Exploring the relationship between SARS-CoV-2 infection and headache: comprehensive systematic review

Explorando a relação entre infecção por SARS-CoV-2 e cefaleia: revisão sistemática abrangente

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ABSTRACT

BACKGROUND AND OBJECTIVES: Addressing secondary headaches in SARS-CoV-2 infection is crucial for effective management and care optimization. This review aims to synthesize data on headache characteristics and the impact of pre-existing headache conditions on these symptoms in SARS-CoV-2 infection.

CONTENTS: A systematic search was conducted across multiple databases, including PubMed/Medline, Cochrane Collaboration, Web of Science, Scopus, LILACS, Embase, Open Grey, and Google Scholar, to identify studies on headache characteristics associated with SARS-CoV-2. The search focused on headache symptoms, characteristics, onset, duration, and response to treatment during and post-infection. Twenty-three studies met the inclusion criteria. Approximately 42.1% of individuals with SARS-CoV-2 reported headaches, resembling tension-type headaches and migraines. These headaches often manifested within the first three days of infection and could persist for up to four months. The data suggest that trigeminovascular activation and pro-inflammatory mediators play a significant role in headache pathogenesis, with pre-existing headache conditions exacerbating the symptoms. The importance of effective pain management strategies must be emphasized.

CONCLUSION: Headache is a prevalent symptom among SARS-CoV-2 infected individuals, with significant implications for patient care. The findings emphasize the importance of recognizing headache characteristics in SARS-CoV-2 management and suggest that tailored clinical approaches are essential for effective symptom relief.

Keywords: COVID-19, Headache, Pain, Pandemic, SARS-CoV-2.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A abordagem das cefaleias secundárias na infecção pela SARS-CoV-2 é crucial para um manejo adequado e otimização do cuidado. Esta revisão tem como objetivo sintetizar os dados sobre as características da cefaleia e o impacto das condições pré-existentes de cefaleia sobre esses sintomas na infecção pela SARS-CoV-2.

CONTEÚDO: Uma pesquisa sistemática foi realizada em vários bancos de dados, incluindo: Pubmed/Medline, *Cochrane Collaboration*, *Web of Science*, Scopus, LILACS, Embase, *Open Grey* e *Google Scholar*, com o objetivo de identificar estudos sobre as características da cefaleia associadas à SARS-CoV-2. A pesquisa se concentrou nos sintomas, nas características, no início, na duração e na resposta ao tratamento da cefaleia durante e após a infecção. Vinte e três estudos atenderam aos critérios de inclusão. Aproximadamente 42,1% dos indivíduos com SARS-CoV-2 relataram dores de cabeça, semelhantes a dores de cabeça do tipo tensional e enxaquecas. Essas cefaleias geralmente se manifestavam nos primeiros três dias de infecção e podiam persistir por até quatro meses. Os dados sugerem que a ativação trigeminovascular e os mediadores pró-inflamatórios desempenham um papel importante na patogênese da cefaleia, com condições preexistentes de cefaleia exacerbando os sintomas. A importância de estratégias eficazes de controle da dor deve ser enfatizada.

CONCLUSÃO: A cefaleia é um sintoma prevalente entre os indivíduos infectados pela SARS-CoV-2, com significativas implicações no atendimento ao paciente. Os achados deste estudo enfatizam a importância do reconhecimento das características da cefaleia no manejo da SARS-CoV-2 e sugerem que abordagens clínicas personalizadas são essenciais para o alívio eficaz dos sintomas.

Descritores: Cefaleia, COVID-19, Dor, Pandemia, SARS-CoV-2.

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INTRODUCTION

Headache is a common type of pain experienced in the head, face, or neck[1,2], classified as primary or secondary based on underlying causes (ICHD-3)[3,4]. This condition is a significant public health concern, with about 50% of the population reporting complaints within a year, and over 90% experiencing them at some point in life[4]. At the same hand, headache is frequently reported as a symptom in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-infected individuals[5-7], with a prevalence ranging from 13% to 74.6%[8]. Coronavirus Disease 2019 (COVID-19) patients often develop severe respiratory distress, requiring intensive care and social isolation to prevent transmission through close contact[9]. Social isolation, movement restrictions, fear, lack of information, and loss of social interactions contribute to increased psychological problems, including anxiety and depression[10]. These factors can worsen conditions such as Temporomandibular Disorders (TMD), bruxism, and headaches[11].

Specific information on headaches and long-term follow-up data regarding secondary headaches during or after SARS-CoV-2 infection is limited[9]. The potential effect of SARS-CoV-2 infection on the headache history of infected individuals remains unclear[7]. Investigating headache pathogenesis in this context is crucial given the potential long-term sequelae of this infection. This knowledge plays a crucial role in understanding, early diagnosis, and effective pain management of secondary headaches in SARS-CoV-2-infected individuals, providing valuable insights for public health and contributing to preventive and therapeutic strategies in the face of potential lasting impacts on the quality of life of those affected. Therefore, the present study's objective was to synthesize data on characteristics and symptoms of headache associated with SARS-CoV-2 during or post-infection. Additionally, the review aimed to explore the potential impact of pre-existing headache history on the characteristics and symptomatology of headaches during and post-infection of SARS-CoV-2 infection.

CONTENTS

This systematic review was performed according to the guidelines presented by the Cochrane Handbook for Systematic Reviews of Interventions[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13]. The study protocol was registered in Open Science Framework (OSF) platform under registration DOI 10.17605/OSF.IO/PU5ME.

