Pain Symptoms in COVID-19

Tülay Şahin, MD, MSci, Aylin Ayyıldız, MD, MSci, Kardelen Gencer-Atalay, MD, Cem Akgün, MD, MSci, Hacı Mustafa Özdemir, MD, MSci, and Banu Kuran, MD, MSci

Objective: The clinical manifestations of COVID-19 range from mild symptoms to severe pneumonia and severe organ damage. When evaluated specifically for pain, the data so far have shown that myalgia, headache, and chest pain can be seen in patients at varying rates; myalgia and headache, especially, are among the initial symptoms.

Design: This retrospective chart review, followed by a descriptive survey design study, was carried out by examining patients afflicted with COVID-19. After discharge, patients were asked about the severity and the body region of their pain, their use of analgesics, their mood and mental health, and their overall quality of life.

Results: A total of 206 patients with a mean age of 56.24 ± 16.99 yrs were included in the study. Pain during COVID-19 was found to be higher compared with the preinfectious and postinfectious states. The most frequent painful areas were reported to be the neck and back before the infection, whereas the head and limbs during the infection. The most frequently used analgesic during infection was paracetamol. There was no relationship between the patients' pain and anxiety and depression; the quality of life was found to be worse in patients with persistent pain.

Conclusions: This study showed that the head and limbs were the most common painful body regions during COVID-19. It was also found that pain can continue in the postinfection period.

Key Words: COVID-19, Headache, Infection, Pain

(*Am J Phys Med Rehabil* 2021;100:307–312)

What Is Known

- The data so far have shown that myalgia, headache, and chest pain can be seen in patients at varying rates; myalgia and headache, especially, are among the initial symptoms.

What Is New

- This study showed that the head and limbs are the most common painful body regions, and pain in the neck and back is also increased during COVID-19. It was also found that pain can continue in the postinfection period.

The first cases of the novel coronavirus infection, later named COVID-19 by the World Health Organization, were reported in late December 2019 in Wuhan province in China.[1,2] Since then, COVID-19 has infected more than 77.4 million people and killed more than 1.7 million people worldwide.[3] There are different treatment modalities applied for different stages and manifestations of the disease.[4] Clinical trials have been started to test the efficacy of antiviral therapies, such as nucleoside analogs, hydroxychloroquine, and protease inhibitors.[5] The human vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are currently being tested in phase 1–3 trials.[4]

The clinical manifestations of patients infected with COVID-19 range from mild symptoms to severe organ damage and severe pneumonia. Common symptoms include fever (77.4%–98.6%), cough (59.4%–81.8%), fatigue (38.1%–69.6%), dyspnea (3.2%–55.0%), myalgia (11.1%–34.8%), sputum production (28.2%–56.5%), and headache (6.5%–33.9%), whereas sore throat, rhinorrhea, chest pain, hemoptysis, conjunctival congestion, diarrhea, nausea, and vomiting are rare symptoms.[6]

When explicitly evaluated for pain, the data so far have shown that myalgia, headache, and chest pain can be seen in patients at varying rates; myalgia and headache, especially, are among the initial symptoms.[7] Widespread tissue and organ damage caused by the infection, damage to tissues such as muscles and joints, and increased cytokines are responsible for the pathogenesis of pain. Su et al.[8] reported possible pain mechanisms due to COVID-19. This study emphasized the angiotensin-converting enzyme 2 (ACE2) receptor, which is used by the virus to enter the cell. It has been determined that the ACE/Ang II/AT1 receptor pathway facilitates the transmission of pain in the spinal dorsal horn, and the ACE2/Ang (1–7)/Mas receptor pathway can relieve pain. With the transmission of COVID-19 to ACE2-positive cells in the spinal dorsal horn, the reduction of functional ACE2 may result in subsequent Ang II accumulation, and Ang (1–7) reduction could cause pain.[8] The pain pathogenesis is multifactorial. The pathogenesis of pain in COVID-19 is still under investigation. Therefore, many factors other than cytokines may be responsible for the pathogenesis of COVID-19 pain. Therefore, pain is a clinical symptom of COVID-19 infection and one of the major causes of disease-related disability. This study aimed to investigate the painful body regions and their severity before, during, and after COVID-19 infection. This study also aimed

