Received: 27 November 2020 | Accepted: 21 February 2021

DOI: 10.1002/ejp.1755

ORIGINAL ARTICLE

EJP European Journal of Pain

Prevalence and characteristics of new-onset pain in COVID-19 survivours, a controlled study

Felipe Henriques Carvalho Soares[1] | **Gabriel Taricani Kubota**[1] | **Ana Mércia Fernandes**[1] | **Bruno Hojo**[1] | **Catarina Couras**[1] | **Bárbara Venturoti Costa**[1] | **Jorge Dornellys da Silva Lapa**[1] | **Luíza Mansur Braga**[1] | **Matheus Merula de Almeida**[1] | **Pedro Henrique Martins da Cunha**[1] | **Vítor Hugo Honorato Pereira**[1] | **Adriano Donizeth Silva de Morais**[1] | **Manoel Jacobsen Teixeira**[1] | **Daniel Ciampi de Andrade**[1,2] | **"Pain in the Pandemic Initiative Collaborators"**

[1]Pain Center, Department of Neurology, University of São Paulo, São Paulo, Brazil

[2]Pain Center, Instituto do Câncer do Estado de São Paulo Octavio Frias de Oliveira, University of São Paulo, São Paulo, Brazil

Correspondence
Daniel Ciampi de Andrade, Av. Dr. Enéas de Carvalho Aguiar, 255, 5 andar, sala 5084, Cerqueira César 05403-900, São Paulo, SP, Brazil.
Email:ciampi@usp.br

Funding information
The study was funded by the Pain Center, Dept of Neurology, University of São Paulo, SP, Brazil. The authors report no disclosures.

Abstract

Background: We assessed whether COVID-19 is associated with de novo pain and de novo chronic pain (CP).

Methods: This controlled cross-sectional study was based on phone interviews of patients discharged from hospital after COVID-19 compared to the control group composed of individuals hospitalized during the same period due to non-COVID-19 causes. Patients were classified as having previous CP based on the ICD-11/IASP criteria, de novo *pain* (i.e. any new type of pain, irrespective of the pain status before hospital stay), and de novo CP (i.e. persistent or recurring de novo pain, lasting more than 3 months) after COVID-19. We assessed pain prevalence and its characteristics, including headache profile, pain location, intensity, interference, and its relationship with fatigue, and persistent anosmia. Forty-six COVID-19 and 73 control patients were included. Both groups had similar sociodemographic characteristics and past medical history.

Results: Length of in-hospital-stay and ICU admission rates were significantly higher amongst COVID-19 survivours, while mechanical ventilation requirement was similar between groups. Pre-hospitalisation pain was lower in COVID-19 compared to control group (10.9% vs. 42.5%; $p = 0.001$). However, the COVID-19 group had a significantly higher prevalence of de novo pain (65.2% vs. 11.0%, $p = 0.001$), as well as more de novo headache (39.1%) compared to controls (2.7%, $p = 0.001$). New-onset CP was 19.6% in COVID-19 patients and 1.4% ($p = 0.002$) in controls. These differences remained significant ($p = 0.001$) even after analysing exclusively (COVID: $n = 40$; controls: $n = 34$) patients who did not report previous pain before the hospital stay. No statistically significant differences were found for mean new-onset pain intensity and interference with daily activities between both groups. COVID-19

Felipe Henriques Carvalho Soares and Gabriel Taricani Kubota contributed equally to the work

The List of Pain in the Pandemic Initiative Collaborators are defined in Appendix.

pain was more frequently located in the head/neck and lower limbs ($p < 0.05$). New-onset fatigue was more common in COVID-19 survivours necessitating inpatient hospital care (66.8%) compared to controls (2.5%, $p = 0.001$). COVID-19 patients who reported anosmia had more new-onset pain (83.3%) compared to those who did not (48.0%, $p = 0.024$).

Conclusion: COVID-19 was associated with a significantly higher prevalence of de novo CP, chronic daily headache, and new-onset pain in general, which was associated with persistent anosmia.

Significance: There exists de novo pain in a substantial number of COVID-19 survivours, and some develop chronic pain. New-onset pain after the infection was more common in patients who reported anosmia after hospital discharge.

1 | INTRODUCTION

The new coronavirus disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), started in Wuhan (China) in the end of 2019 and rapidly expanded worldwide (Li et al., 2020; World Health Organization, 2020a). Since the early reports of the disease, some characteristics have become clear: (a) the largest proportion of infected patients will likely survive the disease (World Health Organization, 2020b); (b) the virus has neurotropic propensity (World Health Organization, 2020b). Indeed, it has been proposed that the virus has the capacity to invade the central nervous system (Satarker & Nampoothiri, 2020; World Health Organization, 2020b), leading, amongst other symptoms, to anosmia (Tong et al., 2020) and dysautonomia (Wu, Guo, et al., 2020), putatively due to gut myenteric nerve plexus-vagus nerve-brainstem invasion (Ellul et al., 2020; Garg, 2020). One of the hallmarks of the disease is the dissociation between oxygen desaturation and lack of overt dyspnea, which is currently credited to brainstem dysfunction (Rogers et al., 2020). The combination of the large number of survivours and propensity for neuronal invasion leads to the possibility that survivours may face not only chronic respiratory symptoms, shortness of breath and difficulty returning to usual activity (ie, long-COVID) (Nabavi, 2020), but also, long-term neurologic sequelae such as dysautonomia, neuromuscular weakness (Toscano et al., 2020; Valent et al., 2020) fatigue, cognitive impairment and anxiety.

Chronic pain affects 18% of the general population and is the most common symptomatic disease worldwide (Sá et al., 2019), it is the first reason why patients seek healthcare and is the most common cause of years lived with disability worldwide (GBD, 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Chronic pain patients are at risk of facing pain aggravation due to constrained spatial mobility to seek treatment, shortage of medication supply, access to rehabilitation facilities, which increases pandemic-related stress and mood symptoms. But added to these problems, there may be new-onset pain associated with the COVID-19 infection itself (Karos et al., 2020; Treede et al., 2015). In this case, new-onset chronic pain patients would be added to the health care system, with potential human, ethical, logistical and financial challenges to society.

Since the beginnings of the pandemic, some have hypothesized pain to be an important persistent symptom amongst COVID-19 survivours (Clauw et al., 2020; Kemp et al., 2020; Su et al., 2020; Vittori et al., 2020). Pain has been proposed to be the result of indirect mechanisms, such as muscle wasting and critical illness neuropathy due to prolonged immobilisation and mechanical ventilation, as well as corticosteroid and neuromuscular blocking drugs use; painful sequelae from neurological complications of the disease (e.g. Guillain-Barre syndrome and stroke); and psychological aspects, specially intensive care-related post-traumatic stress disorder (Kemp et al., 2020; Vittori et al., 2020). Nonetheless, direct consequences of SARS-CoV-2 infection have also been implied to play a significant role (Kemp et al., 2020; Vittori et al., 2020). Garvin et al suggested that an imbalance between ACE2 and ACE enzymes in lung cells would lead to an increase in bradykinin levels, a molecule widely associated with pain sensitisation mechanisms (Garvin et al., 2020). It was also put forward that the direct infection of ACE2-receptor-expressing neurons and microglia in the spinal dorsal horn would facilitate pain transmission (Su et al., 2020). Direct viral invasion to skeletal muscle, synovium and cortical bone has also been proposed, and would contribute to pain development (Disser et al., 2020).