Search strategies and selection process

The review question for this study was: "What are the characteristics and symptoms of headache associated with SARS-CoV-2 during or post-infection, and how does a personal history of headaches prior to infection influence headache symptomatology?" In line with the PECOT framework, the study components were defined as follows: population - individuals infected with SARS-CoV-2; exposure - headache during or post-SARS-CoV-2 infection; comparison - not applied; outcomes - characteristics and symptomatology of headaches during and post SARS-CoV-2 infection; and study type - observational or experimental clinical studies.

Two independent reviewers conducted a systematic search in eight electronic databases and portals, including Pubmed/Medline, Cochrane Collaboration, Web of Science, Scopus, LILACS, Embase, and Open Grey. Additionally, a simplified search was conducted on Google Scholar, examining the first 100 results. The search was last performed on April 20, 2022. Customized search strategies were developed for each database, using terms such as "COVID-19," "SARS-CoV-2," "Orofacial Pain," "Migraine," and "Facial Pain." The inclusion criteria encompassed all observational or experimental clinical studies (including Randomized Controlled Trials - RCTs) and retrospective/prospective studies that reported headache characteristics and symptoms pre-, during, or post-SARS-CoV-2 infection. Studies that were inaccessible for full-text reading or lacked relevant headache-associated information were excluded. Case reports and case series with fewer than 10 individuals were also excluded to avoid studies with a small number of observations. The detailed search strategy can be found in table 1.

Data collection

Duplicates were removed using EndNote X7 software (Thomson Reuters®, NY, USA). Data extraction was performed using a standardized spreadsheet (Microsoft Corporation, Redmond, WA, USA), which included the following information: author, year, journal, title, headache symptoms and characteristics (pre, during, or post-SARS-CoV-2), the onset of pain (pre, during, or post-infection), pain characteristics (frequency, intensity, location, duration, and recovery time), association with a previous history of headache symptoms, comorbidity associations, treatment, follow-up, and measurement instrument. Attempts were made to contact authors for missing or unpublished data. Studies were included only if the missing information was provided.

Risk of bias assessment

The risk of bias for each study was independently assessed by two reviewers using the Risk of Bias Analysis Instrument developed by the Joanna Briggs Institute[14]. A score was assigned to each study based on its quality, calculated by evaluating the responses to each criterion on a scale of 0 to 10. The studies were categorized according to the score obtained: (0-3) low quality, (4-6) medium quality, and (7-10) high quality. All studies approved through the selection process were included in the review, regardless of their quality outcome.

RESULTS

The initial search strategy resulted in 7026 papers. After removing duplicates, 4630 publications were screened. Of these, 46 studies underwent full-text evaluation, and 23 were excluded due to the lack of headache characteristics (Figure 1). The final selection for the systematic review included 15 cross-sectional studies[3,15-28], 2 case-control studies[5,6], 2 cohort studies[29,30], and 4 case series[31-34].

Table 1. Headache-associated symptomatology in SARS-CoV-2-infected individuals assessed in the included studies

Authors	Headache Area	Quality	Start	Intensity	Symptoms Associated with Headache	Duration of Symptomatology
Barut et al.[15]	Bilateral headache (90.8%). Front orbital (40.6%), Diffuse locations (21.8%).	The most common type of headache was throbbing (45.8%), followed, in order, by compressive, dull, combined, and stabbing. Nausea and vomiting occurred in 83 (58.5%) patients and 30 (21.1%) described light and voice sensitivity during infection.	-	The VAS mean of headache pain score from infected individuals was 5.91.	Nausea and vomiting (58.5%), light and sound sensitivity (21.1%), and loss of taste and smell (57%).	-
Bilge, Kesmez and Alay[16]	-	-	-	Mild (25.8%), moderate (61.3%), and severe (12.9%) headache in infected individuals.	Commonly related to cough and fever.	-
Caronna et al.[5]	-	-	-	Severe pain (24.7%).	Patients with headache had more anosmia/ageusia (54.6% versus 18.2%). Commonly reported symptoms were nausea and vomiting (worsening during movement), photo/phonophobia, and vertigo.	-
Carvalho-Schneider et al.[31]	-	-	-	-	-	-
Demiryurek et al.[32]	Bilateral headache.	-	-	Individuals reported an average VAS value of 5.3.	Hyposmia-anosmia (79.2%) and other complaints (35.9%).	The mean duration of seizures per day was 5.6 ± 2.9 hours.
García-Azorín et al.[17]a	-	-	Headache was the first symptom (26.0%) self-reported in clinical examination (87.5%).	-	-	-
García-Azorín et al.[41]b	Bilateral pain (80%), predominantly frontal (71%).	Pain with pressing quality (75%) and severe intensity.	In the first day (40.7%), second day (12.1%), third day (14.3%), fourth day (9.8%) and fifth day or later (23.1%).	The median intensity of the headache was 7 out of 10, with a degree of disability of 50% due to symptomatology.	Photophobia (33.3%), phonophobia (32.3%), and cranial autonomic symptoms (24.8%), increased with head movements (31.2%).	The median period of reported symptomatology was seven days and persisted after 1 month.
Gonzalez-Martinez et al.[6]	Holocranial (42%) and temporal (37%).	Oppressive quality in 94% of individuals.	In the first week (30%) and around the first and second week (50% - day 9).	Mild in 45% and/or moderate in 40% of individuals.	Pharyngitis, ageusia, arthralgia, nausea, and vomiting.	-
Hussein et al.[18]	-	Tension headache (72.48%), tension-like phenotype (52%), and trigeminal autonomic characteristics (6.7%).	-	The median headache intensity assessed by VAS was 7.	Fever and dehydration.	-

Continue...