From the Division of Pain Medicine, Department of Physical Medicine and Rehabilitation, Science Health University, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey (TŞ); Department of Physical Medicine and Rehabilitation, Science Health University, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey (AA, BK); Physical Medicine and Rehabilitation Department, Marmara University Medical Faculty, Istanbul, Turkey (KG-A); Department of Neurosurgery, Science Health University, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey (CA); and Department of Orthopedics and Traumatology, Science Health University, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey (HMÖ).

All correspondence should be addressed to: Tülay Şahin, MD, MSci, Division of Pain Medicine, Department of Physical Medicine and Rehabilitation, Science Health University, Şişli Hamidiye Etfal Training and Research Hospital, Şişli Etfal Eğitim ve Araştırma Hastanesi 34377 Şişli, Istanbul, Turkey.

Aylin Ayyıldız is in training.

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ajpmr.com).

ISSN: 0894-9115
DOI: 10.1097/PHM.0000000000001699

to reveal the relationship between pain severity and features of the disease.

METHODS

This retrospective chart review, followed by a descriptive survey design study, was carried out by analyzing COVID-19 probable, possible, and/or confirmed patients hospitalized in the authors' hospital between March 13, 2020, and May 13, 2020. Patients were determined as possible, probable, and confirmed cases according to the European Centre for Disease Prevention and Control, a case definition for COVID-19, as of May 29, 2020.[9] The case definitions are as follows: (1) possible case, any person meeting the clinical criteria; (2) probable case, any person meeting the clinical criteria with an epidemiological link or any person meeting the diagnostic criteria, including radiological evidence for COVID-19; (3) confirmed case, any person meeting the laboratory criteria.[9] Ethics committee approval was received for this study from the local ethics committee of Health Sciences University, Şişli Hamidiye Etfal Training and Research Hospital (Protocol No: 2811, ClinicalTrials.gov Identifier: NCT04454333) and the Ministry of Health. This study conforms to all Strengthening the Reporting of Observational Studies in Epidemiology guidelines and reports the required information accordingly (see Supplemental Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B210). Verbal informed consent, which was approved by the ethics committee, was obtained from all patients during the phone call. A third-year resident in physical medicine and rehabilitation reviewed the hospital records and conducted the interviews that took approximately 30 mins by telephone calls during weekdays. This interview involved questions about comorbidities, COVID-19 symptoms, duration of symptoms, length of hospital stay, pain status, anxiety and depression levels, and overall quality of life.

The patients were asked about their painful body region(s), including the neck, back, head, and upper and lower limbs and the severity of their pain (using a numeric rating scale [NRS]) before, during, and after COVID-19. Pain before COVID-19 was accepted only if the patients had experienced chronic pain in a specific region of their body for more than 3 mos. The type and duration of analgesic drug usage were also recorded. Anxiety and depression levels were evaluated using the Turkish version of the Hospital Anxiety and Depression Scale (HADS), and quality of life was evaluated using the Turkish version of the 12-item Short Form Survey (SF-12). Using an NRS, patients scored their pain levels between 0 and 10 points. Higher scores indicate a worse outcome. The HADS is a 14-item self-report screening scale. It contains two 7-item subdomains: one for anxiety and one for depression, both with a score range of 0–21. Higher scores indicate a worse outcome. Two summary scores are reported from the SF-12: a mental component score and a physical component score. Higher scores indicate better outcomes.

Disease severity was graded according to the clinical situation. Patients who needed intensive care were classified as severe, whereas patients who were treated in the service and required oxygen support were classified as moderate, and patients with mild pneumonia without oxygen support were classified as mild.

Hospital records also noted the results of real-time reverse transcriptase polymerase chain reaction tests and chest computed tomography. The drugs used to treat the COVID-19 infection, the drugs used to treat pain, specifically, and laboratory parameters (white blood cell count, leukocyte count, renal functional test, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, procalcitonin level, D-dimer, and ferritin levels) were also recorded.

