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Long-Term Persistent Headache After SARS-CoV-2 Infection: A Follow-Up Population-Based Study

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ABSTRACT

Background: Headache is a symptom of the long-COVID syndrome. The incidence and characteristics of *de novo* post-COVID headaches remain unclear. Our aim was to characterize new-onset headaches in a population-based prospective cohort of COVID-19 patients from the first pandemic wave.

Methods: This study followed a prospective cohort of 732 COVID-19 patients consecutively diagnosed between March and June 2020. Neurological follow-up was performed face-to-face or by phone at 3, 12, and 24 months. A structured clinical questionnaire was used to characterize headaches before infection and 24 months postinfection.

Results: Overall, 448 patients completed the 24-month follow-up, with a mean age of 51.6 years at SARS-CoV-2 infection; 272 (60.7%) were women. A prior history of headaches was reported by 115 (25.7%). Patients with either pre-existing or *de novo* persistent headaches were younger, more often women, and exhibited hyposmia, hypogeusia, and headache during the acute phase of infection. *De novo* persistent headaches occurred in 54 of 333 (16.2%) headache-naïve patients. Of these, 35 (64.8%) fulfilled migraine-like headache (MLH) criteria (mean age of 49.1 years at 24-month follow-up), with a cumulative incidence of 42/1000/year.

Conclusions: *De novo* persistent headaches are common 2 years after COVID-19, with MLH being the most frequent type. MLH incidence after COVID-19 is elevated and *de novo* "migraineurs-like" tend to be older compared to the general population. This is an important finding with potential implications for healthcare and quality of life, considering the high number of COVID-19 cases and the global burden of migraine.

1 | Introduction

COVID-19 is associated with persistent neurological symptoms and/or late-onset complications, collectively referred to as "post-COVID syndrome." This syndrome includes symptoms such as headache, cognitive dysfunction, insomnia, and fatigue, among others [1]. Headache is one of the most frequent neurological symptoms during the acute phase of SARS-CoV-2 infection, but it can also persist for months after infection [2]. The terms "post-COVID headache" and "persistent headache after COVID-19" describe any chronic headache with an onset temporally linked to confirmed SARS-CoV-2 infection. The World Health Organization (WHO) defines post-COVID-19 conditions as if it "occurs in individuals with a history of probable

or confirmed SARSCoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" [3]. Headache has been included among these symptoms, either as a new onset headache following recovery from the acute phase of COVID-19 or as a persistent headache since the initial illness. Such headaches are often moderate to severe in intensity, refractory to treatment, [4–6], and can become long-lasting, persisting for up to 9 months [7]. Given the high prevalence of primary headache disorders, such as migraine, in the general population, it is expected that worsening or changes in headache patterns could be common among those with pre-existing headache disorders during COVID-19 infection [8]. However, this is not typically categorized as part of the long-COVID syndrome, due to the multiple factors influencing migraines, [9] including stress-related psychosocial factors such as disrupted sleep and dietary habits, increased anxiety and depressive symptoms, and the possible presence of a nocebo effect, which can affect migraine patterns [9–13].

We took advantage of an ongoing prospective study of COVID-19 patients to characterize *de novo* persistent headaches and assess patient characteristics over a 24-month follow-up period. We aim to characterize *de novo* headache 2 years after SARS-CoV-2 infection, specifically, *de novo* persistent headache incidence, and describe those meeting migraine-like features.

2 | Methods

A prospective population-based cohort study of consecutive patients diagnosed with SARS-CoV-2 infection between March 1 and June 30, 2020. During the first pandemic wave, molecular diagnosis was centralized, allowing the evaluation of patients across the full spectrum of disease severity. All participants remained under follow-up at our University Hospital.

For the current study, the inclusion criteria were as follows: age > 18 years; detection of SARS-CoV-2 RNA by real-time reverse transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal or oropharyngeal swabs. Patients with moderate to severe dementia and nonresident foreigners were excluded. Disease severity groups were defined according to the required invasiveness during the acute phase of the infection as: mild—nonhospitalized patients; moderate—hospitalized patients, but not requiring ICU admission; severe—hospitalized patients admitted to the ICU [14]. Asymptomatic patients who tested positive upon hospital admission or during their stay due to other reasons were classified as having mild severity, as they did not meet the criteria for hospitalization due to COVID-19 [14, 15].