Table 1. Headache-associated symptomatology in SARS-CoV-2-infected individuals assessed in the included studies – continuation

Authors	Headache Area	Quality	Start	Intensity	Symptoms Associated with Headache	Duration of Symptomatology
Kacem et al.[19]	Frontotemporal (51.2%).	-	During the first 3 days of the disease (62.3%).	Mainly mild or moderate (59.1%).	Fever.	3h (range: 15 min to 24 h).
Karadaş et al.[20]	Frontal (54%), occipital (15.6%) and frontotemporal (3.6%).	The most reported headache characteristic was throbbing and or pressed.	-	-	Loss of appetite, weight loss, diarrhea, nausea, photophobia, and phonophobia.	The average dur9.00 ± 5.20 hours.
Leth et al.[33]	-	-	-	-	-	-
López et al.[3]	Bilateral (84.9%), hemicranial (15.1%). Frontal (83.0%), periocular (41.5%) and temporal (32.1%).	Pressing (75.5%), pulsating (21.7%), tipping (14.2%), burning (2.8%), and electric (0.9%).	In the first 24 hours (38.7%), 48 hours (62.3%), and 72 hours (73.6%).	Mild (3.8%), moderate (32.1%), and intense (64.1%).	.	-
Liu et al.[21]	-	-	-	-	-	-
Magdy et al.[22]	Diffuse majority at 52.9%.	Pressing (40.7%).	-	Median intensity.	Fever and dehydration.	-
Osikomaiya et al.[23]	-	-	-	-	-	-
Planchuelo-gómez et al.[24]	Frontal localization was the most common in 83% of cases.	The most frequent pain quality was pressure, present in 75.4% of individuals.	-	-	Increased pain intensity and the presence of nausea were related to lymphopenia.	-
Poncet-Megemont et al.[29]	-	-	-	-	Headaches were not associated with anosmia or ageusia.	-
Rocha-filho et al.[25]	Bilateral headache (94%).	Migraine phenotype (51%), tension-type (5.5%).	More frequent on the first day of symptoms.	The severe intensity in 53% of cases.	Hyposmia, anosmia, hypogeusia, ageusia.	Continuous headache (15%), with a mean duration of seizures of 120 minutes.
Soares et al.[26]	Unilateral (50%).	Pulsatile quality (38.9%).	-	Moderate to severe intensity.	-	-
Trigo et al.[30]	-	-	Headache (26.0%) was present within 24 (38.5%), 48 (62.5%), and 72 hours (74.0%).	-	Anosmia, arthralgia, cough, dizziness, and myalgia.	-
Uygun et al.[27]	Bilateral.	Pulsating, pressure, and stabbing binges pain.	-	Mild intensity (26.6%), moderate (47.7%), severe (23.4%), and very severe (hospitalization) (2.3%).	Anosmia, ageusia, and gastrointestinal complaints.	-
Vacchiano et al.[28]	-	Tension (86%).	-	-	Muscle pain, arthralgia, and headache.	-

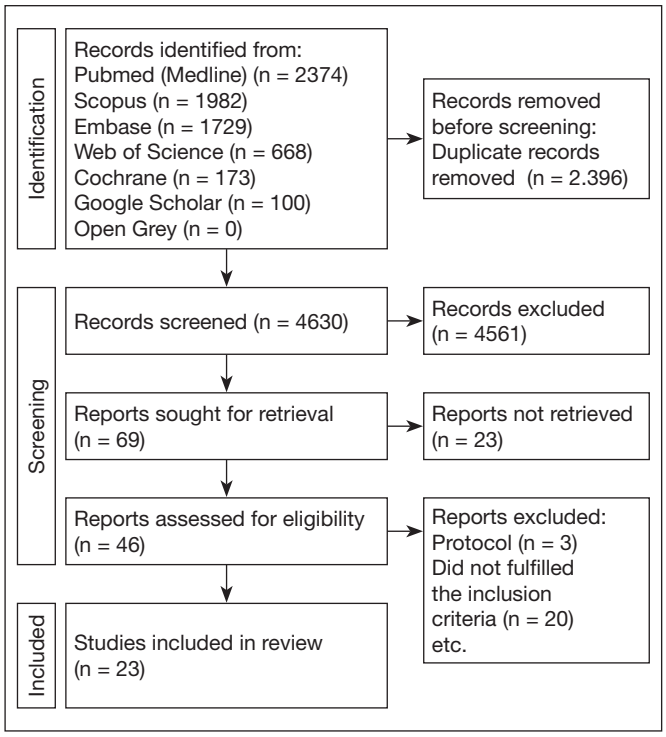

Figure 1. Systematic review flowchart according to PRISMA[13]

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Risk of bias

The Risk of Bias Analysis Instrument was used to assess the quality of the included studies. Among the selected studies, 4 were rated as low quality[15,23,27,28], 11 were rated as medium quality[16-22,24-26,34], and 8 were rated as high quality[3,5,6,29-33]. The main bias observed in the studies was the failure to identify confounding factors, regardless of the study design. Cross-sectional studies lacked objective and standardized criteria for measuring the condition of outcome measures, as well as their validity and reliability. Case series studies had shortcomings in providing demographic data and information about data collection locations/clinics. Case-control studies had a bias related to the non-identification of confounding factors. Cohort studies did not have any loss of follow-up, as all included studies had a complete individual follow-up. More details on the risk of bias assessment for each study can be found in table 2.