Statistical analysis of the study was performed using SPSS for Windows 20.0. The normal distribution of quantitative values was assessed by the histogram, Q-Q graph, and Shapiro-Wilk test. Because the distribution was not normal, the Wilcoxon test was used to compare NRS scores before and during COVID-19 infection and before and after COVID-19 infection. The Mann-Whitney *U* test was used to compare the HADS and SF-12 subgroup scores in patients with and without persistent pain after COVID-19 infection. Logistic regression analysis was used to examine the factors related to the severity of pain during illness. Bonferroni correction was considered statistically significant at a *P* value of less than 0.025 for evaluating the results of the Wilcoxon test. Otherwise, a statistical significance level of a *P* value of less than 0.05 was accepted.

RESULTS

A total of 466 patients hospitalized with a diagnosis of COVID-19 at the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital, were retrospectively screened. Of these patients, 212 did not answer the telephone calls and 34 patients could not be reached because incorrect phone numbers were recorded in their hospital records. Four of the patients had communication problems due to language differences, and 10 patients did not want to complete the questionnaire. Therefore, 206 patients were contacted and completed the questionnaires and answered questions about their pain in the head, neck, back, and upper and lower limb areas before, during, and after COVID-19 as well as about their levels of anxiety and depression after COVID-19 and their overall quality of life (Fig. 1).

The mean age of the patients was 56.24 ± 16.99 yrs; 51% were female. The demographic characteristics and predisease clinical characteristics of the patients are shown in Table 1. The initial symptom was fever in 57.8% of the patients, cough in 60.2%, dyspnea in 22.8%, and runny nose in 0.5%. It was shown that 29.6% of the patients were confirmed cases, whereas 68.9% were probable and 1.5% were possible cases. In terms of disease severity, 74.3% of the total patients had mild disease, 23.3% had moderate disease, and 2.4% had severe disease. The mean hospitalization time of all patients was 7.82 ± 4.67 days. Four patients stayed in the intensive care unit; the average length of stay in the intensive care unit was 6 ± 3.94 days (Table 2).

It was found that 40.7% of the patients experienced chronic pain in a specific region of their bodies for at least 3 mos before COVID-19, and this rate increased to 82.5% during COVID-19 and to 55.1% after COVID-19. Before the infection, the most painful regions were the neck and back. During infection, patients mostly experience pain in the head and limbs. The severity of pain increased in all body regions during the infection when compared with the patients' preinfection state. This increase remained after recovery from the infection in all regions, except for the back. During hospitalization, paracetamol was administered to 68 patients (33%), nonsteroidal anti-inflammatory drugs (NSAIDs) to five patients (2.4%), and opioid agents to one patient (0.5%). After recovery from the disease, 24 patients used

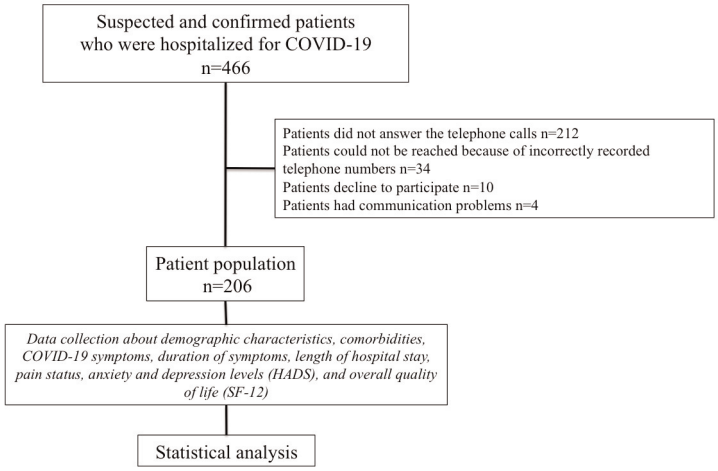

FIGURE 1. Participant flow diagram.

paracetamol (11.7%), 16 patients used NSAIDs (7.8%), 3 patients used corticosteroids in (1.5%), and no patients used opioid agents (Table 3).

