Review Article

COVID-19 and pain: any relation?

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Abstract: A year on since the beginning of the pandemic, we can start to sum up the data on the clinical damage the virus has caused to date. Patients with COVID-19 present various painful symptoms, such as sore throat, headache, arthralgia/myalgia, chest and abdominal pain. The incidence rate is 0.7–47.1% for sore throat, 1.5–61.0% for myalgia/arthralgia, 1.7–33.9% for headache, 1.6–17.7% for chest pain, and 1.9–14.5% for abdominal pain. This review summarizes the current data on reported painful symptoms during and after SARS-CoV-2 infection. The most recent hypothesis of pathophysiological mechanisms of COVID-19-disease and the possible links with related pain symptoms were reported. Acute but also persistent pain and all other comorbid symptoms following recovery from COVID-19 were explored. In addition to the direct effects of COVID-19-related pain, its consequences that negatively affecting quality of life in survivors, and the indirect effects on all the painful syndromes, including pre-existing ones, are also considered. Finally, emphasis is placed on how COVID-19 pandemic negatively involved patients with chronic painful diseases even if not infected. Individuals with central sensitization pain syndromes may have been at higher risk of developing psychological distress during the pandemic. This analysis poses a new perspective for the health care system. It should be noted that the problem of pain is much larger and more complicated than just the appearance of hospitalization. These findings suggest that new concepts in the planning, development, and prioritization on interventions to improve pain care and to prevent the worsening of symptoms during the continuing COVID-19 pandemic.

Keywords: Pain; COVID-19; SARS-CoV-2; pathophysiology; symptom

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Introduction

This review aims to update on pain as a relevant COVID-19 complication and explores the mechanisms of persistent pain and other comorbid symptoms following recovery from COVID-19. The direct effects of COVID-19-related pain, its consequences in survivors, and the indirect effects on all the painful syndromes, including pre-existing ones, are also discussed. The MEDLINE database was searched for the free text terms “COVID-19” or “SARS-CoV-2” combined with the terms “acute pain” or “chronic pain”, and other synonyms as “arthralgia”, “abdominal pain”, “chest pain”, “headache”, “myalgia”, “neuralgia”, “neuropathic pain” and “sore throat” in adults. The research was conducted among the publications in English language only until January 2020. From the analysis of the literature, it emerges that pain is the only symptom that when it is established, then accompanies the disease in all its phases, being in fact, perhaps one of the few symptoms that leaves consequences beyond the duration of the infection. From this perspective, the most typical forms of pain are described in parallel to the course of COVID infection. Finally, the important

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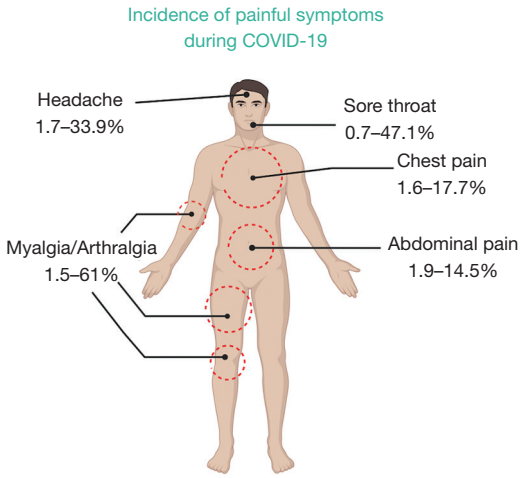

Figure 1 The incidence rate of painful symptoms during COVID-19 infection.

social impact of the virus in those patients with chronic painful diseases that fortunately have not been infected, but are equally and heavily involved in the pandemic is highlighted.

Pain during COVID-19 infection

SARS-CoV-2, the etiologic agent of COVID-19, can cause various manifestations of pain, reflecting the invasion and damage of different body systems.