Qualitative and descriptive analyses

The comprehensive review of the included studies revealed a notable prevalence of headache associated with SARS-CoV-2 infection, approximately 42.1% (Figure 2)[5,6,15,16,18-21,23,25-30,32-34]. A detailed examination of demographic characteristics indicated that the highest prevalence of headaches was observed among individuals aged 37 to 67 years old[3,5,6,15-17,19-21,23,24,26,27,29-32]. Moreover, a slightly higher proportion of women were reported among the infected, with a prevalence of 51.6% (Tables 1 and 2)[3,5,6,15-33].

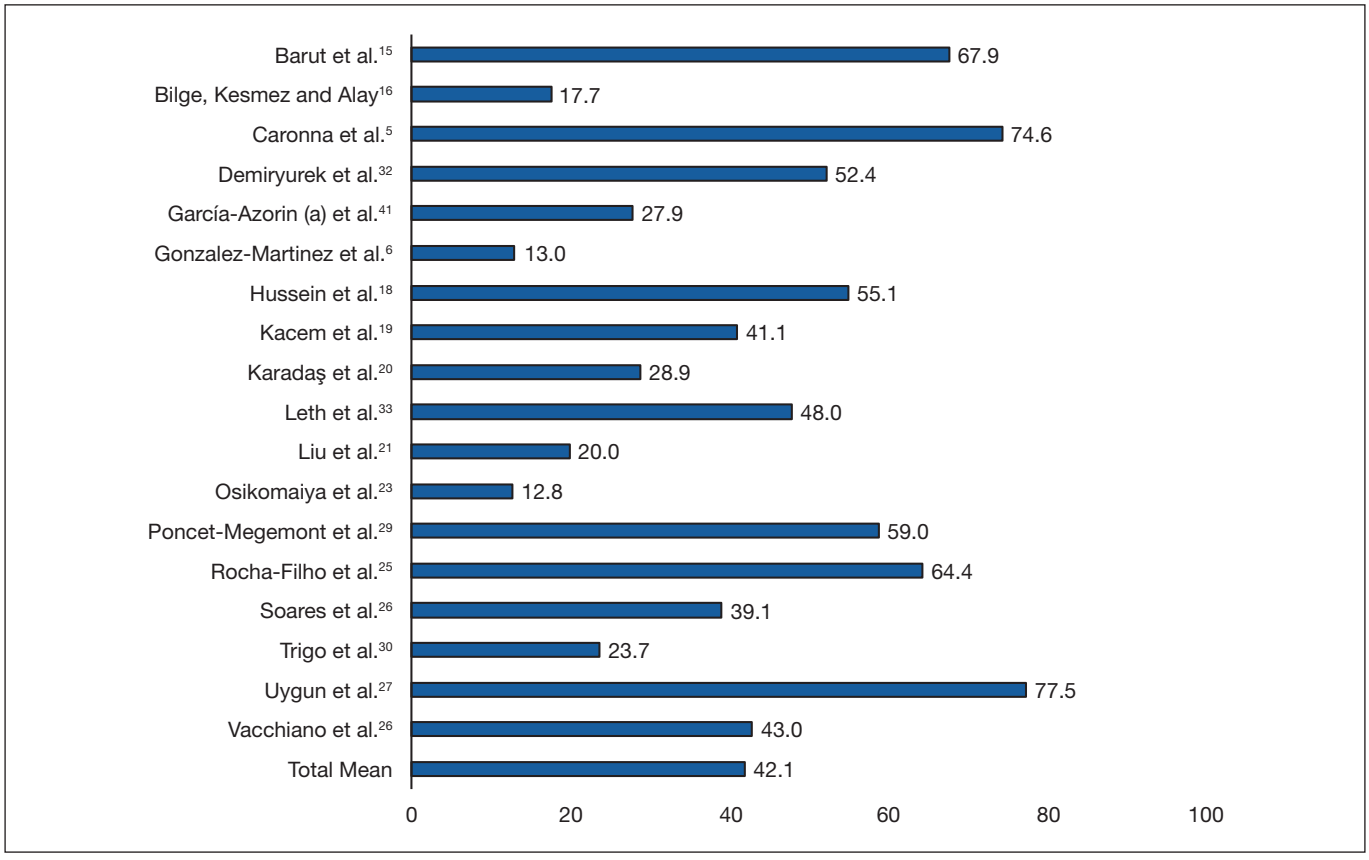

Figure 2. Percentage of secondary headache prevalence associated with SARS-CoV-2-infected individuals from included studies

Table 2. Headache-associated characteristics in SARS-CoV-2-infected individuals assessed in the included studies

