ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 25(4); August 2021 DOI: 10.35975/apic.v25i4.1582

NARRATIVE REVIEW CORONA EXPERIENCE

Post-COVID pain syndrome

Dmytro Dmytriiev [1], Oleksandr Dobrovanov [2]

Authors affiliations:

1. Professor, Department of Anesthesiology & Intensive Care Vinnytsya National Pirogov Memorial Medical University, str. Amosova 9, 21000, Vinnytsia, Ukraine. E-mail: dmytrodmytriiev@gmail.com, ORCID: http://orcid.org/0000-0001-6067-681X

2. Associate Professor, A. Getlik Clinic for Children and Adolescents, Slovak Medical University and University Hospital of Medicine, str. Antolska 11, 85107, Bratislava, Slovakia. E-mail: brovan.oleksandr@gmail.com, ORCID: https://orcid.org/0000-0002-9025-9141

Correspondence: Dmytro Dmytriiev; E-mail: dmytrodmytriiev@gmail.com; Phone: +380674309449

Abstract

The COVID-19 pandemic has affected the lives and health of people all around the world. Although majority of patients with COVID-19 experience respiratory symptoms, pain is also a very important symptom. The condition of 15-20% of patients is serious and requires hospitalization. Despite the fact that the disease was initially referred to as a respiratory disease, it often affects other systems as well; the most common are the cardiovascular, urologic and nervous system. Multi-organ involvement increases the need for intensive care and treatment of several consequences caused by the disease. Due to severity of the disease, the management of complications following release from hospital should also be considered. The provision of multidisciplinary care that supports both physical and mental recovery in the initial stages of hospitalization can minimize the damage. Cognitive, physical and mental dysfunction reported by COVID-19 patients after discharge may have significant impact on the quality of human life. Pain is usually part of the dysfunction. The post-COVID-19 pain syndrome is still not completely understood, in particular the way it affects patients after they have recovered from COVID-19. There is limited information on the clinical characteristics, treatment, results and pain management in COVID-19 patients. The aim of our article is to provide an overview of the impact COVID-19 has on conditions associated with acute and chronic pain.

Key words: Acute pain; Chronic pain; Co-morbidity; Pain syndrome; Pandemic COVID-19; SARS-CoV-2

Citation: Dmytriiev D, Dobrovanov O, Post-COVID pain syndrome. Anaesth. pain intensive care 2021;25(4):505–512. **DOI:** 10.35975/apic.v25i4.1582

1. Introduction

The COVID-19 pandemic has severely affected the lives and health of people all around the world and may have further serious consequences in the future. Major changes resulting from the pandemic that have had a fast impact on the lives of people have impaired and affected the everyday routine of many individuals, including those suffering from chronic pain.[1] The condition of approximately 15-20% of patients infected with SARS-CoV-2 progresses to a serious one which requires hospitalization. [2] The severity of the course of COVID-19 is also affected by the presence of accompanying diseases: diabetes mellitus, obesity, arterial hypertension, cardiovascular diseases, immunodeficiency and bronchial asthma. However, the condition of patients with no co-morbidities may also progress and become serious. Even if the disease was initially referred to as a respiratory syndrome, in acute stage we see damage to other organs and systems as well.

The International Association for the Study of Pain (IASP) defines chronic pain as persistent or repeated pain lasting for more than 3 months or longer than the usual period in which tissues tend to heal. [1] The overall prevalence of chronic pain in the normal population is approximately 30%. Treatment of chronic pain presents a great burden on the individual and the country in terms of personal and socio-economic consequences and costs[3]. The COVID-19 pandemic