Patients were followed by a study neurologist at 3, 12, and 24 months postinfection. At the 3-month follow-up, assessments were conducted by phone using a structured interview due to social contact restrictions at that time. Follow-ups at 12 and 24 months were performed through face-to-face assessments (preferred) or by phone if social contact restrictions or travel limitations to the hospital were in place. Baseline data include demographic information, acute disease severity, and non-neurological and neurological complaints during the acute phase of COVID-19, such as headache, hypogeusia, and hyposmia. For hospitalized patients, clinical information related to the acute phase of SARS-CoV-2 infection and treatment was obtained from electronic health records and confirmed during follow-up. For nonhospitalized patients, this information was collected during the 3-month follow-up.

During follow-up, post-COVID neurological complaints, previous history of headache, vaccination, and re-infection were evaluated using a structured questionnaire. Participants who reported either a previous headache or a new-onset headache persistent at 24 months were invited to complete an additional screening questionnaire, consisting of 12 questions assessing headache features. This questionnaire included inquiries about the quality, intensity, and frequency of pain, pain location, preference for rest, associated symptoms (such as photophobia, phonophobia, and nausea/vomiting), and interference with activities of daily living. *De novo* persistent headache was defined as occurring in patients with no prior history of headaches who reported headache onset following SARS-CoV-2 infection, persisting for more than 24 weeks [16]. Headaches were subclassified as migraine-like headaches (MLH) when they met the criteria set by the International Classification of Headache Disorders (ICDH-3) for migraine without aura [at least five headache attacks lasting 4–72 h (untreated or unsuccessfully treated), with at least two of the four characteristics (unilateral location; pulsating quality; moderate or severe pain intensity; aggravation by or causing avoidance of routine physical activity) and with at least one of the following during headache (nausea and/or vomiting; photophobia and phonophobia); and not better accounted for by another ICHD-3 diagnosis] or for probable migraine [attacks fulfilling all but one of the criteria for migraine, not fulfilling or better accounted for by another ICHD-3 diagnosis] [17]. The European Headache Federation consensus on the technical investigation of primary headache disorders defines a cut-off of ≥ 50 years old to differentiate between an underlying disorder and primary migraine in this age group [18]. We used this cut-off to categorize participants based on the theoretical probability of a *de novo* persistent MLH triggered by COVID-19 infection (versus a new primary headache disorder).

The local ethics review board approved the study, and all patients provided informed consent (068-DEFI 069-CE).

3 | Statistical Analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), and compared using independent sample Student's t-test, Mann–Whitney U test, or one-way ANOVA, as appropriate. Categorical variables are presented as counts (%) and compared using the chi-square test or Fisher's exact test, as appropriate. The cumulative incidence of *de novo* persistent MLH in patients is calculated considering the median study follow-up time. It is reported as crude rates, with a 95% confidence interval (CI) calculated using the Poisson distribution. Statistical significance was set at $p < 0.05$. Statistical analysis and graphical representations were conducted using IBM SPSS Statistics v28 (IBM, New York, USA).

4 | Results

During the pandemic's first wave in Portugal, from March to June 2020, 732 SARS-CoV-2 infections were diagnosed at Centro Hospitalar Universitário de Santo António (CHUdSA), of which 305 (41.7%) resulted in hospitalization. Eighty-eight (12.0%) patients were excluded from the present study: 37 demented, 48 refusals, and three nonresidents in Portugal (Figure 1). During the study period, 104 (14.2%) patients died (86 within the first 3 months) and 92 (12.6%) patients were lost to follow-up. There was no difference in age or sex when comparing the patients who refused participation ($n = 48$) or were lost to follow-up ($n = 92$) with those included in the study. Overall, 448 (61.2%) patients completed 24-month follow-up, with a median follow-up time of 30 months (IQR: 24–32). Patients' mean age was 51.6 years, 272 (60.7%) were women, and 326 (72.8%) had mild disease (Table 1). A previous history of headache was reported in 115 (25.7%) patients. Among the 333 headache-naïve patients, 54 (16.2%) developed *de novo* persistent headache (clinical characteristics in Table 2). Compared to patients without headaches, those with headaches (either previous or *de novo*) were younger and more frequently women. Additionally, patients with *de novo* persistent headaches and those with a prior history of headache frequently experienced headaches during the acute phase (88.9% and 81.7%, respectively). Hyposmia and hypogeusia were also more prevalent in patients with headaches ($p < 0.001$). Headache characterization regarding the study groups (previous headache vs. *de novo* persistent headache) is detailed in Table 2. A pressing quality of pain prevailed in both groups, being more frequent in the *de novo* persistent headache group. No significant differences were found regarding associated symptoms such as photophobia, phonophobia, and nausea/vomiting. Patients with *de novo* persistent headaches reported significantly more interference in activities of daily living than patients with previous headaches. Figure 2 illustrates the prevalence of *de novo* persistent headaches across the follow-up evaluations.