A logistic regression analysis did not reveal a clear relationship between the severity of patients' pain during their illness, the severity of their disease, educational levels, comorbidities, drugs used during illness, length of hospital stay, and duration of mechanical ventilation. Comparing patients who experienced pain before COVID-19 with those who did not have pain before COVID-19, the HADS anxiety subdomain was higher, and physical component score was lower ($P = 0.006$, $P < 0.001$, respectively). In patients with persistent pain after COVID-19 compared with those who did not have pain after COVID-19, physical component score was lower ($P < 0.001$), whereas there was no difference in the mental component score and HADS subdomains (Table 4).

DISCUSSION

This study investigated the painful conditions that occurred during the course of COVID-19. Epidemiological and clinical data on COVID-19 emphasize that advanced age and concomitant chronic disease are risk factors for this infection.[10] Consistent with this, the average age of patients in this study was older than 50 yrs, and more than half of them had one or more comorbidities. Their most common symptoms were fever, cough, and dyspnea. Similarly, studies and reviews conducted worldwide since the onset of COVID-19 have determined that the main symptoms are fever, cough, and dyspnea; a small subset of patients experience gastrointestinal symptoms, such as nausea and diarrhea.[11]

Among the painful conditions seen during the disease, the most frequently reported in the literature is widespread muscle myalgia and headache. Their frequency varies between studies and can affect up to 40% of patients.[12–15] Thus, pain treatment has an important role in the response to this disease. In this study, 40.7% of patients reported experiencing pain before the disease, whereas the rate of patients reporting pain during the infection was 82.5%. Studies have reported that headache and widespread myalgia are the most frequently observed focus of pain during the disease, whereas back pain and neck pain follow closely behind. In this study, pain in the head and limbs was reported more frequently than in the literature, which may be due to several patients experiencing pain before the infection. Because this study conducted intensive pain-oriented inquiries, this may have increased patients' awareness of their pain, which may have affected the results. Patients reported an increase in back and neck pain, and as far as the authors know, no other study has examined patients' pain in detail, including these areas.

TABLE 1. Demographic features of patients

Age, yr	56.24 ± 16.99
Sex	
Female	105 (51)
Male	101 (49)
Education	
No formal education	10 (4.9)
Primary school	42 (20.4)
Middle school	31 (15)
High school	87 (42.2)
University	36 (17.5)
Occupation	
Employee	85 (41.3)
Housewife	75 (36.4)
Retiree	41 (19.9)
Unemployed	4 (1.9)
Student	1 (0.5)
Comorbidity	
None	96 (46.8)
Hypertension	73 (35.4)
Diabetes mellitus	35 (17)
Coronary artery disease	33 (16)
Chronic Respiratory disease	15 (7.3)
Rheumatologic disease	10 (4.1)
Cancer	8 (3.9)
Multiple	48 (23.4)

Data are presented as mean ± SD or *n* (%).

TABLE 2. Clinical features of the patients obtained from hospital records

Symptoms	
Fever	119 (57.8)
Cough	124 (60.2)
Dyspnea	47 (22.8)
Rhinorrhea	1 (0.5)
Symptom duration, *d*	6.62 ± 4.86
Severity of disease	
Mild	153 (74.3)
Moderate	48 (23.3)
Severe	5 (2.4)
RT-PCR test	
Positive	61 (29.6)
Negative	145 (70.4)
Thorax CT	
Confirmed pneumonia	203 (98.5)
Medications	
Hydroxychloroquine	201 (97.6)
Azithromycin	25 (12.1)
Oseltamivir	104 (50.5)
Favipiravir	12 (5.8)
Lopinavir + ritonavir	3 (1.5)
High-dose vitamin C	4 (1.9)
Corticosteroid	8 (3.9)
Tocilizumab	2 (1)
Low–molecular-weight heparin	74 (35.9)
Duration of hospitalization, *d*	7.82 ± 4.67
Patients required mechanical ventilation	3 (1.5)
Duration of mechanical ventilation, *d*	6 ± 3.64
Duration since discharge, *d*	45.99 ± 14.64

Data are presented as mean ± SD or *n* (%).
RT-PCR, reverse transcriptase polymerase chain reaction.

