Clinical profile of pain in post-COVID-19 patients: systematic review

Perfil clínico da dor em pacientes no pós-COVID-19: revisão sistemática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Although research shows that pain is more frequent during COVID-19 infection, little is known about the characterization of pain and factors that influence its permanence after infection. Therefore, the objective of this study was to describe the clinical profile of pain in post-COVID-19 patients.

CONTENTS: This is a systematic review conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations. Articles were searched from November 2021 to November 2022 in the Pubmed, Embase, Web of Science, Scopus, Cochrane and PsycINFO databases. Five observational studies were included for qualitative synthesis. There was an increase in the intensity of pain in all regions of the body during the infection when compared to the pre-infection state, remaining after the infection. The most reported post-COVID-19 pains are: neuropathic pain, generalized pain and pain in the cervical region. The average duration of post-COVID-19 pain was six months.

CONCLUSION: There is persistence of pain after infection with the new coronavirus, with the presence of "new pain" and "new chronic pain", and the worsening of pain in specific groups that had COVID-19.

Keywords: COVID-19, Pain, Pain measurement.

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HIGHLIGHTS

- This study reinforces the importance of knowing the clinical profile of pain after COVID-19 infection, as it will guide strategies for prevention and rehabilitation of pain complaints.
- There is an increase in pain severity in all body regions during COVID-19 infection, when compared to the pre-infection state, and it is maintained after infection.
- Biological, psychological, and social factors influence the intensity of pain.

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RESUMO

JUSTIFICATIVA E OBJETIVOS: Embora as pesquisas evidenciem o quadro álgico mais frequente durante a infecção da COVID-19, pouco se sabe sobre a caracterização da dor e fatores que influenciam sua permanência após a infecção. Portanto, o objetivo deste estudo foi descrever o perfil clínico de dor em pacientes pós-COVID-19.

CONTEÚDO: Trata-se de uma revisão sistemática conduzida conforme as recomendações *Preferred Reporting Items for Sistematic reviews and Meta-Analyses (PRISMA*)**.** Os artigos foram pesquisados no período de novembro de 2021 a novembro de 2022, no banco de dados Pubmed, Embase, *Web of Science*, Scopus, Cochrane e PsycINFO. Foram incluídos cinco estudos observacionais para síntese qualitativa. Evidenciou-se um aumento da intensidade da dor em todas as regiões do corpo durante a infecção quando comparado com o estado pré-infecção, mantendo-se após a infecção. As dores mais relatadas pós-COVID-19 foram dor neuropática, dor generalizada e dor na região cervical. A média de tempo da dor no pós-COVID-19 foi de seis meses.

CONCLUSÃO: Há persistência da dor após infecção pelo novo coronavírus, com a presença de "dor nova" e "dor crônica nova", e a piora da dor em grupos específicos que tiveram COVID-19.

Descritores: COVID-19, Dor, Medição da dor.

INTRODUCTION

COVID-19 virus has caused more than 4.6 million deaths and has spread through more than 200 countries, becoming a public health issue due to its easy transmissibility and high lethality. In view of this, the World Health Organization (WHO) declared the infection by the new coronavirus as a pandemic. In this sense, it has become a health crisis that has been challenging health systems, and it still has a clinical management with many gaps[1-3]. Infected with SARS-CoV-2 may be asymptomatic or develop some symptoms that include dry cough, dyspnea, sore throat, taste and smell disturbance, fever, headache, weakness, and myalgia. However, before the onset of respiratory symptoms, many patients present with anorexia, abdominal pain, nausea, vomiting, and diarrhea. According to the severity of the infection, respiratory complications such as pneumonia, acute respiratory failure, acute respiratory distress syndrome, and other systemic involvement may develop. In this sense, pain is part of the broad spectrum of symptoms and sequelae of SARS-CoV-2[4-6] infection. Pain, according to the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or

potential tissue damage". Recent studies[6,7] have shown the prevalence and persistence of pain in patients during COVID-19 infection, with symptoms including headache, myalgia, arthralgia, abdominal pain, and chest pain[6,7].

