2	
Painkiller	43	20.0	21	14.9	
Rest and painkiller	72	33.5	28	19.9	
Additional symptom during headache					0.115
No	116	54.0	88	62.4	
Yes	99	46.0	53	37.6	

*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

The average headache duration was less than one hour, with no difference in headache duration between COVID-19 and non-COVID-19 groups (62.3% vs. 61%) (**Table 2**). However, those suffering from COVID-19 had a higher frequency of headaches (>2 times or more per week or almost every day) (40.5%), while in non-COVID-19 group the headaches generally occurred 1–2 times per month (69.5%).

The majority of COVID-19 patients (61.4%) described their headache as pulsating, while 20.9% described it as a pressing sensation. The non-COVID-19 patients, on the other hand, described it as fiery, in addition to pulsating and pressing sensation (20.6%, 31.2%, and 36.2%, respectively). COVID-19 patients experienced headache moderate pain (46.5%), while non-COVID-19 patients experienced mild pain (56.7%). In both COVID-19 and non-COVID-19 patients, having activities/being tired was a factor that worsened headaches, while resting, taking pain killers, or a combination of resting and taking pain killers reduced the pain (**Table 2**).

Data suggested that the severity (indicated by having taken painkillers and the headache severity score), location, frequency, factors that made headaches worse or better, and the type of symptom during headache were significantly different between COVID-19 and non-COVID-19 patients (**Table 2**).

Quality-of-life between of the patients

Data indicated that the pain, emotional well-being, and general health were significantly different between COVID-19 and non-COVID-19 patients, with $p<0.001$, $p<0.001$, $p=0.030$, respectively (**Table 3**).

Table 3. Mean scores of quality-of-life domains between COVID-19 and non-COVID-19 patients (n=356)

QoL domain	Mean ± SD		*p*-value
	COVID-19	Non-COVID-19	
Physical functioning	205.58 ± 139.31	209.22 ± 151.61	0.778
Role limitations due to physical health	675.12 ± 225.11	697.80 ± 248.78	0.244
Role limitations due to emotional problems	186.98 ± 103.30	190.07 ± 111.68	0.601
Pain	112.35 ± 41.01	132.02 ± 40.11	<0.001**
Energy/fatigue	180.00 ± 55.30	172.06 ± 56.11	0.102
Emotional well-being	553.21 ± 111.63	488.87 ± 126.18	<0.001**
Social functioning	134.88 ± 41.84	128.65 ± 40.80	0.305
General health	328.26 ± 95.40	310.62 ± 87.11	0.030*
Total quality of life	2254.05 ± 531.53	2212.00 ± 559.99	0.495

*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

The QoL in COVID-19 and non-COVID-19 patients with headache are presented in **Table 4**. The three domains of QoL (pain, emotional well-being, and social functioning) were significantly different between COVID-19 and non-COVID-19 groups (all $p<0.001$). Non-COVID-19 patients had a slightly better QoL than COVID-19 patients in the pain domain (35.5% vs 17.7%), while COVID-19 participants had a slightly better QoL regarding emotional well-being and social functioning domains (38.1% vs 20.6% and 55.3% vs 36.2%, respectively) (**Table 4**).

Factors associated with patients' quality-of-life

Unemployment and having a non-health-related work were associated with poor QoL in COVID-19 patients (OR: 0.28; 95%CI: 0.12–0.67, $p=0.004$ and OR: 0.22; 95%CI: 0.11–0.46, $p<0.001$, respectively). Other demographic data, such as age, gender, and monthly income, were not associated with QoL in COVID-19 patients (**Table 5**). In non-COVID-19 patients, none of the sociodemographic characteristics were associated with poor QoL.

Participants who used painkillers had 2–3 times more chances for poor QoL compared to those who did not, both in headache patients with COVID-19 and non-COVID-19 (OR: 3.25; 95%CI: 1.75–6.05 with $p<0.001$ and OR: 2.34; 95% CI: 1.09–5.00 with $p=0.029$, respectively). Headache duration between 1–6 hours was associated with an increased risk of having poor QoL compared to participants who experienced the headache for less than one hour in both COVID-19 and non-COVID-19 groups (OR: 3.35; 95%CI: 1.64–6.83 and OR: 3.56; 95%CI: 1.42–8.94,

respectively). In COVID-19 patients, a headache that got worse with activities was associated with poor QoL compared to the absence of a worsening factor (OR: 1.98; 95% CI: 1.01–3.90), and a combination of activity and noise as worsening factors was associated with an increase of nearly eight times the odds of poor QoL compared to the absence of a worsening factor (OR: 8.38; 95%CI: 1.78–39.56, with p=0.007). Meanwhile, in non-COVID-19 patients, bright light and a combination of activity/tired, bright light and noise increased the odds of poor QoL compared to the absence of worsening factors (OR: 6.00 and OR: 10.91, respectively).