There is an increasing body of evidence describing long-lasting symptoms, in general, amongst COVID-19 survivours, especially attentional deficits, fatigue and respiratory symptoms (Carfì et al., 2020; Carvalho-Schneider et al., 2020; Tenforde, 2020; Wang et al., 2020). There are also a number of studies that have discussed the indirect burden of the sanitary measures to contain the pandemic

on chronic pain patient's assessment and care (Cohen et al., 2020; Eccleston et al., 2020; El-Tallawy et al., 2020; Karos et al., 2020; Majumdar et al., 2020; Murphy and Latif 2021; Parodi et al., 2020; Shanthanna et al., 2020). However, to date, there are only a few reports specifically addressing the development of new-onset persistent pain or aggravation of previous pain in COVID-19 survivours. These few studies focused exclusively on headache were not controlled and had short follow-ups (Caronna et al., 2020; Rocha-Filho & Magalhães, 2020; Trigo et al., 2020).

The aim of this cross-sectional prospective controlled study was to describe the presence of de novo pain and de novo chronic pain in COVID-19 survivours, compared to a control COVID-19-free group composed of patients hospitalized during the same time period. We have also collected original data on pain location, interference with daily life, the presence of fatigue and associated symptoms in order to propose a framework for COVID-19 pain classification.

2 | METHODS

This was a controlled cross-sectional study, part of the Pain in the Pandemic Initiative of the Pain Center, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo. It was approved by the Institution's Ethics Review Board (# 4.248.387). All patients were volunteers and were informed about research by phone. All interviews were performed by a line phone or by a video-call in some instances. No financial compensation was provided for study participation.

2.1 | Patients

Patients were evaluated by five neurologists after a series of group training aimed at standardising the call procedures as previously described (Leão Ferreira et al., 2016). Interviewers were working as part of the out-patient team and did not work in any of the three hospital buildings assisting in-patients during the 2020 pandemic. All participants were discharged from our institution after hospitalisation during April and August 2020. During the 2020 COVID-19 pandemic the Hospital das Clínicas Complex was divided into two sections, one being the Central Institute, with 900 beds, exclusively dedicated to COVID-19 care and two other Institutes (Cancer and Heart Institutes, 1,034 beds) dedicated to patients admitted due to non-respiratory causes. We have recruited patients who had been hospitalized in the COVID-19 sector and were discharged to their respective homes. Patients without COVID-19 infection hospitalized during this same time period in the COVID-free areas were also contacted and formed the control group.

Inclusion criteria for the COVID-19 group were: (a), confirmed the hospitalisation of the adult patient (older than 18 years old) due to COVID-19 from April to August 2020; (b), hospital discharge to home after infection by COVID-19; (c), COVID-19 infection confirmed by either: positive real-time polymerase chain reaction positivity for COVID-19, and/or a positive serologic test (IgM positivity); (d), willingness to participate and having the capacity to understand the questions posed by the researcher via telephone; (e), not presenting subsequent hospitalisation or new health status aggravation after hospital discharge.

The control group consisted of adult patients who were already followed at the Clínicas Hospital Complex (national public health care system) who had non-surgical health status aggravations (usually due to heart or cancer causes) demanding hospitalisation during the COVID-19 pandemic. Inclusion criteria were: (a) hospitalisation and hospital discharge between April and August 2020; (b) negative COVID-19 tests (RT-PCR and/or serologic tests) during hospitalisation; (c) willingness to give consent to participate and capability to understand the questions posed by the researchers by telephone or by a video-call; (d) denying a subsequent hospitalisation due to health status deterioration after hospital discharge. Exclusion criteria for both groups were: (a), inability to communicate, (b) inability to understand the questions, (c) readmission to the hospital after the initial discharge within the study period; (d) detection of new COVID-19 infection (for the COVID-19 group) or detection of first-time COVID-19 infection (for the control group) from the time of hospital discharge and to the moment of the interview.

2.2 | Assessments

Participants were assessed during a phone (or video, when available) interview using the REDCap software platform (Tennessee, USA). Some measures were adopted to minimize non-response bias including: training of interviewers, standardisation of the interview (identification of the research staff, introduction of the aim of the study) and routine callbacks in case of failed contact (Ortiz et al., 2016). Each selected telephone number was contacted up to 6 times on different week-days and at different time-periods of each day (from 8 a.m. to 21 p.m.) (Neville et al., 2008). Calls were made during one week of each month from May to August 2020. The week in each month when calls were made was chosen randomly. Patients' phone number were randomly selected from a list of patients who had been discharged from the COVID-19 and the COVID-19-free sectors of the hospital. At the end of each week, a list of patients' hospital registration codes from the COVID-19 and non-COVID-19 sectors were downloaded from the hospital registration system and subjects were randomly chosen to

be contacted on one specific day of the following week. COVID-19 and non-COVID-19 patients had two separate lists and were contacted in parallel. The subjects were contacted once at random timepoints since hospital discharge. If an eligible subject agreed to participate, verbal informed consent was obtained. The refusal rate and the time spent in each interview were recorded. Interviews were performed with the patients themselves, and, in cases of hearing impairment, a family member was invited to mediate the interview. We collected sociodemographic data, medical comorbidity status, and medication use, as well as information related to the hospital stay from medical charts and from the patients' report. Additionally, medication classes were also detailed, according to the medication quantification scale (MQS) (Gallizzi et al., 2008). Concomitantly, parts of classic pain questionnaires were used to assess pain and fatigue, as detailed below:

2.2.1 | Scales, questionnaires, and classifications

The following questionnaires were used to assess pain in COVID-19 and controls.

1. Patients were firstly inquired about pre-existing chronic pain (previous to hospitalisation) based on the current IASP definition (Raja et al., 2020; Treede et al., 2015). If present, data about its body site, as well as its evolution (improvement/stability/aggravation) after hospital discharge were obtained. Then, patients were assessed for de novo pain, i.e. any new pain after discharge from the hospital. Patients were free to report any type of new pain they desired given it was not simply an aggravation of previous existing pain. De novo pain could include pain in an otherwise pain-free individual, or pain in a different body location, or of different characteristics in relation to a previously existing chronic pain. De novo chronic pain was defined as any de novo pain recurring or persisting after hospital discharge up to the date of the interview, lasting longer than three months according to the current IASP definition (Raja et al., 2020; Treede et al., 2015). If data on the frequency of de novo pain were missing, it was considered that criteria for de novo CP could not be fulfilled. Clinical features and evolution since hospital discharge for de novo pain and de novo CP were also inquired. Prevalence of de novo pain and de novo CP were calculated for the whole sample of patients in each group (main outcome), for the subset of subjects who were interviewed after 3 months of hospital discharge (secondary analyses), and also for participants who did not present any CP before hospital stay (secondary analyses).
2. Brief Pain Inventory (BPI): was adapted to measure average pain intensity (in the last 7 days, each ranging from 0- no pain to 10- maximal pain imaginable). Pain interference was assessed through a numerical rating score (0–10, where higher scores mean higher inference of pain in daily activities). Patients were asked to classify their pain outcome after hospital discharge as 'improved', 'unchanged' or 'worsened' (Cleeland & Ryan, 1994; Ferreira et al., 2011).
3. Body spatial pain distribution as reported by patients was marked on a predetermined manikin on a REDCap template by the reviewers. Patients were asked to report the sites where they experienced worse pain most of the time.
4. Headache: Patients were classified as having de novo headache if they reported a de novo pain located in the head, as pointed on the manikin mentioned above. Chronic daily headache was defined as based on current definitions (Ahmed et al., 2012; Headache Classification Committee of the International Headache Society, 2018) (ie, headaches occurring on 15 or more days in a month for at least three months). De novo chronic daily headache was defined as a de novo headache which fulfilled such criteria for chronic daily headache. Characteristics of the headache (pulsatile, neck irradiation, unilaterality, presence of osmo-, photo-, phono-phobia, or presence of nausea and vomiting) were enquired. Presence of precipitating factors was recorded.
5. Fatigue: prevalence of previous fatigue before hospitalisation as well as of de novo fatigue after hospital discharge were enquired. The patients ranked the evolution of their fatigue after hospital leave as 'worsening', 'unchanged', or 'improved'.
6. Self -reported presence of anosmia, hypogeusia only amongst COVID-19 patients at the time of assessment was reported.
7. Use of analgesic medication for the treatment of de novo pain and de novo CP was enquired during the interview. The type of such medication, according to its respective pharmacological class, was also questioned.