In this context, after contamination, the mechanism of action of the disease acts when SARS-CoV-2 virus binds to ACE2 (angiotensin-converting enzyme 2) protein receptor and activates transmembrane serine protease 2 (TMPRSS2) to help the cell invasion process. Although the pathogenesis of pain in COVID-19 is still under investigation, it is known that the damage caused to organs, tissues, and joints, in addition to the cytokine storm, may account for the onset of this symptom. In this sense, pain complaint is part of the broad spectrum of symptoms and sequelae of SARS-CoV-2 infection, considered a diffuse and multisystemic inflammatory condition[8-10].

Although research shows the most frequent pain during infection, little is known about the characterization of pain and factors that influence its permanence after infection. In this context, knowing the clinical profile of pain in post-COVID-19 patients, as well as understanding the persistence of pain, will provide scientific subsidies to guide the management and treatment of pain in these patients. Based on this, the present study aimed to describe the clinical pain profile of patients in post-COVID-19 period.

CONTENTS

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] and is registered in the International prospective register of systematic reviews (PROSPERO) database under the number CRD42021290734. Articles were searched from November 2021 to November 2022 in Pubmed, Embase, Web of Science, Scopus, Cochrane, and PsycINFO databases. The keywords used were: COVID-19; Pain; Pain measurement.

In order to develop a high-sensitivity search strategy, the following search string was used: "COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] AND "pain"[MeSH Terms] OR Pain[Text Word] OR "Pain, Burning" OR "Burning Pain" AND "pain measurement"[MeSH Terms] OR pain measurement [Text Word] OR "Measurement, Pain" OR "Measurements, Pain" OR "Pain Measurements" OR "Assessment, Pain".

The research question was guided by the PICO strategy, being P: patients in the post-COVID-19; I: Not applicable; C: Not applicable; O: pain intensity: "What is the clinical pain profile of patients in post-COVID-19?".

Study selection

The selection criteria consisted of randomized clinical trials and observational studies that reported on the clinical characteristics of pain, e.g. type, location, intensity, affective and emotional aspects, pain catastrophizing, kinesiophobia, assessment methods, relief factors, and aggravating factors in post-COVID-19 patients.

Only human studies with pain assessment and associated characteristics of post-COVID-19 patients, studies with patients who started reporting pain after COVID-19 infection, and studies with patients who reported pain intensification after COVID-19 infection were included. On the other hand, exclusion criteria consisted of studies that did not report pain manifestations from patients in post-COVID-19 period.

Data analysis and extraction

The articles were systematically selected for inclusion or exclusion of studies based on title and abstract, according to the eligibility criteria. Of the studies that met the inclusion criteria, the following data were analyzed and extracted: authors, year of publication, experimental design, characteristics of the subjects, methodological instruments, clinical characterization of pain, and results.

Evaluation of study quality

After the search with keywords in databases, the titles and abstracts of the studies were read and then selected according to the inclusion and exclusion criteria. The included studies were read in their entirety, and a methodological evaluation was performed with the tool developed by the Joanna Briggs Institute (JBI) study group for observational studies[12] and, for intervention studies, the Physiotherapy Evidence Database (PEDro)[13]. The methodological quality of the included studies was evaluated by two reviewers, but a third reviewer would be consulted in case of any divergence.

After searching the databases, 1398 studies were identified, of which 340 articles were excluded for duplicity. Subsequently, the titles and abstracts were evaluated and 1058 records that did not meet the research objectives were excluded. After careful reading of the 11 selected articles, 5 studies[14-18] were included for qualitative synthesis, as shown in figure 1. The excluded studies evaluated a specific pain, but included patients in the inflammatory phase of COVID-19; therefore, they did not answer the review question, since they did not address patients in the post-COVID-19 phase.

