



# Pain during and after coronavirus disease 2019: Chinese perspectives

Feng Jiang<sup>a,\*</sup>, Wan-Li Yang<sup>a</sup>, Jia-Wei Wang<sup>b</sup>, Zhen Zhu<sup>b</sup>, Ceng Luo<sup>c</sup>, Lars Arendt-Nielsen<sup>d</sup>, Xue-Jun Song<sup>e</sup>

## Abstract

The coronavirus disease 2019 (COVID-19) global pandemic poses a major threat to human health and health care systems. Urgent prevention and control measures have obstructed patients' access to pain treatment, and many patients with pain have been unable to receive adequate and timely medical services. Many patients with COVID-19 report painful symptoms including headache, muscle pain, and chest pain during the initial phase of the disease. Persistent pain sequela in patients with COVID-19 has a physical or mental impact and may also affect the immune, endocrine, and other systems. However, the management and treatment of neurological symptoms such as pain are often neglected for patients hospitalized with COVID-19. Based on the China's early experience in the management of COVID-19 symptoms, the possible negative effects of pre-existing chronic pain in patients with COVID-19 and the challenges of COVID-19 prevention and control bring to the diagnosis and treatment of chronic pain are discussed. This review calls to attention the need to optimize pain management during and after COVID-19.

**Keywords:** Global pandemic, COVID-19, Pain management, SARS-CoV-2

## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has dramatically changed the way people live around the world. In particular, it has had a profound impact on normal medical activities and required repositioning health care personnel to front line services. To cope with the risk of hospital-acquired infection, medical institutions have had to multiply health care costs and resource use.<sup>5</sup> However, patients with pain may not get better care despite the increased health care spending. Importantly, to

reallocate resources to the emergency department, many non-emergency departments at medical institutions have been completely or partly closed, including many pain management departments.<sup>16</sup> This review, based on the Chinese experience, attempts to uncover the increased risk of pain that patients with COVID-19 may face and outline that pain may not only be a symptom of COVID-19 but also one of the risk factors that influence the improvement of COVID-19 and other patients. This review will highlight and discuss China's early experience in the management of COVID-19 symptoms, including pain, and apply this in a global context.

### 1.1. COVID-19 infection increases the risk of pain

Although pulmonary infection is the major symptom of SARS-CoV-2 infection, more than a third of the patients with COVID-19 had different neurological symptoms which may involve the central nervous system (dizziness, headache, impaired consciousness, ataxia, and epilepsy) and the peripheral nervous system (sensory system impairments and neuralgia) and skeletal muscle damage/pain or chest pain.<sup>41</sup> In some patients, neurological symptoms may be the first or only manifestation of COVID-19.<sup>2</sup> In addition, patients with more severe SARS-CoV-2 infection are more likely to show neurological symptoms.<sup>41</sup> Although severe pain is rare, different forms of pain are important clinical manifestations. In a large study based on 1,099 patients (926 nonsevere and 173 severe) collected in 552 Chinese hospitals, 150 (13.6%) had headache and 164 (14.9%) had muscle or/and joint pain and 153 (13.9%) with sore throat.<sup>24</sup> Because of the differences in study objectives, a very wide range of pain prevalence was reported.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

These authors contributed equally to this article.

<sup>a</sup> Translational Institute for Cancer Pain, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Chongming Branch, Shanghai, China, <sup>b</sup> School of Life Sciences, Shanghai University, Shanghai, China, <sup>c</sup> Department of Neurobiology, School of Basic Medicine, Fourth Military Medical University, Xi'an, China, <sup>d</sup> Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark, <sup>e</sup> SUSTech Center for Pain Medicine, School of Medicine, Southern University of Science and Technology, Shenzhen, Guangdong, China

\*Corresponding author. Address: Translational Institute for Cancer Pain, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Chongming Branch, Shanghai, China 202150. Tel.: 86-21-69691756. E-mail address: fengjiang@xinhua.com.cn (F. Jiang).