The clinical expression of COVID-19 is very ample and it seems to correspond to tissues and systems invasion order (1). The primary infection produces direct invasion of the respiratory system (with sore throat, fever, cough, and other pneumonia-associated symptoms), to which may be added other symptoms that show a subsequent invasion of the nervous system (as headaches, dizziness, and confusion), the gastrointestinal tract (abdominal pain, diarrhea), and the cardiovascular system (chest pain and cardiac injury). The incidence rate is 0.7–47.1% for sore throat, 1.5–61.0% for myalgia/arthralgia, 1.7–33.9% for headache, 1.6–17.7% for chest pain, and 1.9–14.5% for abdominal pain (*Figure 1*, *Table 1*) (2).

Currently, convincing evidence demonstrates that SARS-CoV-2 infection can also result in neurological damage and alterations. These neurological disorders are divided into several categories, ranging from non-specific moderate symptoms, such as headache, myalgia, and hyposmia, to severe symptoms, including cerebrovascular disease and intracranial infections. Poor prognosis occurs in minority of patients when acute cerebrovascular disease takes over. However, most COVID-19 patients only exhibit minor or mild neurological symptoms (3). Nevertheless, physicians should be attentive to patients reporting early neurological symptoms due to potential viral neurotropism with possible medullary damage during the incubation period. Hu *et al.* evidenced how headache may be a predictive factor of intermittent negative status in patients with COVID-19, with a probability of 60%. They describe intermittent negative status as a COVID-19 patient with re-detectable viral RNA following a negative reverse transcription-polymerase chain reaction (RT-PCR) test result. The authors found that most patients with headaches displayed delayed SARS-CoV-2 elimination and high mortality rate, suggesting the need for follow-up even after negative testing for COVID-19, to possibly prolong their isolation and hospitalization (4). The possible pathophysiological mechanisms of central and peripheral nervous system involvement are still unclear, but some have been hypothesized. First, the elevated cytokine levels in the serum of COVID-19-affected, such as tumor necrosis factor, interleukin 2, and granulocyte macrophage-colony stimulating factor. This immune response to viral infections, can produce headaches. Second, lung tissue SARS-CoV-2 invasion can produce, through alveolar gas exchange disorders, brain hypoxia and headache due to cerebral ischemia and congestion. Moreover, headaches may result from the direct invasion of SARS-CoV-2 into the nervous system. Besides headache, some patients also present neurological symptoms, such as dizziness, nausea, and vomiting. Autopsy findings and genome sequencing studies in COVID-19-affected cerebrospinal fluid reveal the congestion and edema of brain tissue, where some neurons degenerate (1,2). The routes of this neuro-invasion remain unclear. Olfactory nerve, the vascular endothelium, migration of leukocytes towards the blood-brain barrier, and trans-synaptic transfer through infected neurons have been suggested as points of entry. The SARS-CoV-2 spike protein and the angiotensin-converting enzyme 2 (ACE2) receptors, also expressed in the blood-brain barrier, have been suggested as the key mechanism in the infection of cells. Likewise, from the gastrointestinal tract the virus is able to enter the central nervous system (CNS) through blood vessels, lymphoid pathways, or by retrograde transport through peripheral nerves such as the vagus nerve. It remains unclear the main route and the significance of CNS involvement (5,6).

A rapidly increasing number of reports on the

Table 1 Painful symptoms, depression and PTSD incidence during and after COVID-19 infection

Population	Incidence of pain	Sore throat	Myalgia	Arthralgia	Headache	Chest pain	Abdominal pain	Depression/ PTSD
COVID-19-affected	–	0.7–47.1%	1.5–61%	2.5%	1.7–33.9%	1.6–17.7%	1.9–14.5%	–
COVID-19-survivors, new-onset chronic pain	55.1–65.2%, 19.6%	–	38%	–	39.1%	10.8–11%	–	15.97%/21.94%
General population	10.4–14.3%	–	–	–	47%	20–40%	–	4.4%/4%

PTSD, post-traumatic stress disorder.

neurological effects of COVID-19 are appearing in the literature. Headache seems to be the leading neurological symptom, being reported in 11–34% of hospitalized COVID-19 patients, but the clinical features of the headaches in these cases have not been provided. The overall rate for symptomatic COVID-19 patients is lower, with round 6–10% reporting headache as a presenting symptom. The significant features of headache presentation in this latter group are new onset, moderate-severe intensity, and bilaterality with a pulsating or pressing quality in the temporoparietal, forehead, or periorbital regions. The most wondering features of the reported headaches were sudden to gradual onset, poor response to common analgesics, and a high recurrence rate only during the active phase of COVID-19 (5,6).

