The Emergence of a New Form of Headache in COVID-19 Pandemic Era

Özge Uygun (ozz_uygun@hotmail.com)

Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, https://orcid.org/0000-0001-9786-5892

Mustafa Ertas

Istanbul Universitesi Istanbul Tip Fakultesi

Esme Ekizoğlu

Istanbul Universitesi Istanbul Tip Fakultesi

Hayrunnisa Bolay

Gazi Universitesi Tip Fakultesi

Aynur Özge

Mersin Universitesi Tip Fakultesi

Elif Kocasoy Orhan

Istanbul Universitesi Istanbul Tip Fakultesi

Arif Atahan Çağatay

Istanbul Universitesi Istanbul Tip Fakultesi

Betül Baykan

Istanbul Universitesi Istanbul Tip Fakultesi

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Abstract

Background

Headache is the most common COVID-19-related neurological symptom. But, diagnostic clues of headache for COVID-19 infection are not well known.

Methods

We developed a detailed web-based questionnaire screening the characteristics and course of headaches besides clinical COVID-19 features. The participants were grouped according to being diagnosed with COVID-19 infection or not, and having previous or new-onset headaches. The COVID-19 related headache features and their associations with other clinical features were investigated. A binary logistic regression model was performed to differentiate the characteristics of headache related to COVID-19.

Findings

3458 participants (2341 females;67.7%, 1495 healthcare workers;43.2%) with a mean age of 43.21±11.2 years experiencing headache during pandemic contributed to the survey. Among them, 262 participants had COVID-19 and 126(48.1%) were male. The rate of males in the group without COVID-19 was 31% (991 out of 3196 participants) showing significant gender difference between groups ($p<0.000$). COVID-19 related headaches were more closely associated with anosmia/ageusia and gastrointestinal complaints (RR=3.7 and RR=1.33, respectively), showed different characteristics like pulsating, pressing, and even stabbing quality. Logistic regression analyses showed that bilateral headache, duration over 72 hours, analgesic resistance and having male gender were significant variables to differentiate COVID-19 positive patients from those without COVID-19 ($p<0.000$ for all variables). A worsening of previous primary headaches due to the pandemic-related problems was not the rule in majority of patients.

Interpretation

Bilateral, long-lasting headaches, resistance to analgesics and having male gender were more frequent in people with COVID-19 in conjunction with the anosmia/ageusia and gastrointestinal complaints. These features may be helpful for COVID-19 diagnosis in the clinical evaluation of headache patients during the pandemic.

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Introduction

Coronavirus disease-19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) first emerged in Wuhan towards the end of 2019.[1] The pandemic has now been influencing the whole world and is causing a large number of deaths, besides many other medical and social

consequences. The most common clinical picture of COVID-19 is characterized by mainly manifestations of the respiratory system, as the name of the virus implies. However, many other complaints such as anosmia, ageusia, diarrhea and also headache have been noted in the clinical spectrum, with an increasing number of patients.[2] A handful of reports disclosed that headache is among the COVID-19-related symptoms with highly variable rates across the studies.[3-5]To date, there are some studies and reviews highlighting that the most common neurological symptom is headache, often accompanied by high fever, whereas headache can occasionally be seen alone as the first sign of the disease.[2, 6] Therefore, detailed questioning of the presence of headaches in patients who admitted to the emergency and outpatient departments is still an important step in the prompt recognition of the infection in some patients.

In clinical observations and small case series, COVID-19 related headache was described as acute at onset, usually occurring in different character unlike previous headaches.[7, 8] However, there are no systematic data on the headache characteristics.

Another important problem is the situation of patients with previous severe headaches like migraine in the COVID-19 pandemic era. COVID-19 itself or its psycho-sociological effects may cause more headache burden, along with the problems of quarantine and these points are not investigated thoroughly, yet. Considering that there are no detailed data on the course of pre-existing headaches as well as new-onset ones during the pandemic, we designed this study to investigate the COVID-19 related headache characteristics and its associations with other clinical features.

Methods

After the emergence of COVID-19 for the first time in March 2020 in our country, the complaints of peculiar headaches by consulted cases and some distinctive features in admitted patients have attracted our attention. For this reason, a detailed questionnaire was developed focusing on headache characteristics, besides some clinical COVID-19 features by a panel of headache experts, after rounds of online discussions. To optimize the attention during answering the survey, the number of the questions was tried to keep in an acceptable limit and the survey was tested before its submission by five patients for clarity of the questions. The web-based, user-friendly technical design was planned by the experts of the Istanbul University Department of Informatics.

The participants were invited by means of social media of the headache experts using a web-based link, suitable also for smart phones, after the Ethics Committee approval (17.04.2020/520). The questionnaire was applied to eligible participants, who had a COVID-19 infection including headache among its symptoms or who had any type of headache before the pandemic, or developed new-onset headaches. These patients were grouped according to being diagnosed with COVID-19 infection or not. In our country's protocol only those patients who had polymerase chain reaction (PCR) positivity, were diagnosed with COVID-19. Especially, healthcare workers were encouraged to attend the study. Figure 1 shows the PRISMA flowchart of our study.