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The International Association for the Study of Pain. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

PR9 6 (2021) e931

<http://dx.doi.org/10.1097/PR9.0000000000000931>

### 1.2. Headache

Headache is one of the most frequent forms of pain during SARS-CoV-2 infection. The exact incidence of headaches caused by the virus needs further study, while most studies suggest headache prevalence ranged between 6% and 21%.<sup>15,58</sup> Whether the headache is caused by the virus invading the nervous system directly or indirectly remains uncertain. An autopsy report showed damage to the central nervous system (CNS) as evidenced by brain edema and partial neuronal degeneration.<sup>63</sup> The presence of SARS-CoV-2 in the cerebrospinal fluid was confirmed by genome sequencing, indicating that the virus may penetrate and cause damage to the CNS.<sup>4</sup> Existing knowledge about coronaviruses suggests that the coronavirus family has a certain tropism for the CNS.<sup>8</sup> Neuronal pathways allow the virus to enter the CNS.<sup>1</sup> The virus can infect sensory and motor nerve endings to migrate, then achieve retrograde or anterograde transport by movement protein, dynein protein, and dynamic neurons to invade nerve tissues and cause infection of immunocompetent microglia, astrocytes, and macrophages in the CNS.<sup>3,56,57</sup>

### 1.3. Muscle pain

Muscle pain is another common symptom in patients with COVID-19. When comparing the existing studies, the incidence of muscle pain ranged between 7% and 32%.<sup>24,36,66</sup> Since the target receptor of SARS-CoV-2, ACE2, is present in almost all tissues, including muscle tissues, the virus can attack skeletal muscle cells directly, causing skeletal muscle weakness, fatigue, pain, and injury.<sup>20,27,43,53</sup> Rhabdomyolysis has been found in patients with severe SARS-CoV-2 infection.<sup>13,19,29,58</sup> Apart from the direct cause, the inflammatory response induced by SARS-CoV-2 infection may be another important cause of muscle pain.<sup>59</sup> Muscle injury caused by COVID-19 is characterized by a significant increase in the levels of creatine kinase and lactate dehydrogenase, and its pathophysiology is primarily believed to be caused by excessive inflammation.<sup>33</sup>

### 1.4. Chest pain

Chest pain, while relatively rare, generally occurred in patients with more severe symptoms especially when lesions are close to the pleura with abundant nerves.<sup>7</sup> A descriptive study of the epidemiology and clinical characteristics of 99 cases of new coronavirus pneumonia in Wuhan in 2019 showed that when admitted to the hospital, most patients had fever or cough, and some patients had chest pain (2%).<sup>11</sup> Compared with the patients with mild symptoms, the incidence of chest pain and dyspnea is higher in critical patients. In the severe patients, chest pain may be caused by the inflammatory reaction of the pleura. Their alveolar tissue is severely damaged, resulting in dyspnea.

### 1.5. Other kinds of pain

Other types of pain are also found during the process of clinical diagnosis. Researchers from Anglia Ruskin University found that among 83 interviewees, there was a significant increase in eye pain in the confirmed patients; 16% reported eye pain as one of their symptoms.<sup>34</sup> Sore throat was reported in 5% to 17.4% of patients with COVID-19 in China.<sup>11,21,60</sup> Of 76 patients with acute abdominal pain, 9 patients (11.8%) were eventually diagnosed with COVID-19.<sup>54</sup>

### 1.6. Pain sequela after COVID-19 in patients with or without chronic pain

Those patients with COVID-19 who experience intense pain and distress during their stay in the intensive care unit (ICU) seem to be at a higher risk of developing chronic pain after discharge.<sup>32,39</sup> Unfortunately, in the ICU, pain is often overlooked as being low priority and thus poorly managed, even in a well-staffed and skilled environment.<sup>50</sup> It is important to consider how to implement effective pain management in the ICU to reduce acute pain and reduce the risk of chronic pain in patients with COVID-19.<sup>31,50</sup> Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU have been developed and adopted in many ICUs.<sup>14</sup> This strategy can obviously strengthen pain management of patients through multidisciplinary management of symptoms, mobility, and communication. Although there is not yet substantial evidence to support the statement that pre-existing chronic pain may worsen the pain during and after COVID-19, many severe chronic diseases such as coronary artery disease, diabetes, cancer, and chronic obstructive pulmonary disease are often accompanied by pain and also heighten the risk of death during COVID-19. Patients with chronic pain already experiencing depression, inattention, fatigue, and insomnia may find COVID-19 symptoms especially disturbing.