All articles included for qualitative synthesis were observational studies (Table 1)[14-18]. These studies showed persistence of pain af-

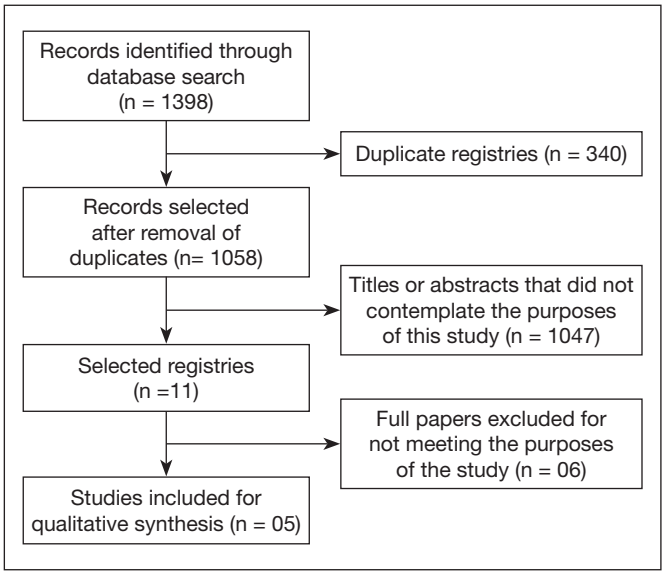

Figure 1. Flowchart for obtaining relevant studies to review

ter infection by SARS-CoV-2 with moderate to severe intensity. As for the number of publications on the subject, was observed a growth over the years, with a predominance of the publication of studies in the years 2021 (40%) and 2022 (60%). No publications were identified in the year 2020.

The quality analysis of the included articles was performed using the critical appraisal tool developed by the Joanna Briggs Institute (JBI), since the included studies were observational research. The tool is composed of 11 questions, called items, which aim to assess the methodological quality of observational studies and determine to what extent a study has addressed the possibility of bias in its design, conduct, and analysis (Table 2)[12].

The synthesis of the included studies methodological quality is described in Table 3[14-18]. The five studies are relevant to the review in question, since they are able to establish satisfactory correlations, "yes" being the answer, in the great majority of the already described tool topics[14-18].

Table 1. Data extraction from elected articles

Sahin et al.[14]	Observational study	Investigating the painful body regions and their severity before, during and post-COVID-19, as well as revealing the relationship between pain intensity and disease characteristics	206 patients, mean age 56.24±16.99 years, 51% female.	Location; intensity; correlations with anxiety, depression and and quality of life
Soares et al.[15]	Cross-sectional observational study	Investigating the presence of new pain symptoms in post-COVID-19 patients	46 patients, mean age 56.30±15.00 years, 45.7% male	Location; intensity; correlations with activities of daily living, presence of fatigue, headache and chronic pain
Bilgin, Kesik and Özdemir[16]	Retrospective observational study	To evaluate pain intensity in patients diagnosed with COVID-19 and correlate with biological, psychological and social factors	149 patients, mean age 32.87±11.32 years, 75.2% were female.	Pain intensity; correlations with biological, social and psychological factors (anxiety); presence of fatigue; level of activity
Büyükşireci et al.[17]	Cross-sectional observational study	To assess pain intensity, anxiety, depression, disease activity, and post-COVID-19 neuropathic pain in patients with fibromyalgia (FM)	77 patients, mean age 46.92 ± 8.72, female only.	Pain intensity and location; symptom severity; disease activity (FM); anxiety and depression; neuropathic signs and symptoms
Herrero--Montes et al.[18]	Cross-sectional observational study	To investigate the prevalence of neuropathic pain symptoms and to analyze the correlation with pain-related, cognitive and psychological variables in patients with post-COVID-19 pain complaint	77 patients, mean age 60 ± 11.5 years, 37.6% were female.	Pain intensity and location neuropathic pain symptoms anxiety and depression, pain catastrophizing, kinesiophobia