In the COVID-19 group, having headache two times or more per week was associated with poor QoL when compared to participants who only had a headache once or twice per month (OR: 4.24; 95%CI: 2.13–8.41). Patients with additional symptoms accompanying headache were nearly four times more likely to have poor QoL (OR: 3.79, 95%CI: 2.02–7.09). In non-COVID-19 patients, neither of these two characteristics were associated with poor QoL.

Table 4. Quality of life between COVID-19 and non-COVID-19 patients (n=356)

Domain	COVID-19		Non-COVID-19		p-value
	n	%	n	%	
Physical functioning					0.484
Good	88	40.9	63	44.7	
Poor	127	59.1	78	55.3	
Role limitations due to physical health					0.235
Good	99	46.0	74	52.5	
Poor	116	54.0	67	47.5	
Role limitations due to emotional problems					0.250
Good	74	34.4	57	40.4	
Poor	141	65.6	84	59.6	
Pain					<0.001**
Good	38	17.7	50	35.5	
Poor	177	82.3	91	64.5	
Energy/fatigue					0.625
Good	41	19.1	24	17.0	
Poor	174	80.9	117	83.0	
Emotional well-being					<0.001**
Good	82	38.1	29	20.6	
Poor	133	61.9	112	79.4	
Social functioning					<0.001**
Good	119	55.3	51	36.2	
Poor	96	44.7	90	63.8	
General health					0.772
Good	25	11.6	15	10.6	
Poor	190	88.4	126	89.4	
Total quality-of-life					0.720
Good	71	33.0	44	31.2	
Poor	144	67.0	97	68.8	

*Statistically significant at p<0.05
**Statistically significant at p<0.01

Discussion

This study was conducted to examine the characteristics of headache between COVID-19 and non-COVID-19 patients and to compare the QoL between these groups. The results suggested that the characteristics of headache between COVID-19 and non-COVID-19 patients were slightly different in terms of location, pain sensation, pain intensity, and frequency. Although most participants complained of pain all over the head (bilateral), COVID-19 patients also reported that the pain was usually concentrated in one particular area or point, whereas non-COVID-19 patients reported pain usually only on one side of the head (left or right), thus resembling a migraine.

Table 5. Factors associated with quality-of-life (good vs poor) in COVID-19-associated headache and non-COVID-19 headache