Pain during COVID-19 can occur through various mechanisms. In the literature, in COVID-19, very few studies have investigated both pain characteristics and pain mechanisms. The most studied area in this regard has been headache.[16,17] A review was recently published that included 20 studies examining headache in COVID-19.[18] In this study, possible mechanisms of headache are described. The first of these mechanisms is the inflammatory mechanism in which nociceptive sensory neurons are activated by cytokines and chemokines, similar to migraine and other headaches. Viral neuroinvasion, hypoxia due to pulmonary involvement, and thrombosis due to hypercoagulopathy are listed as other mechanisms. In this review, the lack of studies regarding the specific features of pain in COVID-19 has been emphasized.[18] In their published study on the mechanisms and features of headache, Bolay et al.[16] emphasized the necessity of investigating the characteristics of headache to guide further research. Although there are no specific detailed studies on musculoskeletal pain involving neck, back, and limbs, similar mechanisms with headache may also be effective in the musculoskeletal system. COVID-19 enters the cells via the ACE2 receptor using serine protease (TMPRSS2).[19] These molecules are known to be found in various cells in the musculoskeletal system.[20,21] Therefore, direct damage to these tissues may cause pain, and cytokines and proinflammatory molecules may also cause damage to the musculoskeletal tissue. In this study, the average time after infection was approximately 45 days (7–78 days), and 55.1% of patients still experienced pain. It has been reported in the literature that the effects of immune system changes and systemic inflammation on the nervous system (both the central nervous system and the peripheral nervous system) may be effective in the chronicity of pain.[22] The fact that the patients' postinfection pain rates were higher than the preinfection rates showed that for some patients, the pain continues after recovery from COVID-19. This finding suggests that pain control is also required after recovery and supports the need to investigate the characteristics of pain.

TABLE 3. Painful regions of patients

	Before SARS-CoV-2[a]			During SARS-CoV-2[b]			After SARS-CoV-2[c]				
		NRS (0–10)			NRS (0–10)			NRS (0–10)		$P^{a,b}$	P^{a-c}
	n (%)	Median	95% CI	*n* (%)	Median	95% CI	*n* (%)	Median	95% CI	Wilcoxon	
Pain	83 (40.7)			170 (82.5)			113 (55.1)				
Neck	63 (30.6)	4	3.84–4.6	96 (46.6)	5	4.34–5.08	75 (36.6)	4	3.61–4.29	**<0.001**	0.014[d]
Back	70 (34.1)	4	3.89–4.6	104 (50.7)	5	4.53–5.22	80 (38.8)	4	3.61–4.3	**<0.001**	0.096
Head	34 (16.5)	3	2.82–4.01	127 (61.7)	5	4.35–5.08	62 (30.4)	3	2.6–3.37	**<0.001**	**<0.001**
Upper limbs	42 (20.5)	3.5	3.13–3.97	113 (55.1)	5	4.19–4.87	65 (31.6)	3	2.8–3.56	**<0.001**	**<0.001**
Lower limbs	49 (23.8)	4	3.43–4.32	126 (61.5)	5	4.48–5.17	77 (37.4)	3	2.87–3.65	**<0.001**	**<0.001**
Analgesic usage											
Paracetamol				68 (33)			24 (11.7)				
NSAIDs				5 (2.4)			16 (7.8)				
Opioids				1 (0.5)			0 (0)				

Bold indicates significant $P < 0.05$.
[a]Before SARS-CoV-2.
[b]During SARS-CoV-2.
[c]After SARS-CoV-2.
[d]$P < 0.05$.
CI, confidence interval.

