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ORIGINAL INVESTIGATION

Chronic pain after hospital discharge on patients hospitalized for COVID-19: an observational study

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Abstract
Background: There are few studies related to Coronavirus Disease 2019 (COVID-19) on the prevalence and nature of pain symptoms after hospital discharge, especially in individuals who develop moderate to severe disease forms. Therefore, this study aimed to evaluate the presence of chronic pain in patients discharged after hospitalization for COVID-19, and the relationship between the presence of chronic pain and intensive care stay, demographics, and risk factors for the worst Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outcome.
Methods: A cross-sectional observational study was carried out on patients with COVID-19 who recovered after hospitalization. Patients were recruited at the least 3 months after discharge and their hospital's health files were prospected. The variables evaluated were demographics, the severity of SARS-CoV-2 infection (considering the need for intensive care), and the presence of chronic pain. The results were shown in a descriptive manner, and multivariate analysis expressed as Odds Ratios (ORs) and respective Confidence Intervals (CIs) for the outcomes studied. Statistical significance was set at $p < 0.05$.
Results: Of 242 individuals included, 77 (31.8%) reported chronic pain related to COVID-19, with no correlation with the severity of infection. Female sex and obesity were associated with a higher risk for chronic pain with ORs of 2.69 (Confidence Interval [95% CI 1.4 to 5.0]) and 3.02 (95% CI 1.5 to 5.9). The limbs were the most affected areas of the body.
Conclusion: Chronic pain is common among COVID-19 survivors treated in hospital environments. Female sex and obesity are risk factors for its occurrence.

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Introduction

Coronavirus Disease 2019 (COVID-19), a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was officially declared by the World Health Organization as a pandemic on March 11, 2020.[1] This infection is known to cause acute onset of respiratory symptoms 4−5 days after exposure to the virus, which lasts for 7 −10 days. However, up to 87.5% of hospitalized patients have persistent symptoms that continue for several weeks or even months and include a variety of pain complaints. [2–4] Although initially believed to be a disease that exclusively affects the respiratory system, it is now known that it is a systemic illness that can lead to multiple organ failures during the acute phase, affecting the renal, nervous, circulatory, and hematological systems.[5] For this, many patients demand intensive care treatment and may develop post-intensive therapy syndrome, characterized by physical, cognitive, and psychiatric dysfunctions.[6]

In data collected between February and April 2020 in the United Kingdom, it was observed that the demand for intensive care of patients hospitalized for COVID-19 was approximately 17%, of which 50% required mechanical ventilation. Of these individuals, 27% required continuous care after the infection, to the detriment of only 20% who were discharged without further repercussions.[5] Thus, dysfunctions related to post-intensive care syndrome may be observed, including chronic pain as one of them, and may have a commonality with the so-called post-acute COVID-19 syndrome.

Post-acute COVID-19 syndrome is a multisystem condition that more frequently affects patients with mild to severe COVID-19 and is characterized by fatigue, dyspnea, cough, pain, anosmia, and manifestations related to persistent organ dysfunction.[7,8] The pathophysiology of late sequelae of COVID-19 is not clear and may be related to, but not limited to, direct organ damage, persistent hyperinflammatory state, hypercoagulable state, or poor host immune response.[9]

Chronic pain is defined by the International Association for the Study of Pain as persistent or recurrent pain that persists for more than 3-months or beyond the normal period of tissue recovery.[10,11] However, the effect of chronic pain on patients surviving SARS-CoV-2 infection remains poorly understood.[5] Even though nowadays there is a lower risk of severe COVID-19 infection due to mass vaccination,[12] we still have a large number of survivors living with chronic pain as a consequence of this disease. To date, few studies have characterized how hospitalized patients are affected by chronic pain after recovery from SARS-CoV-2 infection.

We hypothesized that patients with COVID-19 who present with more severe forms of infection (treated with intensive care) might be more susceptible to the presence of chronic pain after recovery. Therefore, this study aimed to evaluate the presence of chronic pain in survivors hospitalized for treatment of SARS-CoV-2 infection. As secondary outcomes, we studied the relationship between the presence of chronic pain and the use of intensive care, demographics, and risk factors for the worst disease outcome.

Methods

Study design

A cross-sectional observational study was carried out on patients with COVID-19 who recovered after hospitalization between 2020 and 2021. The study followed the research guidelines described by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of studies Conducted using Observational Routinely collected health Data statement (RECORD).[13,14]

Setting and variables

The study was performed in a tertiary teaching hospital at Sao Paulo State University's Medical School, Brazil. Data were obtained through telephone interviews with respect to the social distancing imposed during the pandemic. The interviewers read and explained the informed consent term before beginning the survey questionnaire application.