With the designed questions, the features of previous headaches were screened and diagnosed according to International Classification of Headache Disorders, 3rd version (ICHD-3 criteria).[9]Possible changes in the headache course during the pandemic along with perceived precipitating factors and related characteristics were queried with scrutiny. Important characteristics such as the duration, frequency, course, localization, the severity of headaches, and treatment response have been asked separately before and during the COVID-19 pandemic. The questionnaire has also asked the symptoms of COVID-19 infection in detail, for relevant patients. Even if the patient is not diagnosed with COVID-19, the factors that are secondary to the pandemic lifestyle, such as wearing a mask as a possible trigger before the headaches, having the fear of infection, etc. were evaluated. The questionnaire has included a total of 39 questions, and based on four different parts, in terms of demographics, previous headache features, reported COVID-19 infection features, and details of the headaches after the pandemic.

The duration of survey implementation was planned as 15 days, starting on 1 May 2020. In power analysis, it has been calculated that at least 201 individuals were needed with a %95 confidence interval, %5 precision, and %16.4 for prevalence rate of migraine in Turkey. Although reaching this needed number in a few hours, the survey was continued to the end of this period to include more patients with COVID-19 related headaches. Discharged COVID-19 patients of the Istanbul University Department of Infectious Diseases and Clinical Microbiology were invited by text messages to volunteer the survey, in order to increase the number of patients with COVID-19 infection-related headache.

Statistical analysis:

Descriptive analyses were applied for four main groups of participants (Figure 1, Table 1); the participants with or without COVID-19 were compared in relation to the presence or absence of previous headaches before the pandemic of COVID-19 in regard to headache characteristics by the chi-square test and t-test where appropriate. A binary logistic regression model was performed to explore the differentiating headache variables between COVID-19 positive and negative cases. Relative risks and odds ratios were calculated for significant infection-related features, such as anosmia/ageusia and gastrointestinal complaints like diarrhea. IBM SPSS Statistics Version 22 was used and $p<0.05$ was considered as statistically significant.

Results

A total of 3458 participants (2341 females) contributed to our survey. Of this main group with and without headache during the pandemic, 262 patients have been diagnosed with COVID-19 by PCR. These patients were grouped as COVID-19 positive; and this group consisted of 136 females (51.9%); 89 healthcare workers (9.8%) versus 114 other participants (10.8%) were diagnosed with COVID-19, with similar rates.

During the pandemic, 1968 participants reported headache attacks. Among them 714 (36.3%) had migraine and 1077 (54.7%) participants were diagnosed as tension type headache (TTH) according to

ICHD-3 criteria. The headache characteristics, accompanying features, treatment responses of those experiencing headache during the pandemic were shown in Table 1, comparatively.

The characteristics of patients with COVID-19 infection

In the COVID-19 positive group, the rate of males was 48.1% (126 out of 262 patients), whereas in the COVID-19 negative group (3196 patients) this rate was 31% (991 patients), showing a significant gender difference between the groups ($p<0.000$). Headaches over 72 hours were reported by 10.3% of COVID-19 infected patients versus by 4.1% of the COVID-19 negative group (27 of 262 versus 130 of 3196 participants, $p<0.000$).

The severity of the previous headaches did not relate to receiving COVID-19 diagnosis; COVID-19 positive patients had reported headaches of mild intensity in 26.6%, moderate-intensity in 47.7%, severe in 23.4% and very severe headaches (dependent to bed/hospital) in 2.3% of the group, whereas the corresponding rates of headache intensity were 27.7%, 46.7%, 21%, and 4.6% in COVID-19 negative participants, consecutively.

The great majority (79.5%) of COVID-19 patients with previous headaches reported that their new emerging headaches during the infection period were different from their usual headaches; among them, 50% disclosed that this new headache was totally different, whereas 29.5% reported some differences despite some similar properties resembling previous headache features. On the other hand, among the participants without COVID-19 diagnosis but with previous headaches, 62.7% disclosed that their headaches were identical to the pre-existing episodes. Among them, only 13.9% reported entirely different attacks, whereas 23.4% reported partly different headaches.

Among all 262 patients diagnosed with COVID-19, 40% reported high fever (over 38˚C), 49.2% prominent cough, 48.3% sore throat and 33.5% shortness of breath, whereas diarrhea/stomachache was present in 57.7% and lastly anosmia/ageusia was present in 60.4% of this group. There were 59 COVID-19 positive patients who had previous headaches (22.5%), who did not experience headaches during the pandemic period of 2 months at the time of their participation in the survey. At least one close contact with the disease was present in 65.4% of the COVID-19 positive patients and 90.1% of the patients lived under quarantine.

The course of participants with pre-existing headache during the pandemic

The triggers of headache reported by the participants are shown comparatively in COVID-19 positive and negative cases in the Figure 2; the second part of this figure shows the triggers reported by healthcare workers compared to the others.

The various changes of headache in participants with previous headaches after the pandemic were shown in Figure 3. Among these patients, 23.3% reported an increase in severity of headache, 28.7% reported an increase of the headache duration, and lastly, 14% reported deterioration of the accompanying symptoms. The decreased headache frequency in 12.3% of the group was remarkable.

Our analysis showed that among the patients with pre-existing migraine diagnosis, the frequency of pulsating headache character decreased from 60.5% (328 out of 542 pts) to 55% (22 out of 40 pts) in those receiving COVID-19 diagnosis. But this latter rate was still significantly higher in comparison to 34.1% (31 out of 91 pts) compared to COVID-19 positive patients without previous headache (p=0.033).