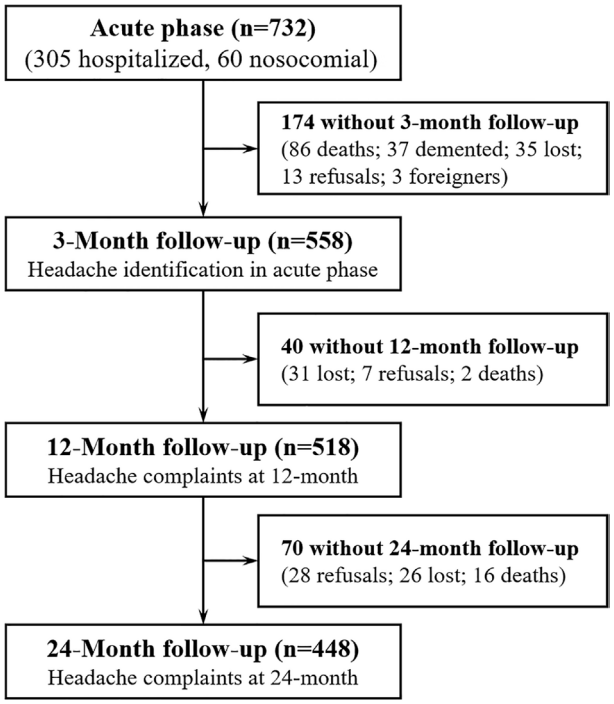

FIGURE 1 | Flowchart depicting the study cohort.

TABLE 1 | Clinical and demographic information and acute COVID-19 complaints according to previous history of headache and *de novo* persistent headache.

			Previous headache				*De novo* persistent		
	All ($n = 448$)		No ($n = 279$)		Yes ($n = 115$)		Headache ($n = 54$)		
	n	%	*n*	%	*n*	%	*n*	%	*p*
Mean age (SD), y	51.6	(16.8)	64.3	(17.5)	47.0	(15.2)	47.1	(13.6)	**< 0.001**
Women	272	60.7	134	48.0	99	86.1	39	72.2	**< 0.001**
Acute phase									
Hyposmia	275	61.4	149	53.4	82	71.3	44	81.5	**< 0.001**
Hypogeusia	294	65.6	164	58.7	85	73.9	45	83.3	**< 0.001**
Headache	273	60.9	131	47.0	94	81.7	48	88.9	**< 0.001**
Disease severity									0.393
Mild	326	72.8	196	70.3	89	77.4	41	75.9	
Moderate	47	10.5	29	10.4	13	11.3	5	9.3	
Severe	75	16.7	54	19.4	13	11.3	8	14.8	
Sleep disturbances at 24 months	153	34.2	74	26.5	54	47.0	25	46.3	**< 0.001**
Vaccination rate	437	97.5	272	97.5	111	96.5	54	100.0	0.394
Re-infection	89	19.9	42	15.1	35	30.4	12	22.2	**0.002**

Note: Bold values represent $p < 0.05$, indicating statistical significance.
Abbreviation: SD, standard deviation.

TABLE 2 | Headache characterization according to previous history of headache or *de novo* persistent headache.