2.3 | Statistics

We have based our target sample size to be within similar ranges as those previously reported for long-term (up to 3 months) complications of new viral diseases such as in de Laval et al., 2018 ($n = 49$) (de Laval et al., 2018) and da Silva et al., 2017 ($n = 40$) (da Silva et al., 2017) for Zika vírus. The COVID-19 and non-COVID-19 list of patients to be contacted by phone were independent, and the non-COVID-19 list was relatively larger than the COVID-19 list. These convenience samples of participants ended up providing a larger

number of non-COVID-19 than COVID-19 participants. However, our target sample size (n = 40–45) was based on the size of the COVID-19 group, and when the desired sample was reached, inclusion has terminated. Thus, the control group was not matched to the COVID-19 group. Categorical variables were represented by frequencies, percentages, and absolute numbers. Continuous variables were presented as means ± standard deviation (minimal - maximal values) and tested for normal distribution using Kolmogorov-Smirnoff tests, Q-Q plots and histograms. The Mann-Whitney test was applied for comparisons of non-parametric quantitative variables between the two groups. The Chi-square was used to compare the nominal and ordinal qualitative variables between groups according to the sample size. When an expected table cell sample size was < 5, the Fisher's exact test of independence was used. As this was an exploratory study and the main results from multiple tests had to be combined for one final conclusion, no correction for multiple testing was deemed necessary (Bender & Lange, 2001). The level of significance considered was 5%.

3 | RESULTS

A total of 69 COVID-19 patients and 96 controls were screened for participation in the study (Figure S1, study flowchart). Data from 46 COVID-19 patients and 73 controls were available for analysis. Clinical characteristics of participants are displayed in Table 1 and Table S1. Both groups had similar sociodemographic characteristics and similar past medical history profile, except for previous heart disease, which was more common in the control group. COVID-19 patients were in-hospital for a significantly longer period of time (22 ± 26.6 days) compared to controls (9.7 ± 16.5; p =0.001), and were more frequently admitted to the intensive care unit (ICU) (45.7%) compared to controls (20.5%, p =0.014). However, the number of COVID-19 patients requiring invasive mechanical ventilation (28.3%) was similar to those from the control group (16.4%, p = 0.304) (Table 1). The average times since hospital discharge until the interview were 112 ± 43 days for COVID-19 subjects and 69.5 ± 34.6 for controls (p = 0.001; Table 1).

TABLE 1 Demographical profile of the subjects included in the study

	COVID−19 (n = 46)	Control (n = 73)	p
Age (years)[a]	56.3 ± 15.0 (27–81)	54.8 ± 16.2 (19–89)	0.794
Male sex, n (%)	21 (45.7)	28 (38.4)	0.554
Past medical history, n (%)			
Diabetes	13 (28.3)	21 (28.8)	0.953
Hypertension	22 (47.8)	41 (56.2)	0.375
Stroke	2 (4.3)	8 (11)	0.206
Peripheral artery disease	7 (15.2)	8 (11)	0.496
Chronic kidney disease	6 (13.0)	4 (5.5)	0.148
Cancer	0 (0)	3 (4.1)	0.164
Heart disease	5 (10.9)	40 (54.8)	0.001*
Liver disease	2 (4.3)	1 (1.4)	0.313
Lung disease	4 (8.7)	16 (21.9)	0.060
Gastrointestinal disease	3 (6.5)	4 (5.5)	0.814
Autoimmune disease	4 (8.6)	7 (9.6)	0.870
Anxiety	3 (6.5)	13 (17.8)	0.079
Depression	4 (8.7)	9 (12.3)	0.536
Other psychiatric diseases	0 (0)	1 (1.4)	0.425
In-hospital duration (days)[a]	22.7 ± 26.6 (5–159)	9.7 ± 16.5 (1–93)	0.001*
Time since hospital discharge (days)[a]	112 ± 43 (3–170)	69.5 ± 34.6 (4–162)	0.001*
ICU admission, n (%)	21 (45.7)	15 (20.5)	0.014*
Use of invasive mechanical ventilation, n (%)	13 (28.3)	12 (16.4)	0.304

[a]Values are presented in mean ± SD (minimum and maximum).

*p < 0.05.

Prevalence of previous chronic pain before hospitalisation was lower in the COVID-19 compared to the control group (10.9% vs. 42.5%; $p = 0.001$, respectively) (Table S2). However, COVID-19 patients had a significantly larger proportion of patients with new-onset pain after the hospital stay (65.2%) compared to patients from the control group (11.0%, $p = 0.001$) (Table 2). When including exclusively patients without CP previous to the hospital stay, similar results were found for de novo *pain* in the COVID-19 (70.0%) and in the control groups (20.6%); $p = 0.001$, as well as for de novo CP (25% vs. 3%, respectively; $p = 0.025$).

TABLE 2 Pain after hospital discharge in the COVID-19 and Control groups

	COVID−19 ($n = 46$)	Control ($n = 73$)	p
Prevalence of de novo pain, *n* (%)	30 (65.2)	8 (11)	0.001*
Prevalence of de novo chronic pain, *n* (%)	9 (19.6)	1 (1.4)	0.002*
Location of de novo pain, *n* (%)			
Head and neck	20 (66.7)	2 (25)	0.034*
Upper limbs	5 (16.7)	0 (0)	0.215
Thorax and/or abdomen	5 (16.7)	4 (50)	0.049*
Dorsal and/or low back	14 (46.7)	3 (37.5)	0.643
Lower limbs	11 (36.7)	0 (0)	0.042*
Widespread pain	7 (23.3)	0 (0)	0.130
Frequency of de novo pain, *n* (%)			
< 15 days per month	4 (13.3)	2 (25)	0.672
≥ 15 days per month	15 (50)	4 (50)	
Not informed	11(36.7)	2 (25)	
De novo pain intensity[a]	6.7 ± 1.6 (3–9)	6.5 ± 2.6 (2–9)	0.794
De novo pain interference in daily activities[a]	6.0 ± 2.6 (0–9)	6. 5 ± 3.8 (0–10)	0.328
Trend of d*e novo* pain after hospital discharge, *n* (%)[b]			
Improved	5 (17.2)	1 (12.5)	0.052
Unchanged	13 (44.8)	3 (37.5)	
Worsened	0 (0)	2 (25)	
Not informed	11 (37.9)	2 (25)	

[a]According to the numeric rating scale (0 – none; 10 –highest imaginable). The values are presented as mean ± *SD* (minimum and maximum).

[b]For inferential analysis between groups, subjects who informed de novo pain to have remained unchanged since hospital discharge and those who reported it to have worsened were polled together and compared with those who described de novo pain improvement.

*$p < 0.05$.