The age plots of the participants with COVID-19 in relation to worsening of previous headache and analgesic unresponsiveness did not show any difference.

Differentiating variables of COVID-19 related headache

The important differentiating variables for COVID-19 infection patients suffering from headaches were summarized in Figure 4 with calculated relative risks (RR) and Odds ratios (OR).

Additionally, binary logistic regression was computed with significant headache variables which could be observed in everyday practice to distinguish COVID-19 related headaches. We did not enter infection-related features in this analysis, because they are clear clues for COVID-19 and do not appear in control cases. The results of this analysis shown in Table 2.

Discussion

This first careful analysis of emerging headache characteristics in the pandemic showed that COVID-19 related headaches are more closely associated with anosmia/ageusia and gastrointestinal complaints, in comparison to other usual infection findings. Moreover, bilateral headache, duration over 72 hours, male gender, and analgesic resistance are highly important variables to differentiate between COVID-19 positive patients from negative ones. Although we expected prominent worsening of primary headaches due to the pandemic-related problems, it came out that this happened only for less than 1/3 of participants, mostly related to stress.

Gender difference of COVID-19 related headaches

Despite the well-known predominance of headaches in females and the fact that more than 2/3 of participants answering our survey consisted of females, COVID-19 related headaches were reported by male patients at a high rate. This interesting finding is somewhat in line with the predominance of COVID-19 in males with changing reported rates around 56-73%.[10-12]It could be hypothesized that this reversed gender dominance may relate to comorbidities like atherosclerosis and hypertension which are more frequent in males. However, females with nearly three times higher rates of migraine, could have still been outnumbered in COVID-19 related headaches.[10,13] Therefore, this finding is a striking point that needs further careful elaboration. Given the higher risk of male gender in COVID-19 cases, a protective role of female hormones or X chromosome location of Angiotensin-converting enzyme 2 (ACE-2) could be speculated.[7,10] Moreover, ACE-2 expression level which is critical for the SARS- CoV-2 entry to the cells was found different between genders[12]. There is some evidence that immune activity is more efficient in females, in other viral infections.[14] It is tempting to speculate that SARS-CoV-2 may trigger some silenced

genes related to innate immunity in the X chromosome, so two X chromosomes may serve for a more effective and balanced war against COVID-19 related hyperactivation of immune pathways. Moreover, estrogens and progesterone have anti-inflammatory actions partially through inflammasome activation in some models.[15]ACE also affects the display of major histocompatibility complex (MHC) class I and MHC class II peptides.[16] Thus, further work with these gender-related differences may give us some clues to find out novel protective ways against COVID-19.

Possible mechanisms underlying COVID-19 related headaches in the light of our findings

The underlying mechanisms of headache related to COVID-19 are not clear at this early moment.[7]A direct invasion of trigeminal nerve endings in the nasal or oral cavity by the virus seems one of the most reasonable mechanisms underlying headache according to our results showing the close relation between headache and anosmia/ageusia. Some coronaviruses were shown to be neurotropic and former SARS-CoV has been observed in the human brain.[17,18] Therefore, it is highly likely that SARS-CoV-2 may also enter the nervous system via the cranial nerves. Regarding the frequency, since the first observations in China, there are many worldwide reports with heterogeneous prevalence figures around 5-85% of loss of smell.[19, 20] These differences may relate to the viral load in conjunction with a different individual immune response between younger milder symptomatic outpatients, who are eager to report their symptoms, and contrarily severe COVID-19 inpatients with prominent respiratory problems who probably under-report this relatively milder problem. It is well-known that methodological differences exist between questionnaire studies and objective measurements, being the former mostly with lower prevalence. Despite this fact, the rate of anosmia/ageusia was high in our study. These two distinct problems caused by different nerves were not easy to differentiate from each other in daily life, therefore anosmia and ageusia were evaluated together, in our study. It was remarkable that nasal obstruction and rhinorrhea were frequently reported but not strictly correlated with anosmia and ageusia according to our results. Although the trans-synaptic transfer of SARS-COV-2 is not proven yet, this possibility of the trans-synaptic route was documented for other coronaviruses.[21]Entrance from the nasal cavity to the olfactory bulb, then spreading to the brainstem via the piriform cortex with both passive diffusion and axonal transport has been demonstrated.[22]

Besides the described headache characteristics and COVID-19 related respiratory tract symptoms, abdominal pain and diarrhea should be taken into account to evaluate these patients.[3-5,23] Our study found a high rate of gastrointestinal symptoms like diarrhea/stomachache in more than half of the COVID-19 cases along with high rates of nausea (71%) as an accompanying symptom of headache. A previous interesting report from China on non-classical symptoms indicated that 21.6% of patients with gastrointestinal symptoms associated with headache which is a higher number in comparison to patients without gastrointestinal symptoms.[24]The intriguing relationship of headache with gastrointestinal symptoms also reminds several interesting mechanisms including increased circulating Calcium gene related peptide (CGRP) levels and “gut-brain axis” concept where several inflammatory mediators like Interleukin-1β (IL-1 β), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Tumor necrosis factor-α (TNF-α), besides

gut microbiota, and neuropeptides including CGRP are thought to play a role in this interaction. More relevant consideration will be systemic CGRP increase, possibly induced by both angiotensin II and IL-6 levels, as CGRP is clearly associated with trigemino vascular activation resulting in headache, increased gastrointestinal (GI) motility leading to diarrhea, further triggering inflammation and vascular edema.[7,25] Taken together with the unusually high rate of ageusia-anosmia (60.4%) this data may lead us to the footsteps of the viral pathway in the brain. Thus we may also suggest that neuronal invasion of this new coronavirus may cause the dysfunction of the network at brainstem sites, in addition to headache. Nausea and vomiting are associated GI symptoms of migraine headache, yet the diarrhea is a distinct GI feature associated with headache in COVID-19, which clearly shows opposite influencers play role in SARS-CoV-2 infected gut and trigeminal nerve.

