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Pain paths among post-COVID-19 condition subjects

a prospective cross-sectional study with in-person evaluation

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PAIN PATHS AMONG POST-COVID-19 CONDITION SUBJECTS: A PROSPECTIVE CROSS-SECTIONAL STUDY WITH IN-PERSON EVALUATION

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Significance

COVID-19-related pain usually follows a chronic course and is non-neuropathic. Its possible courses and phenotypes are associated with distinct clinical and epidemiological features. This suggests differing underlying mechanisms, which may have significant prognostic and therapeutic implications.

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Abstract

Background: New-onset chronic pain has been acknowledged as part of the post-COVID-19 condition. However, available fine-grained data about its clinical phenotype, trajectories and main associated characteristics remain scarce. We described the distinct temporal evolutions of post-COVID-19 pain, their epidemiological and phenotypical features.

Methods: A prospective cross-sectional study enrolled post-COVID-19 condition patients (i.e. who had persisting COVID-19-related symptoms over 30 days since their first positive laboratorial test), whose COVID-19 diagnosis had been supported by RT-PCR of oral/nasopharyngeal swab or serology. They underwent in-person evaluations with structured interview, pain and quality-of-life-related questionnaires and thorough physical examination. Chronic pain (CP) and probable neuropathic pain (NP) were defined according to *IASP* criteria.

Results: The present study included 226 individuals, 177 (78.3%) of whom presented over 3 months since their first COVID-19 symptom. New-onset pain occurred in 170 (75.2%) participants and was chronic in 116 (68.2%). A chronic course was associated with COVID-19-related hospitalization, new-onset fatigue, lower cognitive performance, motor and thermal sensory deficits, mood and sleep impairments, and overall lower quality of life levels. Probable NP occurred in only 7.6% new-onset pain patients, and was associated with pain chronification, new-onset fatigue, motor and thermal sensory deficits, mechanical allodynia, and lower rates of SARS-CoV-2 vaccination. Previous CP was reported by 86 (38.1%) individuals and had aggravated after the infection in 66 (76.7%) of them, which was associated with orthostatic hypotension.

Conclusions: Post-COVID pain phenomena follow different paths, which are associated with specific clinical and epidemiological features, and possibly distinct underlying mechanisms, prognostic, and therapeutic implications.

Keywords: SARS-CoV-2, COVID-19, post-COVID condition, pain, neuropathic pain

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1. Introduction

Since it was first described in December 2019, COVID-19 has accounted for over 600 million cases and 6 million deaths worldwide as of October 2022 (WHO, 2022). Although its lethality is less than 1% (COVID-19 Forecasting Team, 2022), approximately three quarters of survivors develop persistent and frequently burdensome symptoms (Lopez-Leon et al., 2021; Nasserie et al., 2021). This condition has been referred to by varying terms such as 'long-COVID-19' and 'post COVID-19 syndrome', being coded in the International Classification of Diseases (ICD-10) since September 2020 as "Post COVID-19 Condition" (PCC, code U09.9) (Soriano et al., 2022; WHO, 2021).

PCC is a broad term that encompasses over 50 symptoms, which frequently overlap (Lopez-Leon et al., 2021; Taquet et al., 2021). New-onset chronic pain has been acknowledged as one of them. A cross-sectional study with 273.618 COVID-19 survivors in the UK has found incidences of 5.71% for chest/throat pain, 4.63% for headache, and 7.19% for other pain after 3 to 6 months from the infection (Taquet et al., 2021). Furthermore, headache and myalgia were observed 1 year after hospital discharge among 2.3 and 7.9% of COVID-19 survivors from Wuhan, China, respectively (Zhang et al., 2021). A recently published meta-analysis has observed that almost 10% of those infected by SARS-CoV-2 will suffer from musculoskeletal post-COVID-19 pain at some time during the first year of infection (Fernández-de-Las-Peñas et al., 2022).

However, few studies have provided details about new chronic pain related to PCC. These have reported incidences ranging from 15.1 to 45.1% (Fernández-de-Las-Peñas et al., 2021; Fernández-De-las-Peñas et al., 2022; Fernández-De-Las-Peñas et al., 2022; Fernández-de-las-Peñas et al., 2023; Karaarslan et al., 2022). Yet, most of them were based on phone interviews, and have focused on musculoskeletal pain (Bakılan et al., 2021; Fernández-de-Las-Peñas et al., 2021; Fernández-De-las-Peñas et al., 2022; Karaarslan et al., 2022), while few data is available for neuropathic pain (Herrero-Montes et al., 2022; Magdy et al., 2022). Furthermore, the relationship between COVID-19 and persisting pain is complex. The infection may lead to novel chronic painful symptoms either directly (e.g., viral-mediated tissue damage and inflammation) (Bauer et al., 2022), or indirectly (e.g., treatment-related complications) (Kemp et al., 2020). Although interview-only assessments allow for investigating the frequency of post-COVID-19 pain, they may be limited to describe phenotypical characteristics and associated epidemiological factors. To date, few fine-grained information stemming from broader in-person assessments of COVID-19 pain types are available. Also, data remain scarce about the magnitude of chronic pain patients that will have their symptoms

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aggravated by the infection, the incidence of new chronic pain among non-European populations, and how many will have neuropathic pain based on clinical examination.

Therefore, we conducted the present study with the objective of describing the distinct characteristics of different evolutions of post-COVID-19 pain, both musculoskeletal and neuropathic, and their association with epidemiological and clinical pain features through standardized in-person evaluations. These original data may help shed light on the possibly distinct underlying mechanisms that may lead to pain among these patients and help shape individually-tailored treatment and preventive strategies.

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2. Methods

2.1. Study design

This was a prospective cross-sectional study, conducted at the Pain Center of the Hospital das Clínicas of the University of São Paulo, Brazil. It is part of the larger project *Pain in the Pandemic Initiative,* aimed at examining the epidemiology, clinical characteristics, and prognosis of the pain phenomena among COVID-19 survivors. This study's protocol has been approved by the local Institutional Review Board (# 4.258.387).

2.2. Subjects

The patients were invited to participate in the study through open advertisements, made public through digital media and the local university newspaper and contact with primary care providers. Enrollment occurred from March to November of 2021. The subjects were considered eligible if they fulfilled the following criteria: i. diagnosis of COVID-19 supported by reverse transcription polymerase chain reaction (RT-PCR) of oral/nasopharyngeal swab samples and/or serology obtained at least one month before study inclusion, ii., reported any COVID-19-related symptom persisting beyond 30 days after the date of the first positive RT-PCR or serology test (i.e., PCC). COVID-19-related symptom was considered as any symptom the patient deemed to be newly occurring after the infection. This definition for PCC is supported by the one previously proposed by the United States' Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2022). The presence of pain or chronic pain was not an inclusion criterion, and it was not specifically mentioned on the advertisement for participation material. Individuals who were unable to give informed consent or to understand the study's questionnaires (e.g., due to severe cognitive disability) were excluded. Written informed consent was obtained from all enrolled subjects before they underwent the study's assessments.