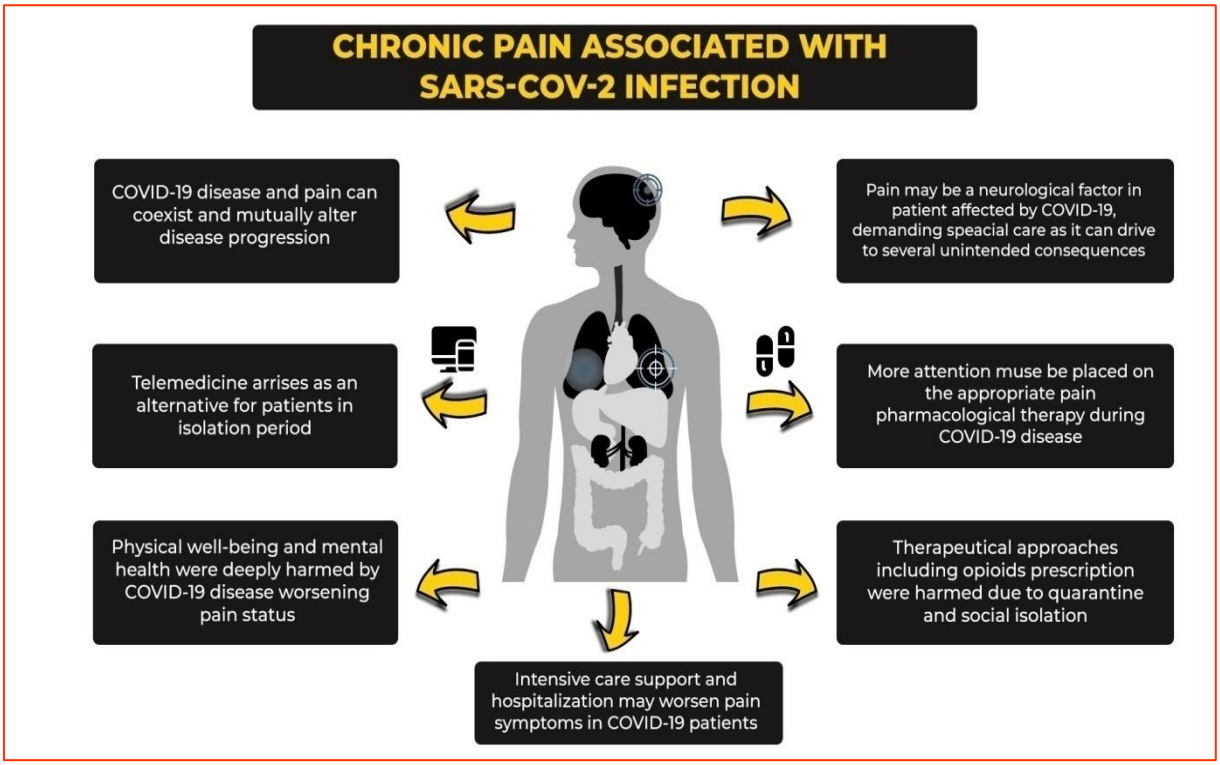

Figure 1: Chronic pain associated with SARS-CoV-2 infection

*[**Source:** adapted by the authors according to various sources of literature]*

has increased the risk of chronic pain due to viral infection, social isolation and for other causes. An obvious risk factor of chronic pain is the association with acute pain. Therefore, it is very important to take this fact into account during the treatment of acutely hospitalized patients. Those patients who can remember the pain and fear they experienced while being hospitalized at the intensive care unit (ICU) or Covid ward have a higher risk of chronic pain following discharge to home or outpatient care. [2] It is very likely that patients who had a serious course of COVID-19 are exposed to a higher risk of chronic diseases and chronic pain.

Cognitive, physical and mental dysfunctions reported by COVID-19 patients may have a serious impact on their quality of life. [2] Chronic pain is usually part of the dysfunction, but it is still not understood well. Multi-organ involvement increases the need for intensive care and treatment of several consequences of COVID-19. Multidisciplinary interventions supporting both physical and mental recovery in the initial stages of hospitalization may minimize the damage. [4]

Moreover, patients with COVID-19 and chronic pain are at a higher risk of developing depression[5]. Social isolation itself is a risk factor for the onset of depression and depressive symptoms. A population suffering from chronic pain was seriously affected by the pandemic and 'the home detention' as part of the measures aimed to reduce the risk of spreading the COVID-19 infection. Healthcare facilities and services providing medical help, including pain management, worked in a limited regime which seriously affected (worsened) the condition of patients suffering from chronic pain. [4, 6] The physical well-being and mental health of many people have been impaired during the pandemic, which has resulted in an increased incidence of depression, anxiety, sleep disorders, chronic and acute pain and suicides. All of this has impaired the quality of life. The combination of chronic pain, mental disorders related to COVID-19 and social isolation may have a very bad prognosis for patients with chronic pain.

2. Effect of COVID-19 on pain

Our efforts are aimed to describe the potential health impacts of COVID-19 on the development of the pain

syndrome, and to provide a summary of the known facts related to the development and management of chronic pain following the viral infection (SARS-CoV-2), organ damage associated with COVID-19 and worsening of chronic pain due to exacerbation of existing diseases (Figure 1).

3. Stages of pain development

Since pain is a frequent symptom accompanying COVID-19, we have tried to systematize both the pain and some symptoms associated with it:

3.1. The pre-disease stage and the onset of the disease are often associated with a non-specific discomfort, such as sore throat and body pain.