Headache in relation with a systemic viral infection, (without signs of meningo-encephalitis) is described in the International Classification of Headache Disorders-3 classification. The underlying mechanisms of this entity are not illuminated so far. Regarding its characteristics, diffuse pain of moderate/severe intensity, commonly with fever was noted.[9]However, in our analyses, the association of headache with fever seems not to be decisive (in all COVID-19 patients with headache, only 40% reported high fever). Also, rhinosinusitis and other respiratory tract symptoms did not seem to explain the headaches in many of these cases, as seen in Table 1. Therefore, for this emerging COVID-19 related headache, the simplistic view of a "causal" relationship with fever or upper respiratory symptoms is not explanatory.

The course of previous headaches during the pandemic and reported triggers for headache

Most of the patients with pre-existing headaches easily noticed that this was a different problem if they have COVID-19 related headache according to our survey. On the other hand, it was also intriguing that 22.5% of the COVID-19 positive cases with previous headaches did not suffer from headache during the pandemic and during the infection. There is no clear explanation for the lack of headache in these cases; causes related to viral load, transmission route, or individual differences may play a role. Other interesting data were the stabile course (53%) or even decrease of the attack frequencies (12%) and reduced severity of the pre-existing headaches in the pandemic period despite the apparent stressful conditions. Social isolation may help to avoid stressful social interactions, a healthy diet, and mild sports activities are possible with more time at home, also reducing the stress of daily-work life during the pandemic; these points were the possible reasons for the better headache outcome than expected.

The triggers for headaches showed significant differences between participants with and without COVID-19 infection. Headache was triggered more frequently by stress and social isolation in patients without COVID-19, whereas the patients diagnosed with COVID-19 reported also infection itself and the drugs as triggers of headache. Furthermore, wearing masks as well as stress both were the main triggers of headache and were more frequently reported by healthcare workers than by the others. Standard hygiene precautions seem to reduce the risk for the healthcare workers, who did not show an increased risk for COVID-19 compared to other participants in our study. It was reported from Germany an overall

seroprevalence of SARS-CoV-2 in a tertiary hospital was low, given the standard hygiene measures were taken.[26]

Other differentiating features and associations of COVID-19 related headache

Headache as the leader of the COVID-19 related neurological symptoms is also the most frequent complaint in outpatient clinics.[27] Thus it is essential to recognize those patients with COVID-19 in the beginning of the visit or even in telemedicine visits. In this study, we provided evidence that long-lasting bilateral headaches over 48-72 hours and headaches resistant to analgesics suggested the likelihood of being infected by COVID-19 similarly to other secondary headaches. The interesting distributions of pulsating and pressing characters in COVID-19 patients, as seen in Table 1, showed that pulsating type was more pronounced in patients with previous headaches; this may indicate that individual backgrounds are important in the final phenotypic presentation of COVID-related headache. COVID-19 infection may play a synergistic role in nociception using similar pathways of trigeminovascular complex, with underlying primary headache such as migraine. However, different characteristics like pulsating, pressing, and even stabbing quality may indicate that more than one mechanism is involved in COVID-19 related headache emergence. A case report by a headache expert diagnosed with COVID-19 also indicated that several types of headaches can be seen during COVID-19 infection based on a single case (himself).[28] Our data had a cross-sectional design; and many participants have chosen only one type despite the availability of multiple choices. Thus instead of several headache types in one patient, it seems more likely that, headache types may differ between individual backgrounds. Another intriguing finding was that photophobia was more frequently experienced by infected participants than those without COVID-19, reaching statistical significance between the subgroups without prior headache. Moreover, osmophobia was more frequently seen in the group with COVID-19, which may also be related to the olfactory dysfunction. Further basic studies are needed to clarify the mechanism of COVID-19-related headache and to unravel the mysteries of the environmental factors including viruses for the headache mechanisms, to make the pandemic disaster an opportunity.

Limitations And Strengths Of The Study

There are some limitations to this study. First of all, we investigated headache characteristics via questionnaire; the results were based on the answers of the patients. Secondly, the patients with COVID-19 were not examined by a physician or headache specialist. Furthermore, our questionnaire was a web-based survey, therefore, only individuals, who were able to use new technological devices, thus probably younger and educated people could participate in the study. Among the participants, there may also be some patients who were not tested for COVID-19 due to the lack of other accompanying symptoms. Moreover, patients with severe COVID-19, at the time of the survey could not be included.

The main strength of our study was the participation of a large number of people in a very short period during the increasing phase of the pandemic. We used a detailed dedicated questionnaire investigating various characteristics of previous and current headaches, including also cross-questions to avoid

misunderstandings. The answers given by participants were also examined meticulously to minimize discrepancies. Furthermore, the presence of healthcare workers, reaching nearly half of the participants has increased the reliability of the study.