Table 2. Analyzed variables and the instruments used

Authors	Variables	Instruments
Sahin et al.[14]	Socio-demographic and clinical data Location of pain Pain intensity Anxiety and depression Quality of life	Records and Interview (via telephone) Numeric Rating Scale (NRS) Hospital Anxiety and Depression Scale (HADS), (Turkish version). Short from Survey (SF-12) (Turkish version)
Soares et al.[15]	Sociodemographic and clinical data Interferences in activities of daily living Presence of fatigue, headache and chronic pain Pain intensity and location	Interview (via telephone and/or video call), REDCap software platform Brief Pain Inventory (BPI) adapted to Portuguese Use of a mannequin
Bilgin, Kesik and Özdemir[16]	Pain intensity Biological factors Social factors Presence of fatigue Psychological factors (anxiety) Activity level	Visual Analog Scale (VAS) Online survey (on Google Forms) Chalder Fatigue Scale (CFS) Anxiety Scale (CAS) Pain-Activity Standards Measurement Scale (POAM-P) (Turkish version)
Büyükşireci et al.[17]	Pain intensity and location Severity of symptoms Disease activity (FM) Anxiety and depression Neuropathic signs and symptoms	Numerical Rating Scale (NRS) Widespread Pain Index (WPI) Symptom Severity Scale (SSS) Fibromyalgia Impact Questionnaire (FIQ) Hospital Anxiety and Depression Scale (HADS) Leeds Neuropathic Signs and Symptoms Assessment Scale (LANSS) (Turkish version)
Herrero--Montes et al.[18]	Pain intensity and location Neuropathic pain symptoms Anxiety and depression Pain catastrophizing and kinesiophobia	Numerical Rating Scale (NRS) Self-Report Leeds Assessment of Neuropathic symptoms (S-LANSS) Hospital Anxiety and Depression Scale (HADS) Pain Catastrophizing Scale (PCS) Tampa Scale for Kinesiophobia (TSK -11) (Spanish version)

Table 3. Joanna Briggs Institute critical assessment tool

	Yes	No	Confusing	Not applicable
1- Is there congruence between the stated philosophical perspective and the research methodology?				
2- Is there congruence between the research methodology and the research question or objectives?				
3- Is there congruence between the research methodology and the methods used to collect the data?				
4- Is there congruence between the research methodology and the data representation and analysis?				
5- Is there congruence between the research methodology and the interpretation of the results?				
6-Is there a statement locating the researcher culturally or theoretically?				
7- Is the influence of the researcher on the research and vice-versa addressed?				
8- Are the participants and their voices adequately represented?				
9- Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by a competent body?				
10- Do the conclusions drawn in the research report flow from the analysis or interpretation of the data?				
11- Were the specific guidelines used by the research appropriate?	Include	Exclude	Search for more information	
General Evaluation				
Comments (including reason for exclusion)				

Table 4. Quality evaluation of articles according to Joanna Briggs Institute critical assessment tool

General evaluation	Include	Exclude	Search for more information
Sahin et al.[14]	X		
Soares et al.[15]	X		
Bilgin, Kesik and Özdemir[16]	X		
Büyükşireci et al.[17]	X		
Herrero-Montes et al.[18]	X		

As for the number of participants, according to Table 4, the five articles included involved 555 participants, with a predominance of females, age ranging from 32.8 to 60 years. All participants were in the post-COVID-19 period, in a time interval of three months or more, with a predominance of patients with a history of hospitalization by COVID-19[14-18].

Also, according to table 4, the clinical variables most evaluated in the studies were: sociodemographic characteristics, pain intensity and location, symptom severity, level of physical activity, presence of anxiety, depression, kinesiophobia, pain catastrophizing, fatigue, headache, chronic pain, interference in quality of life and daily life activities. The instruments used for such records ranged from the analysis of medical records, interviews with the use of scales, to the use of platforms and software with worldwide access[14-18].