3.2. Acute pain associated with SARS-CoV-2.

3.3. Para infectious pain:

3.3.1. Headache,

3.3.2. Myalgia,

3.3.3. Neuropathic pain.

3.4. Abdominal pain.

3.5. Neurological manifestations.

3.6. Chronic pain: due to COVID-19 itself or secondary diseases associated with the SARS-CoV-2 infection, including Guillain-Barre syndrome, polyneuritis, polyneuropathy or central pain following strokes.

3.6.1. It may be a complication of treatment at the ICU.

3.1. Acute pain associated with COVID-19

COVID-19 is defined as an air-borne infection characterized by the ability to spread quickly by droplets and contact. The fecal-oral rout is also possible, in particular in breast fed babies and infants wearing nappies (viral replication in the gastrointestinal tract). The inducer is the new coronavirus (SARS-CoV-2) which causes symptoms of a respiratory disease (dry cough, breathlessness, sore throat, fever, fatigue, muscle pain, gastrointestinal symptoms) with a wide range of severity, from asymptomatic to critical course: acute hypoxemic respiratory failure to complete failure (bilateral pneumonia, ARDS). [6, 7] As with the majority of viral infections, patients with COVID-19 commonly suffer from headache, sore throat, myalgia, arthralgia or peripheral neuralgia.[6]

3.2. Parainfectious pain

Myalgia is one of the most common manifestations observed in COVID-19 patients, present in nearly 36% of cases. [8] Analysis of statistical data has shown that in 14.8% the disease was associated with myalgia or arthralgia. [2, 6] In the Chinese province of Hubei, one of the first areas affected, myalgia or fatigue was present in 32.1% patients. [9] The fast release of cytokines; interleukin-6 (IL-6), IL-10 and tumor necrotizing factor-alpha (TNF-α),[7] elevation of inflammatory markers; C-reactive protein (CRP), lactate dehydrogenase (LDH), and accelerated erythrocyte sedimentation rate (ESR) in COVID-19 patients point to the presence of a generalized inflammatory response, [10, 11] which could explain the presence of myalgia. Weakness and hyporeflexia of the lower extremities have also been reported in association with COVID-19. It is not a usual pain, but weakness in the lower extremities, which may be an indication of peripheral motor neuropathy and could be present even before occurrence of the first signs and clinical manifestation of COVID-19. [12] It seems that neuropathy is related to the autoimmune reaction or involvement of the peripheral neuromuscular system or central nervous system due to the viral infection.

3.3. Abdominal pain

Gastrointestinal symptoms are less common in COVID-19, but they are part of the syndromes. Abdominal pain has been reported in the case of gastrointestinal problems in 2-6% of infected adults, adolescents or children. [13] In children, gastrointestinal problems often belong to dominating symptoms in the case of multisystem inflammatory syndrome (PIMS-TS / MISC). [14-18]

In the majority of cases, the pain was associated with diarrhea or an eating disorder. [19] Gahide et al. (2020) have described cases of patients diagnosed with COVID-19, who during hospitalization suffered from acute abdominal pain without severe respiratory symptoms or fever, which is a confirmation of the fact that abdominal pain is a relevant symptom in diagnosing COVID-19. [47] Poggiali et al. (2020) have described 10 patients with fever, nausea, loss of appetite, abdominal pain and diarrhea. [21]

The angiotensin-converting enzyme 2 (ACE2) is highly expressed in the human small intestine and is the primary described cell receptor for the new coronavirus. [20] Diarrhea occurs secondarily, following interaction between the ACE2 receptor and SARS-CoV-2. Recent studies show that the RNA of the SARS-CoV-2 virus can be detected in stool samples, which confirms the fecal-oral route. [21] These data prove that abdominal pain, as one of the symptoms of COVID-19, to be taken into account in differential diagnosis. Generalized inflammation in the gastrointestinal tract (gastroenteritis) is regarded as a potential mechanism for the development of abdominal pain in patients with COVID-19. It is also important to note that patients diagnosed with inflammatory bowel disease or chronic liver disease do not present a higher risk in terms of the infection with SARS-CoV-2 compared to the normal population. [13]

3.4. Neurological manifestations

Central pain is potential neurological manifestation of COVID-19 [7], which raises our concerns regarding the increase of new patients with pain syndrome with the continuing pandemic and pandemic measures. Headache is very common in patients with COVID-19, and in some surveys as many as 90.5% of infected patients listed headache as their first sign (26%) or a symptom that occurred within 48 hours (62.5%) from the development of the disease. [22, 23] Headache is often accompanied by anosmia, arthralgia, cough, dizziness and myalgia. [23] Generalized inflammation, cytokine storm, damage to vascular endothelium and activation of macrophages are thought to be involved in the mechanism of pain development. [7, 23, 24] Expression of ACE2 receptors in spinal neurons is important for pain sensation. However, further research and studies are needed to detect exact mechanisms that lead to the development of central pain, in correlation with the severity of COVID-19. [20, 23]