Although COVID-19 infection may be characterized by recurring headaches in a proportion of patients, a recent review of more than 41,000 COVID-19 patients included in clinical studies, of whom 8–12% presented headache, failed to offer a characterization of this symptom. According to a review paper by Belvis, headaches related to COVID-19 can be classified into the 2 phases of the disease: acute headache due to systemic viral infection, primary cough headache, tension-type headache, and headache due to heterophoria, which may appear in the first phase (influenza-like); and headache attributed to hypoxia, and a newly described type of headache, difficult to fit into the International Classification of Headache Disorders (ICHD-3), which may appear in the case of a cytokine storm phase of COVID-19. All of these headaches described are specified in the ICHD-3, except for one form that occurs from the 7th day after clinical onset. This headache is probably related to the cytokine storm that some patients suffer, and may be similar to the ICHD-3 headache attributed to other non-infectious inflammatory intracranial disease forms. Although the reported prevalence of headaches as a symptom of COVID-19 infection is relatively low, the above evidence shows that its actual incidence is most probably underestimated (7).

Outside the context of COVID-19 infection, the cause of headache has many different origins. Globally, the prevalence of headache in the general population is 47%, and lifetime prevalence is 66%. For individuals, this condition can cause suffering, reduced quality of life, and even disability. A study of 203 corporate sector professionals and 325 undergraduate and postgraduate university students, all of whom worked from home during the pandemic, revealed an increase in more persistent feelings of sleepiness, with significantly increased daytime nap duration, and depressive symptomatology relative to pre-lockdown conditions. Moreover, the chronic stress of living through a pandemic led to a host of physical symptoms, including headaches, insomnia, digestive problems, hormonal imbalances, and fatigue (8).

Myalgia during viral infection is due to inflammation mediated by interleukin-6, which leads to myalgia or arthralgia. Skeletal muscle damage can be assessed by creatine kinase (CK) and lactate dehydrogenase (LDH) levels. Mao *et al.* found higher levels of CK and LDH in COVID-19-affected with muscle symptoms than those without muscle symptoms (9). Myalgia might be due to skeletal muscle injury. SARS-CoV-2 may bind with skeletal muscle ACE2 receptors. However, the autopsy results of SARS-CoV-affected did not indicate any SARS-CoV infection in skeletal muscle. Hence, the mechanism underlying myalgia in COVID-19 still needs further study. Second, muscle pain can occur when peripheral pain receptors are stimulated by cytokines and prostaglandin E2. In addition, skeletal muscle injury can also be a manifestation of nervous system damage with the pathogenetic mechanisms above mentioned. The occurrence of myalgia is closely related to SARS-CoV-2 test positivity and can be used as one of the strongest predictors. Arthralgia is also common in COVID-19-affected, but

only approximately 2.5% of patients reported joint pain as an initial presentation (2). In contrast, coronaviruses are usually associated with arthralgia but not frank arthritis. Data on rheumatic manifestations during COVID-19 infection are limited. Most studies suggest that patients with rheumatic disease are not at an increased risk of acquiring COVID-19. Importantly, accumulating evidence suggests that COVID-19 can cause a recurrence of rheumatic disease, especially in some subsets, such as inflammatory arthritis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Therefore, joint pain symptom must be considered in this context (10).

Sore throat is the pain caused by tissue inflammation at the back of the throat, usually caused by viruses. This mechanism is not yet been demonstrated in COVID-19 affected but only suspected due to the similarity of symptoms between SARS-CoV-2 and influenza virus in the upper respiratory tract. Sore throat is not as common as fever in COVID-19-affected, but these patients should still be considered as potential carriers of COVID-19 especially in young adults among which a higher incidence was found than in older infected patients (2).