Participants

We invited adult patients of both sexes to participate in the study, with a past diagnosis of COVID-19 disease confirmed by real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) test and who required hospitalization for the treatment of mild to severe SARS-CoV-2 infection. Patients were recruited 3-months after discharge from the hospital in accordance with the list of individuals admitted to a tertiary teaching hospital for COVID-19 treatment from April 2020 to March 2021. The exclusion criteria were as follows: participants with cognitive impairment easily observed during the phone interview by asking patient's name and age, weekday, and the time that interview has been conducted; those who presented significant hearing loss or speech problems; or individuals with chronic pain not related to SARS-CoV-2 infection in accordance with the participant's perception. Participants with incomplete data were excluded.

Interviewers

The interviewers were third- and fifth-year undergraduate medical students who acted voluntarily; therefore, they did not receive any financial compensation. Participants were evenly divided among participating students. The interviews were conducted from January to May 2021.

Variables

A questionnaire formulated by the researchers was hosted on Google Forms to facilitate data collection. The variables evaluated were: demographic data, the severity of SARS-CoV-2 infection based on the need for intensive care, potential risk factors associated with severe illness, and the presence or absence of chronic pain (defined as any pain recurring or persisting after hospital discharge up to the date of the interview, lasting longer than 3 months according to the current International Association for the Study of Pain definition).[10,11] The Brief Pain Inventory (BPI) was used for the evaluation of chronic pain (location, pain intensity

measured by a numeric scale 0 to 10, frequency, treatment in use, and the impact of pain on daily life activities).[15] For the completion of the pain diagram of the BPI, we requested the patients to describe the locations where the pain was present. We also have requested the patient to score their frequency of pain one week before the interview and the pain treatment in use.

If the patient presented with chronic pain, we asked their opinion if it was a consequence of COVID-19 or a result of another context.

Data sources/measurement

The research questionnaire consisted of three parts. The first one included the identification of patients, basic demographics, and information related to hospitalization data that was collected from the patient hospital's health file, including the period of admission and the need for intensive care and mechanical ventilation. Risk factors considered to be most frequently associated with SARS-CoV-2 infection at the time of hospital admission were documented. These risk factors included in the study were hypertension, obesity, and chronic lung and cardiovascular diseases.[16]

The second part was composed of questions related to the presence of chronic pain and its relationship to SARS-CoV-2 infection. The last part of the questionnaire was composed of the BPI.[15] As the interviews were performed through phone calls, the body diagram on the BPI was replaced by oral questions on pain sites.[17] The interviews were pre-scheduled to include participants on the best day and time of their preference. The interviews did not last for more than 15 minutes.

Ethical considerations

This study was approved by the Institutional Research Ethics Committee (CAAE 39112720.0.0000.5411, opinion number 4.340.406) prior to its execution. All participants were informed that their participation would only consist of answering questionnaires about sociodemographic aspects, health status, and pain. The requirement for informed consent on paper was waived by the Institutional Research Ethics Committee, as it was only necessary to read it aloud with the verbal acceptance of the invited individual.

Statistical analysis

Sample size was determined as convenience. Qualitative variables were presented as absolute and relative frequencies, and quantitative variables as medians and quartiles, as they did not present a normal distribution in the histogram analysis and the Shapiro-Wilk test. The Chi-Square and Fisher's exact tests were used to compare qualitative variables with the final outcome (occurrence of chronic pain related to COVID-19), and the Mann-Whitney test was used for qualitative variables.

The variables that presented p-values up to 0.20 in the associations with the main outcome of pain related to COVID-19 (female sex, number of risk factors for worst outcome of COVID-19, obesity, and diabetes) were analyzed in a binary logistic regression model to assess the independence of association. In univariate analyses, a cut-off points of 0.20 was chosen to maintain the model's parsimony and to reduce the risk of type 2 error. The Hosmer-Lemeshow test was used to assess the degree of agreement between the model and the results of the analysis. Multivariate data were expressed as Odds Ratios (ORs) and respective Confidence Intervals (CIs) for the outcome studied. Statistical significance was set at $p < 0.05$.

Results

A total of 341 patients were discharged from the hospital after admission for COVID-19 treatment from April 2020 to March 2021. However, we did not include 91 patients due to misinformation in the telephone numbers (79 individuals), refusal to participate (8 individuals), or death after hospital discharge (4 individuals). In addition, four participants were excluded due to hearing impairment, three due to speech disorders, and one with missing hospitalization data (Fig. 1).