2.3. In-person assessments and data collection

All subjects were evaluated in-person concomitantly by two researchers and all cases were reviewed with two other specialists in pain and COVID-19. These researchers assessed each subject together as a panel and according to a standardized protocol, and if uncertainty existed concerning the classification of the participant's symptoms, this was discussed with a board composed of neurologists, pain specialists and doctors with experience with COVID-19 management until a unanimous position was reached. Participants initially underwent a structured interview, which gathered data

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about demographic features, COVID-19 diagnosis and treatment, vaccination status, medical conditions, and previous chronic pain. During this interview, the individuals were also investigated about the development of new-onset pain during the SARS-CoV-2 infection, its body location, duration, and characteristics. COVID-19-related *de novo* pain was defined as any new-onset pain which started up to one month since the beginning of COVID-19 symptoms. Patients with previous chronic pain (PCP) were also inquired about its location and evolution after the infection (i.e., resolved, improved, persisted similarly, or worsened). Individuals with PCP who developed a new-onset pain, which was clearly different from their previous one (e.g., affecting a distinct body part, or with different pain characteristics), and which fulfilled the aforementioned criteria, were also considered to have developed COVID-related *de novo* pain (New-COVID-P). This type of pain was classified as probable neuropathic if it fulfilled the previously published *International Association for the Study of Pain* (IASP) criteria and grading system after neurological examination (Finnerup et al., 2016). Chronic pain was defined according to the IASP as a persistent or recurrent pain lasting longer than 3 months (Treede et al., 2015), and pain lasting less than 3 months was classified as acute. Quality of life and sleep, anxiety, and depression levels, as well as New-COVID-P characteristics and interference, were examined with the questionnaires and instruments presented below. Data about the development of new-onset fatigue, loss of smell and/or taste, were also collected.

Thereafter, all subjects underwent a standardized in-person physical examination by two senior neurologists concomitantly with expertise in pain medicine. In this examination, these researchers examined motor strength for superior and inferior limbs, and thermal sensory functions for cold stimuli, according to a protocol, described in detail in supplementary material 1. Heart rate and blood pressure were also measured in horizontal decubitus and after 2 minutes of standing position. Orthostatic hypotension was defined as a difference ≥ 20mmHg in the systolic blood pressure or ≥ 10mmHg in the diastolic blood pressure between these positions, and a significant heart frequency variation as an increase in ≥ 30ppm between them. Cognitive impairment was also screened with the semantic verbal fluency test for the category 'names of animals' (S-VFT). Thermal and mechanical allodynia were assessed objectively through sensory examination of the site the subjects reported pain.

All collected data were stored and managed using REDCap electronic data capture tools hosted at the Hospital das Clínicas of the University of São Paulo. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies (Harris et al., 2009, 2019).

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2.4. *Questionnaires and other assessment instruments*

The enrolled subjects were examined with the following instruments:

- Verbal numeric rating scale (NRS): self-reported 11-point scale that measures pain intensity from 0 (no pain) to 10 (highest possible). This scale was also used to assess the general impression of health, in which 0 indicates the lowest and 10 the highest possible.
- Brief pain inventory (BPI): this questionnaire allows for the characterization of the average pain intensity, its body location and interference (Ferreira et al., 2011). Interference levels were classified according to a numeric scale, varying from 0 (none) to 10 (highest possible).
- Douleur Neuropathique-4 questionnaire (DN-4): 10-item screening tool for identifying neuropathic pain (Santos et al., 2010). A score ≥ 4 has been shown to indicate the presence of neuropathic pain in the Brazilian population with 100% sensitivity and 93.2% specificity (Santos et al., 2010).
- Neuropathic Pain Symptoms Inventory (NPSI): a questionnaire that characterizes the clinical profile of peripheral and central neuropathic pain (de Andrade et al., 2011). It describes scores ranging from 0 (none) to 10 (highest possible) for each of the following clinical pain features: burning (superficial) spontaneous; pressing (deep) spontaneous; paroxysmal; evoked; and paresthesia/dysesthesia (Bouhassira et al., 2004). NPSI also allows for the classification of this type of pain in clinical clusters, which may have distinct responses to the treatment alternatives (Bouhassira et al., 2021).
- EuroQol 5D-3L questionnaire (EQ-5D3L): widely used instrument that examines quality of life and functionality across five dimensions (i.e., mobility, self-care, usual activities, pain and discomfort, anxiety, and depression) (Menezes et al., 2015; Santos et al., 2016).
- Visual analogue scale (VAS): self-report scale which was used in this study to quantify the subjects' impressions of their current quality of sleep, depression, and anxiety levels. It consists of a 100mm horizontal line, anchored by the ratings "none" at the left side (score 0) and "worst possible" at the right side (score 100).
- Semantic verbal fluency test (S-VFT): widely used screening cognitive test, which focuses on executive functions (Caramelli et al., 2007). It examines the number of elements of a given category the individual can recall within 1 minute. In this study, the category "names of animals" was assessed. Normative data of the S-

VFT for the Brazilian population, according to the education level, has been previously published elsewhere (Carvalho and Caramelli, 2020).

In this study, the previously validated Brazilian-Portuguese versions of the BPI (Ferreira et al., 2011), DN-4 (Santos et al., 2010) and NPSI (de Andrade et al., 2011) were used.

2.5. Data analysis

We included a convenience sample of consecutive patients with laboratory evidence of COVID-19 associated with long-lasting symptoms. Participants were first divided between those who did not develop *de novo* pain (no New-COVID-P) and those who did. The latter were then classified according to their new-onset pain evolution up to the day of their interview: acute resolved; acute persisting; chronic resolved; and chronic persisting. The relative proportions of subjects in each of these groups and their general demographic features were then examined. Sequentially, data from subjects without current New-COVID-P (i.e., acute resolved or no New-COVID-P) were grouped and compared with those who had chronic pain at the time of the interview (i.e., whose new-onset pain was chronic persisting).

Moreover, the incidence of probable neuropathic pain in each of these groups was described. Clinical pain phenotype and demographic features were compared between subjects with neuropathic and non-neuropathic chronic persisting *de novo* pain. The subset of PCP patients without current New-COVID-P was also examined. These individuals were further divided into 2 groups: those who had reported that their previous pain had worsened after the SARS-CoV-2 infection (aggravated PCP); and those who did not (non-aggravated PCP). Data from these groups were then compared and described. Finally, among subjects with current chronic pain, demographic features and clinical phenotype were compared between those whose pain was COVID-related (New-COVID-P without PCP), and the ones who had COVID-unrelated pain (non-aggravated PCP without New-COVID-P).