A research[14] evidenced that pain is more prevalent during COVID-19 when compared to pre- and post-infectious states. The study in question found that 40.7% of patients experience chronic pain before COVID-19 and this percentage increased to 82.5% during infection, and to 55.1% after COVID-19. Patients with persistent pain after COVID-19 have a significantly lower physical component score and poorer quality of life. There was also an increase in pain intensity in all body regions during infection when compared to the pre-infection state, and it was maintained after infection, except in cervical spine. The study did not reveal a clear relationship between the severity of the patient's pain during the disease, nor with the severity of the disease, with educational levels, comorbidities, drugs used during the disease, length of stay and duration of mechanical ventilation[14].

A cross-sectional prospective controlled study[15] aimed to investigate the presence of "pain again", i.e. any new pain that appeared after discharge, or even a new feature of a preexisting pain, and "chronic pain again" (any recurrent or persistent "pain again" lasting more than three months) in patients who are post-COVID-19. For this, the participants were divided into two groups, one of survivors of SARS-COV-2 infection (46 patients), and another group being the control, composed of patients hospitalized during the same period, but unrelated to COVID-19 (73 patients)[15]. It was evidenced that the prevalence of previous chronic pain was lower in COVID-19 individuals when compared to group 2. However, COVID-19 patients developed more recent onset pain after hospitalization than the control group. Added to this, COVID-19 group had a higher percentage of "headache again" when compared to control group. When analyzing the presence of "pain again" and "chronic pain again" in patients without previous chronic pain, it was observed that COVID-19 group had higher prevalences. The results of this study showed that the "pain again" by COVID-19 has moderate intensity, similar to control group, and more frequent in the head and neck regions. Also, higher pain intensity scores were associated with greater interference with activities of daily living. Recent onset fatigue was more common in COVID-19 survivors who required hospital admission (66.8%), compared with control group. SARS-CoV-2 infected patients who reported anosmia had more recent onset pain (83.3%) compared with those who did not report it[15].

A study conducted in February and March 2021 in Turkey assessed pain intensity in patients diagnosed with COVID-19 and correlated it with biological, psychological (anxiety), and social

factors[16]. The biological factors investigated were post-COVID-19 time, hospitalization status, and need for respiratory support. Among the participants, 49.7% had post-COVID-19 time ranging from 3 to 5 months and 9.4% required hospitalization. The assessment of fatigue perception showed high severity and a direct and positive association with pain intensity. The same was found when pain intensity was correlated with the presence of anxiety. In addition to that, the participants had low levels of physical activity, which directly affected pain intensity[16]. The findings of this research showed that biological, psychological and social factors directly influence pain intensity. Among the limitations of the study, it is noteworthy that the sample was composed of a young population, which restricted the generalizability of these results to older populations. The study also reports the possibility of memory bias, given its methodological characteristics.

A cross-sectional observational study aiming to assess the impact of COVID-19 on fibromyalgia patients showed in its results higher levels of anxiety and generalized pain index in FM patients infected with SARS-CoV-2. There were no differences between the fibromyalgia groups without COVID-19 and post-COVID-19 regarding the variables physical functionality, well-being, absenteeism and presenteeism, pain intensity, fatigue, neuropathic pain symptoms, morning tiredness, stiffness and depression. Regarding the fibromyalgia and post-COVID-19 group, the authors also found no differences in the clinical presentation of COVID-19 between patients who were using drugs such as pregabalin and duloxetine and patients without this pharmacological treatment[17].