In Conclusion

The COVID-19 pandemic seems to have a particular effect on the characteristics and the course of headaches in individuals with and without COVID-19 diagnosis, according to our findings. We disclosed that having male gender, bilateral, long-lasting headaches, and resistance to analgesics were more frequently seen in people with COVID-19 infection in conjunction with the anosmia/ageusia and gastrointestinal complaints, besides other infection findings. We propose that these features may be diagnostic for COVID-19 infection in the clinical evaluation of headache patients during the pandemic. We think that COVID-19 related headache should be considered as a separate entity among the infection-related secondary headaches, with this different profile.

Abbrevations

COVID-19: Coronavirus disease 2019

SARS-CoV 2:Severe acute respiratory syndrome coronavirus 2

ACE-2: Angiotensin converting enzyme

TNF- α: Tumor necrosis factor-α

IL-1β: Interleukin-1β

IL-6: Interleukin-6

IL-8: Interleukin-8

CGRP: Calcium gene related peptide

TTH: Tension type headache

ICD-3: International Classification of Headache Disorders, 3rd Edition

PCR: Polymerase chain reaction

MHC: Major histocompatibility complex

RR: Relative risk ratio

OR: Odds ratio

GI: Gastrointestinal

Declarations

Consent for Publication:

Not applicable

Ethics Approval and consent to participate:

Istanbul University Istanbul Faculty of Medicine Ethics Committee approved the study (17.04.2020/520).

Availability of Data and Materials:

This study is a web-based questionnairre, the data is not applicable.

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We received limited support from the Istanbul University Clinical Research Committee at the stages of creating appropriate questionnaires and reaching patients.

Declaration of interests:

We declare no competing interests.

Contributors

HB, AO, EKO, EE, BB designed the survey. ME did statistical analyses. All authors drafted the manuscript.

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Tables

Table 1: Demographic features of participants and characteristics headache of experienced during the pandemic period

(n=1968)	COVID-19 positive*			No COVID-19#				
	Prior headache (n=116)	No prior headache (n=87)		Prior headache (n=138)	No prior headache (n=383)			
			p			**p**	**p (1-3)**	**p (2-4)**
Age year,mean (SD)	39.7 (11)	38.2 (11)	.370	41.0 (10)	42.2 (11)	.061	.175	**.004**
Sex (male %)	36.2	46.0	.104	22.9	31.6	**.000**	**.001**	**.008**
Healthcare worker(%)	44.0	43.7	.541	46.1	48.3	.239	.366	.255
Headache duration hours mean (SD)	52.1 (57)	45.3 (53)	.430	38.4 (53)	45.9 (63)	**.039**	**.014**	.949
Headache characteristics								
Pulsating %	50.9	32.5	**.008**	55.5	42.5	**.000**	.202	.064
Pressing %	31.9	43.7	.058	29.0	38.6	**.000**	.289	.227
Fiery %	2.6	2.3	.633	2.7	5.0	**.022**	.625	.219
Stabbing %	12.9	16.1	.330	11.1	11.2	.497	.315	.142
Accompanying symptoms								
Nausea %	70.8	71.3	.538	53.5	52.9	.450	**.000**	**.002**
Phonophobia %	67.0	67.9	.509	71.2	66.6	.056	.198	.465
Photophobia %	63.9	63.0	.508	60.5	51.2	**.002**	.276	**.038**
Osmophobia %	39.0	50.0	.090	30.4	28.5	.292	**.044**	**.000**
Allodynia %	31.9	-	-	41.8	-	-	**.024**	-
Anosmia/ageusia %	74.5	73.2	.479	19.1	23.1	.073	**.000**	**.000**
Sore throat, rhinorrhea %	62.2	70.4	.152	41.8	54.4	**.000**	**.000**	**.006**
Stinging, burning, tearing in the eyes	63.2	64.6	.481	44.8	49.8	.063	**.000**	**.011**
Use of analgesics %	84.3	79.8	.257	82.8	69.8	**.000**	.389	**.042**
No response to analgesics %	16.5	22.4	.227	7.1	8.0	.353	**.002**	**.002**

Partial response to analgesics ≤50%) %	38.1	38.8	.530	25.5	37.6	**.000**	**.006**	.484
Improved with analgesics >50%	32.0	25.4	.231	26.1	27.4	.362	.129	.436
Completely recovered with analgesics %	12.4	11.9	.568	39.2	26.2	**.000**	**.000**	**.008**

***** Diagnosed by positive PCR test; **#** No COVID-19 symptoms or diagnosis; **p (1-3)** p value between the patients with prior headache with or without positive COVID-19 test; **p (2-4)** p value between the patients with no prior headache with or without positive COVID-19 test (significant test values are marked as bold)

Table 2: The logistic regression analysis model to differentiate patients with COVID-19 from those without COVID-19 based on headache characteristics

Variables						**Exp(B)**	**95% C.I. for EXP(B)**	
	B	S.E	Wald	df	Sig.		Lower	Upper
Bilateral headache	-1.391	0.254	30.081	1	0.000	0.249	0.151	0.409
Gender	-0.897	0.173	27.012	1	0.000	0.408	0.291	0.572
Analgesic resistance	-1.005	0.236	18.153	1	0.000	0.366	0.231	0.581
Duration>72 hours	-0.509	0.248	4.214	1	0.040	0.601	0.370	0.977
Constant	0.179	0.329	0.297	1	0.586	1.196		

B: beta (regression coefficient); SE, standard error; d.f., degree for freedom; Sig., significance; Exp (B), OR: exponential B, odds ratio.