When questioned specifically about headache, patients from the COVID-19 also had a lower prevalence of this symptom before hospital admission (2.2%) compared to those from the control group (12.3%; $p = 0.052$). However, new-onset headache after the hospital stay was significantly more common in COVID-19 patients (39.1%) compared to controls (2.7%, $p = 0.001$) (Table 3). Phone and video interviews occurred at random time points after in-hospital stay. It means that some patients were interviewed a few weeks after discharge, while others were interviewed several months thereafter. Still, we found a significant proportion of patients experiencing new-onset chronic pain in the COVID-19 group (19.6%) compared to the control group (1.4%, $p = 0.002$). Also, when only the subset of subjects interviewed after 3 months from hospital discharge was analysed ($n = 25$, 54.3% of COVID-19 patients and $n = 19$, 27.4% of controls), COVID-19 group still had a significantly higher prevalence of de novo CP (36% vs. 5.2%; $p = 0.016$). It should be noticed that only 3 of the 54 (5.5%) controls and 6 of the 20 (30%) COVID-19 survivours who were assessed lesser than 3 months after hospital discharge reported recurring and persistent new pain.

Analogously, new-onset chronic daily headache was present in 13% of COVID-19 patients compared to none in the control group ($p = 0.007$). The COVID-19 and control groups used a similar amount and similar profile of analgesic after discharge from hospital for the treatment of de novo *pain* (Table 4). Opioids were rarely used for pain analgesia in our sample. Pain after COVID-19 had an average intensity of 6.7 ± 1.6 and interference of 6.0 ± 2.6, which did not differ from the control groups. COVID-19 de novo pain was more frequently of moderate intensity and was more commonly located in the head/neck and in the lower limbs compared to controls (Figure 1, Tables 2 and 3). As expected, higher pain intensity scores were associated with more severe pain interference in activities of daily living (coefficient = + 0.718, $p = 0.001$).

New-onset headache amongst COVID-19 survivours was unilateral in 50%, had a pulsating quality in 38.9% and a moderate to severe intensity in all (Table 3). Nausea and/or vomiting were reported by 44% of these patients, whereas phonophobia and photophobia by 38.9% and 27,8%, respectively.

For fatigue, although patients from the control group had more complaints before hospital admission, new-onset fatigue was significantly more common in COVID-19 survivours (68.8%) compared to controls (2.5%, $p = 0.001$) (Table S3). In the COVID-19 group, 39.1% of patients reported having new-onset anosmia, while 50.3% reported experiencing hypogeusia. Interestingly, patients with anosmia presented more frequently new-onset pain (83.3%), when compared to those without this symptom (48.0%, $p = 0.024$).

TABLE 3 Headache after hospital discharge

	COVID−19 ($n = 46$)	Control ($n = 73$)	p
Prevalence of previous chronic daily headache, *n* (%)	1 (2.2)	9 (12.3)	0.052
Prevalence of de novo headache, *n* (%)	18 (39.1)	2 (2.7)	0.001*
Prevalence of de novo chronic daily headache, *n* (%)	6 (13)	0 (0)	0.007*
Clinical features, *n* (%)[a]			
Unilateral	9 (50)	1 (50)	–
Pulsating quality	7 (38.9)	2 (100)	–
Neck irradiation	4 (22.2)	0 (0)	–
Intensity, *n* (%)[a]			
Mild	0 (0)	1 (50)	–
Moderate	7 (38.9)	0 (0)	
Severe	10 (55.6)	1 (50)	
Not informed	1 (5.6)	0 (0)	
Associated symptoms, *n* (%)[a]			
Photophobia	5 (27.8)	1(50)	–
Phonophobia	7 (38.9)	0 (0)	–
Osmophobia	2 (11.1)	0 (0)	–
Nausea/vomit	8 (44.4)	1 (50)	–
Aggravating factors, *n* (%)[a]			
Routine physical activity	5 (27.8)	2 (100)	–
Valsalva manoeuvre	3 (16.7)	0 (0)	–
Orthostasis	2 (11.1)	0 (0)	–

[a]Percentages from subjects with de novo headache. No inferential analysis between groups was possible as only two control subjects developed de novo *headache*.

*$p < 0.05$.

4 | DISCUSSION

This is an original report of a controlled prospective assessment of pain and headache epidemiology and clinical features in COVID-19 infection survivours. We have found that COVID-19 survivours had more frequent new-onset pain after hospital discharge, affecting almost two-thirds of our sample compared to patients without COVID-19 infection with similar sociodemographic and health profile who were also hospitalized during the 2020 pandemic. We reported the original finding concerning the occurrence of de novo chronic pain after COVID-19 infection, present in 19.6% of survivours. These are outstanding figures, especially if one considers that based on our study's cross-sectional design, chronic pain could not be detected in those potentially *en route* to develop it, but who had the interview performed within the first three months after hospital discharge (thus precluding the diagnosis of chronic pain). This means that, based on our results, there were at least 19.6% of new-onset chronic pain patients after COVID-19 infection. Given the usual high pain prevalence in the general population (Sá et al., 2019), these data speak for a net increase in chronic pain patients during, and possibly after the 2020 pandemic. Importantly, 66% of our COVID-19 patients presented head or neck pain. Indeed, new-onset headaches after the COVID-19 infection was reported in 39.1% of our sample. Diagnostic criteria for de novo chronic-daily headache were fulfilled in 13% of the participants. Headache and pain, in general, have been reported during COVID-19 since the early reports, along with rhabdomyolysis and muscle pain during the acute infection (Chen et al., 2020). However, few studies have specifically addressed long-term COVID-19-related pain. All these reports have focused exclusively on headache and were not controlled. Also, their follow-ups were relatively short, and therefore chronic pain could not have been assessed (Table 5). Our data, if confirmed, will serve to help the health care system be prepared to assist and treat a substantial number of new pain patients.

Besides the head, pain after COVID-19 was also more commonly located in the lower limbs. Due to the restrictions of time imposed by phone/video interviews and current limitation to perform non-urgent consultations, we could not

TABLE 4 Use of analgesic medication for de novo pain and de novo chronic pain

	De novo Pain[a]			De novo Chronic Pain[b]	
	COVID−19	Control	*p*	COVID−19	Control
Prevalence of analgesic medication use	14 (46.7)	5 (62.5)	0.727	6 (66.6)	1 (100)
Methimazole	12 (85.7)	4 (80)	0.764	5 (55.5)	1 (100)
Paracetamol	1 (7.1)	1 (20)	0.421	1 (11.1)	0 (0)
Non-steroidal anti-inflammatory	2 (14.3)	1 (20)	0.764	0 (0)	1 (100)
Muscle Relaxant	3 (21.4)	1 (20)	0.946	2 (22.2)	1(100)
Tramadol[c]	0 (0)	2 (40)	–	0	0
Codeine[c]	0 (0)	1 (20)	–	0	0

Note: Values are presented in *n* (%).

[a]Percentages from subjects with de novo pain who reported using analgesic medications.

[b]Percentages from subjects with de novo chronic pain who reported using analgesic medications. As only one control subject fulfilled the criteria for de novo chronic pain, inferential statistical analysis was not possible.

[c]Inferential analysis between groups was not possible for weak opioid use in de novo pain due to the low frequency of use of these medications in our sample.