For inferential statistical analysis, categorical variables were compared with chi-square test, or Fisher's exact test when appropriate. Quantitative variables were tested for normality through the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as through visual inspection of histograms and normal Q-Q plots. Parametric variables were analyzed with Student's t test; and the non-parametric ones with the Mann-Whitney U and Kruskal Wallis test. Correlations were examined by the Spearman test. Statistical significance was set at $p<0.05$.

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Furthermore, clinical and epidemiological variables found to be significantly different between the compared groups were selected for logistic regression analyses. For these, only independent variables with over 15 cases were included into the regression equation; and their outliers were excluded. Outliers were defined as cases with standardized residual values greater than 2.5 standard deviations. For each regression, multicollinearity was examined through inspection of correlation coefficients and tolerance values. Model adequacy was tested with the Hosmer and Lemeshow goodness of fit test, and the variation explained by it was calculated with Nagelkerke R^2 method. The regression equation's sensitivity and specificity, as well as the contribution of each of its independent variables were reported. All analyses were conducted with the IBM SPSS Statistics software for Windows, Version 20.0 (Armonk, New York).

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3. Results

3.1 General demographic data

A total of 325 subjects were screened and 226 were found eligible and enrolled in this study. The reason for non-enrollment in all cases was lack of available laboratorial testing that supported COVID-19 diagnosis. The general demographic features of the included patients are presented in Table 1. Most of our sample was female (n=167, 73.9%) and the mean age was 46.9 ± 13.6 years. Diagnosis of COVID-19 was supported by RT-PCR of naso/oropharyngeal swab in 212 (93.8%) individuals, and COVID-19-related hospitalization occurred in 65 (28.8%), with a mean duration of 13.4 ± 9.6 days. Mean time from the first COVID-19 symptom and enrolment was 8.3 ± 5.1 months, and more than 3 months had elapsed from symptom appearance and the present assessment in 177 (78.3%) subjects (Figure 1).

3.2 Pain paths among COVID-19 survivors

New-COVID-P was reported by 170 (75.2%) participants, it was acute in 69 (30.5%) individuals, and had already completely resolved in 54 (23.9%) at the time of the assessment. On the other hand, this pain was chronic in 100 (44.2%) subjects and was present up to the time of the assessment in 97 (42.9%). Previous chronic pain (PCP) was reported by 86 (38.1%) subjects and was aggravated after COVID-19 in 66 (76.7%) of them. Further details of the pain subtypes within the studied sample are in Table 2.

3.3 Clinical and demographic characteristics of chronic persisting COVID-19 de novo pain

The clinical features and burden of chronic persisting New-COVID-P were described in Table 3. It was reported to occur on most days of the previous month in 84 (88.4%) subjects, with an average pain intensity of 7.3 ± 1.4. The most common pain sites were the lower limbs (n=46, 47.4%), and the head/neck (n=27, 27.8%). Analgesic medications were used by 71 (73.2%) of those who experienced this type of pain. Opioid use was, however, relatively uncommon (n=11, 11.4%). Chronic persisting New-COVID-P resulted in moderate interference in general activities, mood, walking, work performance and sleep (Table 3).

When compared to subjects with no current New-COVID-P (i.e. those who did not develop new-onset pain or only suffered from acute pain that was subsequently totally resolved), individuals with chronic persisting *de novo* pain were more likely to have been hospitalized due to COVID-19 (35.4% vs. 19.1%, p=0.008) and to have developed new-onset fatigue after infection (95.2 vs. 83.3, p=0.012); and less likely to have PCP

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(25.8% vs. 49.1%, p=0.001) (Table 4). Cognitive performance was lower among these subjects (16 ± 4.4 vs. 17 ± 4.8, p=0.021). The frequencies of motor (6.5% vs. 2.8%, p=0.013) and thermal sensory (13.4% vs. 2.7%, p=0.004) deficits were also higher in such patients, although their spatial distribution did not differ significantly from subjects without current New-COVID-P.

Furthermore, individuals with current New-COVID-P reported higher levels of anxiety (64.6 ± 30.2 vs. 55.2 ± 30.1, p=0.014) and depression (41.6 ± 32.5 vs. 28.5 ± 30.8, p=0.004), and more severe sleep impairment (55.3 ± 34.5 vs. 44.7 ± 36.3, p=0.045) compared to patients without New-COVID-P, respectively. New-COVID-P individuals also reported a lower overall impression of their health status (5.5 ± 1.7 vs. 6.8 ± 1.6, p<0.001) and quality of life levels in all assessed dimensions: mobility (p<0.001), self-care (p=0.035), usual activities (p<0.001), pain and discomfort (p<0.001), and anxiety and depression (p=0.007) (Table S1) compared to those without New-COVID-P, respectively.

Logistic regression analysis included the all the variables above, except for motor and thermal sensory deficits, due to low case counts. No evidence of multicollinearity between them was identified. The resulting model had an adequate fit (Hosmer and Lemeshow test p=0.282), and explained 28.4% of the observed variance for developing chronic persisting New-COVID-P, with a sensitivity of 64.6% and a specificity of 70.5%. Hospitalization (OR 3.01, 95%CI 1.36-6.67), new-onset fatigue after COVID-19 (OR 5.22, 95%CI 1.33-20.51), previous chronic pain (OR 0.41, 95%CI 0.19-0.89) and semantic verbal fluency (OR 0.87, 95%CI 0.80-0.94) contributed significantly to this model (Table S2).

In order to assess whether the presence of previous chronic pain (PCP) patients in the No-New-COVID-P group was not driving the findings described above, we conducted analyses comparing patients with New-COVID-P against those without New-COVID-P, this time removing PCP patients. Interestingly, except for anxiety scores, all the findings remained significant in these *ad hoc* analyses (Table S3).

3.4 Neuropathic pain among COVID-19 survivors

Probable neuropathic pain criteria were fulfilled by 13 (7.6%) New-COVID-P subjects. This type of pain was significantly more frequent among chronic persisting New-COVID-P patients (10.3%) compared to those with no current *de novo* pain (1.8%, p=0.009). Of note, DN-4 retained a high accuracy for identifying probable neuropathic pain in our sample of chronic persisting New-COVID-P subjects (sensitivity = 90%, specificity = 90.8%, Figure S1). Three patients with probable neuropathic pain had acute

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pain that persisted until the assessment date (persisting pain), while ten had an insidious and chronic persisting course.