Figures

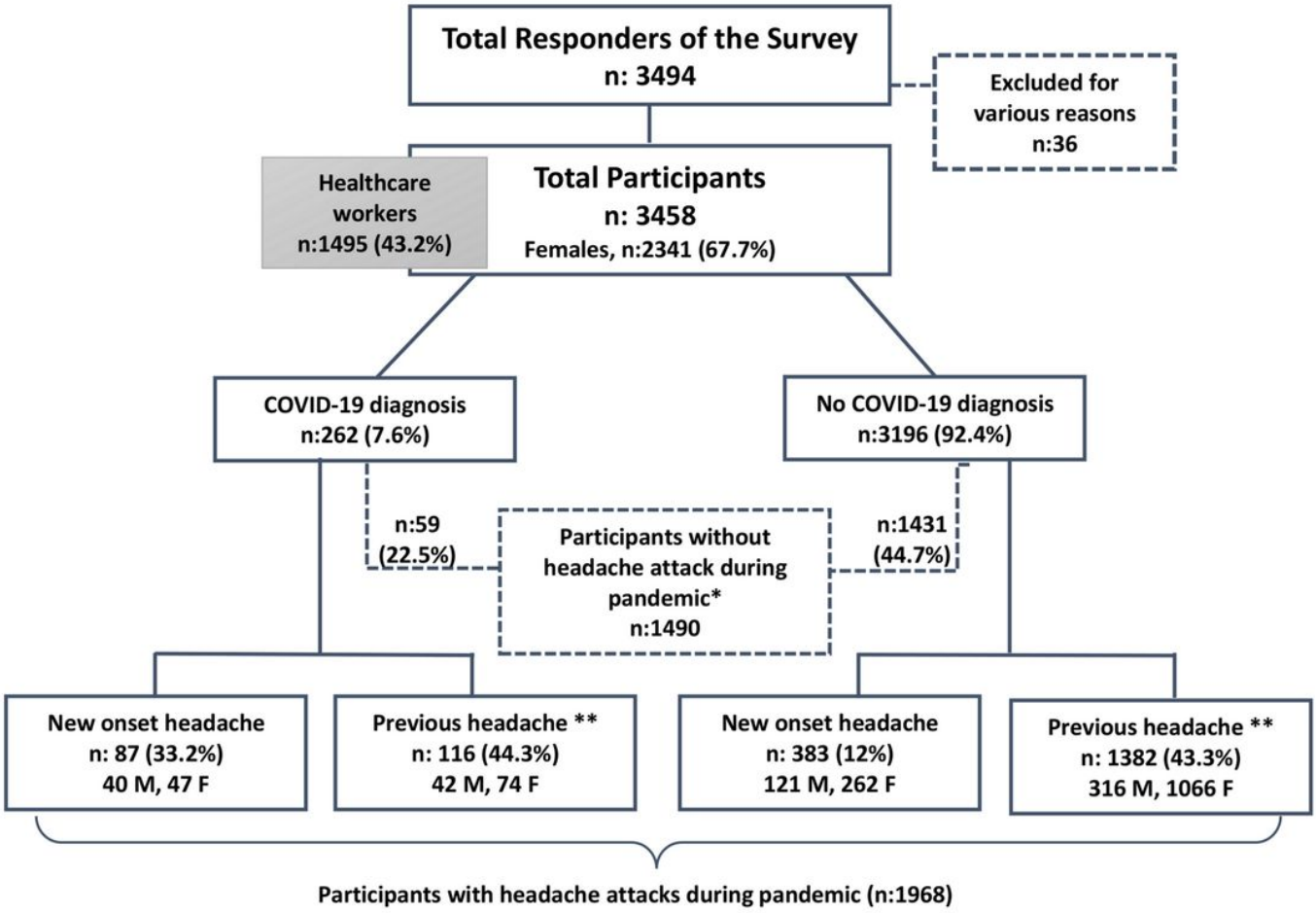

Figure 1

Flowchart of the study Legend *Please note that some participants with previous headaches did not experience headache attacks during pandemic (March-April 2020). **Only those participants with headache attacks during the pandemic could be included in the analyses, done in terms of before-after pandemic comparisons. M; male, F; female