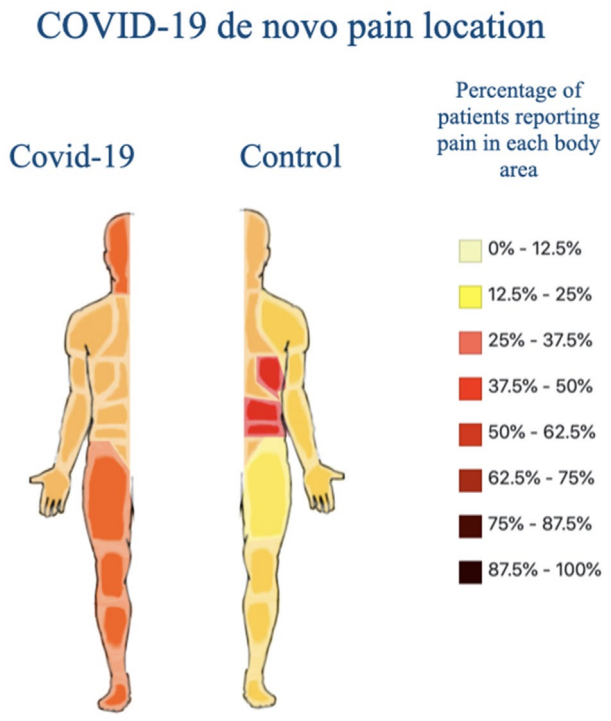

FIGURE 1 Pain distribution in the COVID-19 and control groups. Colours indicate the percentage range of the prevalence of pain in each body location in patients with de novo pain

examine these patients yet. Thus, lower limb pains could actually be due to joint pain, or perhaps neuropathic pain due to peripheral length-dependent neuropathy, but these assumptions remain theoretical so far.

Despite the general similarity in baseline health antecedents, controls had a significantly higher prevalence of previous cardiac diseases and, consequently, had significantly more fatigue and baseline chronic pain before hospitalisation. In fact, our study included control patients those who were already followed for health conditions in our tertiary and university hospital complex. In contrast, COVID-19 patients came from the general population have become ill during the pandemic. Still, COVID-19 patients had a significantly higher proportion of fatigue, new-onset pain and headache after hospital stay. While it would be possible that the presence of pre-hospitalisation chronic pain could have biased the assessment of new-onset pain after hospital stay, both de novo pain and de novo CP remained significantly more frequent amongst COVID-19 survivours in an analysis excluding patients with previous CP. COVID-19 patients stayed longer in-hospital and had higher rates of ICU admission, but used mechanical ventilator in the same proportion as controls. This is a very important point, given the use of neuromuscular blocks and high-dose sedatives necessary during orotracheal intubation and mechanical ventilation, along with the systemic inflammatory response syndrome occurring during sepsis and shock all lead to critical patient neuromuscular disease and pain, which would be obvious bias in our study (Kemp et al., 2019; Zhou et al., 2014). Unfortunately, details on other ICU stay information and other in-hospital complications were limited in our sample.

One interesting point is related to the development of anosmia and the presence of de novo pain. This is an intriguing finding that links the development of pain to signs of central nervous system dysfunction. It has been hypothesized that SARS-CoV-2 could invade the CNS through the circulation, cerebral spinal fluid or via cranial nerves/olfactory bulb, by synapse-connection or by direct endocytic paths (similar

TABLE 5 Published studies that have assessed pain after COVID-19

	Type of study	Sample size	Type of pain	Method of assessment	Control group	Maximum time since COVID−19[a]	Evaluation of chronic pain	Main findings
Trigo et al., 2020	Retrospective cohort	576	Headache	Retrospective review of medical charts	No	61	No	One hundred and thirty-seven (23.7%) patients reported new-onset headache after COVID−19. Headache was associated with lower risk of mortality (OR 0.39, 95% CI 0.17–0.88)
Caronna et al., 2020	Prospective cohort	130	Headache	Face-to-face and phone interviews	No	42	No	Ninty-seven (74.6%) patients reported headache as a COVID−19 symptom. At the 6-week follow-up, 28 of these patients (37.8%) reported on-going headache.
Rocha-Filho & Magalhães, 2020	Cross-sectional	73	Headache	Face-to-face interviews	No	<30	No	Forty-seven (64.4%) reported headache related to COVID−19. Anosmia/hyposmia and/or ageusia/hypogeusia was associated with headache development (OR 5.39; 95% CI 1.66–17.45)
Present Study, 2021	Cross-sectional case-control	119 (46 with COVID−19)	Any pain	Phone interviews	Yes	162	Yes	When compared to controls, COVID−19 survivours reported significantly higher prevalence of new-onset pain (65;2% vs. 11.0%; $p = 0.001$) and new onset chronic pain (19.6% vs. 1.4%; $p = 0.002$). New-onset headache was also statistically more frequent amongst COVID−19 patients (39.1% vs. 2.7%; $p = 0.001$)

Note: Studies assessing the prevalence of pain after COVID-19 and: 1. a size sample $n > 10$ employed, 2. well-established diagnostic/classification criteria.

[a]Values are presented in days. All the reported times considered hospital/ED admission as the initial time-point, except for our study, which considered hospital discharge as the initial time-point.

to ZIKA virus) (Baptista et al., 2020; Channappanavar & Perlman, 2017). Indeed, COVID-19 is capable to invade astrocytes, neuroblasts, and neurons via the direct binding to the ACE2 receptor (Baptista et al., 2020). This would lead to the dysfunction of ACE2-mediated cascades with potential implications in neuroinflammation, neurodegeneration, and neurotoxicity processes. From the clinical perspective, patients with COVID-19 in Wuhan presented acute CNS symptoms, such as dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and convulsions (Morfopoulou et al., 2016; Turgay et al., 2015; Wu, Xu, et al., 2020). SARS-CoV had been detected in the human and experimental animal central and peripheral nervous systems. It remains fully speculative whether anosmia represents long-term sequelae of a treated disease, or some kind of marker of a potential latent inflammatory activity, associated with new-onset pain after the disease. Importantly, these assumptions must be taken cautiously since anosmia was not looked for in the control group. Despite the general acknowledgement that COVID-19 is specifically linked to anosmia in a larger proportion than in other viral infections, one cannot assume it was only present in post-COVID-19 cases. New prospective clinical and experimental studies will need to be conducted to explore these new perspectives. The literature on neuro-virology is full of examples of long-term neurological sequelae of viral infections such as Zoster, Zika, Dengue and Chikungunya (de Andrade et al., 2010), to cite a few examples. Although our controls were assessed after a significantly shorter period since hospital discharge than COVID-19 survivours, very few controls actually developed new-onset persistent pain and CP after hospital discharge.

Our study has several limitations. First, data collection was conducted only by phone interviews, due to sanitary restrictions to presential assessments during the study period. This limited the evaluation of some relevant clinical features, such as allodynia, hyperpathia, pain triggers and worsening factors. Also, data about previous chronic pain may have been liable to recall bias. While we have described several characteristics of new-onset chronic pain after COVID-19, several important aspects of pain such as pain-related catastrophism, mood symptoms and quality of life were not assessed. Also, pain treatment is based on the mechanistic classification of pain into nociceptive, neuropathic or nociplastic (Freynhagen et al., 2018; Kosek et al., 2016), which was not performed here due to time limitations. While we tried to obtain information on new-onset headache characteristics and precipitating factors, our data was very limited and a deeper temporal profile and fine-grained spatial description of post-COVID-19 headache was not provided here. Another major limitation is that we have not assessed potential prodromal pain or pain during full-blown infection, and one cannot determine, based on our data, whether acute pain during in-hospital stay is a risk factor or is a necessary element to develop chronic post-COVID-19 pain. This information would have potential value for preventive approaches to post-COVID-19 pain.