Authors	Triggered *versus* reasons	Previous History	Headache *versus* Comorbidity	Recovery Time	Headache *versus* COVID-19 Severity	Response to Analgesia
Barut et al.[15]	-	Headache before COVID-19 (33.5%) and other headache types (51.2%).	-	-	-	-
Bilge, Kesmez and Alay[16]	-	-	Headache and concomitant diseases (16.1%): hypertension (6.4%), chronic obstructive pulmonary disease (3.2%), chronic kidney disease (3.2%), and hypothyroidism (3.2%).	Headache improved with the completion of the course of the disease.	Mild (25.8%), moderate (61.3%), and severe (12.9%) clinical pain.	-
Caronna et al.[5]	-	Previous headache (32.0%).	-	6 weeks of continuous headache (37.8%).	-	-
Carvalho-Schneider et al.[31]	-	-	-	30th day (36%) and 60th day (21.5%) of the disease.	-	-
Demiryurek et al.[32]	Headache triggered with cough (23.8%). Of these, only headache with cough (9.52%), migraine phenotype (7.93%), and tension headache phenotype (6.34%). Tension headache without exacerbation by cough (12.7%).	-	-	The mean time to reduce symptoms related to headache was 5.1 ± 2.1 (1 to 9-day) minimum of 1 and a maximum of 9 days.	-	-
García-Azorín et al.[17]a	-	Previous headache (57.7%) with migraine (16.3%) and tension headache (28.8%).	-	-	-	-
García-Azorín et al.[41]b	-	Previous headache (48.8%), being migraine (18.2%).	Prior history of hypertension (21.4%), pulmonary disorders (11.6%), cardiac disorders (10.7%), diabetes (8.1%).	-	-	Paracetamol in 82.9%.
Gonzalez-Martinez et al.[6]	.	Previous headache (65%) and other types of anterior headache (47%).	No underlying pathologies.	End symptoms after the course of the disease (84%).	-	-
Hussein et al.[18]	.	-	Comorbidities were reported (29.7%), but with no association with headache.	-	-	Good response to analgesic (79.8%); or ineffective analgesic response (20.2%).
Kacem et al.[19]		-		Persistent headache after the course of the disease (16.8%).	-	-
Karadaş et al.[20]		No previous headaches (85.5%).	Diabetes mellitus and stroke were associated with headaches.	_	-	Good response to 1000 mg intravenous paracetamol (59%), and responses to major occipital nerve blocks (85%).

Continue...

Table 2. Headache-associated characteristics in SARS-CoV-2-infected individuals assessed in the included studies – continuation

Authors	Triggered *versus* reasons	Previous History	Headache *versus* Comorbidity	Recovery Time	Headache *versus* COVID-19 Severity	Response to Analgesia
Leth et al.[33]		-	-	After 6 weeks, 24% of the subjects had a headache, and after 12 weeks, 27% had a headache as a persistent symptom.	-	-
López et al.[3]	Exacerbation with walk movements (10.4%), head movement (31.1%), eye movement (18.9%), cough (33.0%), muscle flexion (6.6%), and sneezing (1.8%).	Previous headaches (48.2%), this headache increasing were similar to other infections in (45.1%).	Hypertension (34.0%), diabetes (11.3%), cardiac disorders (8.5%), pulmonary disorders (22.6%), cancer (12.3%), immunocompromised patients (4.7%), and smokers or former smokers (11.3%).	The headache had resolved in parallel with the improvement or resolution of SARS-CoV-2 (54.7%).	Headache worsened in parallel with the worsening of the disease in 39.6% of cases.	-
Liu et al.[21]	-	-	-	-	-	-
Magdy et al.[22]	-	-	Individuals with comorbidities had significantly higher frequency and intensity of headaches when associated with 'SARS-CoV-2.	-	Headache frequency and intensity were significantly higher in individuals with SARS-CoV-2 with moderate symptoms.	Good response to steroids (40.7%).
Osikomaiya et al.[23]		-	No association between comorbidities and SARS--CoV-2.	Headache was persistent until 2 weeks after the end of infection (12.8%).	-	-
Planchuelo-Gómez et al.[24]	-	Previous history of headache (57.5%): similar to anterior headache (32.5%).	-	-	-	-
Poncet-Megemont et al.[29]		-	-	Persistent headache 1 month after remission of fever and dyspnea (3.6%).	-	-
Rocha-Filho et al.[25]	Migraine and tension--type headache phenotype triggered by cough (16.4%).	Migraine phenotype is more frequent in individuals with a previous migraine. Previous headache before infection by SARS-CoV-2 (64%). Current headaches different from the previous ones (80%).	-	-	No differences in the duration of symptoms compared to individuals who did not present headaches.	-
Soares et al.[26]	-	-	-	-	-	-
Trigo et al.[30]	-	Previous headaches associated with systemic viral infections (47.2%). The current episode was similar to the previous one (46.0%).	Hypertension, smoking, cardiac disorders, and chronic neurological disorders.	-	All-cause hospital mortality was 20.0% in the entire sample and 5.8% in individuals with headaches.	Systemic steroids were applied for individuals with headache (55.9%) and without headache (40.1%)
Uygun et al.[27]	_	Previous headache associated (79.5%): different from the usual headaches (50%) and similar (29.5%).	-	-	-	-
Vacchiano et al.[28]	Tension-type pain	-	-	-	-	Responsive to paracetamol (86%).

Regarding the headache intensity, data was gathered through self-reports using various methodologies[3,15]. Two studies specifically used a numerical scale with a score ranging from 0 to 10[3,15] to classify the intensity of secondary headache attributed to SARS-CoV-2 infection, indicating an average value of 5.91 on the VAS scale for headache intensity[15]. The quality of headaches varied across the included studies and were commonly described as oppressive, tensional, pulsating, and throbbing. Less frequently, descriptions such as stabbing, burning, electrical, and acute were reported[15,18,27].