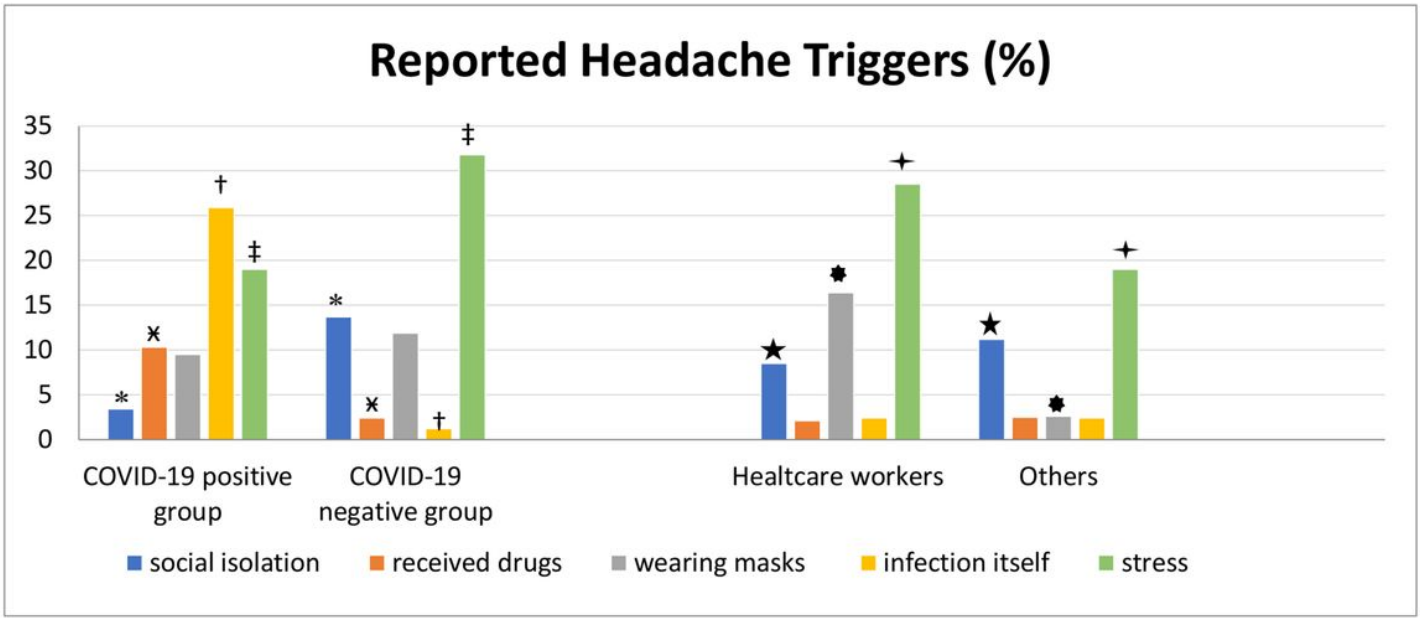

Figure 2

Reported triggers for headache were shown comparatively in COVID-19 positive and negative cases. The second part of the figure shows the triggers reported by healthcare workers compared to the others. Legend *p:0.0006, ⁎p:0.0002, †p:0.0001, ‡p:0.0015 showing statistically significant differences between each reported trigger in COVID-19 positive and negative patients; and ★p:0.049, ✸p:0.0001, ✦p:0.0001showing statistically significant difference between healthcare workers and others, with Pearson Chi Square Test.