Chest pain is often reported as generic discomfort or pain between the neck and upper abdomen that can affects 20–40% of general population over the course of a lifetime. The mechanisms underlying chest pain in COVID-19-affected remain unclear; however, we can speculate that it may involve cardiac injury or inflammation of the pleura due to infection. On the basis that ACE2 receptors are highly expressed in the normal human heart and the SARS-CoV-RNA was found in SARS patient heart samples, we speculate that the virus, through ACE2, is able to invade cardiomyocytes directly causing cardiac damage. Moreover, patients with cardiac injury present higher concentrations of inflammatory markers (e.g., leukocytes, C-reactive protein, and procalcitonin), as it occurs following a cytokine storm syndrome. This event can be the explanation of chest pain, both through the myocardial damage and for pleural irritation by the inflammatory mediators spreading. In addition, cardiac damage can also result from respiratory disfunction and hypoxemia induced by COVID-19 (2).

Abdominal pain is usually a symptom of disordered gastrointestinal motility, affecting most people at least once over the course of a lifetime. Few studies have offered an explanation for the mechanism of abdominal pain caused by SARS-CoV-2. Luo *et al.* provided evidence showing that SARS-CoV-2 reaches the gastrointestinal system where ACE2 is widely represented, especially in the small and large tract. As a result, SARS-CoV-2 may invade the digestive system by binding to ACE2, causing abdominal pain (11).

There is accumulating evidence on coronavirus induction of multiple neurological disorders, including polyneuropathy, encephalopathy, ischemic stroke, and even demyelinating lesions, such as multiple sclerosis (MS) and Guillain-Barré syndrome (GBS). Among these neurological impairments, the demolition of myelin appears to be a visible complication in patients with severe infection: demyelination was reported in cases of COVID-19, and autopsy reports confirm the presence of SARS-CoV particles and genome sequences in various organs of the body (12).

Pain in COVID-19 seems to have a specific distribution and precise timing which was reported both in patients with infection-related pain (*de novo* pain) but also in those with pre-existing chronic pain worsened by infection (COVID-19-aggravated pain). In a recent retrospective chart review, Şahin *et al.* produced a map of COVID-19-related pain. In a total of 206 patients examined after discharge, the areas of the body most frequently reported to experience pain prior to infection were the neck and back (in 40.7% of patients), whereas the head and limbs were the areas most frequently affected during infection (in 82.5% of patients) (*Figure 2*). The severity of pain increased in all body regions during COVID-19 infection compared with the patients' pre-infection state. This increase in severity remained after recovery from the infection in all regions, except for the back. Indeed, pain may continue following recovery from COVID-19, negatively affecting quality of life. More than half of all patients (55.1%) continued to experience pain once negative for SARS-CoV-2 infection, and the average time that pain persisted after infection was approximately 45 days (7–78 days) (13).

Pain in COVID-19 survivors

Survivors of a critical disease have been shown to have a high prevalence of moderate to extreme chronic pain, which is an essential factor affecting their ability to return to work and to restore quality of life for up to 5 years following discharge. Critically ill patients with COVID-19 are an especially susceptible population to develop the post-intensive care syndrome (PICS). However, with current knowledge, there are no studies related to treatment of chronic pain after a critical disease, particularly in patients with COVID-19 (14).