### 1.7. Presence of pain may affect the recovery from COVID-19

To concentrate available resources during the initial wave of COVID-19, most medical institutions had to close nonintensive care services including pain management departments.<sup>55</sup> Besides the increased burden on the medical staff, patients with severe chronic pain, the disabled, and the elderly had reduced access to psychological and interdisciplinary treatments.<sup>30</sup> A lack of face-to-face counseling services complicates individual assessment of analgesic use risk. When pain cannot be effectively assessed and treated, quality of life is reduced and treatment of underlying diseases may be impaired.<sup>47,64</sup> The presence of chronic pain can activate the hypothalamus–pituitary–adrenal axis and alter the function of the immune and endocrine systems.<sup>26,28,46,49,68</sup> At the Renmin Hospital of Wuhan University, a total of 663 patients with COVID-19 admitted between January 2020 and February 2020 were enrolled in a retrospective cohort study. Muscle pain was significantly associated with severe COVID-19 ( $P = 0.028$ ) and to the patients' hospital course ( $P < 0.001$ ). Muscle pain, expectoration, and decreased albumin were believed to be independent risk factors influencing patients' improvement during follow-up.<sup>66</sup> Furthermore, groups such as the poor, the widowed elderly, and the homeless are more likely to suffer from chronic pain and comorbidities,<sup>42</sup> have less access to health care, and are a high-risk group for severe COVID-19.<sup>6</sup>

Online pain management programs where patients are in contact with health care providers remotely are promising.<sup>62</sup> Online resources can disseminate pain education and can develop online training programs on pain self-management for health care professionals, patients with pain, and relevant personnel. Although much of the existing research is optimistic about eHealth Care, studies may not adequately assess groups without access or ability to use these services, including children, the elderly, or those with intellectual disabilities.<sup>16</sup>

### **1.8. China's approaches to pain control during and after COVID-19**

China's response to COVID-19 has been rigorous. After the outbreak, the Central Government's Leading Group for Epidemic Work swiftly formulated a response plan which put people's lives as the top priority. With the precise decision of the Chinese government and the joint efforts of volunteers from all over the country, the further expansion of the epidemic was finally controlled, which laid a solid foundation for the Chinese control of the epidemic throughout the country. Many of China's practices are worthy of discussion and reference.

### **1.9. Popularization of COVID-19 knowledge**

Popularizing science and improving citizens' scientific quality are long-term concern of the Chinese government. This ensures that the public can properly understand and scientifically protect against the COVID-19 epidemic. In the very early days of the epidemic, China published the basic knowledge of novel coronavirus, the key points of self-protection, and the relevant national epidemic prevention and control policies to the public on the official government media, such as the Xinhua News Agency and China Central Television. At the same time, authoritative medical organizations, such as the Chinese Medical Association, China Preventive Medicine Association, and Chinese Association for the Study of Pain, educated the public through their official information release platforms. Through their professional guidance, self-health management of patients during the epidemic period was strengthened. For example, the Chinese Association for Science and Technology issued an article on home care and rehabilitation guidance for patients with shoulder joint pain during the epidemic.<sup>13</sup> It is worth noting that new media platforms, which are more easily accepted by the people, have played a huge role in the prevention and control of the epidemic. Only when most people are familiar with the correct knowledge and prevention measures of COVID-19 can epidemic prevention work be performed more effectively.

### **1.10. Setting up professional diagnosis and treatment department**

After the SARS epidemic and experience in 2003, China set up professional fever clinics in general hospitals grade II and above (grade III is the highest grade). All patients with fever, cough, and pain were to be admitted to the fever clinic for diagnosis and treatment. During the period of regular epidemic prevention and control, the registration, imaging examination, nucleic acid testing, isolation, reporting, treatment, and referral of patients with fever and pain can be conducted in this department. The fever clinics performed strict terminal disinfection operations. On December 3, 2020, the State Council's Joint Prevention and Control Mechanism Press Conference announced that more than 7,000 fever clinics had been completed nationwide.<sup>45</sup>

### **1.11. Standardize the use of analgesic and febrifuge drugs**

Fever and pain are important early diagnostic indications for most patients with COVID-19. The China National Drug Administration issued an administrative order to further regulate the use of analgesic and antipyretic drugs, even those not typically thought of as drugs of abuse.<sup>17</sup> Meanwhile, the National Health Committee issued the "Expert Consensus on the Management and Guidance of the Rational Use of Home Medications for

Common People During the Epidemic Period"<sup>18</sup> and provided pain management and pain medication training to all medical staffs. The purpose of these measures is to guide both medical staffs and patients on the correct use of medicines and correct reporting of early symptoms.