Factor	COVID-19-associated headache					Non-COVID-19 headache				
	n	%	Poor QoL n (%)	OR (95%CI)	p-value	n	%	Poor QoL n (%)	OR (95%CI)	*p*-value
Age group (year)										
20–29 (*Reference group* (*R*)	55	25.6	39 (70.9)	1		70	49.6	46 (65.7)	1	
30–39	98	45.6	60 (61.2)	0.65 (0.32–1.32)	0.230	48	34.0	32 (66.7)	1.04 (0.48–2.27)	0.915
40–49	41	19.1	27 (65.9)	0.79 (0.33–1.89)	0.597	11	7.8	8 (72.7)	1.39 (0.34–5.73)	0.648
>50	21	9.8	18 (85.7)	2.46 (0.64–9.53)	0.192	12	8.5	11 (91.7)	5.74 (0.70–47.14)	0.104
Gender										
Male (R)	65	30.2	39 (60.0)	1		56	39.7	39 (69.6)	1	
Female	150	69.8	105 (70.0)	1.56 (0.85–2.85)	0.154	85	60.3	58 (68.2)	0.94 (0.45–1.94)	0.860
Employment										
Unemployed (*R*)	47	21.9	40 (85.1)	1		47	33.3	30 (63.8)	1	
Employed	168	78.1	104 (61.9)	0.28 (0.12–0.67)	0.004**	94	66.7	67 (71.3)	1.41 (0.67–2.96)	0.369
Health–related worker										
No (*R*)	76	35.3	65 (85.5)	1		64	45.4	43 (67.2)	1	
Yes	139	64.7	79 (56.8)	0.22 (0.11–0.46)	<0.001**	77	54.6	54 (70.1)	1.15 (0.56–2.34)	0.707
Monthly income (Indonesian Rupiah)										
<3 million (*R*)	46	21.4	29 (63.0)	1		50	35.5	35 (70.0)	1	
3–5 million	112	52.1	74 (66.1)	1.14 (0.56–2.33)	0.717	46	32.6	28 (60.9)	0.67 (0.29–1.55)	0.348
5–10 million	45	20.9	33 (73.3)	1.61 (0.66–3.93)	0.294	34	24.1	23 (67.6)	0.90 (0.35–2.29)	0.819
>10 million	12	5.6	8 (66.7)	1.17 (0.31–4.48)	0.816	11	7.8	11 (100.0)	7×10^{8} (0.00–NA)	0.999
Had painkillers for the headache										
No (*R*)	61	28.4	29 (47.5)	1		80	56.7	49 (61.3)	1	
Yes	154	71.6	115 (74.7)	3.25 (1.75–6.05)	<0.001**	61	43.3	48 (78.7)	2.34 (1.09–5.00)	0.029*
Location										
Only in one point/area (*R*)	36	16.7	15 (41.7)	1		3	2.1	2 (66.7)	1	
Right side	20	9.3	13 (65.0)	2.60 (0.84–8.07)	0.098	25	17.7	20 (80.0)	2.00 (0.15–26.73)	0.600
Left side	11	5.1	9 (81.8)	6.30 (1.19–33.44)	0.031*	25	17.7	19 (76.0)	1.58 (0.12–20.69)	0.726
Whole head	102	47.4	74 (72.5)	3.70 (1.68–8.17)	0.001**	55	39.0	36 (65.5)	0.95 (0.08–11.13)	0.966
Cannot be described	46	21.4	33 (71.7)	3.55 (1.41–8.94)	0.007**	33	23.4	20 (60.6)	0.77 (0.06–9.37)	0.837
Duration (hour)										
Less than 1 (*R*)	134	62.3	78 (58.2)	1		86	61.0	49 (57.0)	1	
1–6	68	31.6	56 (82.4)	3.35 (1.64–6.83)	0.001**	40	28.4	33 (82.5)	3.56 (1.42–8.94)	0.007**
7–12	4	1.9	2 (50.0)	0.72 (0.10–5.25)	0.744	10	7.1	10 (100.0)	1×10^{9} (0.00–NA)	0.999
More than 12	9	4.2	8 (88.9)	5.74 (0.70–47.23)	0.104	5	3.5	5 (100.0)	1×10^{9} (0.00–NA)	0.999
Frequency										
1–2 times/month (*R*)	96	44.7	51 (53.1)	1		98	69.5	63 (64.3)	1	
1–2 times/week	32	14.9	21 (65.6)	1.68 (0.73–3.87)	0.219	31	22.0	24 (77.4)	1.91 (0.75–4.87)	0.178
>2 times or more	87	40.5	72 (82.8)	4.24 (2.13–8.41)	<0.001**	12	8.5	10 (83.3)	2.78 (0.58–13.40)	0.203
Characteristic of the headache										
Pulsating (*R*)	132	61.4	85 (64.4)	1		44	31.2	26 (59.1)	1	
Pressing	45	20.9	27 (60.0)	0.83 (0.41–1.66)	0.598	51	36.2	39 (76.5)	2.25 (0.93–5.44)	0.072