	Previous headache ($n=115$)		*De novo* persistent headache ($n=54$)		
	n	**%**	***n***	**%**	***p***
Quality of pain					**0.030**
Pressing	56	48.7	38	70.4	
Throbbing	46	40.0	12	22.2	
Other	13	11.3	4	7.4	
Unilateral pain	39	33.9	16	29.6	0.579
Photophobia	58	50.4	24	44.4	0.467
Phonophobia	51	44.3	16	29.6	0.068
Nausea/vomiting	42	36.5	16	29.6	0.379
Interference with ADL	32	27.8	31	57.4	**<0.001**
Median intensity (IQR)	6	(5–8)	6	(5–7)	0.176
≥10 monthly episodes			21	38.9	
Intensity worsening	21	18.3	10	18.5	0.968
Frequency worsening	31	27.0	9	16.7	0.142
Different headache type after infection	11	9.6			
Increased need for analgesic treatment	22	19.1			
Migraine or probable migraine criteria	66	57.4	35	64.8	0.359

Note: Bold values represent $p < 0.05$, indicating statistical significance.
Abbreviations: ADL, activities of daily living; IQR, interquartile range.

MLH was identified in 66 of 115 patients with pre-existing headaches (57.4%) and in 35 of 54 patients who developed *de novo* persistent headaches (64.8%). The cumulative annual incidence of MLH in headache-naïve patients was 42/1000 (95% CI, 29–58). The *de novo* MLH group had a mean age of 49.1 years at the 2-year follow-up, and more than half (54.3%) were older than 50. As expected, photophobia, phonophobia, and nausea/vomiting were significantly more common in MLH patients. Also, MLH exhibited a tendency ($p=0.061$) to be more intense and to interfere more frequently with activities of daily living ($p=0.094$) when compared to *de novo* persistent headache without migraine criteria. No differences in sex, age, or acute phase symptoms were observed between patients with *de novo* headaches, regardless of whether they had migraine features. Similarly, the two groups did not differ in pain quality, the number of monthly episodes, or frequency worsening during the pandemic (Table 3).

5 | Discussion

In this population-based cohort of 448 individuals diagnosed with SARS-CoV-2 infection during the first pandemic wave and followed for 24 months, 16.2% of headache-naïve patients developed *de novo* persistent headaches. Remarkably, 64.8% of these patients fulfilled the ICDH-3 migraine (or probable migraine) criteria. Leveraging our study design, we estimated an annual incidence of *de novo* persistent MLH of 42/1000. Importantly, this headache frequently and severely impacts patients' quality of life.

Our cohort showed a higher MLH incidence compared to the only migraine incidence study in an American population [19]. The cumulative lifetime migraine incidence from the American Migraine Prevalence and Prevention study (which included 120,000 United States households) showed that approximately 75% of new-onset cases occurred before 35 years in both men and women [19]. In contrast, almost half of patients in our cohort developed a *de novo* persistent MLH after the age of 50, considered a late-onset migraine-like disease. This, along with the temporal association with COVID-19, supports the hypothesis that SARS-CoV-2 infection may trigger headaches with migraine-like features in older adults [18]. The pathophysiology of persistent headaches in the post-acute phase remains under debate [20, 21]. Bobker and Robbins suggest that early COVID-19-related headaches are likely caused by systemic infection, whereas later-onset headaches may result from neuroinvasion and cytokine release storms [22]. The ongoing activation of inflammatory mechanisms, including the release of mediators such as interleukins and TNF-α, could lead to cerebral inflammation [23, 24]. Additionally, activation of the trigeminovascular system may trigger neuron sensitization, particularly in individuals with a migraine history [25]. The common association of headaches with hyposmia and hypogeusia in COVID-19 might be due to an inflammatory response in the nasal mucosa and the activation of meningeal nociceptors [26]. Other theories suggest that autoimmune mechanisms, triggered during the acute phase of the disease, contribute to post-COVID conditions [8, 27]. Moreover, common forms of migraine may arise from genetic factors interacting with environmental influences, increasing their susceptibility [28]. Acute infections could potentially trigger migraine attacks in those with an underlying predisposition, linking the condition to a complex interplay of biological and environmental factors [7]. The lack of immunization at the infection could have amplified this effect due to a naïve virus-host interaction.