Of those 242 patients analyzed, 77 (31.8%) presented chronic pain considered by the participant as caused by COVID-19. More than 75% of the patients were hospitalized for less than 15 days. Hospitalization occurred exclusively in the ward in 71.4% and 72.2% of those with or without chronic pain, respectively. There was no difference in the incidence of chronic pain after COVID-19 according to the place of hospitalization (ward or Intensive Care Unit [ICU]) or the presence of mechanical ventilation; however, female patients and those with obesity showed higher occurrences of chronic pain in the univariate analysis (Table 1). The odds for the occurrence of COVID-19-related chronic pain remained higher among female patients (p = 0.002; OR = 2.69; 95% CI 1.43–5.05) and those with obesity (p = 0.001; OR = 3.02; 95% CI 1.53–5.94) after multivariate analysis (Table 2).

When present, the pain was scored by the participants as a median of 6 and the limbs were the most frequent site of its occurrence. In the week prior to the interview, 75.3% of the participants described their pain as often or uninterrupted. Non-opioid analgesics, such as acetaminophen and metamizole, and opioids were used by 44.2% and 6.5% of patients with pain, respectively, while 24.6% did not use any kind of analgesics (Table 3).

Pain represents variable impacts on different daily life activities. General activities, walking, and enjoyment of life were the most impacted (median scores 7, 6, and 6, respectively), while personal relations were the least impacted activity (median score 2) (Table 4).

Discussion

This observational study evaluated the occurrence of chronic pain after hospitalization for the treatment of moderate-to-severe forms of COVID-19. Our study was unable to establish a correlation between the severity of COVID-19 (considering the site of hospitalization) and the presence of chronic pain. However, COVID-19-related chronic pain after hospitalization was detected in a considerable number of participants, representing 31.8% of the analyzed sample.

A review of the literature points to the incidence of chronic pain ranging from 36.5% to 62.5% of those infected.[18] One study that included a smaller number of

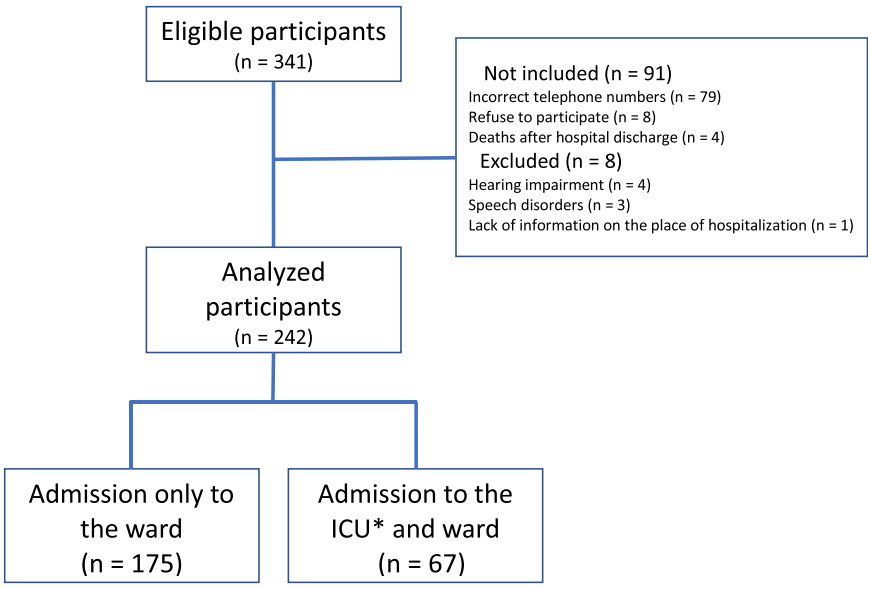

Figure 1 Participants flowchart. *ICU, Intensive Care Unit.

patients after discharge for COVID-19 treatment found an incidence of chronic pain of 19.6%, while other research found *de novo* pain in 33.7% of COVID-19 survivors.[19,20] Although fatigue and dyspnea are the most frequently reported symptoms by patients who have recovered from the disease, pain, more specifically joint and chest pain, is reported by 15% to 20% of individuals.[21] In patients mildly affected by COVID-19, the most painful sites were the head/face, chest, lower extremities, and migratory locations. Generalized pain was self-reported by 75% of participants, and a diagnosis of fibromyalgia, according to the 2016 criteria, was suspected in 40% of participants.[22] In our study, the most affected areas were the limbs and torso; likewise, in the study of Fernández-de-las-Peñas et al., 2022, where torso was the most affected area, followed by generalized body pain.[20]

A similar study through telephone interviews with hospitalized patients, without defining whether there was a need for intensive care, was conducted in Turkey. The estimated post-COVID-19 pain among patients was 7.9%. Also in this study, the highest occurrence of pain was observed in patients aged > 50 years (16.1%). These authors did not observe significant associations between sex, body mass index, presence of chronic diseases, and the occurrence of post-COVID-19 pain.[23] In our study, only obesity and female sex were risk factors for the presence of chronic pain.