Among chronic persisting New-COVID-P subjects, those with probable neuropathic pain were less likely to have received vaccination for SARS-CoV-2 (60% vs. 93.1%, p=0.009) and to have developed new-onset fatigue after COVID-19 (75% vs. 97.4%, p=0.044). On the other hand, motor (40% vs. 8.4%, p=0.016) and thermal sensory (100% vs. 3.4%, p<0.001) deficits as well as mechanical allodynia in the pain site (40% vs. 1.2%, p<0.001) were more frequent among these individuals (Table S4). Probable neuropathic pain was associated with higher interference with work performance (8.1 ± 3.0 vs. 6.4 ± 3.3, p=0.022); and depression (13.7 ± 15.4 vs. 45 ± 32.5, p=0.004), as well as a less affected quality of sleep (26.3 ± 33.5 vs. 58.8 ± 31.2, p=0.006), compared to those without it (Table S4). Probable neuropathic pain occurred in most days of the month in 9 (90%) individuals and had a moderate-to-high average mean intensity (7.6 ± 7.5). Its most frequent descriptors were burning (n=8, 80%) and tingling (n=8, 80%). The most frequent NPSI clusters among probable neuropathic pain were “deep pain” (n=5, 50%) and “pinpointed pain” (n=4, 40%, Table S5).

Logistic regression analysis was not possible for prediction of probable neuropathic pain among chronic persisting New-COVID-P because of the low frequency of patients with this condition (n=10).

3.5 Aggravation of previous chronic pain among subjects without current COVID-19-related de novo pain.

Previous chronic pain (PCP) was reported by 54 (49.1%) subjects without current New-COVID-P, of whom 36 (66.6%) had suffered a significant aggravation of their pain after the infection (Table S6). Orthostatic hypotension was more frequent among aggravated PCP individuals (8.8% vs. 33.3%, p=0.047). Other physical examination findings did not differ significantly between these groups (Table S6). Although the frequency of probable neuropathic pain did not differ significantly between aggravated and non-aggravated PCP patients, the former had higher DN-4 scores (2.0 ± 2.9 vs. 3.5 ± 2.6, p=0.001) and a trend to higher NPSI scores (9.7 ± 8.4 vs. 4.2 ± 3.7, p=0.050) (Table S6). Aggravated PCP was also associated with higher mean pain intensity (5.4 ± 2.9 vs. 3.5 ± 2.6, p=0.020); and a higher interference with mood (5.8 ± 3.6 vs. 3.2 ± 3.7, p=0.022), work performance (5.5 ± 3.5 vs. 2.9 ± 3.4, p=0.027), social relations (3.9 ± 3.6 vs. 2.3 ± 3.1, p=0.031), sleep (5.8 ± 3.7 vs. 3.0 ± 3.5, p=0.006) and enjoyment of life (4.6 ± 3.5 vs. 1.3 ± 3.0, p=0.004), when compared to non-aggravated PCP (Table S6). Patients of this group also reported higher levels of anxiety (59.3 ± 28.3 vs. 44.3 ± 27.8, p=0.024) and depression (39.7 ± 35.9 vs. 15.2 ± 18.1, p=0.012), and more severe sleep

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impairment (59.1 ± 35.6 vs. 30.2 ± 34.4, p=0.005) (Table S6). Although global impression of health status did not differ significantly between these groups, aggravated PCP was associated with higher burden on the following quality of life dimensions: usual activities (p=0.002), and anxiety and depression (p=0.006) (Table S6).

Logistic regression included global impressions of anxiety, depression and sleep quality. Orthostatic hypotension was not selected for this analysis due to its low frequency in the sample (n=8). No evidence of multicollinearity between the included variables was identified. The resulting model had an adequate fit (Hosmer and Lemeshow test p=0.745), and explained 55.9% of the observed variance for PCP aggravation, with a sensitivity of 53.3% and a specificity of 88.9%. Global impression of anxiety levels (OR 1.04, 95%CI 1.01-1.07) and global impression of sleep quality (OR 1.04, 95%CI 1.01-1.07) contributed significantly to this model (Table S7).

3.6 Comparison between subjects with exclusively COVID-19-related versus exclusively COVID-19-unrelated persisting chronic pain.

Data from participants with current chronic pain which was exclusively COVID-19-Related (i.e., chronic persisting New-COVID-P individuals who never had previous chronic pain; n=72) were compared with those from subjects with current chronic pain which was entirely unrelated and uninfluenced by COVID-19 (i.e. non-aggravated PCP patients without current New-COVID-P; n=18), and presented in Table S6. The COVID-related chronic pain group reported higher mean pain intensity (5.6 ± 2.0 vs. 3.9 ± 2.4, p=0.002) and significantly more neuropathic pain symptoms (Table S8) compared to those with COVID-unrelated chronic pain. Cognitive functioning was more affected (15.9 ± 4.3 vs. 19.1 ± 4.7, p=0.023), and development of new-onset fatigue after the infection was more frequent among the COVID-related (96.9% vs. 70%, p=0.016) than COVID-unrelated chronic pain subjects (Table S8). Moreover, COVID-related chronic pain individuals reported lower impression of health status (5.7 ± 1.6 vs. 6.6 ± 1.5, p=0.027); higher burden on quality-of-life dimensions usual activities (p<0.001), and pain and discomfort (p=0.008, Table S6); higher levels of anxiety (65.0 ± 30.3 vs. 37.8 ± 29.4, p=0.001) and depression (34.4 ± 30.8 vs, 13.6 ± 17.1, p=0.002); as well as more severe sleep impairment (54.6 ± 34.1 vs. 29 ± 34.2, p=0.010) when compared to COVID-unrelated chronic pain.

Moreover, when compared to the COVID-unrelated chronic pain patients, those with COVID-related had higher interference in general activities (6.4 ± 2.9 vs. 4.4 ± 3.3, p=0.014), mood (6.3 ± 3.3 vs. 3.6 ± 3.4, p=0.004), walking (5.3 ± 3.7 vs. 3.1 ± 3.7, p=0.042), work performance (6.4 ± 3.3 vs. 3.2 ± 3.4, p=0.001), social relations (4.1 ± 3.8

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vs. 2.9 ± 3.5, p=0.024), sleep (5.1 ± 3.7 vs. 2.9 ± 3.5, p=0.036) and enjoyment of life (4.7 ± 3.5 vs. 1.7 ± 3.0, p=0.002), respectively (Table S8).