The location of headache pain was a significant finding, with 52.1% of the included studies reporting painful symptoms in four orofacial areas, being often associated with multiple areas[3,6,15,19,22,23-27,32,33]. Bilateral pain[3,15,25,27,32], followed by frontal[19,20,24] and diffuse or holocranial pain[5,15,22,32] were predominantly reported. The onset of headache symptoms typically occurred within the first three days of infection, highlighting headaches as an early manifestation of SARS-CoV-2 infection[3,17,19,25,34-37] (Table 3).

The investigation into headache duration during the acute phase of SARS-CoV-2 infection revealed variability, contrasting with the typical durations of tension-type headaches (30 minutes to 7 days) and migraines (4 to 72 hours)[37]. Notably, 15% of infected individuals experienced continuous headaches, with a mean duration of episodes reported at 120 minutes. The longest duration noted was approximately 9 hours and the average was 5.6 hours[32].

Trigger factors for headaches, akin to those for tension-type headaches or migraines such as stress and hormonal changes, were evaluated in the context of SARS-CoV-2 infection. Fever (29.2%), cough (11.3%), and asthenia (11.3%) were primarily associated with the onset of headache crises. Activities such as walking, head movement, and eye movement were identified as exacerbating factors[3]. A specific cough headache pattern was observed in 16% of patients[25], whereas a significant 94.3% of hospitalized cases during the acute phase met the criteria for headache attributed to systemic viral infection[3].

Clinical assessments and laboratory tests underscored common symptoms among SARS-CoV-2 infected individuals, including anosmia, ageusia, fever, gastrointestinal complaints, cough, and myalgia[5,6,15,16,18,19,22,25,27,32,34-40]. Dehydration was associated with worsened pain or headaches[18,22], along with photophobia, phonophobia[5,15,20,34], and lymphopenia[24]. However, the correlation between headache presence and anosmia or ageu-

Table 3. Headache-associated characteristics and symptomatology of most common primary headaches (i.e., migraine and tension type-headache) and secondary headaches associated with SARS-CoV-2 infection

	Types of Headaches		
Characteristics and symptomatology	Migraine	Tension type-headache	Secondary headache associated with SARS-CoV-2 Infection
Prevalence	14%[46]	26%[46] 30% – 78%[4]	39.68%[3,5,6,15-34]
Age range	18 – 44[39]	30 – 39[4]	33 – 59[16,17,20,22,29,34]
Area	Unilateral pain. Mainly frontotemporal[4].	Bilateral pain[4].	Four orofacial areas. Bilateral pain[3,15,25,27,32]. Frontal pain[19,20,24]. Diffuse or holocranial pain [15,22,34].
Triggers	Routine physical activity[4].	Not aggravated by routine physical activity[4].	Cough[3,25,32]. Head movements[25].
Pathophysiology	Activation and sensitization of trigeminovascular pathways, as well as the brain stem and diencephalic nuclei[49]. Activation of descending pathways that facilitate the processing of neuronal pain signals in the spinal cord[49]. Suppression of inhibitory descending pathways of pain processing[49]. Activation of peripheral sensory fibers that innervate intracranial blood vessels and dura mater[47].	Neurobiological basis with both peripheral and central mechanisms contributing to the pain[45]. Sensitization of peripheral myofascial nociceptors[48]. Sensitization of secondary neurons in the dorsal horn of the spinal cord or trigeminal nucleus[48]. Sensitization of supraspinal neurons[48]. Decreased antinociceptive activity of supraspinal structures[48].	Direct viral invasion of the trigeminal nerve by the SARS-COV-2 virus[35]. Involvement of endothelial cells with high expression of angiotensin-converter enzyme 2 (ACE2), and inflammatory process[35]. Coagulopathy or hypoxemia[35]. Stress[8]. Intracranial pressure[8].
Phenotypic features	Pulsating quality. Moderate or severe pain intensity[4].	Pressing or tightening (non-pulsating) quality. Mild or moderate intensity[4].	Oppressive symptomatology[3,15,25,27,32]. Pulsatile pain especially in individuals with headaches pre-infection[7,25].
Duration of headache symptomatology	4 to 72 hours[4].	30 min to 7 days[4].	Mean of 5.6 hours[32].
Drug treatment	Simple analgesics, nonsteroidal anti-inflammatory drugs, triptans, gepants, lasmiditan[42].	Simple analgesics and non-steroidal anti-inflammatory drugs [42].	Simple analgesics[20,28,34].

sia remains uncertain, with one study not establishing a clear relationship[29]. Conversely, individuals with anosmia exhibited a higher prevalence of infection, lower headache severity, and more favorable clinical indicators compared to those with both headaches and anosmia[12], suggesting that specific symptoms like anosmia could influence the headache experience during SARS-CoV-2 infection.

The dynamics of headache symptoms post-infection of SARS--CoV-2 reveal considerable variability. A notable reduction in headache symptoms post-infection was reported within four days[30,32]. Persistently, 61% of individuals experienced daily and constant headache pain six weeks after the acute stage, with this condition more prevalent among women, those with a history of headaches, and a limited response to acute pain treatment[5]. The prevalence of headaches was observed to increase from 24% at 6 weeks post-infection to 27% at 12 weeks[33].