Factor	COVID-19-associated headache					Non-COVID-19 headache				
	n	%	Poor QoL n (%)	OR (95%CI)	p-value	n	%	Poor QoL n (%)	OR (95%CI)	*p*-value
Fiery	4	1.9	2 (50.0)	0.55 (0.08–4.05)	0.560	29	20.6	17 (58.6)	0.98 (0.38–2.54)	0.968
Stabbing	11	5.1	10 (90.9)	5.53 (0.69–44.54)	0.108	1	0.7	1 (100.0)	1×10^{9} (0.00–NA)	1.000
Combination of 2 characteristics	20	9.3	17 (85.0)	3.13 (0.87–11.25)	0.080	10	7.1	10 (100.0)	1×10^{9} (0.00–NA)	0.999
Combination of 3 or 4 characteristics	3	1.4	3 (100.0)	9×10^{8} (0.00–NA)	0.999	6	4.3	4 (66.7)	1.39 (0.23–8.38)	0.723
Severity (on a pain scale of 0–10, where 0 is no pain and 10 is very painful)										
0 (*R*)	3	1.4	0 (0.0)	1		5	3.5	5 (100.0)	1	
1–3	88	40.9	49 (55.7)	2×10^{9} (0.00–NA)	0.999	80	56.7	48 (60.0)	0.00 (0.00–NA)	0.999
4–6	100	46.5	75 (75.0)	5×10^{9} (0.00–NA)	0.999	50	35.5	39 (78.0)	0.00 (0.00–NA)	0.999
7–9	22	10.2	18 (81.8)	7×10^{9} (0.00–NA)	0.999	4	2.8	3 (75.0)	0.00 (0.00–NA)	0.999
10	2	0.9	2 (100.0)	3×10^{18} (0.00–NA)	0.999	2	1.4	2 (100.0)	1.00 (0.00–NA)	1.000
What makes the headache worse										
None (*R*)	56	26.0	29 (51.8)	1		23	16.3	11 (47.8)	1	
Activity	97	45.1	66 (68.0)	1.98 (1.01–3.90)	0.047*	76	53.9	50 (65.8)	2.10 (0.82–5.40)	0.125
Light	10	4.7	4 (40.0)	0.62 (0.16–2.44)	0.495	13	9.2	11 (84.6)	6.00 (1.08–33.32)	0.041*
Noise	15	7.0	13 (86.7)	6.05 (1.25–29.33)	0.025	7	5.0	6 (85.7)	6.55 (0.68–63.33)	0.105
Activity and light	4	1.9	4 (100.0)	2×10^{9} (0.00–NA)	0.999	5	3.5	3 (60.0)	1.64 (0.23–11.70)	0.624
Activity and noise	20	9.3	18 (90.0)	8.38 (1.78–39.56)	0.007**	3	2.1	3 (100.0)	2×10^{9} (0.00–NA)	0.999
Light and noise	4	1.9	4 (100.0)	2×10^{9} (0.00–NA)	0.999	3	2.1	3 (100.0)	2×10^{9} (0.00–NA)	0.999
All three (activity, light and noise)	9	4.2	6 (66.7)	1.86 (0.42–8.19)	0.411	11	7.8	10 (90.9)	10.91 (1.19–99.69)	0.034*
What makes the headache better										
None (*R*)	24	11.2	15 (62.5)	1		10	7.1	7 (70.0)	1	
Rest	76	35.3	48 (63.2)	1.03 (0.40–2.66)	0.954	82	58.2	49 (59.8)	0.64 (0.15–2.64)	0.534
Painkiller	43	20.0	29 (67.4)	1.24 (0.44–3.53)	0.683	21	14.9	17 (81.0)	1.82 (0.32–10.34)	0.499
Rest and painkiller	72	33.5	52 (72.2)	1.56 (0.59–4.13)	0.371	28	19.9	24 (85.7)	2.57 (0.46–14.32)	0.281
Additional symptom during headache										
No (*R*)	116	54.0	63 (54.3)	1		88	62.4	57 (64.8)	1	
Yes	99	46.0	81 (81.8)	3.79 (2.02–7.09)	<0.001**	53	37.6	40 (75.5)	1.67 (0.78–3.59)	0.186

*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

Non-COVID-19 headache patients experienced a pain with pressing followed by pulsating and fiery sensation (36.2%, 31.2%, and 20.6% respectively). Meanwhile, 61.4% of the COVID-19 patients complained of a pulsating headache and 20.9% had a pressing headache. Those with COVID-19 reported more pain intensity (moderate to severe) than non-COVID-19 (mild to moderate) while also reporting the use of medication. Similar results were reported by other studies. For instance, pulsating, or pressing sensation, high risk of drug resistance and recurrence appear to be more common in COVID-19 patients [23-25]. Frontal pain, pulsating type, higher pain intensity, and presence of nausea in COVID-19 patients were associated with lymphopenia, low C-reactive protein, and procalcitonin levels [26]. Viral infections other than COVID-19 - such as dengue - have shown headache sensation of throbbing (59.2%) or pressing (40.7%) patterns more frequently [27].