3.5. Chronic pain

Chronic pain as a result of worsened existing pain, physical or mental difficulties, may lead to severe depression. [5] Patients with chronic pain who remain without appropriate treatment have a high level of depressive disorders. [25] Specific serotonergic path from the dorsal raphe nucleus to lateral habenula, via the central amygdala, is regarded to be the key nervous circuit controlling depressive symptoms in chronic pain. [26, 27]

Chronic pain may cause depression and vice versa and depression may lead to abnormal sensation and modulation of pain, with increased risk of the development of chronic pain. [26, 28] Severe anxiety or the presence of anxiety disorder has been observed in more than 50% of patients with chronic pain. Neuroimaging studies suggest that overlapping parts of the brain, such as the thalamus, prefrontal cortex and anterior cingulated cortex are activated by both chronic pain and anxiety or another mental/depressive disorder. [29, 30]

According to various studies on patients with COVID-19, the most frequently reported problems were pain/discomfort (19.0%) and anxiety/depression (17.6%). Logistic regression models show that the risk of factors provoking pain/discomfort and anxiety/depression associated with mental disorders has increased significantly in specific groups of people. [31, 32, 33] They include the elderly and persons with chronic diseases, people with low income and persons affected by stress (such as physicians, employees at Covid wards, etc.). [31, 32, 33]

Individual with chronic diseases develop mental symptoms more frequently compared to the rest of the population. [34] Social isolation due to the COVID-19 pandemic has only made the symptoms more pronounced. Social isolation, which is added to all the reported effects since the outbreak of COVID-19, is therefore regarded as a risk factor for the development of mental diseases and makes worse existing conditions that could, by contrast, have an adverse effect on the results of treatment associated with pain. [35] Besides that, the number of people suffering from mental diseases following a major event is often higher and the consequences of such an event may persist longer [33], in particular in people with chronic diseases, elderly and persons on a low income.

3.6. Chronic pain due to exacerbation of accompanying diseases

Chronic pain is a widespread symptom associated with high costs of treatment and reduction of the quality of life. Chronic pain means a medical issue that requires medial, economic and social efforts. [36] It is worth

noting that chronic pain occurs to a great degree in the old age group, which is already a high risk for severe course of COVID-19. [6, 10] Patients are more likely to develop pain or discomfort and anxiety/depression when in fear of contracting SARS-CoV-2; therefore, these individuals may develop more severe symptoms of COVID-19. [33] The disease reaches its peak in the elderly, people with chronic diseases and persons on a low income or those who concerned about contracting COVID19 during the COVID-19 pandemic. [33] These data point to the need for pain management during the pandemic and lockdown.

During the COVID-19 pandemic, we have witnessed the increase in the number of patients with chronic neuropathy, neck and back pain, orofacial pain, including dental pain, and headache. It is associated with the fact that some healthcare facilities have limited their activity and operation in the efforts to fight COVID-19. Unpleasant feelings, discomfort and persistent pain are frequent in patients hospitalized at an ICU who require or required intensive care, artificial lung ventilation, etc. [7] Moreover, during their treatment at the ICU, COVID-19 patients often cannot report the pain scale themselves, which is why the pain is often underestimated. It means that it is advisable to use other rating tools at ICUs [7] – for example, pain score in intubated patients (Critical Care Pain Observation Tool, CPOT) [37] or patients under sedation (Behavioral Pain Scale, BPS). [38] These scores are helpful in pain monitoring and management during hospitalization already, and prevent further decline of patient condition not only during hospitalization but also after overcoming COVID-19.

4. Treatment of chronic pain associated with COVID-19

Patients suffering from any type of pain during the COVID-19 pandemic require special attention, since pain may be induced by many factors, including neurological ones, [7] and may result in chronic pain. This condition often develops in patients after overcoming COVID-19 and requires professional help and appropriate analgesia in order to relieve the pain. [20] Therefore, healthcare professionals are currently calling for continuous care for acute and chronic pain in such patients.