On the other hand, some studies noted a decline in headache symptoms either at the conclusion of the infection period or within an average span of 5 days[16,25]. Over a longer term, a post-hoc multicenter ambispective study indicated that headaches persisted in 19% of individuals 3 months post-infection, reducing slightly to 16% at 9 months. Interestingly, the intensity of headaches during the acute phase was linked to more extended durations of headache, yet no significant difference was noted concerning individuals' prior headache history[41], providing insight into the potential impact of pre-existing headache conditions on the development and intensity of headaches during SARS-CoV-2 infection.

The treatment of headache symptoms associated with SARS-CoV-2 infection encompasses a range of pharmacological interventions. For tension-type headaches, non-steroidal anti--inflammatory drugs (NSAIDs) and simple analgesics are commonly used for acute relief, with tricyclic antidepressants suggested for preventive measures[42].

Acute migraine treatment involves the use of triptans, NSAIDs, simple analgesics, and antiemetics, with gepants and lasmiditan being recent additions for selected scenarios[39,45]. It is important to note that the effectiveness of these treatments in the context of SARS-CoV-2-related headaches has not been specifically evaluated in clinical trials[25]. Paracetamol has been identified as a potential treatment for mild SARS-CoV-2-associated headaches, though a non-negligible proportion (20.2%) of patients, particularly older individuals with comorbidities and severe infections, exhibited an ineffective analgesic response[18,20,28,34], highlighting the complexity of managing headache symptoms in this specific population.

DISCUSSION

The pathogenesis of headache symptoms in the SARS-CoV-2 infection can be attributed to several potential mechanisms, including direct invasion of the trigeminal nerve by the virus, involvement of endothelial cells expressing angiotensin-converter enzyme 2 (ACE2) leading to trigeminovascular activation, the influence of pro-inflammatory mediators and viral cytokines, coagulopathy, and hypoxemia[35]. Other hypotheses suggest stress-related pain or increased intracranial pressure as contributing factors[8]. Despite these insights, the complete pathophysiology of headaches associated with SARS-CoV-2 infection remains to be fully elucidated.

Comparatively, headache characteristics and symptomatology between common primary headaches (i.e., migraine and tension-type headache) and secondary headaches associated with SARS-CoV-2 infection reveal significant overlaps and distinctions. According to the International Classification of Headache Disorders (ICHD-3)[3], headaches occurring alongside another disorder are classified as secondary, which encompasses those associated with viral infections like SARS-CoV-2 infection, meeting the criteria for Headache Attributed to Systemic Viral Infection (9.2.2)[4]. Additionally, the exacerbation of headache symptoms was reported by individuals with pre-existing primary headaches in close temporal association with the viral infection, indicating a complex interaction between pre-existing headache conditions and the SARS-CoV-2 infection[3].

This section delves into the nuanced findings regarding headache duration and triggers within the context of SARS-CoV-2 infection. The discrepancy in headache durations compared to conventional tension-type and migraine headaches suggests a unique influence of the virus on headache pathophysiology. The association of specific symptoms and physical activities with headache exacerbation highlights the complex interplay between the infection's physiological impacts and headache manifestation.

The exploration of comorbidities reveals a varied influence on headache occurrence in infected individuals, with some studies indicating a heightened headache frequency and intensity in the presence of certain comorbid conditions[5,20,22,25,41,42]. This variability underscores the necessity for further research to delineate the role of pre-existing systemic conditions in the headache experiences of COVID-19 patients.

Moreover, the discussion on anosmia and headache severity brings to light intriguing aspects of SARS-CoV-2 infection's clinical scenario. The differential impacts on individuals with anosmia, as opposed to those suffering from both headaches and anosmia, suggest potential pathways for further investigation into the virus's effects on sensory perception and headache severity.

The persistence of headache symptoms post-SARS-CoV-2 infection highlights the intricate interplay of contributing factors. The multisystemic inflammatory response may increase the likelihood of persistent symptoms post-infection. The virus-induced immunological response triggers elevated production of inflammatory mediators, particularly in severe cases, exacerbating the disease factors[5,21,23]. This observation is congruent with WHO reports that delineate average recovery times, pointing to extended recovery periods for severe SARS-CoV-2 infection conditions[9].

From a prognostic perspective, some studies have showed intriguing patterns, for instance, individuals enduring headaches reported shorter durations of infection, with negligible impact on mortality or hospital stay lengths compared to those without headaches[3,30]. Meta-analyses further shed light on the potential of headaches serving as markers of inpatient survival, yet a direct

correlation between headaches and the worsening prognosis or severity of infection remained elusive[43,44].

The influence of pre-existing headache history on the manifestation of headaches during and post- SARS-CoV-2 infections draws attention to the nuanced impact of prior headache conditions. Individuals with a history of headaches, particularly migraines, reported a higher frequency of pulsatile pain, alongside an increase in osmophobia and phonophobia[7]. The literature presents mixed findings about the effect of pre-infection headache history on the symptomatology of post-infection headaches. While one study noted that nearly 40% of infected individuals experienced an exacerbation in headache symptomatology attributable to their pre-infection headache history[3], another study found no discernible differences in the duration or intensity of headache characteristics between individuals with and without a pre-existing headache condition[25].

Notably, a significant proportion of individuals with a history of headaches prior to SARS-CoV-2 infection showed exacerbated symptoms, especially those with migraines, suggesting a potential predisposition to more severe headache symptoms post-infection[3,5,6,15,17,25,27]. Moreover, a retrospective analysis revealed a strong association between individuals with a self-reported history of headaches before SARS-CoV-2 infection and the occurrence of headaches linked to other viral respiratory tract infections[30].