Reports of COVID-19-related pain also reveal the need to provide updated nomenclature approaches. Here we have initially considered as de novo pain any new pain that was reported by the patients, even if the patient already presented previous chronic before hospital admission. Although this particular instance was relatively rare in the COVID-19 group, a supplementary analysis including exclusively patients without any chronic pain before hospitalisation provided similar results, suggesting that there was, indeed, more 'new pain' present after COVID-19 infection compared to controls. Hence, here we propose, as has been performed in other instances (Mylius et al., 2020), the use of three classification terms: i. COVID-19-unrelated pain, for patients who had chronic pain before the infection, but no change in their pain pattern has occurred after the COVID-19; ii, COVID-19-directly related pain: for de novo pain occurring after the infection in previously pain-free patients; iii: COVID-19-aggravated pain, for patients with preceding chronic pain who had pain aggravation after the infection.

In view of our preliminary results, future controlled studies are needed to corroborate our findings and better characterize the predictors, clinical features, underlying mechanisms, morbidities and burden of COVID-19 directly related pain. Indeed, in-person assessments, when sanitary conditions will allow, may provide a better clinical description as well as invaluable data from physical examination (e.g. allodynia, myofascial syndrome, signs of peripheral neuropathy). The use of validated clinical tools, such as the Douleur Neuropathique 4 (Bouhassira et al., 2005; Santos et al., 2010) and the Neuropathic Pain Symptom Inventory (Bouhassira et al., 2004; de Andrade et al., 2011) could contribute to the identification and description of an eventual neuropathic component to COVID-19 directly related pain. Furthermore, quantitative sensory testing and neurophysiological evaluations may help shed light on its underlying mechanisms. The evaluation for persistent changes in certain serum biomarkers (such as bradykinin and interleukin-6 for general pain, and perhaps CGRP for headache) amongst COVID-19 directly related pain patients may also provide an insight to these mechanisms.

The description of pain after COVID-19 is in its infancy. To date, one can ascertain that there exist pain and chronic pain after the infection, and a large proportion of COVID-19 survivours will develop it. Post-COVID-19 pain is of at least moderate intensity and has a significant impact on daily activities, being associated with new-onset anosmia. Future studies will better define the deeper characteristics of COVID-19-related pains and, hopefully, give insights into its prevention and treatment.

5 | AUTHORS' CONTRIBUTIONS

FHCS: study design, data collection and analyses of data. GTK: study design, analyses of data, writing of the draft and review of the draft. AMF: analyses of data and writing of the draft. BH: study design and data collection. CC: study design and data collection. BVC: study design and data collection. JDSL: study design and data collection. LMB: study design and data collection. MMA: study design and data collection. PHMC: study design and data collection. VHHP: study design and data collection. ADSM: study design and data collection. MJT: writing of the draft and review of the draft. DCA: study design, analyses of data, writing of the draft and review of the draft.

ORCID

Daniel Ciampi de Andrade https://orcid.org/0000-0003-3411-632X

REFERENCES

Ahmed, F., Parthasarathy, R., & Khalil, M. (2012). Chronic daily headaches. *Ann Indian Acad Neurol*, *15*, S40–S50. https://doi.org/10.4103/0972-2327.100002

Baptista, A. F., Baltar, A., Okano, A. H., Moreira, A., Campos, A. C. P., Fernandes, A. M., Brunoni, A. R., Badran, B. W., Tanaka, C., de Andrade, D. C., da Silva Machado, D. G., Morya, E., Trujillo, E., Swami, J. K., Camprodon, J. A., Monte-Silva, K., Sá, K. N., Nunes, I., Goulardins, J. B., … & Zana, Y.. (2020). Applications of Non-invasive Neuromodulation for the Management of Disorders Related to COVID-19. *Front Neurol*, *11*.1248

Bender, R., & Lange, S. (2001). Adjusting for multiple testing–when and how? *Journal of Clinical Epidemiology*, *54*, 343–349. https://doi.org/10.1016/S0895-4356(00)00314-0

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lantéri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., & Vicaut, E. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*, *114*, 29–36. https://doi.org/10.1016/j.pain.2004.12.010

Bouhassira, D., Attal, N., Fermanian, J., Alchaar, H., Gautron, M., Masquelier, E., Rostaing, S., Lanteri-Minet, M., Collin, E., Grisart, J., & Boureau, F. (2004). Development and validation of the neuropathic pain symptom inventory. *Pain*, *108*, 248–257. https://doi.org/10.1016/j.pain.2003.12.024

Carfì, A., Bernabei, R., & Landi, F., Gemelli Against COVID-19 Post-Acute Care Study Group. (2020). Persistent symptoms in patients after acute COVID-19. *JAMA*, *324*, 603–605. https://doi.org/10.1001/jama.2020.12603

Caronna, E., Ballvé, A., Llauradó, A., Gallardo, V. J., María Ariton, D., Lallana, S., Maza, S. L., Gadea, M. O., Quibus, L., Restrepo, J. L., Rodrigo-Gisbert, M., Vilaseca, A., Gonzalez, M. H., Gallo, M. M., Alpuente, A., Torres-Ferrus, M., Borrell, R. P., Alvarez-Sabin, J., & Pozo-Rosich, P. (2020). Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. *Cephalalgia*, *40*, 1410–1421. https://doi.org/10.1177/0333102420965157

Carvalho-Schneider, C., Laurent, E., Lemaignen, A., Beaufils, E., Bourbao-Tournois, C., Laribi, S., Flament, T., Ferreira-Maldent, N., Bruyère, F., Stefic, K., Gaudy-Graffin, C., Grammatico-Guillon, L., & Bernard, L. (2020). Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clinical Microbiology and Infection*, *27*, 258–263.

Channappanavar, R., & Perlman, S. (2017). Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. *Seminars in Immunopathology*, *39*, 529–539. https://doi.org/10.1007/s00281-017-0629-x

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet*, *395*, 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Clauw, D. J., Häuser, W., Cohen, S. P., & Fitzcharles, M.-A. (2020). Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain*, *161*, 1694–1697. https://doi.org/10.1097/j.pain.0000000000001950

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the brief pain inventory. *Ann Acad Med Singap*, *23*, 129–138.

Cohen, S. P., Baber, Z. B., Buvanendran, A., McLean, B. C., Chen, Y., Hooten, W. M., Laker, S. R., Wasan, A. D., Kennedy, D. J., Sandbrink, F., King, S. A., Fowler, I. M., Stojanovic, M. P., Hayek, S. M., & Phillips, C. R. (2020). Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. *Pain Med*, *21*, 1331–1346. https://doi.org/10.1093/pm/pnaa127

de Andrade, D., Ferreira, K. A. S. L., Nishimura, C. M., Yeng, L. T., Batista, A. F., de Sá, K., Araujo, J., Stump, P. R. N. A. G., Kaziyama, H. H., Galhardoni, R., Fonoff, E. T., Ballester, G., Zakka, T., Bouhassira, D., & Teixeira M. J. (2011). Psychometric validation of the Portuguese version of the Neuropathic Pain Symptoms Inventory. *Health and Quality of Life Outcomes*, *9*(1), 107. http://dx.doi.org/10.1186/1477-7525-9-107

da Silva, I. R. F., Frontera, J. A., Bispo de Filippis, A. M., & Nascimento, O. J. M. D., RIO-GBS-ZIKV Research Group (2017). Neurologic complications associated with the Zika Virus in Brazilian Adults. *JAMA Neurol*, *74*, 1190–1198. https://doi.org/10.1001/jamaneurol.2017.1703

de Andrade, D. C., Jean, S., Clavelou, P., Dallel, R., & Bouhassira, D. (2010). Chronic pain associated with the Chikungunya fever: Long lasting burden of an acute illness. *BMC Infectious Diseases*, *10*, 31. https://doi.org/10.1186/1471-2334-10-31

de Laval, F., d'Aubigny, H., Mathéus, S., Labrousse, T., Ensargueix, A. L., Lorenzi, E. M., Le Flem, F. X., André, N., Belleoud, D., Leparc-Goffart, I., Rousset, D., Simon, F., & Briolant, S. (2018). Evolution of symptoms and quality of life during Zika virus infection: A 1-year prospective cohort study. *Journal of Clinical Virology*, *109*, 57–62.