During the period of isolation (as part of the epidemiologists' efforts to reduce the spread of infection), those with a greater burden of pain (including chronic pain) had a higher incidence of COVID-19 infections. The consequences of abruptly suspended/modified provision of healthcare associated with a disrupted approach to healthcare have increased the number of patients with pain [4], and the consequences of insufficient treatment may even deepen in the future. [4] Despite the fact that adverse effects of medications and the addiction syndrome may develop during the treatment of pain and associated syndromes,[39, 40] opioids and non-steroidal anti-inflammatory drugs are commonly used to treat both acute and chronic pain. [40, 41, 42] Termination of treatment due to the COVID-19 pandemic may thus lead to several unwanted consequences: worsening of pain, reduced function, opioid addiction, and potentially increased morbidity. [43, 44]

The effects of opioids on the immune system are complex and have to do with the infection and chronic treatment of pain with opioids. Therefore, they should be used cautiously and to a limited extent in patients with weakened immunity. [35, 44, 45] During the COVID-19 pandemic we have seen an increase in incorrect use of opioids, which is why greater attention should be paid to their appropriate prescribing. Therefore, there are several non-opioid strategies (for example the use of clonidine) and strategies for the treatment of patients with the risk of opioid withdrawal proposed.[44]

Irrespective of the previously mentioned facts, treatment of chronic pain during the COVID-19 pandemic must be regarded as an equally important part of continuous supportive care. During the COVID-19 pandemic and following the approval of telemedicine, there have been problems with prescribing analgesic agents [6], which may impact the future incidence of chronic pain.

E.B. de Moraes et al. have assessed a great number of publications dealing with pain during and after COVID-19 and have prepared recommendations on how to cope with chronic pain associated with COVID-19 (Figure 2).

The work procedure proposes the use of telemedicine for the screening of painful conditions and pain intensity, as well as the use of colored signaling intervention packages depending on the severity (green, yellow and red). [46] New studies only confirm the role of the mental component in the development of pain during or after COVID-19, and therefore stress

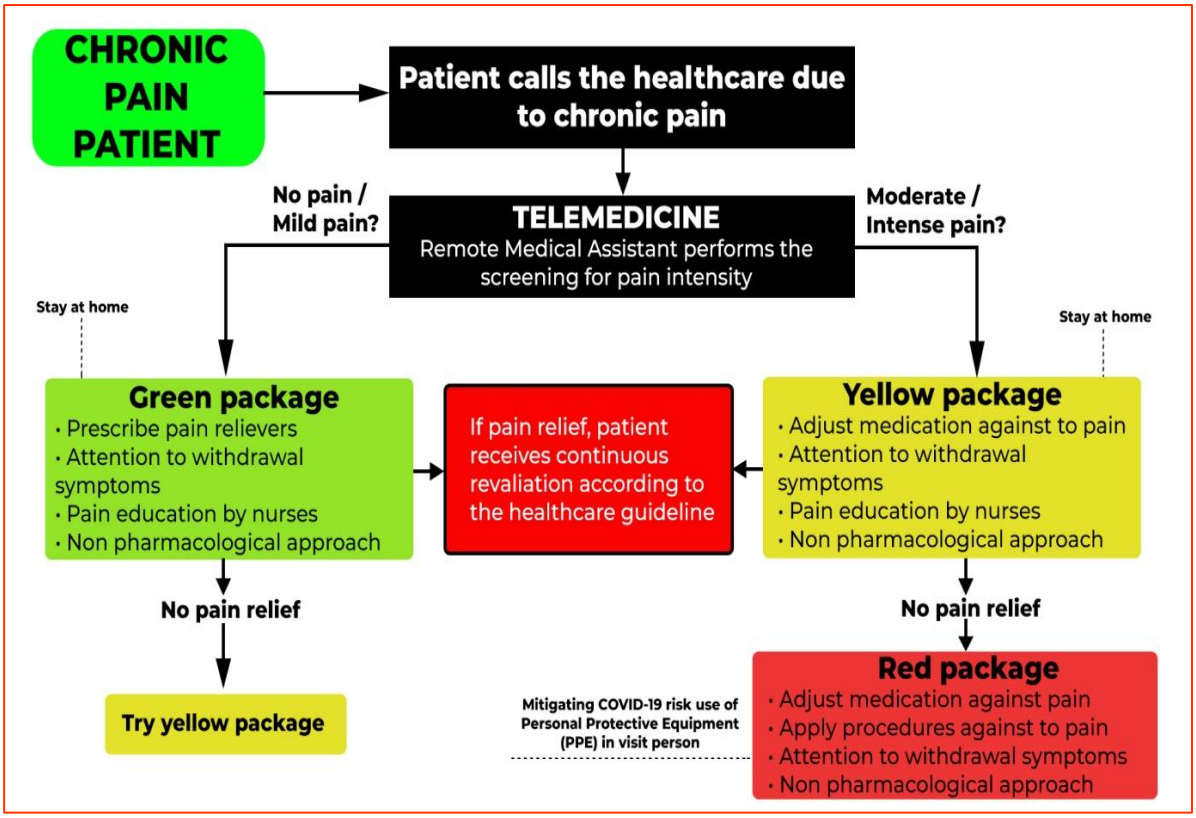

Figure 2: Chronic pain management during the COVID-19 pandemic
*[**Source:** Adapted from E.B. de Morales et al.[46]]*

the need for appropriate healthcare and psychologist interventions during the treatment of the pain syndrome in COVID-19. [48, 49, 50]