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4 Discussion

Our study provided a detailed characterization of the potential unfolding of pain after COVID-19 (Figure 2). Approximately a third of New-COVID-P resolved completely, generally within 12 weeks. Meanwhile, over half had a chronic course, most of which (97%) persisted for several months and were still present at the moment of the assessment. This was associated with hospitalization due to COVID-19, development of new-onset fatigue, lower cognitive performance, motor and thermal sensory deficits mood and sleep impairments, resulting in lower quality of life levels. In particular, hospitalization, new-onset fatigue and lower cognitive performance provided an altogether small-to-moderate contribution for the probability of pain chronificiation. Neuropathic pain was associated with a higher pain chronification probability, and was present in 7.6% of New-COVID-P patients, being associated with new-onset fatigue, motor and thermal sensory deficits, mechanical allodynia in the pain site, and lower rates of SARS-CoV-2 vaccination. We also observed that DN-4 had high accuracy for identifying probable neuropathic pain in our sample. Finally, COVID-Related chronic pain, was found to be more intense, leading to a higher burden on overall functionality, sleep and mood, and higher cognitive impairment when compared to the COVID-Unrelated pain.

Pain was reported to occur in 30 to 70% of patients during acute COVID-19 (Jena et al., 2022; Karaarslan et al., 2022; Knox et al., 2021; Kubota and Moisset, 2022; Kurçaloğlu et al., 2021; Murat et al., 2020; Oguz-Akarsu et al., 2022; Ojeda et al., 2022; Şahin et al., 2021). However, few studies are available on its natural history beyond the first months of the infection. In fact, to the best of our knowledge, five researches have specifically addressed chronic New-COVID-P incidence. The first was a relatively small prospective case-control study where we reported that approximately 20% of COVID-19 survivors developed new-onset chronic pain, after a mean of 4 months since hospital discharge (Soares et al., 2021). Four larger subsequently published cohorts, which assessed subjects between 6 to 13.2 months from the infection, found incidences ranging from 15.1 to 45.1% (Fernández-de-Las-Peñas et al., 2021; Fernández-De-las-Peñas et al., 2022; Fernández-De-Las-Peñas et al., 2022; Fernández-de-las-Peñas et al., 2023; Karaarslan et al., 2022). Female sex (Fernández-de-las-Peñas et al., 2023; Karaarslan et al., 2022), anosmia (Soares et al., 2021), myalgia and/or headache at admission (Fernández-de-Las-Peñas et al., 2021; Fernández-de-las-Peñas et al., 2023), length of hospitalization and history of musculoskeletal pain (Fernández-de-las-Peñas et al., 2023) were associated with new-onset chronic pain. Data gathered by these pioneering reports are of great value, however some gaps of knowledge remained. All the aforementioned studies were conducted through phone interviews among previously

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hospitalized subjects, and the largest ones focused specifically on musculoskeletal pain. Therefore, detailed information about physical examination findings, non-European populations and pain subtypes were not available. Furthermore, data about New-COVID-P natural history, the distinct paths it may follow, and their associated individual phenotypical features, have been addressed by few of these studies, and are available only for musculoskeletal pain (Fernández-de-las-Peñas et al., 2023).

Currently, most available studies have examined New-COVID-P by focusing on two specific categories: musculoskeletal and neuropathic pain. Musculoskeletal pain has been investigated by the majority and the largest studies in this field. (Bakılan et al., 2021; Fernández-De-Las-Peñas et al., 2022; Fernández-de-Las-Peñas et al., 2022; Fernández-de-las-Peñas et al., 2023; Karaarslan et al., 2022). These observed that it most commonly affects the spine and lower limbs, and has a widespread distribution in up to two thirds of cases. It was also found that musculoskeletal New-COVID-P was associated with fatigue and myalgia at admission (Fernández-De-Las-Peñas et al., 2022; Fernández-de-Las-Peñas et al., 2022). While previous data indicated that this subtype of pain may be associated with more severe inflammatory response (i.e. leukopenia and D-dimer elevation) during the acute phase (Bakılan et al., 2021), a recent larger study found that serological biomarkers of acute COVID-19 severity has small association with New-COVID-P, although this latter work did not examine directly inflammatory markers. Most of chronic persisting New-COVID-P subjects of our study had non-neuropathic pain (89.7%, 87/97) and, consistently with previous research, they reported new-onset fatigue more frequently than those with a neuropathic mechanism. We also observed that they had higher levels of anxiety and depression, and lower sleep quality, which have been described in models of chronic inflammatory pain, e.g., fibromyalgia associated with rheumatologic conditions (Sarzi-Puttini et al., 2020).

Contrastingly, very few data are available for neuropathic pain. A recently published metanalysis has estimated it to occur in 10% (95%CI 5-15%) of patients during acute/subacute COVID-19 (di Stefano et al., 2023), but few studies have assessed its frequency and characteristics in the long run. Chronic neuropathic pain has been reported to occur in 24.6% of new-COVID-P patients (Herrero-Montes et al., 2022). However, our study found this frequency to be significantly lower (7.6%). This may be explained by the fact that most of our sample had not required hospital admission, while previous research examined subjects who had been hospitalized (Herrero-Montes et al., 2022). Also, neuropathic pain definition differed as we used IASP criteria through in-person examination, instead of self-administered questionnaires (Herrero-Montes et al., 2022). Conversely, in line with currently published data (Magdy et al., 2022), neuropathic pain occurred more frequently in the limbs and its most frequent descriptor was 'burning'.

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Moreover, neuropathic pain has been associated with depression, use of azithromycin, COVID-19 severity and duration, higher serum ferritin levels during the acute phase, anxiety and kinesiophobia levels (Herrero-Montes et al., 2022; Magdy et al., 2022). Although our results did not support its association with anxiety nor depression levels, we did observe lower vaccination rates in these patients. This finding may be indirect, as vaccination has been shown to correlate with shorter disease duration and lower severity (Ronchini et al., 2022; Tenforde et al., 2021), and therefore possibly to a lower incidence of neuropathic pain. Nevertheless, vaccination might also lead to lower viremia, and less neural tissue invasion by SARS-CoV-2.

Yet, no definite single mechanism has been proved to account for post-COVID-19 conditions. The most frequently discussed hypotheses are: i. the sequelae of direct viral invasion and destruction of neural and other tissues; ii. persistent immunological imbalance after the infection. SARS-CoV-2 particles have been isolated from neurons and other cells in the cortex, substantia nigra, brainstem and cranial nerves in up to 53% autopsied patients (Bauer et al., 2022). But infection seems to be restricted only to a subset of cells, and the association between tissue viral load and severity of neuropathological changes seems loose (Bauer et al., 2022; Matschke et al., 2020; Solomon et al., 2020). Meanwhile, mounting data points to persistent inflammatory abnormalities after COVID-19. A recently published cohort observed persistent abnormalities in a series of cytokines after a median of 8 months since infection, of which elevated TNF-α, IL-1β and IL-6 were associated with post-COVID-19 condition (Schultheiß et al., 2022). A long-lasting immune dysregulation may occur due to many potential causes, including persisting viral reservoirs, imbalance in renin-angiotensin system, gastrointestinal microbiota dysbiosis and chronic reprogramming of immune cells, particularly lung macrophages (Ramakrishnan et al., 2021; Schultheiß et al., 2022).