TABLE 4. Patients' level of anxiety and depression and quality of life

	Patients Without Pain After SARS-CoV-2c (n = 113)		Patients With Pain After SARS-CoV-2c (n = 93)		
	Median	**95% CI**	**Median**	**95% CI**	***P***
HADS					
Anxiety	3	3.34–5.13	5	4.86–7.07	0.071
Depression	1	3.01–5.06	5	4.28–6.14	0.075
SF-12					
Physical	52.08	46.88–50.53	44.56	41.32–45.06	**<0.001**
Mental	51.29	46.94–50.5	52.72	48.15–51.15	0.401

Bold indicates significant $P < 0.05$.
CI, confidence interval.

In this study, the analgesic drugs used by patients with COVID-19 were also investigated. This study found that 33% of the patients used paracetamol. Only five patients used NSAIDs. Concerns have surfaced after observations that the symptoms of four young patients in France worsened after they used ibuprofen; NSAIDs may increase the level of ACE2 and, therefore, should be avoided.[23] The European Medicine Agency has recommended that there is no evidence to establish a link between NSAIDs and worsening of COVID-19 and no reason for patients who are taking NSAIDs for chronic diseases to discontinue taking them.[24] However, many national treatment guidelines recommend using paracetamol as the first-line option for symptomatic treatment of COVID-19, especially for pain.[24–27] Accordingly, paracetamol was the most preferred analgesic agent in this study. In addition, the mean pain NRS score of the patients was between 3 and 4. The relatively low level of pain severity, which can be responsive to analgesics such as paracetamol, may also have resulted in this finding. Only one patient whose pain could not be managed by paracetamol or NSAIDs had to use an opioid agent for a stronger analgesia during hospitalization. The effects of opioids on the immune system, especially the immunosuppressive effect, may differ depending on the type of opioid agent[27]; however, this is not considered to be a primary factor affecting the outcome of this study. The immunosuppressive effects of opioids are unlikely, but the pathophysiology of COVID-19 pain is still being studied, and it has been approached with suspicion because there is no definitive information.

This study could not reveal a relationship between the patients' pain during their illness and the severity of their disease, comorbidities, drugs used during illness, educational level, hospital stay, and laboratory parameters during hospitalization. Similarly, there was no correlation between pain and educational attainment in this study. There are studies in the literature in which there is a correlation between pain and educational level.[28] The rationale behind why a correlation could not be detected in this study could be attributed to the low number of patients and the milder pain levels of the patients. Considering that tissue damage caused by the increase in inflammatory cytokines during infection plays a role in the mechanism of pain formation, it may be thought that there should be a relationship between disease severity and pain. The fact that the patient group in this study showed relatively mild clinical and laboratory parameters may have affected the results, and the fact that pain sensation is a multifactorial and subjective sensation seems to be a stronger factor.

In this study, different aspects of painful conditions during COVID-19 were investigated. Patients were also asked about their anxiety and depression levels and quality of life. The relationship between chronic pain, anxiety, and depression has been well researched and defined. Acute or chronic painful conditions can affect anxiety and depression levels, and as a result, quality of life can be adversely affected.[29] Thus, it is somewhat surprising that there was no significant difference in the levels of anxiety and depression between those who continued to experience pain after recovery from COVID-19 and those who did not have any pain after an average of 45 days. Therefore, this relationship should be investigated in more detail. In the evaluation using the SF-12 quality of life scale, the fact that the physical scores were significantly low in patients with pain is an important finding that shows the negative effect of pain on the quality of life.

One of the limitations of this study is the retrospective investigation of patients. Another limitation is that the majority of the patient group showed mild and moderate disease severity. The low number of cases with severe disease resulted in an evaluation that included little data for these patients. In addition, the patients could not be interviewed face-to-face, and because of this, myalgia and muscle-joint pain could not be discriminated from limb pain. The last one is that the duration after discharge was quite heterogeneous in the patient population to include more patients in the study. This could have caused memory bias. The strength of the study is that, to the best of the authors' knowledge, it is one of the first studies to focus on COVID-19 and pain, which draws attention to clinicians in the field and concurrently to future studies.