Our findings are supported by previous studies that revealed that acute phase symptoms, including headache, persisted months after the infection, even in patients without a prior history of primary headache [7, 13, 29–35]. However, the current literature on this subject is limited to shorter follow-up studies of patients with post-COVID headaches [7, 29, 32, 36]. The larger study, a multicentric follow-up with 905 patients, showed that 16% of patients still reported headaches at 9 months, with phenotypic

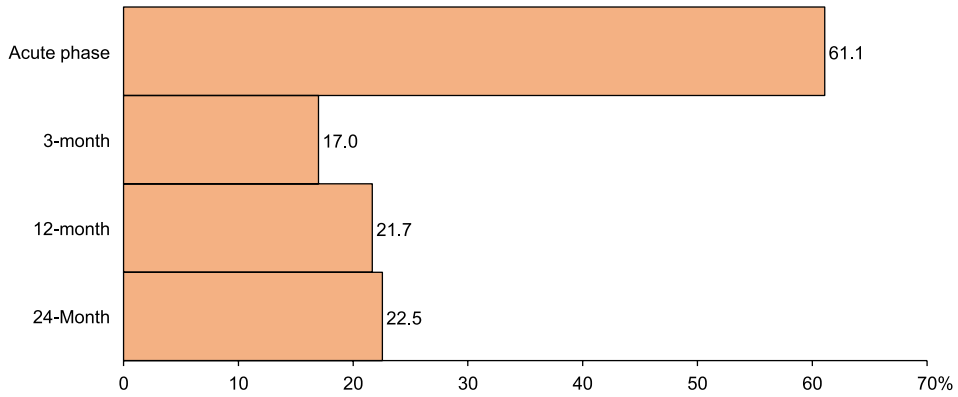

FIGURE 2 | Prevalence of *de novo* persistent headaches across the follow-up evaluations.

TABLE 3 | Demographic information, acute COVID-19 complaints, and headache characterization regarding *de novo* persistent headache (with or without migraine features).

	***De novo* persistent headache**						
			Migraine-like headaches				
	All ($n=54$)		**Yes ($n=35$)**		**No ($n=19$)**		
	n	**%**	***n***	**%**	***n***	**%**	***p***
Mean age at 24 months (SD), y	49.3	(13.7)	49.1	(10.5)	49.7	(18.6)	0.898
≥ 50 years old	28	51.9	19	54.3	9	47.4	0.627
Women	39	72.2	24	68.6	15	78.9	0.416
Acute phase							
Hyposmia	44	81.5	29	82.9	15	78.9	0.724
Hypogeusia	45	83.3	30	85.7	15	78.9	0.524
Headache	20	37.0	12	34.3	8	42.1	0.570
Sleep disturbances at 24 months	25	46.3	16	45.7	9	47.4	0.907
Vaccination rate	54	100.0	35	100.0	19	100.0	
Re-infection	12	22.2	9	25.7	3	15.8	0.402
Quality of pain							0.083
Pressing	38	70.4	22	62.9	16	84.2	
Throbbing	12	22.2	11	31.4	1	5.3	
Other	4	7.4	2	5.7	2	10.5	
Unilateral pain	16	29.6	13	37.1	3	15.8	0.101
Preference to be still	33	61.1	30	85.7	3	15.8	**< 0.001**
Photophobia	24	44.4	21	60.0	3	15.8	**0.002**
Phonophobia	16	29.6	15	42.9	1	5.3	**0.004**
Nausea/vomiting	16	29.6	16	45.7	0	0.0	**< 0.001**
Interference with ADL	31	57.4	23	65.7	8	42.1	0.094
Median intensity (IQR)	6	(5–7)	7	(5–8)	5	(5, 6)	0.061*
≥ 10 monthly episodes	21	38.9	13	37.1	8	42.1	0.721
Intensity worsening	10	18.5	9	25.7	1	5.3	0.065
Frequency worsening	9	16.7	8	22.9	1	5.3	0.098

Note: *Mann–Whitney test. Bold values represent $p < 0.05$, indicating statistical significance.
Abbreviations: ADL, activities of daily living; IQR, interquartile range; SD, standard deviation.