The number of individuals with COVID-19 who require intensive care has already been alarming. It is known that

Table 1 Demographics and Coronavirus Disease 2019 (COVID-19) risk factors for hospitalization and disease severity data of patients admitted to the hospital for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection treatment.

	COVID-19 related chronic pain		*p*
	Yes (n = 77)	No (n = 165)	
Female[a]	47 (61%)	61 (37.2%)	**0.001**
Age (years)[b]	56 (45.0 / 62.5)	57 (44.0 / 67.0)	0.616
Presence of risk factors for COVID-19 worse outcome[a]	67 (87%)	142 (86.1%)	0.841
Number of COVID-19 risk factors for worse outcome	2 (1 / 4)	2 (1 / 3)	0.151
Obesity	34 (44.2%)	39 (23.6%)	**0.001**
Older than 60 years	26 (33.8%)	62 (37.6%)	0.566
Diabetes	30 (46.9%)	54 (35.3%)	0.110
Length of hospitalization[b]	10 (7.0 / 15.0)	10 (7.0 / 15.0)	0.485
Hospitalization place[a]			0.798
Ward	55 (71.4%)	120 (72.7%)	
ICU[c]	22 (28.6%)	45 (27.3%)	
Mechanical ventilation[a]	9 (11.7%)	16 (9.7%)	0.646

Chi-Square and Fisher's tests: qualitative variables with the final outcome (occurrence of pain after COVID-19); Mann-Whitney test: for other qualitative variables.

[a] Data are expressed in absolute and relative frequencies.

[b] Data are expressed as medians and quartiles.

[c] ICU, Intensive Care Unit.

Table 2 Multivariate analyses for binary logistic regression for chronic pain after COVID-19 hospitalization (n = 77).

Variable	Chronic pain related to COVID-19		
	Odds Ratio	Confidence Interval 95%	*p*-value
Female sex	2.69	1.43–5.05	**0.002**
Number of COVID-19 risk factors for worse outcome	0.98	0.78–1.23	0.871
Obesity	3.02	1.53–5.94	**0.001**
Diabetes	1.54	0.75–3.17	0.234

Hosmer Lemeshow: 0.126.

many of these patients survive after hospitalization, but not without multiple consequences for their health. Thus, there is an urgent need to prepare ourselves to continue treating these individuals, which implies adequate treatment of pain.[24] In COVID-19 patients, pain may be the sixth most prevalent symptom 48 days after hospital discharge. Thirty percent of patients admitted to the ICU reported pain during this period compared to 15% of those treated in the ward.[25] In our study, individuals undergoing mechanical ventilation or who were subjected to intensive care treatment, which are associated with more severe infections, presented similar rates of post-COVID-19 chronic pain than those who were affected in a milder way.

However, an interesting study that evaluated the occurrence of a post-COVID-19 syndrome, without specific emphasis on pain but including pain as a symptom related to it, observed that the risk of its incidence was higher among hospitalized individuals. Similar to our results, the authors did not observe an increased risk of its occurrence among those who received intensive care compared to that of ward care.[26] Usually patients who received mechanical ventilation were usually treated in a prone position during moderate to severe acute respiratory distress syndrome due to SARS-CoV-2. In patients treated in prone position, complications such as peripheral nerve injury have been reported, which may lead to chronic neuropathic pain.[27] In our study no nerve injuries were reported by patients.

Central pain and headache are another potential manifestation of post-COVID-19. Generalized inflammation, cell storming, vascular damage, and damage to macrophages may explain the developmental mechanism of pain. Still more research is needed to detect the exact mechanisms that lead to the development of COVID-19 pain.[28] Our study did not specifically assess the presence of chronic pain with neuropathic features.