Data from our study and other published work suggest that chronic musculoskeletal and neuropathic New-COVID-P have different clinical profiles, which may indicate distinct underlying pathophysiology. Musculoskeletal pain appears to be associated with more frequent widespread location, and a plethora of multisystemic symptoms (e.g., fatigue, depression, anxiety, and sleep disorders) which are observed in chronic inflammatory conditions. Conversely, neuropathic pain seems to correlate with factors that would point to more severe tissue injury: use of potentially neurotoxic substances (e.g., azithromycin) (Waetzig et al., 2017), higher serum neurofilament light chain levels (Magdy et al., 2022), and a possibly higher viremia (suggested by the association with lower rates of vaccination and higher disease severity). Evidently, it is unlikely that these pain subtypes would be explained by a single mechanism each, but it is possible that one may be predominant over others.

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One important issue is that the evolution of PCP after COVID-19 has been rarely studied. Indeed, only two studies presented PCP data separately from New-COVID-P (Fernández-de-Las-Peñas et al., 2021; Fernández-De-las-Peñas et al., 2022). Consistently with our findings, it observed that the majority of PCP subjects reported a persistent aggravation of their previous pain after the infection (Fernández-de-Las-Peñas et al., 2021). In our sample, global levels of anxiety and sleep quality contributed moderately to the risk for PCP aggravation. Additionally, we found that PCP worsening was associated with orthostatic hypotension. This is a novel finding, which could suggest a role of central nervous system invasion through the vagus nerve, which contributes to cardiovascular autonomic balance. This hypothesis has been raised by earlier autopsy studies that isolated SARS-CoV-2 in vagus nerve fibers, nuclei and the medulla oblongata (Bulfamante et al., 2021; Matschke et al., 2020; von Weyhern et al., 2020). It must be acknowledged, however, that if this was true, the frequency of orthostatic hypotension would probably also be higher among New-COVID-P individuals, which could not be observed. On the other hand, the differences found between New-COVID-P and aggravated PCP regarding associated epidemiological and clinical factors may indicate that these are distinct entities, with dissimilar underlying mechanisms.

Our data should be interpreted taking in consideration some relevant limitations. This was a cross-sectional study, and therefore it is not able to establish causality nor assess incidence of pain subtypes after COVID-19. Some aspects of our sample should be considered when comparing our results from those of previous and/or future studies: (i) although the definition for PCC our study used was supported by the literature available at its design, its time thresholds differ from the one more recently proposed by the World Health Organization (Soriano et al., 2022); (ii) less than a third of our sample required hospitalization, and therefore average acute COVID-19 severity was probably lower than in previously published research; (iii) recently published research indicated that the viral strain may influence the risk for PCC (Fernández-de-las-Peñas et al., 2022), and our sample was largely infected by SARS-CoV-2 between 2020 and early 2021, when most COVID-19 cases in Brazil were caused by the index virus and its gamma variant (Fiocruz, 2023). Neuropathic pain was defined according to well-established clinical criteria, but no further complementary testing was conducted to assess the presence of injury to somatosensory pathway. The number of individuals who developed this pain subtype was relatively small, limiting the statistical power of our analyses for this group. Also, it is not possible to exclude the possibility of selection bias once recruitment was directed to patients with PCC and those with more severe symptoms could have been preferentially enrolled in the study.

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Conclusions

Our data suggest that patients with chronic persisting New-COVID-P and PCP aggravated after COVID may present different clinical characteristics, and may have nociceptive or neuropathic mechanistic backgrounds, which quite likely has therapeutic and prognostic implications. Together with the available literature, this may support the next step phase in the study of PCC-related chronic pain: the design of therapeutic trials and potential preventive actions aimed at patients with high risk of developing chronic pain after COVID.

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6 Author contributions

GTK has contributed to the conception and design of this study, data analysis and interpretation, and drafting of the manuscript. FHCS has contributed to the conception and design of this study, data acquisition and interpretation. ASF, TSR, GRG, VGF, PHMC have contributed to the conception of the study and data acquisition. ARB and MJT have contributed to the study design and data interpretation. DCA has contributed to the conception and design of this research, data interpretation and drafting of the manuscript. All authors have discussed the results, revised and commented on the manuscript. The final version of the manuscript has been approved by all authors.

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8 Figures titles and legends

Figure 1. Distribution of time since first COVID-19 symptom and enrolment in the study.

Legend: This chart presents the distribution of the included COVID-19 survivors according to time span categories between their first COVID-19 symptom and their enrollment in this study.

Figure 2. Pain paths among post-COVID-19 condition patients

Legend: This figure illustrates the possible clinical paths post-COVID-19 condition patients may follow regarding pain phenomena. Subjects without previous chronic pain may either develop acute COVID-19-related *de novo* pain or persist without any pain symptoms. Meanwhile, those with previous chronic pain may also develop new-onset acute COVID-19 pain; and their previous pain may either aggravate or not. Most *de novo* pain after COVID-19 have a chronic course, i.e. persist even after 12 weeks from the infection. However, in some cases, new-onset pain may resolve before this time period. Additionally, a minority of chronic new-onset COVID-19 pain may also resolve posteriorly.

Table 1. General demographics and COVID-19 characteristics

	COVID-19 survivors (N = 226)
Female sex	167 (73.9)
Age (years)[A]	46.9 ± 13.6 (14-82)
Ethnicity	
White	119 (52.7)
Afrodescendant	105 (46.5)
Asian	2 (0.9)
Years of education	
0 year	0 (0)
1-9 years	18 (8)
10-12 years	82 (36.3)
> 12 years	126 (55.8)
Marital status	
Single	71 (31.4)

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Married / stable union	117 (51.8)
Divorced / separated	28 (12.4)
Widower	10 (4.4)
Pain as a post-COVID-19 condition symptom[B]	154 (68.1)
Previous chronic pain	86 (38.1)
COVID-19 infection and immunization	
Time since first symptom (months)[A]	8.3 ± 5.1 (1-21)
COVID-19 diagnosis	
RT-PCR	212 (93.8)
Serology	14 (6.2)
Hospitalization	65 (28.8)
Length of hospitalization (days)[A]	13.4 ± 9.6 (1-51)
Treated with chloroquine	22 (9.7)
Vaccination	203 (89.8)
1 dose	77 (34.1)
2 doses	124 (54.9)
Oxford	77 (34.1)
Coronavac	84 (37.2)
Pfizer	38 (16.8)
Aztrazeneca	2 (0.9)
Type of vaccine not reported	25 (11.1)

Data presented in n (%), unless otherwise specified.
[A]Data presented in mean ± standard deviation (minimum-maximum)
[B]Defined new-onset pain after COVID-19 or aggravation of previous chronic pain.