A cross-sectional observational research aimed to investigate the prevalence of neuropathic pain symptoms and their correlation with demographic variables and clinical profile given by pain intensity and catastrophizing, kinesiophobia, anxiety and depression. The authors also divided the participants into two groups according to the severity of neuropathic pain symptom. The results showed a higher prevalence of pain in cervical region (14.3%) and the presence of generalized pain in 20.8% of the participants. The analysis of the groups showed that patients with pain characteristic of neuropathic component had higher levels of pain catastrophizing and kinesiophobia. In addition, neuropathic pain symptoms showed a positive association with anxiety and kinesiophobia symptoms. Finally, further regression analyses revealed that kinesiophobia was a significant predictor of neuropathic pain symptom, explaining 12.8% of its variance[18].

DISCUSSION

The main results of this study indicated that post-COVID-19 pain was predominant in female subjects with a mean age between 32.8 and 60 years[14-18]. Pain persisted, on average, six months after infection, especially in people with a history of hospitalization for COVID-19. Pain intensity increased in all body regions, characterized by pain in the cervical region, pain with neuropathic component and generalized pain.

It was also observed that all articles included for qualitative synthesis were observational studies[14-18]. In observational studies, the researcher studies, observes, and records the disease and its attributes and how they relate to other conditions/attributes (exposure), but does not intervene in the research. These studies are useful in describing trends in health indicators, generate hypotheses, and allow the monitoring of health policies[19]. In this sense, these studies[14-18] will serve as a basis for future clinical trials[20].

A relatively tiny amount of subjects were also noted in the studies[14-18], when compared to the gigantic number of those infected with SARS-CoV-2 virus. This may be justified because it is a new clinical condition, which emerged at the end of 2019, and the social restrictions caused by the pandemic, although there is the same proportion of infected subjects by gender[9]. Men are more susceptible to severe COVID-19 with a higher risk of death than women[9], and this difference is justified by biological factors.

The studies have also shown the persistence of pain post-SARS-CoV-2 infection even after a mean period of six months[14-18]. It has been found that the percentage of chronic pain increases during the inflammatory phase of COVID-19 and may persist in a portion of the population in the post-COVID-19 or "long COVID" condition[14]. Since chronic pain is considered a public health problem worldwide, affecting between 20% and 35% of the population[19], the results of this study indicate the need for prevention programs, pain treatment and post-COVID-19 rehabilitation in this population.

An increase in pain intensity was found in all body regions during infection, when compared to the pre-infection state, and this was maintained after infection. The body region and the most reported pain characteristics were cervical region, pain with neuropathic component, and generalized pain[14-18]. This corroborates the results found in a longitudinal study that evaluated the disease effects over time, finding that more than half of the patients after COVID-19 remained with post-infection symptoms. Among the most frequent sequelae were fatigue and headaches[9].

There is a predominance of patients with a history of hospitalization for COVID-19[14-18]. Patients hospitalized due to COVID-19 develop more pain after hospitalization when compared to patients hospitalized unrelated to COVID-19[15]. Even hospitalized patients whose condition was not considered severe suffer long-term physical consequences, and post-hospitalization care is necessary and essential in cases of SARS-CoV-2. A minority of the population reported spontaneous pain before the diagnosis was confirmed, but after the diagnosis of COVID-19 and hospital discharge, this rate increases. In this context, besides the pathophysiological factors, hospitalization often generates immobility with consequent musculoskeletal dysfunctions and greater chances of worsening in pain levels[21].

The main limitation of this research lies in the few studies elected[14-18] and their methodological characteristics that limit the establishment of a causal relationship for post-COVID-19 pain symptoms. In this sense, more studies are needed for better characterization of the post-COVID-19 pain profile, using more representative samples and different sociodemographic and health condition population profiles.

CONCLUSION

This research observed an increase in pain intensity in all body regions during infection, when compared to the pre-infection state, and this was maintained after infection. Biological, psychological and social factors influenced the intensity of pain. The most commonly reported pains were neuropathic pain, generalized pain, and pain in cervical region. The average time of post-COVID-19 pain was six months.

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Data Collection, Methodology, Writing - Preparation of the Original, Writing - Review and Editing
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Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Supervision, Validation

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