Disser, N. P., De Micheli, A. J., Schonk, M. M., Konnaris, M. A., Piacentini, A. N., Edon, D. L., Toresdahl, B. G., Rodeo, S. A., Casey, E. K., & Mendias, C. L. (2020). Musculoskeletal Consequences of COVID-19. *Journal of Bone and Joint Surgery. American Volume*, *102*, 1197–1204. https://doi.org/10.2106/JBJS.20.00847

Eccleston, C., Blyth, F. M., Dear, B. F., Fisher, E. A., Keefe, F. J., Lynch, M. E., Palermo, T. M., Reid, M. C., de Williams, A. C. D. C., (2020). Managing patients with chronic pain during the COVID-19 outbreak: Considerations for the rapid introduction of remotely

supported (eHealth) pain management services. *Pain*, *161*, 889–893. https://doi.org/10.1097/j.pain.0000000000001885

Ellul, M. A., Benjamin, L., Singh, B., Lant, S., Michael, B. D., Easton, A., Kneen, R., Defres, S., Sejvar, J., & Solomon, T. (2020). Neurological associations of COVID-19. *The Lancet Neurology*, *19*, 767–783. https://doi.org/10.1016/S1474-4422(20)30221-0

El-Tallawy, S. N., Nalamasu, R., Pergolizzi, J. V., & Gharibo, C. (2020). Pain management during the COVID-19 pandemic. *Pain Ther*, 1–14. https://doi.org/10.1007/s40122-020-00190-4

Ferreira, K. A., Teixeira, M. J., Mendonza, T. R., & Cleeland, C. S. (2011). Validation of brief pain inventory to Brazilian patients with pain. *Supportive Care in Cancer*, *19*, 505–511. https://doi.org/10.1007/s00520-010-0844-7

Freynhagen, R., Arevalo Parada, H., Calderon-Ospina, C. A., Chen, J., Rakhmawati Emril, D., Villacorta, F. F., Franco, H., Ho, K.-Y., Lara-Solares, A., Li, C.- C.-F., Mimenza Alvarado, A., Nimmaanrat, S., Dolma Santos, M., & Ciampi de Andrade, D.. (2018). Current understanding of the mixed pain concept: a brief narrative review. *Current Medical Research and Opinion*, *35*(6):1011-1018.

Gallizzi, M., Gagnon, C., Harden, R. N., Stanos, S., & Khan, A. (2008). Medication quantification scale version III: Internal validation of detriment weights using a chronic pain population. *Pain Pract*, *8*, 1–4.

Garg, R. K. (2020). Spectrum of neurological manifestations in Covid-19: A review. *Neurol India*, *68*, 560–572.

Garvin, M. R., Alvarez, C., Miller, J. I., Prates, E. T., Walker, A. M., Amos, B. K., Mast, A. E., Justice, A., Aronow, B., & Jacobson, D. (2020). A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. *Elife*, *9*:e59177.

GBD (2016). Disease and injury incidence and prevalence collaborators (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, *390*, 1211–1259.

Headache Classification Committee of the International Headache Society. (2018). Headache classification committee of the INTERNATIONAL Headache Society (IHS) The international classification of headache disorders, 3rd edition. *Cephalalgia*, *38*, 1–211.

Karos, K., McParland, J. L., Bunzli, S., Devan, H., Hirsh, A., Kapos, F. P., Keogh, E., Moore, D., Tracy, L. M., & Ashton-James, C. E. (2020). The social threats of COVID-19 for people with chronic pain. *Pain*, *161*, 2229–2235.

Kemp, H. I., Corner, E., & Colvin, L. A. (2020). Chronic pain after COVID-19: Implications for rehabilitation. *British Journal of Anaesthesia*, *125*, 436–440.

Kemp, H. I., Laycock, H., Costello, A., & Brett, S. J. (2019). Chronic pain in critical care survivors: A narrative review. *British Journal of Anaesthesia*, *123*, e372–e384.

Kosek, E., Cohen, M., Baron, R., Gebhart, G. F., Mico, J.-A., Rice, A. S. C., Rief, W., & Sluka, A. K. (2016). Do we need a third mechanistic descriptor for chronic pain states? *Pain*, *157*, 1382–1386.

Leão Ferreira, K. A. S., Bastos, T. R. P. D., Andrade, D. C. D., Silva, A. M., Appolinario, J. C., Teixeira, M. J., Latorre, M. D. R. D. D. O. (2016). Prevalence of chronic pain in a metropolitan area of a developing country: A population-based study. *Arquivos De Neuro-Psiquiatria*, *74*, 990–998. https://doi.org/10.1590/0004-282x20160156

Li, Y.-C., Bai, W.-Z., & Hashikawa, T. (2020). The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of Medical Virology*, *92*, 552–555. https://doi.org/10.1002/jmv.25728

Majumdar, P., Biswas, A., & Sahu, S. (2020). COVID-19 pandemic and lockdown: Cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. *Chronobiology International*, *37*, 1191–1200. https://doi.org/10.1080/07420528.2020.1786107

Morfopoulou, S., Brown, J. R., Davies, E. G., Anderson, G., Virasami, A., Qasim, W., Chong, W. K., Hubank, M., Plagnol, V., Desforges, M., Jacques, T. S., Talbot, P. J., & Breuer, J. (2016). Human coronavirus OC43 associated with fatal encephalitis. *New England Journal of Medicine*, *375*, 497–498. https://doi.org/10.1056/NEJMc1509458

Murphy, M. T., Latif, U. Pain during COVID-19: A comprehensive review and guide for the interventionalist. *Pain Practice*, *21*(1):132–143.

Mylius, V., Lloret, S. P., Cury, R. G., Teixeira, M. J., Barbosa, V. R., Barbosa, E. R., Moreira, L. I., Listik, C., Fernandes, A. M., de Lacera Veiga, D., Barbour, J., Hollenstein, N., Oechsner, M., Walch, J., Brugger, F., Hägele-Link, S., Beer, S., Rizos, A., Chaudhuri, K. R., & Ciampi de Andrade, D. (2020). The Parkinson's disease pain classification system (PDPCS): results from an international mechanism-based classification approach. *Pain*.

Nabavi, N. (2020). Long covid: How to define it and how to manage it. *BMJ*, *370*, m3489. https://doi.org/10.1136/bmj.m3489

Neville, A., Peleg, R., Singer, Y., Sherf, M., & Shvartzman, P. (2008). Chronic pain: A population-based study. *Isr Med Assoc J*, *10*, 676–680.