Table 2. Overview of the pain phenomena among 226 COVID-19 survivors

COVID-19-related *de novo* pain	
Overall prevalence	170 (75.2)
Self-resolved acute pain	54 (23.9)
Time to acute pain resolution (days)[A]	11.42 ± 11.38 (1-60)
Persistent acute pain	15 (6.6)
Self-resolved chronic pain	3 (1.3)
Time to chronic pain resolution (days)[A]	120 ± 30 (90-150)
Persistent chronic pain	97 (42.9)
Mean persistent chronic pain duration (months)[A]	9.8 ± 4.3 (3-19)
Aggravated previous chronic pain	
Overall prevalence	68 (30.1)
Non-aggravated previous chronic pain	
Overall prevalence	22 (9.7)

Data presented in n (%), unless otherwise specified.

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[A]*Data presented in mean ± standard deviation (minimum-maximum)*

Table 3. Clinical characteristics and burden of COVID-19 *de novo* persistent chronic pain

	COVID-19 survivors who developed *de novo* chronic persistent pain (N = 97)
Average pain intensity in the past week[A]	7.3 ± 1.4 (4-10)
Frequency of > 15 days per month	84 (88.4)
Pain localization	
Head & neck	27 (27.8)
Upper limbs	6 (6.2)
Back pain	12 (12.4)
Thorax	13 (13.4)
Abdomen	1 (1.0)
Lower limbs	46 (47.4)
Perineum	2 (2.1)
Widespread pain	2 (2.1)
Pain interference assessed by the *Brief Pain Inventory*[A]	
General activities	6.7 ± 2.9 (0-10)
Mood	6.2 ± 3.5 (0-10)
Walking ability	5.6 ± 3.5 (0-10)
Normal work	6.5 ± 3.3 (0-10)
Relations with other people	3.9 ± 3.7 (0-10)
Sleep	5.4 ± 3.7 (0-10)
Enjoyment of life	4.6 ± 3.6 (0-10)
General impression of health (NRS) [A]	5.5 ± 1.7 (0-9)
General impression of anxiety (VAS) [A]	64.3 ±30.2 (0-100)
General impression of sleep (VAS) [A]	41.1 ± 32.5 (0-100)
General impression of depression (VAS)[A]	54.7 ± 34.5 (0-100)
Pain medication	
No medication	26 (26.8)
Methimazole	41 (42.3)
Acetaminophen	15 (15.5)
Non-steroidal anti-inflammatory drug	20 (20.6)
Muscle relaxant	13 (13.4)
Codeine	5 (5.2)
Tramadol	6 (6.2)
Strong opioid	0 (0)
Other	12 (12.4)

Data presented in n (%), unless otherwise specified.

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[A] *Data presented in mean ± standard deviation (minimum-maximum)*

Table 4. Comparison between subjects with chronic persistent and no current COVID-19-related *de novo* pain.

	COVID-19-related *de novo* persistent chronic pain (N=97)	**No current COVID-19-related *de novo* pain (N=110)**	**p**
Female sex	76 (78.4)	77 (70)	0.172
Age (years)[A]	46.2 ± 12.8 (14-82)	47.1 ± 14.4 (16-81)	0.671
Ethnicity			
White	*43 (44.3)*	*65 (59.1)*	
Afrodescendant	*53 (54.6)*	*44 (40.0)*	0.058
Asian	*1 (0.9)*	*1 (1.1)*	
Previous chronic pain	25 (25.8)	54 (49.1)	0.001*
Previous fatigue	12 (12.5)	20 (18.2)	0.261
Hospitalization	34 (35.4)	21 (19.1)	0.008*
Treated with chloroquine	14 (14.4)	7 (6.4)	0.055*
Vaccination	87 (89.7)	101 (92.7)	0.451
Anosmia/hyposmia	76 (78.4)	75 (68.8)	0.122
Ageusia/Hypogeusia	72 (75)	71 (65.1)	0.292
New-onset fatigue after COVID-19[B]	80 (95.2)	75 (83.3)	0.012*
Global impression of anxiety levels[A]	64.6 ± 30.2 (0-100)	55.2 ± 30.1 (0-100)	0.014*
Global impression of depression levels[A]	41.6 ± 32.5 (0-100)	28.5 ± 30.8 (0-100)	0.004*
Global impression of sleep quality[A]	55.3 ± 34.5 (0-100)	44.7 ± 36.3 (0-100)	0.045*
Physical Examination[E]			
Orthostatic hypotension	13 (19.4)	5 (9.1)	0.110
Significant heart frequency variation	2 (3)	0 (0)	0.500
Semantic verbal fluency[A]	16 ± 4.4 (8-26)	17 ± 4.8 (9-26)	0.021*
Motor strength deficit	11 (6.5)	3 (2.8)	0.013*
Distal superior limbs	2 (18.2)	0 (0)	1.000
Proximal superior limbs	1 (9.1)	1 (33.3)	0.396
Distal inferior limbs	8 (72.7)	1 (33.3)	0.505
Proximal inferior limbs	3 (30.0)	1 (33.3)	1.000
Tetraparesis	1 (9.1)	2 (66.7)	0.093

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Sensory deficit	13 (13.4)	3 (2.7)	0.004*
Head & neck	3 (23.1)	0	1.000
Upper limbs	3 (23.1)	1 (33.3)	1.000
Dorsal and lumbar	2 (15.4)	0 (0)	1.000
Thorax	0 (0)	1 (33.3)	0.188
Abdomen	1 (7.7)	0 (0)	1.000
Lower limbs	9 (69.8)	3 (100)	0.529
Perineum	0 (0)	0 (0)	---
Thermal allodynia	0 (0)	---	---
Mechanical allodynia	5 (5.5)	---	---
Coordination deficit	2 (2.2)	4 (3.8)	0.688
Gait abnormality	34 (37)	27 (26)	0.097

*Data presented in n (%), unless otherwise specified; * p<0.05*

For this analysis, no current COVID-19-related de novo pain group was composed by subjects who did not develop de novo pain after COVID-19 and those who developed acute new-onset pain which had completely resolved by the time of the enrollment.