In conclusion, this study demonstrated that, independent of other factors, the head and limbs are the most common painful body regions when infected with COVID-19. The quality of life of patients with persistent pain after COVID-19 was shown to be affected. Currently, research is primarily focused on disease prevention strategies and treatment methods. Coping with pain is an important component of the treatment of the disease. Considering that pain can sometimes persist after recovery from the illness and that this may have a negative impact on the quality of life, it is clear that well-designed studies are needed to evaluate painful conditions in COVID-19 in more detail.

REFERENCES

1. Rothan HA, Byrareddy SN: The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020;109:102433
2. Stübinger J, Schneider L: Epidemiology of coronavirus COVID-19: forecasting the future incidence in different countries. *Healthcare (Basel)* 2020;8:99
3. Center for Systems Science and Engineering (CSSE): Coronavirus COVID-19 global cases. Available at: https://coronavirus.jhu.edu/map.html. Published 2020. Accessed January 21, 2021
4. Wiersinga WJ, Rhodes A, Cheng AC, et al: Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324:782–93
5. Ahn DG, Shin HJ, Kim MH, et al: Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). *J Microbiol Biotechnol* 2020;30:313–24
6. Ge H, Wang X, Yuan X, et al: The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis* 2020;39:1011–9
7. Tang D, Comish P, Kang R: The hallmarks of COVID-19 disease. *PLoS Pathog* 2020;16:e1008536
8. Su S, Cui H, Wang T, et al: Pain: a potential new label of COVID-19. *Brain Behav Immun* 2020;87:159–60
9. Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. Available at: https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition. Updated 2020. Accessed January 21, 2021
10. Zhou F, Yu T, Du R, et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62
11. Jiang F, Deng L, Zhang L, et al: Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *J Gen Intern Med* 2020;35:1545–9
12. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020;368:m792
13. Chen N, Zhou M, Dong X, et al: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13
14. Wang D, Hu B, Hu C, et al: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9
15. Jin X, Lian JS, Hu JH, et al: Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020;69:1002–9
16. Bolay H, Gül A, Baykan B: COVID-19 is a real headache! *Headache* 2020;60:1415–21
17. Bobker SM, Robbins MS: COVID-19 and headache: a primer for trainees. *Headache* 2020;60:1806–11
18. Tolebeyan AS, Zhang N, Cooper V, et al: Headache in patients with severe acute respiratory syndrome coronavirus 2 infection: a narrative review. *Headache* 2020;60:2131–8
19. Hoffmann M, Kleine-Weber H, Schroeder S, et al: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.e8
20. Disser NP, De Micheli AJ, Schonk MM, et al: Musculoskeletal consequences of COVID-19. *J Bone Joint Surg Am* 2020;102:1197–204
21. Lee N, Hui D, Wu A, et al: A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348:1986–94
22. Sun W, Gao H, Luo Y, et al: Management of immunity alteration-induced chronic pain during the coronavirus disease-2019 (COVID-19) pandemic. *Front Microbiol* 2020;11:572318
23. Day M: Covid-19: European drugs agency to review safety of ibuprofen. *BMJ* 2020;368:m1168
24. EMA advice on the use of NSAIDs for Covid-19. *Drug Ther Bull* 2020;58:69
25. FDA: FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed January 21, 2021
26. Cohen SP, Baber ZB, Buvanendran A, et al: Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. *Pain Med* 2020;21:1331–46
27. Shanthanna H, Strand NH, Provenzano DA, et al: Caring for patients with pain during the COVID-19 pandemic: consensus recommendations from an international expert panel. *Anaesthesia* 2020;75:935–44
28. Saastamoinen P, Leino-Arjas P, Laaksonen M, et al: Socio-economic differences in the prevalence of acute, chronic and disabling chronic pain among ageing employees. *Pain* 2005;114:364–71
29. Michaelides A, Zis P: Depression, anxiety and acute pain: links and management challenges. *Postgrad Med* 2019;131:438–44