New technologies present an emerging option in the management of chronic pain in particular. An extremely helpful and state-of-the-art technology in the treatment of chronic pain is the use of virtual reality. [51]

5. Conclusion

In the era of the COVID-19 pandemic, it is still necessary to identify many unknown factors to be able to understand their relation to pain in patients infected with COVID-19. Recently, procedures for control of pain caused by the virus have been proposed and should be further investigated. [52] Despite a large number of patients with COVID-19, epidemiological studies of pain are still missing. To better understand the mechanisms involved in the development of the disease and the role of pain in the development of infectious conditions, it is necessary to analyze the pain as a consequence of the disease. Admission of the fact that social isolation plays an especially important role in progression of the disease has led to the extreme need for treatment, management and improvement of the quality of life of patients with chronic pain and other psychiatric comorbidities.

In the future, epidemiological data should help politicians, ministries of health and public health experts, whose goal is to reduce the scope of future pandemics and their consequences, including chronic pain. For a better understanding of the disease, it is especially important to admit that COVID-19 causes chronic pain and worsens existing chronic pains. Besides that, the treatment of acute pain should never be overlooked; as it is important to stop progression to, and reduction of the potential impact of chronic pain during the COVID-19 pandemic.

6. Conflict of interest

None declared by the author

7. Authors' contribution

Both authors took part in literature search and the preparation of this manuscript.

8. References

1. Puntillo F, Giglio M, Brienza N, Viswanath O, Urits I, Kaye AD, et al. Impact of COVID-19 pandemic on chronic pain management: looking for the best way to deliver care. Best Pract Res Clin Anaesthesiol. 2020;34:529–537. [PubMed] DOI: 10.1016/j.bpa.2020.07.001
2. Nanjayya V. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). WHO-China Jt. Mission Coronavirus Dis. 2020;16–24. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
3. Van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014;155: 654–662. [PubMed] DOI: 10.1016/j.pain.2013.11.013
4. Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, et al. Managing patients with chronic pain during the COVID-19 outbreak. Pain. 2020;161:889–893. [PubMed] DOI: 10.1097/j.pain.0000000000001885
5. Williams LS. Prevalence and impact of depression and pain in neurology outpatients. J Neurol Neurosurg Psychiatry. 2003;74:1587–1589. [PubMed] DOI: 10.1136/jnnp.74.11.1587
6. Shanthanna H, Strand NH, Provenzano DA, Lobo CA, Eldabe S, Bhatia A, et al. Caring for patients with pain during the COVID-19 pandemic: consensus recommendations from an international expert panel. Anaesthesia. 2020;75:935–944. [PubMed] DOI: 10.1111/anae.15076
7. Drozdzal S, Rosik J, Lechowicz K, Machaj F, Szostak B, Majewski P, et al. COVID-19: pain management in patients with SARS-CoV-2 infection-molecular mechanisms, challenges, and perspectives. Brain Sci. 2020;10:465. [PubMed] DOI: 10.3390/brainsci10070465
8. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92:577–583. [PubMed] DOI: 10.1002/jmv.25757
9. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J Engl. 2020;133:1025–1031. [PubMed] DOI: 10.1097/CM9.0000000000000744
10. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620–2629. [PubMed] DOI: 10.1172/JCI137244
11. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623. [PubMed] DOI: 10.1016/j.tmaid.2020.101623
12. Abdelnour L, Eltahir Abdalla M and Babiker S. COVID 19 infection presenting as motor peripheral neuropathy. J Formos Med Assoc. 2020;119:1119–1120. [PubMed] DOI: 10.1016/j.jfma.2020.04.024
13. Oba J, Carvalho WB, de Silva CA, Delgado AF. Gastrointestinal manifestations and nutritional therapy during COVID-19 pandemic: a practical guide for pediatricians. Einstein (Sao Paulo). 2020;18:eRW5774. [PubMed] DOI: 10.31744/einstein_journal/2020rw5774
14. Dobrovanov O, Furkova K, Vidiščák M, Húšťavová L. Multisystémový zápalový syndróm u detí spojený s COVID-19/SARS-CoV-2, napodobňujúci Kawasakiho chorobu (Kawa-COVID-19). Pediatria (Bratisl.) 2020; 15(5):300-303.
15. Dmytriiev D, Dmytriiev K, Stoliarchuk O, Semenenko A. Multiple organ dysfunction syndrome: What do we know about pain management? A narrative review. Anaesth Pain Intensive Care. 2019;23(1):84-91. [FreeFullText]
16. Dmytriiev D. Assessment and treatment of postoperative pain in children. Anaesth Pain Intensive Care. 2018;22(3):392-400. [FreeFullText]
17. Kralinsky K, Pisarcikova M, Dobrovanov O, Babela R. Protocol for the diagnosis, management and treatment of pediatric patients with COVID-19 according to the recommendations of the Slovakian Pediatric Society. Ros Vestn Perinatol Pediat. 2020;65(5):93-99. DOI: 10.21508/1027-4065-2020-65-5-93-99
18. Dobrovanov O, Dmytriiev D, Dmytriieva K, Hustavova L. Difficulties in diagnosing and treating Kawasaki disease in children. Ros Vestn Perinatol Pediat. 2020;65(6):122-128. DOI: 10.21508/1027-4065-2020-65-6-122-128
19. Dong ZY, Xiang BJ, Jiang M, Sun MJ, Dai C. The prevalence of gastrointestinal symptoms, abnormal liver function, digestive system disease and L. J Clin Gastroenterol. 2020;55:67–76. [PubMed] DOI: 10.1097/MCG.0000000000001424
20. Su S, Cui H, Wang T, Shen X and Ma C. Pain: a potential new label of COVID-19. Brain Behav Immun. 2020;87:159–160. [PubMed] DOI: 10.1016/j.bbi.2020.05.025
21. Poggiali E, Ramos PM, Bastoni D, Vercelli A, and Magnacavallo A. Abdominal pain: a real challenge in novel COVID-19 infection. Eur J Case Rep Intern Med. 2020;7: 001632. [PubMed] DOI: 10.12890/2020_001632
22. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288:335–344. [PubMed] DOI: 10.1111/joim.13089
23. Trigo J, García-Azorín D, Planchuelo-Gómez Á, Martínez-Pías E, Talavera B, Hernández-Pérez I, et al. Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study. J Headache Pain. 2020;21:1–10. [PubMed] DOI: 10.1186/s10194-020-01165-8
24. Kanberg N, Ashton NJ, Anderson LM, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology. 2020;95:e1754–e1759. [PubMed] DOI: 10.1212/WNL.0000000000010111
25. Choinière M, Dion D, Peng P, Banner R, Barton PM, Boulanger A, et al. The canadian STOP-PAIN project – Part 1: who are the patients on the waitlists of multidisciplinary pain treatment facilities? Can J Anesth. 2010;57:539–548. [PubMed] DOI: 10.1007/s12630-010-9305-5
26. Tappe-Theodor A, Kuner R. A common ground for pain and depression. Nat Neurosci. 2019;22:1612–1614. [PubMed] DOI: 10.1038/s41593-019-0499-8