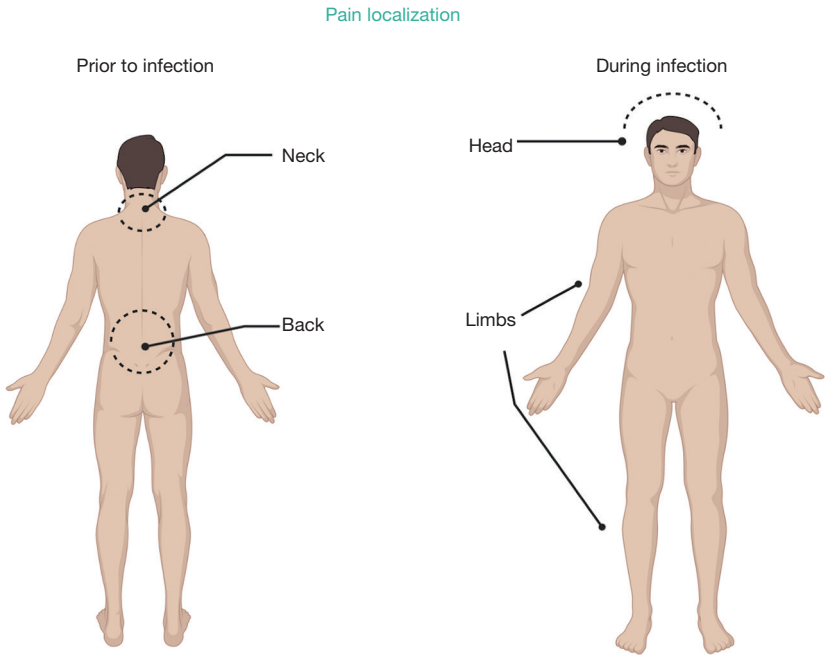

Figure 2 Timing and localization of painful symptoms before and during COVID-19 infection.

The most studied mental health problems during COVID-19 are depression, anxiety, insomnia, post-traumatic stress disorder (PTSD) and psychological distress (PD). In a recent meta-analysis these five symptoms are reported with a significantly higher prevalence in pandemic-affected populations compared to the general population under normal circumstances. In particular prevalence of depression in populations affected by COVID-19 is more than three times higher (15.97%) than in the general population (4.4%); while it is four times higher for anxiety (15.15% *vs.* 3.6%); and five times higher for PTSD (21.94% *vs.* 4%) (15). Actual research indicates that PTSD and chronic pain often co-occur and that similar mechanisms, such as fear, avoidance, and catastrophizing, may maintain both conditions (16).

The cases series by Carfi and colleagues describes COVID-19 symptoms persisting for a mean of 60 days after their onset in patients discharged from COVID-19 hospitalization (17). Symptoms persisting for a mean (± SD) of 110.9 (±11.1) days following hospital admission were also observed. The most frequently reported persistent symptoms were: fatigue (55%), dyspnea (42%), concentration and sleep disorders (28% and 30.8%, respectively), and chest pain (11%). Garrigues *et al.* analyzing a cohort of 279 COVID-19 hospitalized patients with EQ-5D-5L questionnaire, a specific tool that records mobility, self-care, anxiety and depression, usual activity and pain, revealed a mean score [EuroQol Visual Analogue Scale (EQ-VAS)] of 70.3 in 21.5% of patients. Among these, more precisely, it has emerged that a persistent chest pain is reported in 10.8% within 100 days after discharge (18).

Using the International Classification of Diseases/International Association for the Study of Pain (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* chronic pain (i.e., persistent or recurring *de novo* pain, lasting more than 3 months) were observed in 46 COVID-19 and 73 control patients. The COVID-19 group had a significantly higher prevalence of *de novo* pain (65.2% *vs.* 11.0%) and *de novo* headache (39.1%) compared with controls (2.7%). New-onset chronic pain was observed in 19.6% of COVID-19 patients and in 1.4% of controls (*Table 1*). These differences also remained significant when exclusively analyzing patients who did not report any previous pain prior to hospital stay (n=40 COVID-19 patients *vs.* n=34 control patients). COVID-19-related pain was more frequently located in the head/neck and lower limbs (P<0.05). COVID-19 patients who reported anosmia had a higher prevalence of *de novo* pain (83.3%) compared with those who did not (48.0%, P=0.024) (19).

The neurological complications of COVID-19, such as GBS, myelitis, and stroke, were recently revised in relation to their potential to increase the risk for chronic neuropathic pain (20). Data on persistent painful symptoms following clinical manifestations of COVID-19 and their consequences are lacking (21). Similarly, little is known about the indirect effects of the virus which, by inducing lymphocytopenia, can exacerbate serious opportunistic infections, such as herpes reactivation, if further aggravated by certain therapies (e.g., corticosteroids or tocilizumab), potentially leading to additional painful syndromes. On the basis of this assumption, a preliminary single case study was recently reported concerning headache and myalgia in a COVID-19 patient successfully treated with micronized/ultramicronized palmitoylethanolamide (PEA), a medical food supplement. PEA seems to have anti-inflammatory and neuroprotective properties, which might be useful the earliest disease stage. The antioxidant properties of PEA could be fully exploited, since it reduces the expression of cyclooxygenase 2 and nitric oxide synthase 2, which may play a key role in regulating the immune response to infections (22).