The discussion on pharmacological management of SARS-CoV-2-related headaches highlights the adaptation of existing headache treatments to this new context. The lack of clinical trials specifically targeting the treatment of acute-phase SARS-CoV-2 headaches underscores a significant gap in the current understanding and treatment protocols[25]. The observed variability in drug efficacy, especially the limited effectiveness of paracetamol in certain populations, points to the need for tailored treatment approaches that consider individual patient factors such as age, comorbidities, and severity of infection[18,20,28,34].

The methodological challenges and biases identified across studies examining headache treatments in the context of SARS-CoV-2 infection reflect broader issues in researching emergent diseases. High risks of bias in areas such as confounder management and data analysis complicate the interpretation of findings and limit the generalizability of results. These challenges are aggravated by the overlapping symptoms of SARS-CoV-2 with other conditions and the rapid progression of the disease, making it difficult to isolate the specific effects of the virus on headache symptoms. Despite these obstacles, the imperative to synthesize existing data remains. Such synthesis is crucial for enhancing the comprehension of pain development in SARS-CoV-2 infections and for informing future research directions. The call for future studies to extend follow-up periods, standardize methodologies, and employ consistent data measurements is a critical step toward achieving a more comprehensive understanding of the headache characteristics associated with SARS-CoV-2, from pre-infection to long-term post-infection phases[4,39,45-50].

The present study's insights are invaluable for advancing clinical practices in managing secondary headaches related to SARS-CoV-2 infections. They aid healthcare professionals in acute care settings and offer guidance for monitoring long-term symptoms post-infection. Most importantly, this research contributes to a foundational knowledge base that can inform responses to future pandemics, improving the preparedness and understanding of clinical manifestations similar to those observed in long-COVID infections[50].

CONCLUSION

The studies included in this review demonstrated a high prevalence of headache among individuals infected with SARS-CoV-2, typically manifesting within the initial days post-infection and possibly persisting for up to four months. The characteristics of these headaches closely resemble those associated with tension-type headaches and migraines, highlighting the importance of a nuanced approach to pain management that includes a variety of analgesics. This underlines the critical need for further research to fully grasp the impact of viral infections on headache patterns, improving pandemic preparedness and clinical management strategies.

AUTHORS' CONTRIBUTIONS

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Statistical analysis, Data Collection, Conceptualization, Research, Writing - Preparation of the original, Writing - Review and Editing, Visualization

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Statistical analysis, Data Collection, Conceptualization, Research, Writing - Preparation of the original, Writing - Review and Editing, Visualization

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REVIEWS

In view of the commitment made by the Brazilian Journal of Pain to Open Science, the magazine only publishes reviews authorized by all parties involved.

REVIEW 1

SARS-CoV-2, the virus responsible for COVID-19, affects mainly the respiratory system, but it also affects other areas, such as the cardiovascular and nervous systems. Of the various persistent neuromuscular symptoms reported by patients infected with the COVID-19 virus, headache is one of the most prevalent. The article presents a summary of information related to headache secondary to the acute and persistent SARS-CoV-2 infection. In the case of COVID-19 patients, complaints of general pain (including headaches) are more frequent during SARS-CoV2 infection, however, in some of the cases, the pain remains even after the infection has resolved, which further increases the need for research into the topic, since chronic pain is considered a global public health problem. The article is relevant both clinically and for the development of new research. The methodological approach of the systematic review is sound, providing a coherent analysis of the literature data available on the pathophysiology and characteristics of headache secondary to SARS-CoV-2 infection. Furthermore, the comparison with primary headaches, such as migraine and tension-type headache, enriches the article, being useful specially in the clinical and diagnostic context. The authors also listed data on the triggers capable of setting off pain, predictors, prevalence, other symptoms associated with headache secondary to COVID-19 and possible treatments for the condition. This data is essential to guide proper patient management and the development of future protocols. In addition, the systematic review identified a significant gap in the literature regarding the lack of a standardized management protocol for this specific type of headache. This highlights the need for further investigation in future clinical trials to better guide treatment. In the initial version of the manuscript, there was little need for correction. My contributions were occasional, focusing mainly on the methodological description and the clarity of obtained data. These corrections included a more detailed description of the databases used, the reformulation of the acronym PECOT and the inclusion of information on the triggers of headaches secondary to SARS-CoV-2 as well as the predictors for the development of the condition. **APPROVED**.

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REVIEW 2

I can only imagine how much time went into this excellent work and I congratulate the authors on their dedication. However, I suggested that the authors re-evaluate the content of the discussion in its first version in order to make the results found from the systematic review clearer, which the authors promptly did, improving the end result.
The great amount of data analyzed by the authors and the relevance of the work were evident. In the first version, I realized that the authors had chosen to present the results together with the discussion. However, due to the large amount of information, the text seemed confusing to me. The suggestion to rewrite the discussion with an emphasis on the most relevant findings and summarizing the information was accepted by the authors.

Finally, I found it difficult to understand how the authors arrived at the conclusions presented in the first version. However, the second version made the text of the conclusion clearer and more coherent with the objectives and the discussion. **ACCEPTED WITH MINOR REVISIONS.**

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REVIEW 3

Reviewer was not interested in publishing his evaluation opinion.
Article approved with minor changes.