### **1.12. Early detection of close contacts**

Finding close contacts of confirmed patients can help detect potentially infected persons by identifying trajectories and early symptoms, clearly describe the entire transmission chain and transmission network, and make epidemic control more effective.<sup>25</sup> In January 2021, a few local cases were reported in Beijing, Shanghai, Hebei, and other places of China. The local governments immediately organized large-scale epidemiological follow-up. Most subsequent confirmed cases were close contacts identified by epidemiological means. The scattered outbreaks were controlled in only 1 month. Fever, pain, and other symptoms of patients with COVID-19 after infection clearing and discharge should also be included in the epidemiological follow-up.

### **1.13. Improve the public treatment system of COVID-19**

In developing countries, even in many developed countries, the cost of treatment is a heavy burden for most patients with COVID-19. This may lead some patients to report their symptoms untruthfully. The Chinese government has designated special medical hospitals in each city to treat patients with COVID-19. In these institutions, free treatment including pain management for people infected with COVID-19 is provided. All the treatment costs are covered by the national public health insurance fund. This measure has helped implement the "early detection, early isolation, early treatment" guideline and fully guarantees the right of every citizen to have fair access to medical services. According to statistics from the China Medical Insurance Administration, in the first quarter of 2020 alone, China's public medical insurance invested more than 19.3 billion yuan (approx. 3.1 billion US dollars) for the treatment of patients with COVID-19.<sup>52</sup> In addition, to encourage the public to receive the COVID-19 vaccine and ensure that low-income groups can also get the vaccine fairly, China has announced free vaccination for all citizens, the cost of which will be covered by the national public medical insurance fund.

China has adopted multiple channels to ensure the pain control needs of patients without COVID-19 are addressed. The National Ministry of Civil Affairs continues to purchase social medical services for poor people and actively encourages relevant companies to provide pain management services. For example, the Nationwide Hospice Service Program supported by Li Ka-shing Foundation provided free pain management and other services to approximately 15,000 patients with cancer pain during the COVID-19 epidemic.<sup>12,35</sup>

### **1.14. Adjust the measures of pain management**

As COVID-19 has changed the original medical treatment model, pain management measures have been adjusted to minimize the impact of COVID-19 on patients with pain and the probability infection spread by patients with pain receiving unsupervised medical treatment. Based on the experience of effective prevention and treatment of SARS and MERS, 8 updated versions of Diagnosis and Treatment Protocol for Novel Coronavirus

Pneumonia have been issued by the National Health Commission of China.<sup>44</sup>

The experts in the Department of Pain Medicine in Wuhan and Shenzhen have implemented a series of measures to take better care of the most vulnerable patients.<sup>55</sup> After classification of diagnosis and treatment planning, outpatients with moderate and below pain received prescription drugs and received telemedicine support at home. Outpatients with severe pain were sent to clinic for rapid treatment. Any outpatients with confirmed or suspected COVID-19 infection will be sent to the quarantine area for further observation and treatment. For in-patients with severe pain, the necessary pain treatment was ensured as much as possible on the basis of minimizing contact.

Telemedicine is a convenient and safe way of providing pain management service during and after COVID-19, including instructions for taking medicine, relief of psychological symptoms, and at-home exercises.<sup>55</sup> According to reports, the medical staff in Wuhan mobile cabin hospitals organized patients to conduct collective social activities, lead patients to practice square dances and increased theatrical performances.<sup>61</sup>

After discharge from hospital, patients should be followed up to see if sequelae are present.<sup>67</sup> Recently, a book cowritten by Chinese doctors and scientific researchers in the field of COVID-19 prevention and treatment named *COVID-19: The Essentials of Prevention and Treatment* was released worldwide. This book recorded China's experience in prevention, control, and treatment for global reference.<sup>51</sup>