Myalgia in the acute phase was associated with musculoskeletal pain as long-term post-COVID sequelae. From a total 1,200 hospitalized COVID-19 patients, 369 with and 369 without myalgia at hospital admission were assessed an average of 7.2 months (SD ±0.6) after hospital discharge. A greater proportion of patients with myalgia at hospital admission (20%) showed more than three post-COVID symptoms compared with individuals without myalgia (13%). A higher proportion of patients presenting myalgia (odds ratio: 1.41; 95% confidence interval: 1.04–1.90) exhibited post-COVID musculoskeletal pain compared with those without myalgia. The prevalence of post-COVID-19 musculoskeletal pain in the total sample was 38% (*Table 1*). Additionally, half of the patients with pre-existing pain conditions experienced a persistent exacerbation of their previous syndromes (COVID-19-aggravated pain) (19,23).

Preexisting chronic pain during the COVID-19 pandemic

During the pandemic, healthcare systems across the world have imposed to postpone or cancel all elective surgical procedures, outpatient procedures, and patient visits, including pain management services (24,25). An immediate consequence of the postponement of pain management and surgical procedures has been the exacerbation of chronic pain in patients with COVID-19-unrelated musculoskeletal pain, as well as in those waiting for total joint arthroplasty [total hip arthroplasty (THA) and total knee arthroplasty (TKA)] and in those needing orthodontic treatment for temporomandibular disorders (TMD) (26-30). Anxiety, depression, PTSD and PD are known reactions in the general population during COVID-19 pandemic (15,31).

It was shown that central sensitization pain syndromes can develop PD during the pandemic. Indeed, correlations were found between changes in daily routines and emotional distress, sensitization, and pain intensity. Advanced age, difficult access to medical care, changes in daily habits, and reduced social interaction were found as predisposing factors to emotional distress (32). Social distancing for 4–8 weeks has been shown to increase pain severity and pain interference in patients affected by fibromyalgia, chronic spine, or postsurgical pain. Although both pain severity and interference were quite variable among individuals under conditions of social distancing. Several demographics, socioeconomic, and psychosocial factors were associated with greater pain severity and interference during social distancing. Multivariable linear regression demonstrated that the female sex, non-white race, lower education level, disability, fibromyalgia, and higher pain catastrophizing were independently associated with greater pain severity, whereas the female sex and pain catastrophizing were independently associated greater pain interference.

It is therefore reasonable to assume an increase in the incidence of chronic pain that in the general population is actually registered around 10.4% in Europe, 14.3% in the UK and 12% in the USA (33-35). More attention to these findings should be paid in the planning, develop, and prioritizing of interventions in the future to prevent the worsening of symptoms in COVID-19-unrelated chronic pain patient (36).

The diagnostic accuracy of 84 signs and symptoms, including painful symptoms (sore throat, headache, myalgia, arthralgia, chest and abdominal pain), was recently assessed in a systemic review of 44 different studies to determine whether clinical examination alone could accurately diagnose SARS-COV-2 infection in patients being treated in a primary care or hospital outpatient settings. The results were highly variable across the studies. The authors concluded that neither the presence nor absence of specific combinations of signs or symptoms was accurate enough to confirm or rule out COVID-19 diagnosis, although the presence of fever, cough, anosmia, or ageusia may be useful

to identify people for further testing for SARS-COV-2 infection (37).

In conclusion, we can state with a reasonable degree of certainty that pain is an integral part of COVID-19 infection, occurring both directly and indirectly, and may entail both early and late manifestations. SARS-COV-2 may cause the *de novo* presentation of certain forms of pain or the exacerbation of a pre-existing or chronic form of pain. It should be noted that the problem of pain during pandemic is much larger and complicated than just the appearance of hospitalization. Finally, it is obvious how failing to treat pre-existing pain can result, not only in the exacerbation of the underlying conditions, but even in the collapse of health care systems, in terms of the number of patients involved and the severity of the pain to treat, regardless of whether patients have COVID-19 or not. So, to win a war, we must first win the battles: against infection itself and against its consequences.

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Footnote

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