Ortiz, F., Santos, M., Landenberger, T., Emmanuelli, B., Agostini, B., & Ardenghi, T. (2016). Comparison of face-to-face interview and telephone methods of administration on the ecohis scores. *Braz Dent J*, *27*, 613–618. https://doi.org/10.1590/0103-6440201601134

Parodi, I. C., Poeta, M. G., Assini, A., Schirinzi, E., & Del Sette, P. (2020). Impact of quarantine due to COVID infection on migraine: A survey in Genova. Italy. *Neurol Sci*, 1–3. https://doi.org/10.1007/s10072-020-04543-x

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., Keefe, F. J., Mogil, J. S., Ringkamp, M., Sluka, K. A., Song, X.-J., Stevens, B., Sullivan, M. D., Tutelman, P. R., Ushida, T., & Vader, K. (2020). The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain*, *161*(9), 1976–1982. https://doi.org/10.1097/j.pain.0000000000001939

Rocha-Filho, P. A. S., & Magalhães, J. E. (2020). Headache associated with COVID-19: Frequency, characteristics and association with anosmia and ageusia. *Cephalalgia*, *40*, 1443–1451. https://doi.org/10.1177/0333102420966770

Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., Zandi, M. S., Lewis, G., & David, A. S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*, *7*, 611–627. https://doi.org/10.1016/S2215-0366(20)30203-0

Sá, K. N., Moreira, L., Baptista, A. F., Yeng, L. T., Teixeira, M. J., Galhardoni, R., & de Andrade, D. C. (2019). Prevalence of chronic pain in developing countries: Systematic review and meta-analysis. *PAIN Reports*, *4*, e779.–https://doi.org/10.1097/PR9.0000000000000779

Santos, J. G., Brito, J. O., de Andrade D. C., Kaziyama, V. M., Ferreira, K. A., Souza, I., Teixeira, M. J., Bouhassira, D., & Baptista, A. F. (2010). Translation to Portuguese and validation of the douleur neuropathique 4 questionnaire. *The Journal of Pain*, *11*(5), 484–490. http://dx.doi.org/10.1016/j.jpain.2009.09.014

Satarker, S., & Nampoothiri, M. (2020). Involvement of the nervous system in COVID-19: The bell should toll in the brain. *Life Sciences*, *262*, 118568. https://doi.org/10.1016/j.lfs.2020.118568

Shanthanna, H., Strand, N. H., Provenzano, D. A., Lobo, C. A., Eldabe, S., Bhatia, A., Wegener, J., Curtis, K., Cohen, S. P., & Narouze, S. (2020). Caring for patients with pain during the COVID-19 pandemic: Consensus recommendations from an international expert panel. *Anaesthesia*, *75*, 935–944.

Su, S., Cui, H., Wang, T., Shen, X., & Ma, C. (2020). Pain: A potential new label of COVID-19. *Brain, Behavior, and Immunity*, *87*, 159–160. https://doi.org/10.1016/j.bbi.2020.05.025

Tenforde, M. W. (2020). Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States. March–June 2020. *MMWR. Morbidity and Mortality Weekly Report*, *69*(30), 993–998.

Tong, J. Y., Wong, A., Zhu, D., Fastenberg, J. H., & Tham, T. (2020). The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: A systematic review and meta-analysis. *Otolaryngology–head and Neck Surgery*, *163*, 3–11. https://doi.org/10.1177/0194599820926473

Toscano, G., Palmerini, F., Ravaglia, S., Ruiz, L., Invernizzi, P., Cuzzoni, M. G., Franciotta, D., Baldanti, F., Daturi, R., Postorino, P., Cavallini, A., & Micieli, G. (2020). Guillain-Barré syndrome associated with SARS-CoV-2. *New England Journal of Medicine*, *382*(26), 2574–2576. https://doi.org/10.1056/NEJMc2009191

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., … Wang, S.-J. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*, 1003–1007. https://doi.org/10.1097/j.pain.0000000000000160

Trigo, J., García-Azorín, D., Planchuelo-Gómez, Á., Martínez-Pías, E., Talavera, B., Hernández-Pérez, I., Valle-Peñacoba, G., Simón-Campo, P., de Lera, M., Chavarría-Miranda, A., López-Sanz, C., Gutiérrez-Sánchez, M., Martínez-Velasco, E., Pedraza, M., Sierra, Á., Gómez-Vicente, B., Arenillas, J. F., & Guerrero, Á. L. (2020). Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: A retrospective cohort study. *J Headache Pain*, *21*, 94. https://doi.org/10.1186/s10194-020-01165-8

Turgay, C., Emine, T., Ozlem, K., Muhammet, S. P., & Haydar, A. T. (2015). A rare cause of acute flaccid paralysis: Human coronaviruses. *J Pediatr Neurosci*, *10*, 280–281. https://doi.org/10.4103/1817-1745.165716

Valent, A., Dudoignon, E., Ressaire, Q., Dépret, F., & Plaud, B. (2020). Three-month quality of life in survivors of ARDS due to COVID-19: A preliminary report from a French academic centre. *Anaesth Crit Care Pain Med*, *39*(6), 740–741. https://doi.org/10.1016/j.accpm.2020.10.001

Vittori, A., Lerman, J., Cascella, M., Gomez-Morad, A. D., Marchetti, G., Marinangeli, F., & Picardo, S. G. (2020). COVID-19 pandemic acute respiratory distress syndrome survivors: Pain after the storm? *Anesthesia and Analgesia*, *131*, 117–119. https://doi.org/10.1213/ANE.0000000000004914

Wang, X., Xu, H., Jiang, H., Wang, L., Lu, C., Wei, X., Liu, J., & Xu, S. (2020). Clinical features and outcomes of discharged coronavirus disease 2019 patients: A prospective cohort study. *QJM: An International Journal of Medicine*, *113*, 657–665. https://doi.org/10.1093/qjmed/hcaa178

World Health Organization. (2020a). *WHO Coronavirus Disease (COVID-19) Dashboard. Vol. 2020*.

World Health Organization. (2020b). Novel Coronavirus (2019-nCoV): situation report, 22.

Wu, Y., Guo, C., Tang, L., Hong, Z., Zhou, J., Dong, X., Yin, H., Xiao, Q., Tang, Y., Qu, X., Kuang, L., Fang, X., Mishra, N., Lu, J., Shan, H., Jiang, G., & Huang, X. (2020). Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol*, *5*, 434–435. https://doi.org/10.1016/S2468-1253(20)30083-2

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*, *87*, 18–22. https://doi.org/10.1016/j.bbi.2020.03.031

Zhou, C., Wu, L., Ni, F., Ji, W., Wu, J., & Zhang, H. (2014). Critical illness polyneuropathy and myopathy: A systematic review. *Neural Regen Res*, *9*, 101–110. https://doi.org/10.4103/1673-5374.125337

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Soares FHC, Kubota GT, Fernandes AM, et al. Prevalence and characteristics of new-onset pain in COVID-19 survivours, a controlled study. *Eur J Pain*. 2021;25:1342–1354. https://doi.org/10.1002/ejp.1755

APPENDIX

Pain in the Pandemic Initiative: Larissa Iulle Moreira[a], Valquiria A. Silva[a], André Bortolon Bissoli[a], Juliete Melo Diniz[a], Lin Tchia Yeng[a,c], Jefferson Rossi Jr[a,c], Teresa Yae Takagaki[d], Gustavo Corrêa de Almeida[d], Jessica Fernandes Ramos[e], Ana Catharina Seixas Santos Nastri[e].

[a]Pain Center, Department of Neurology, University of São Paulo, São Paulo, Brazil; [b]Pain Center, Instituto do Câncer do Estado de São Paulo Octavio Frias de Oliveira, University of São Paulo, São Paulo, Brazil; [c]Pain Center, Institute of Orthopedics, University of São Paulo, São Paulo, Brazil; [d]Pneumology Division of the Heart Institute, Faculty of Medicine of the University of São Paulo, São Paulo, Brazil; [e]Infectious and parasitic diseases division, Faculty of Medicine of the University of São Paulo, São Paulo, Brazil