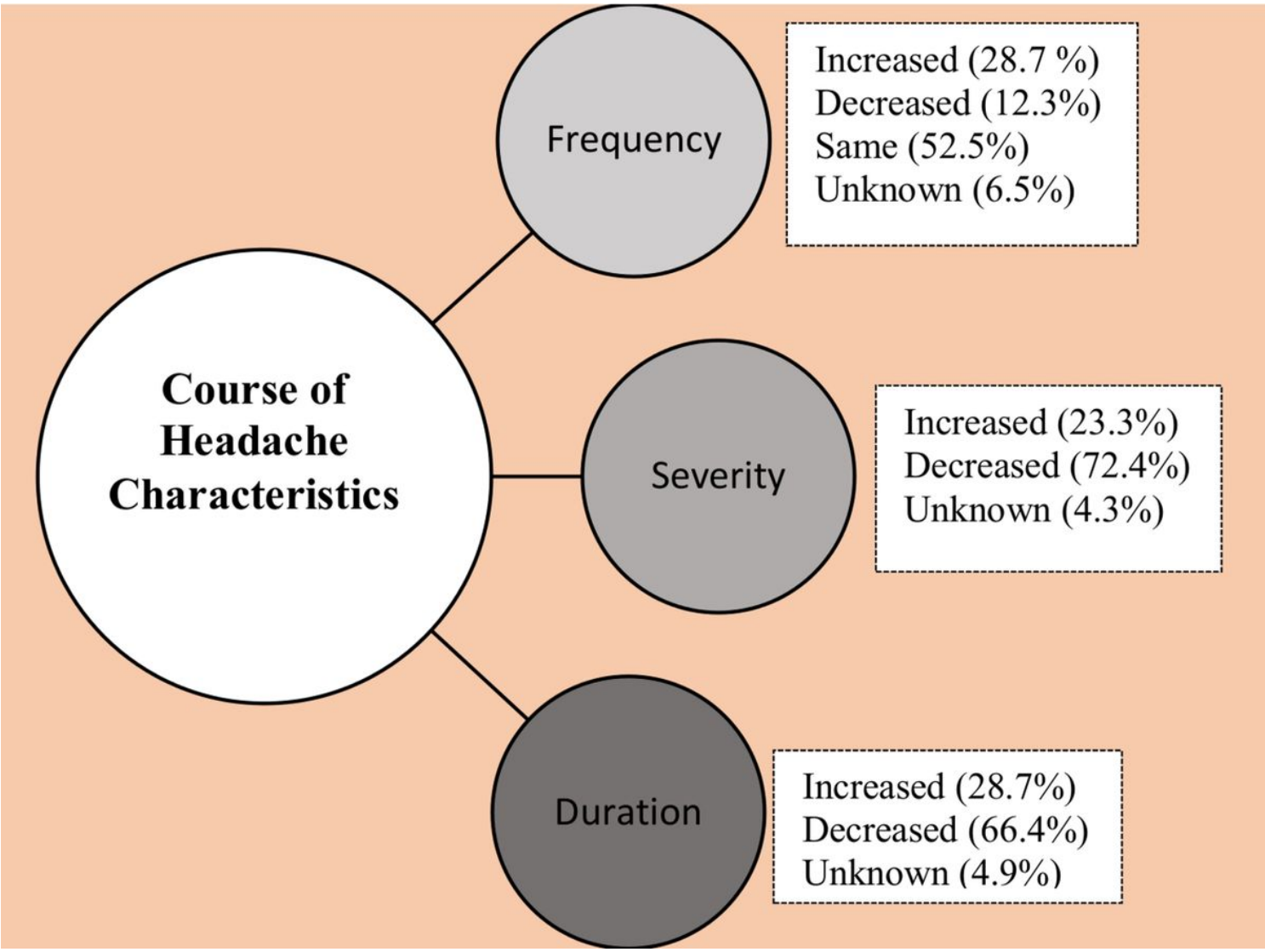

Figure 3

The course of headache characteristics

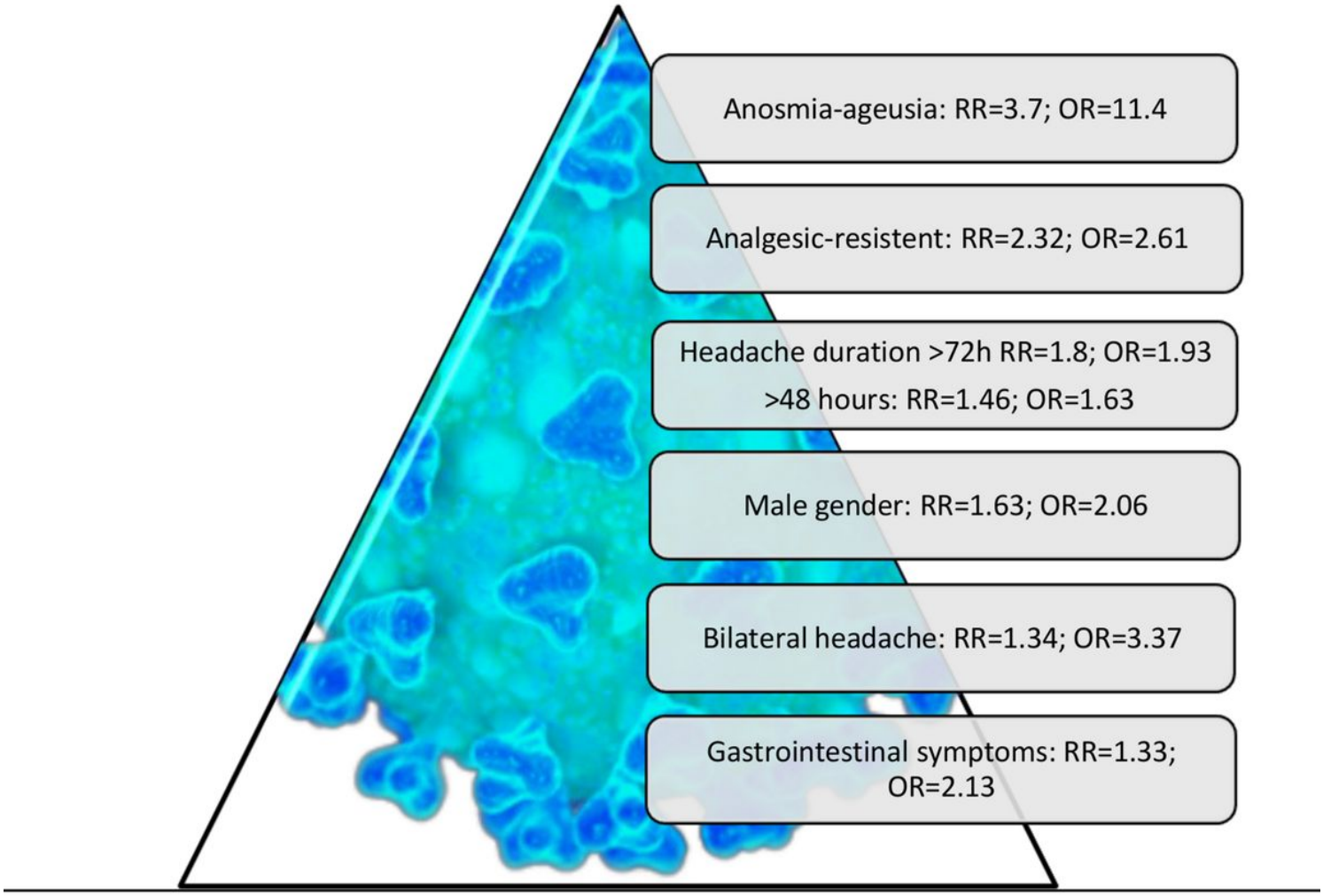

Figure 4

Relative risks and Odds ratios of differentiating variables related to the presence of headache in patients with COVID-19 diagnosis reporting headache during pandemic