27. Zhou W, Jin Y, Meng Q, Zhu X, Bai T, Tian Y, et al. A neural circuit for comorbid depressive symptoms in chronic pain. Nat Neurosci. 2019;22:1649–1658. [PubMed] DOI: 10.1038/s41593-019-0468-2
28. Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. Psychol Med. 2005;35:1275–1282. [PubMed] DOI: 10.1017/S0033291705004952
29. Hsieh JC, Hannerz J, Ingvar M. Right-lateralised central processing for pain of nitroglycerin-induced cluster headache. Pain. 1996;67:59–68. [PubMed] DOI: 10.1016/0304-3959(96)03066-7
30. Davidson RJ, Abercrombie H, Nitschke JB, Putnam K. Regional brain function, emotion and disorders of emotion. Curr Opin Neurobiol. 1999;9:228–234. [PubMed] DOI: 10.1016/s0959-4388(99)80032-4
31. Lei L, Huang X, Zhang S, Yang J, Yang L, Xu M. Comparison of prevalence and associated factors of anxiety and depression among people affected by versus people unaffected by quarantine during the COVID-19 Epidemic in Southwestern China. Med Sci Monit. 2020;36:1–12. [PubMed] DOI: 10.12659/MSM.924609
32. Majumdar P, Biswas A, Sahu S. COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. Chronobiol Int. 2020;37:1191–1200. [PubMed] DOI: 10.1080/07420528.2020.1786107
33. Ping W, Zheng J, Niu X, Guo C, Zhang J, Yang H, et al. Evaluation of health-related quality of life using EQ-5D in China during the COVID-19 pandemic. PLoS One 2020;15:1–12. [PubMed] DOI: 10.1371/journal.pone.0234850
34. Ozamiz-Etxebarria N, Dosil-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. Cad Saude Publica. 2020;36:1–9. [PubMed] DOI: 10.1590/0102-311X00054020
35. Cohen SP, Baber ZB, Buvanendran A, McLean BC, Chen Y, Hooten WM, et al. Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. Pain Med. 2020;21:1331–1346. [PubMed] DOI: 10.1093/pm/pnaa127
36. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123:e273–e283. [PubMed] DOI: 10.1016/j.bja.2019.03.023
37. Kotfis K, Zegan-Barańska M, Strzelbicka M, Safranow K, Zukowski M, Ely EW. Validation of the polish version of the critical care pain observation tool (CPOT) to assess pain intensity in adult, intubated intensive care unit patients: the POL-CPOT study. Arch Med Sci. 2018;14:880–889. [PubMed] DOI: 10.5114/aoms.2017.69752
38. Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29:2258–2263. [PubMed] DOI: 10.1097/00003246-200112000-00004
39. Shamji MF, De Vos C, Sharan A. The advancing role of neuromodulation for the management of chronic treatment-refractory pain. Neurosurgery. 2017;80:S108–S113. [PubMed] DOI: 10.1093/neuros/nyw047
40. Campos ACP, Antunes GF, Matsumoto M, Pagano RL, Martinez RCR. Neuroinflammation, pain and depression: an overview of the main findings. Front Psychol. 2020;11:1825. [PubMed] DOI: 10.3389/fpsyg.2020.01825
41. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. JAMA. 2018;320:2448–2460. [PubMed] DOI: 10.1001/jama.2018.18472
42. Szok D, Tajti J, Nyári A, Vécsei L. Therapeutic approaches for peripheral and central neuropathic pain. Behav Neurol. 2019:8685954. [PubMed] DOI: 10.1155/2019/8685954
43. Deer TR, Sayed D, Pope JE, Chakravarthy KV, Petersen E, Moeschler SM, et al. Emergence from the COVID-19 pandemic and the care of chronic pain: guidance for the interventionalist. Anesth Analg. 2020;131:387–394. [PubMed] DOI: 10.1213/ANE.0000000000005000
44. El-Tallawy SN, Nalamasu R, Pergolizzi JV, Gharibo C. Pain management during the COVID-19 pandemic. Pain Ther. 2020;9:453–466. [PubMed] DOI: 10.1007/s40122-020-00190-4
45. Plein LM, Rittner HL. Opioids and the immune system – friend or foe. Br J Pharmacol. 2018;175:2717–2725. [PubMed] DOI: 10.1111/bph.13750
46. de Moraes ÉB, Santos Garcia JB, de Macedo Antunes J, Daher DV, Seixas FL, Muniz Ferrari MF. Chronic Pain management during the covid-19 pandemic: a scoping review. Pain Manag Nurs. 2021;22:103-110. [PubMed] DOI: 10.1016/j.pmn.2020.11.010
47. Gahide G, Frandon J, Vendrell JF. COVID-19 patients presenting with afebrile acute abdominal pain. Clin Med. 2020;20:E4–E6. [PubMed] DOI: 10.7861/clinmed.2020-0150
48. Serrano-Ibáñez ER, Esteve R, Ramírez-Maestre C, Ruiz-Párraga GT, López-Martínez AE. Chronic pain in the time of COVID-19: Stress aftermath and central sensitization. Br J Health Psychol. 2021;26:544–552. [PubMed] DOI: 10.1111/bjhp.12483
49. Meyer-Frießem CH, Gierthmühlen J, Baron R, Sommer C, Üçeyler N, Enax-Krumova EK. Pain during and after COVID-19 in Germany and worldwide: a narrative review of current knowledge. Pain Rep. 2021;6(1):e893. [PubMed] DOI: 10.1097/PR9.0000000000000893
50. Consonni M, Telesca A, Grazzi L, Cazzato D, Lauria G. Life with chronic pain during COVID-19 lockdown: the case of patients with small fibre neuropathy and chronic migraine. Neurol Sci. 2021 Feb;42(2):389-397. [PubMed] DOI: 10.1007/s10072-020-04890-9
51. Garcia LM, Birckhead BJ, Krishnamurthy P, Sackman J, Mackey IG, Louis RG, Salmasi V, et al. An 8-week self-administered at-home behavioral skills-based virtual reality program for chronic low back pain: double-blind, randomized, placebo-controlled trial conducted during covid-19. J Med Internet Res. 2021 Feb 22;23(2):e26292. [PubMed] DOI: 10.2196/26292
52. Moutal A, Martin LF, Boinon L, Gomez K, Ran D, Zhou Y, et al. SARS-CoV-2 Spike protein co-opts VEGF-A / neuropilin-1 receptor signaling. Pain. 2020;162:243–252. [PubMed] DOI: 10.1097/j.pain.0000000000002097