There are some mechanisms underlying the worsening headache in COVID-19 patients. First, the profound pain of headache is induced by vasodilatation, plasma protein release, and mast cell degranulation in cranial tissues and meninges [28-30]. Second, the receptors of angiotensin-converting enzyme 2 (ACE2) on endothelial vessels make blood arteries prone to SARS-CoV-2 invasion. ACE2 has been linked to various defensive mechanisms in the body, including antinociception and vasodilation. ACE2 also reduces excessive free radical generation, which helps to minimize oxidative stress [31]. In addition, the virus that occupies the receptors may disrupt the vascular homeostasis. The perivascular trigeminal nerve may be damaged as a result, leading in COVID-19 headache [32]. Third, SARS-CoV-2 may infiltrate the trigeminal nerve by indirect pathways as well. Mechanisms such as cytokine storm and vasculopathy are also postulated to explain trigeminal nerve activation during SARS-CoV-2 infection [33-35]. Fourth, another theory explains that COVID-19 headache is induced by SARS-CoV-2 that disturb gas exchange in alveoli. Consequently, COVID-19 patients may have lower blood oxygen levels that triggers ischemia [33, 36].

COVID-19 patients have a higher frequency of headaches than non-COVID-19 patients. They complained of headaches twice a week, sometimes almost every day, while non-COVID-19 patients, who only get sick once or twice a month on average. Headache may impact individual's life both during and between headache attacks, which later affect QoL. Several studies identified headaches as the most distressing symptom, particularly in COVID-19 patients, because they interfere with daily activities [7, 25, 37]. The majority of participants (67.7%) in this study had a poor QoL in terms of pain, social functioning, fatigue, and mental health. Indeed, patients with chronic daily headaches experience emotional disturbances significantly more [38]. Thus, reduced QoL among headache patients poses a major concern because of its widespread prevalence and its debilitating nature [39]. The economic impact that occurs is due to a decrease in work productivity, increased absenteeism and disruption in social and family relations [39].

Poor QoL in COVID-19 patients with headaches were associated with unemployment, non-health-related jobs, use of pain medication, headache duration, frequency of attacks, activities, conditions that aggravate pain, and additional symptoms. In non-COVID-19 individuals, data suggested that poor QoL was associated with pain medication use, headache duration, and factors that aggravated headache pain.

Headaches affect an individual's daily life and QoL negatively. The frequency, severity and other symptoms (such as nausea, phonophobia and photophobia, and also mood disorders) contribute to this negative outcome [40]. A recent study found that post-COVID-19 sequelae increased anxiety and hampered daily activities, such as full-time work and self-care, while also decreasing ones' participation in social activities due to cognitive dysfunction [41].

There are several limitations in this study. For example, the investigation did not assess the types of headaches before COVID-19, which could have contributed to the characteristics of COVID-19 headache. The COVID-19 headache characteristics were not specified for its migraine or tension-type headache-like symptoms. Consequently, it might be indistinguishable from the primary headache disorders, especially on asymptomatic COVID-19 patients. Also, reports on headache characteristics were based on personal complaint that could not be determined accurately. Further studies regarding the processes by which SARS-CoV-2 assaults the CNS and

causes headache are vital for improving our understanding of COVID-19 headache pathophysiology, which determines potential therapeutic strategies.

Conclusions

There are four key differences between COVID-19 and non-COVID-19 headache: location, pain sensation, pain intensity, and frequency. The COVID-19 headache found in this study was bilateral, pain centered in one specific area, with pulsating or pressing sensation; it was also of moderate to severe pain and occurred more than twice a week or every day. Meanwhile, the non-COVID-19 headache was bilateral, the pain centered on one side of the head with pressing or pulsating sensation, with reports of mild to moderate pain, and occurred once or twice a month. These comparisons are critical since headache has a negative impact on patients' QoL. More in-depth research, particularly on the mechanisms of headache in both COVID-19 and non-COVID-19 patients, is still required to gain a better knowledge for headache management.

Ethics approval

The study protocol was approved by the Ethical Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (10/EA/FK-RSUDZA/2022).

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Conflict of interest

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results are available from the corresponding author upon reasonable request.

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