It is known that up to 25% of patients admitted to the ICU for COVID-19 still have persistent inflammation after 3 months of discharge.[29] We believe that future evaluation for persistent changes in certain serum biomarkers, such as bradykinin and interleukin-6 for general pain, and perhaps Calcitonin Gene-Related Peptide (CGRP) for headache, among patients with COVID-19 may provide insight into pain mechanisms.[19] Theories hypothesize that SARS-CoV-2 cytokines and interleukin-induced storms may lead to sensitization of pain pathways in nociplastic pain as a result of the imbalance between neuromodulation systems of nociception. Anxiety levels and the intensity of pain symptoms in COVID-19 survivors are independently associated with central pain sensitization, suggesting a significant overlap with the psychological construct of the presence of pain in these patients.[20] Patients with obesity may be at higher risk for chronic pain after COVID-19 as these individuals present a low-grade chronic inflammation.[30]

In addition to pain, neuropathy and myopathy are very common in critically ill patients due to coronavirus

Table 3 Characteristics of pain after COVID-19 and actual use of analgesics in accordance with the brief pain inventory (n = 77).

Pain characteristics	n (%)
Pain site	
Limbs	30 (39%)
Torso	18 (23.4%)
Other	52 (62.4%)
Pain score – verbal numeric scale (0–10)[a]	6 (5.0 / 8.0)
Pain frequency at the last week	
Rarely	4 (5.2%)
Eventually	3 (3.9%)
Often	24 (31.2%)
Uninterrupted	34 (44.1%)
Missing info	12 (15.6%)
Pain treatment[b]	
None	15 (19.5%)
Non-opioids analgesics	31 (40.3%)
Opioids	5 (6.5%)
Physical therapy	5 (6.5%)
Others	7 (9.1%)
Cannot remember	3 (3.9%)
Missing info	12 (15.6%)

Data are expressed as absolute and relative frequencies.
[a] Data are expressed as medians and quartiles.
[b] More than one treatment could be in use at the same time.

Table 4 Impact of pain after COVID-19 on daily life activities in accordance with the brief pain inventory (n = 77).

Daily life activities[a]	Scores (0–10)
General activities	7 (4.0 / 9.5)
Mood	4 (0.0 / 9.0)
Walking	6 (2.5 / 8.5)
Working	6 (4.0 / 9.0)
Personal relations	2 (0.0 / 6.0)
Sleep	5 (0.0 / 8.0)
Enjoyment of Life	6 (2.0 / 8.5)

[a] Impairment in daily life is measured on a scale from 0 to 10, where 0 represents “no impact” and 10 represents “completely impacted”. Data are expressed as medians and quartiles.

infection. According to current clinical experience, patients receiving ICU treatment for COVID-19 often develop early-stage motor deficits, which may be due to neuropathy superimposed on myopathy.[31] The neuropathy and myopathy may explain the high score for general activity and walking pain interferences observed among the included participants in our study.

The pandemic imposed a restructuring on health systems worldwide, and in this context, most chronic pain services were considered non-essential at peak times of the occurrence of cases. Thus, as in most specialties, outpatient visits were reduced or interrupted to reduce the risk of viral spread. Due to the interruption of services, the treatment of chronic pain has been significantly impacted on a global scale. This circumstance may have complicated the comprehension of the correlation between symptoms and the extent of cases in patients who have recovered.[32] Curiously, patients with chronic pain prior to infection presented a higher risk of hospitalization for COVID-19.[33]

Our study has several limitations. Most importantly, we conducted interviews via telephone owing to sanitary restrictions and did not use a standardized tool to evaluate cognitive impairment of participants. This imposed important restrictions such as the use of a physical exam. In addition, as this was a single-center study carried out with patients treated at a tertiary teaching hospital, the results may not reflect the reality of patients admitted to other less complex health institutions. We must also consider that data on the presence of previous chronic pain may have been liable to recall bias, which is why we may have included participants with pre-existing chronic pain. Data prospect in health files also can be incomplete. In addition, we did not assess the participants' quality of life, although pain interference in daily activities was evaluated. We did not study the presence of neuropathic pain, mood, or catastrophism among the included participants. These results must be interpretated taking in consideration all informed bias.

Conclusion

Thus, we concluded that chronic pain is frequent among patients with COVID-19 after hospital discharge, but the severity of the infection cannot be associated with a higher prevalence of chronic pain. Furthermore, female patients and those with obesity had higher odds of chronic pain after hospital discharge. Future studies may reveal better characteristics of COVID-19-related pain and, hopefully, provide insights into its physiopathology, prevention, and treatment.

Data availability statement

The authors state that the data can be made available upon request.

Ethics approval statement

The study was approved by the Institutional Research Ethics Committee (CAAE 39112720.0.0000.5411, opinion number 4.340.406) before its execution.

Patient consent statement

Patient consent was verbally obtained from all the participants.

Clinical trial registration

As this was not a clinical trial, but an observational study no registration was performed.

Conflicts of interest

The authors declare no conflicts of interest.

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