[A] *Data presented in mean ± standard deviation (minimum-maximum)*

[B] *For this analysis, only subjects who did not report previous fatigue were considered.*

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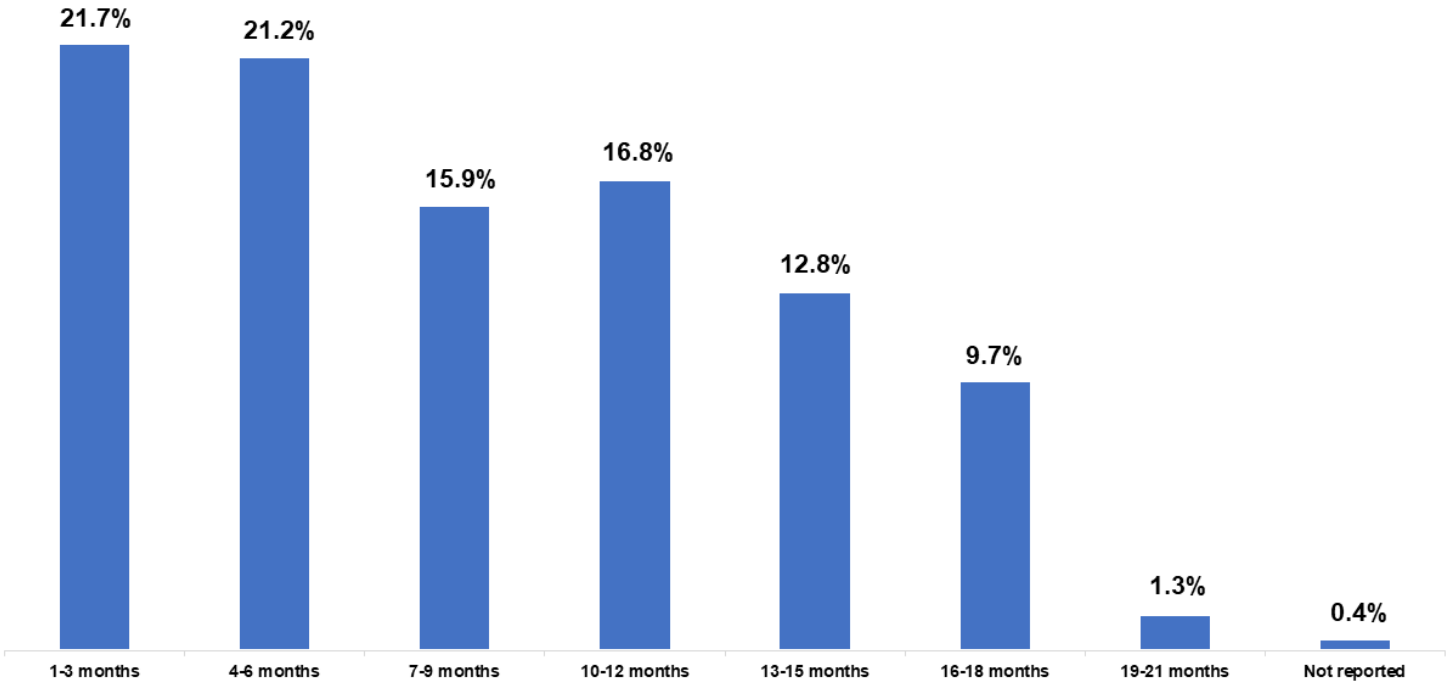

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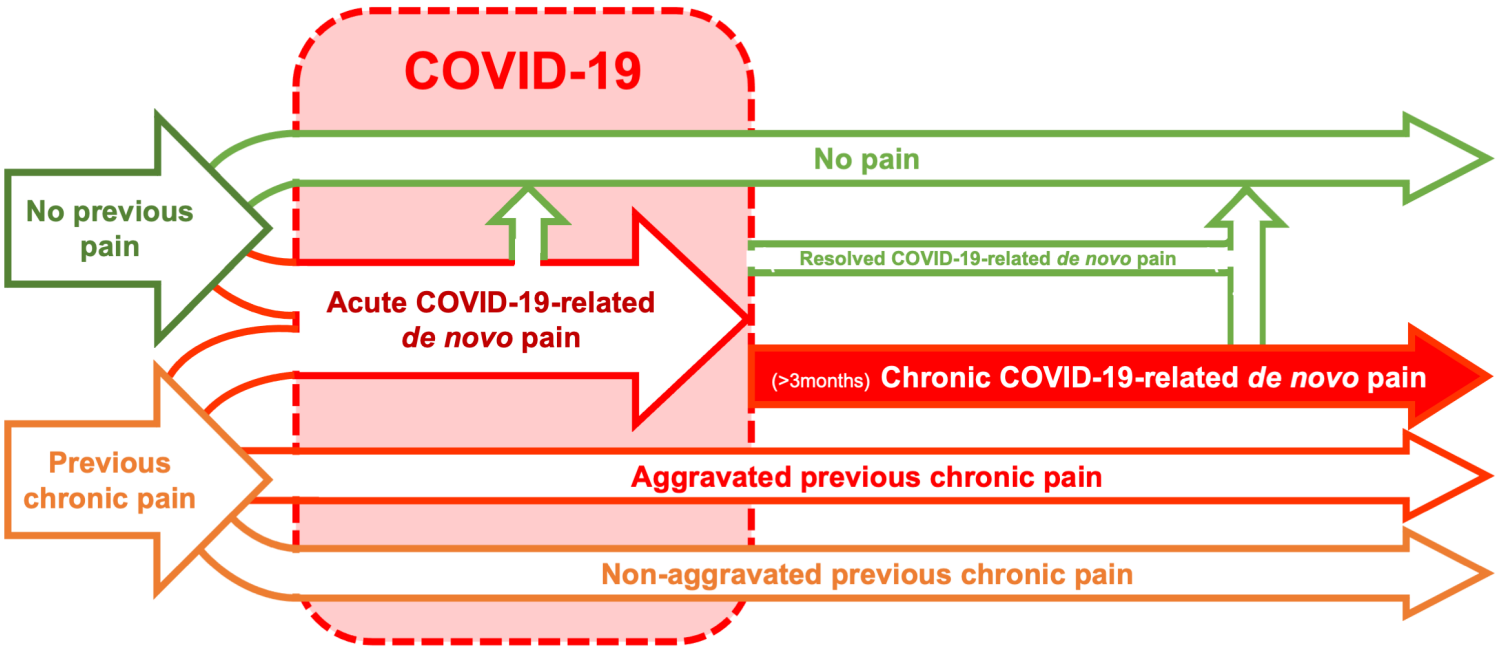

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