features resembling migraine [7]. In a cohort study by Uygun et al., in Turkey, 33.2% of 262 SARS-CoV-2 positive patients developed *de novo* headaches, while 44.3% had a prior diagnosis of headaches. This research also highlighted commonly associated symptoms, namely, nausea (70.8%), photophobia (63.9%–67%), and anosmia/ageusia (74.5%) [5]. In a systematic review of headaches and facial pain attributed to SARS-CoV-2, it was found that migraine-like phenotypes were reported in up to 74%, mainly in the first 2 weeks after infection, and data on headache characteristics after the acute phase of COVID-19 are markedly restricted [37]. In line with previous studies, we found that *de novo* persistent headaches are more prevalent in middle-aged women and are characterized by moderate to severe intensity, bilateral/holocranial, often accompanied by other symptoms such as nausea, photophobia, and phonophobia [2, 7, 9, 20, 25, 37, 38]. As observed in the multicenter study by Garcia-Azorin, we also noted a decrease in overall headache complaints over consecutive evaluations [7]. To our knowledge, no other studies examined the long-term evolution of post-COVID headaches over an extended follow-up period. Our study has several strengths, such as consecutive recruitment, which allowed us to capture a broad spectrum of patients and extrapolate the findings to a representative population, minimizing patient selection bias. Additionally, since our recruitment occurred between March and June 2020, the SARS-CoV-2 variants were likely dominated by clades 20C and 20D, so other variant-specific phenotypes are not mixed [39]. We also focused on unvaccinated patients, avoiding potential confounders such as immunization. However, we acknowledge some limitations of this study, including its single-site nature and the potential for over-reporting subjective complaints. This was mitigated by neurologist validation of the complaints and longitudinal follow-up. It is also important to note that prior headaches were assessed based on retrospective patient reports, which could introduce recall bias. Additionally, since only one probable variant was studied, these results may not be generalizable to other virus variants. Finally, negative information processing during the lockdown period may have negatively influenced self-perceived worsening. The relatively small number of incident cases also limited our ability to adjust incidence calculation for age or sex.

This is the longest follow-up study demonstrating the chronic nature of post-COVID headaches, including *de novo* headache characterization and the persistence of new-onset headaches. Interestingly, most of the *de novo* persistent headache cases fulfill migraine (or probable migraine) diagnostic criteria. Future population-based studies may provide further clarification of our observations and assess their potential impact on healthcare systems, as well as explore broader implications for patient care, quality of life, and healthcare costs. Our findings may serve as a foundation for earlier management of long-term consequences and more efficient resource allocation in future pandemics.

6 | Conclusions

Our study found that *de novo* persistent headaches are common 24 months post-COVID, with migraine-like headaches being the most frequent type. MLH incidence is high, and new "migraineurs-like" tend to be older compared to the general population. This finding is significant and could have a considerable impact on healthcare and quality of life, especially considering the vast number of COVID-19 cases since the pandemic began and the known global burden of migraine.

Author Contributions

Lénia Silva: investigation, formal analysis, writing – original draft. **Joana Fernandes:** investigation. **Rui Lopes:** investigation. **Sara Costa:** investigation. **Sofia Malheiro:** investigation. **Elaine Aires:** investigation. **Diogo Pereira:** investigation. **Joana Fonte:** investigation. **Alexandre Dias:** conceptualization, methodology, data curation, writing – review and editing. **Vanessa Oliveira:** conceptualization, methodology. **Sara Cavaco:** conceptualization, methodology. **Rui Magalhães:** conceptualization, data curation, formal analysis, writing – review and editing. **Manuel Correia:** conceptualization, methodology, supervision, writing – review and editing, validation. **Carlos Andrade:** conceptualization, methodology, writing – review and editing. **Luís F. Maia:** conceptualization, funding acquisition, methodology, project administration, supervision, validation, writing – review and editing.

Conflicts of Interest

The study was conducted under the Helsinki Declaration of 1964, its later amendments, and with relevant international and national regulations governing medical research. The study protocol was submitted and approved by the ethics committee of our university hospital (068-DEFI 069-CE). All patients provided informed and signed consent to participate.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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