### 1.15. Promote traditional Chinese medicine treatment

Another highlight of COVID-19 treatment in China is the use of traditional Chinese medicine (TCM). Traditional Chinese medicine plays an important role in the treatment of patients with COVID-19 in China. China's Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia has included guidance on using TCM to treat patients with COVID-19 at all stages. The essence of Chinese medicine is applying medicine according to symptom-based diagnosis.<sup>9</sup> The main symptoms of the patients with COVID-19 are fever, fatigue, pain, cough, myalgia/arthralgia, gastrointestinal symptoms, and "thick fur on tongue" which can be classified into dampness subtype on the basis of TCM theory.<sup>10,11,65</sup> In TCM, the core pathogenesis of COVID-19 is the discomfort of the lungs and spleen caused by damp cold distemper. Early corresponding treatment should aim at eliminating moisture, thereby releasing lungs and eliminating pathogenic factors, so as to shorten the duration of fever, relieve symptoms including pain, and reduce mortality.<sup>40</sup> There are many prescriptions and proprietary Chinese medicines which have been used in relieving COVID-19 symptoms in China. Most Chinese medicine guidelines define COVID-19 as an endemic, toxic, humid, or warm infectious disease.<sup>48</sup> Licorice is the most frequently used Chinese medicine. Ephedra, bitter almond, astragalus, scutellaria, patchouli, and honeysuckle are also medicines that are frequently used. In Guangdong, a case study of Tou-jie-qu-wen granules was conducted and promoted to 30 designated hospitals as the standard treatment for patients with COVID-19.<sup>22</sup> Pharmacological analysis showed that most of the active components of these herbs have antiviral, immunomodulatory, anti-inflammatory, and analgesic effects.<sup>23</sup> In the process of treating patients with COVID-19, the use rate of traditional Chinese medicine in patients accounted for 90.6%, and the total effective rate was reported as over 90%.<sup>52</sup>

In addition, physicians use traditional nondrug methods such as acupuncture and massage as adjuvant therapy for patients.<sup>67</sup>

According to reports, stimulating the acupoint such as Tianzhu (BL10), BL12, and GV14 can eliminate nasal discharge, pain of the shoulders, and the back, while Neiguan (PC6) and Lieque (LU7), or Jueque (CV14), Qimén (LR14), and Zhaohai (KI6) can relieve chest pain or/and shortness of breath.<sup>37</sup> The traditional exercises named Taiji and Ba-Duan-Jin et al. are also used in rehabilitation training.<sup>38</sup> The combination of TCM and modern medicine is used to treat patients with COVID-19 in China, giving full play to the respective possible strengths of TCM and modern medicine therapy.

### Disclosures

The authors have no conflicts of interest to declare.

### Acknowledgements

The authors are very grateful to Dr. Michael C. Rowbotham for his great assistance in the final completion of the article. This work was funded by Shanghai Health Committee (201840003) to F.J. and supported by the National Nature Science Foundation of China (31671088,32071002) to C.L. and Danish National Research Foundation (DNRF121) to L.A..

### Article history:

Received 1 December 2020

Received in revised form 30 March 2021

Accepted 10 April 2021

### References

- [1] Aghagholi G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. *Neurocrit Care* 2020;13:1–10.
- [2] Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci* 2020;77:8–12.
- [3] Al-Obaidi MMJ, Bahadoran A, Wang SM, Manikam R, Raju CS, Sekaran SD. Disruption of the blood brain barrier is vital property of neurotropic viral infection of the central nervous system. *Acta Virol* 2018;62:16–27.
- [4] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;11:995–8.
- [5] Bartsch SM, Ferguson MC, McKinnell JA, O'Shea KJ, Wedlock PT, Siegmund SS, Lee BY. The potential health care costs and resource use associated with COVID-19 in the United States. *Health Aff (Millwood)* 2020;39:927–35.
- [6] Bavel JJV, Baicker K, Boggio PS, Capraro V, Cichocka A, Cikara M, Crockett MJ, Crum AJ, Douglas KM, Druckman JN, Drury J, Dube O, Ellemers N, Finkel EJ, Fowler JH, Gelfand M, Han S, Haslam SA, Jetten J, Kitayama S, Mobbs D, Napper LE, Packer DJ, Pennycook G, Peters E, Petty RE, Rand DG, Reicher SD, Schnall S, Shariff A, Skitka LJ, Smith SS, Sunstein CR, Tabri N, Tucker JA, Linden SV, Lange PV, Weeden KA, Wohl MJA, Zaki J, Zion SR, Willer R. Using social and behavioural science to support COVID-19 pandemic response. *Nat Hum Behav* 2020;4:460–71.
- [7] Buena AG, Wever PC, Borst DP, Sliker KA. [COVID-19 in the emergency department of bernhoven hospital [in Dutch]]. *Ned Tijdschr Geneesk* 2020;164:D5001.
- [8] Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol* 2020;12:e7352.
- [9] Chan KW, Wong VT, Tang SCW. COVID-19: an update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese-western medicine for the management of 2019 novel coronavirus disease. *Am J Chin Med* 2020;48:737–62.
- [10] Chang, LinM, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside wuhan, China. *JAMA* 2020;323:1092–3.
- [11] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical

- characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- [12] China's Ministry of Civil Affairs and Ministry of Finance. Notice on further improving the basic living conditions of the needy people, 2020. Available at: [http://www.gov.cn/gongbao/content/2020/content\\_5551811.htm](http://www.gov.cn/gongbao/content/2020/content_5551811.htm). Accessed June 3, 2020.
- [13] Chinese Association for Science, Technology. Home care and rehabilitation guidance for patients with shoulder joint pain during the epidemic, 2020. Available at: [https://www.cast.org.cn/art/2020/3/2/art\\_384\\_114846.html](https://www.cast.org.cn/art/2020/3/2/art_384_114846.html). Accessed March 2, 2020.
- [14] Devlin JW, Skrobik Y, Gelin C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochweg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser JC, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825–73.
- [15] Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol* 2020;92:1549–55.
- [16] Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, Palermo TM, Reid MC, Williams ACC. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. *PAIN* 2020;161:889–93.
- [17] Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs* 2017;77:403–26.
- [18] Expert consensus on the management and guidance of rational drug use for home-based medications for the people during the epidemic. *J Adverse Drug React* 2020;130–8.
- [19] Fadila MF, Wool KJ. Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. *N Am J Med Sci* 2015;7:122–4.
- [20] Ferrandi PJ, Alway SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. *J Appl Physiol* 2020;129:864–7.
- [21] Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin YF, Duan Q, Luo G, Fan S, Lu Y, Feng A, Zhan Y, Liang B, Cai W, Zhang L, Du X, Li L, Shu Y, Zou H. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020;80:656–65.
- [22] Fu XX, Lin LP, Tan XH. Clinical study on treatment of cases of COVID-19 with toujie quwen granules. *Chin J Exp Traditional Med Formulae* 2020;26:44–8.
- [23] Gao X, He ZY, Luo P, Jiang Y, Bi JJ, Tang XQ. Research overview of high-frequency single-medicine in Chinese herbal compound against novel coronavirus pneumonia (COVID-19). *World Notes Antibiot* 2020;41:283–9.
- [24] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. China medical treatment expert group for C. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
- [25] Guang Z. The role and influence of epidemiological investigation in China's "anti-epidemic." *Popular Sci Res* 2020;15:7–10+108.
- [26] Guereschi MG, Araujo LP, Maricato JT, Takenaka MC, Nascimento VM, Vivanco BC, Reis VO, Keller AC, Brum PC, Basso AS. Beta2-adrenergic receptor signaling in CD4+ Foxp3+ regulatory T cells enhances their suppressive function in a PKA-dependent manner. *Eur J Immunol* 2013;43:1001–12.
- [27] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- [28] Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol* 2011;11:625–32.
- [29] Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. *Emerg Infect Dis* 2020;26:1618–20.
- [30] Karos K, McParland JL, Bunzli S, Devan H, Hirsh A, Kapos FP, Keogh E, Moore D, Tracy LM, Ashton-James CE. The social threats of COVID-19 for people with chronic pain. *PAIN* 2020;161:2229–35.
- [31] Kemp HI, Bantel C, Gordon F, Brett SJ, Plan, S, Laycock HC. Pain Assessment in INTensive care (PAINT): an observational study of physician-documented pain assessment in 45 intensive care units in the United Kingdom. *Anaesthesia* 2017;72:737–48.
- [32] Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. *Br J Anaesth* 2020;125:436–40.
- [33] Korolnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. *Ann Neurol* 2020;88:1–11.
- [34] Lawrenson JG, Buckley RJ. COVID-19 and the eye. *Ophthalmic Physiol Opt* 2020;40:383–8.
- [35] Li Ka Shing Foundation. Gathering for love- national Hospice project 2020 end-of-year meeting. Available at: <http://www.hospice.com.cn/news.aspx?id=8057>, 2021.1.3. Accessed January 3, 2021.
- [36] Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC, Liu HG. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020;133:1025–31.
- [37] Liu WH, Guo SN, Wang F, Hao Y. Understanding of guidance for acupuncture and moxibustion interventions on COVID-19 (Second edition) issued by CAAM. *World J Acupunct Moxibustion* 2020;30:1–4.
- [38] Liu XD, Liu L, Lu YF, Feng L, Zhao FR, Wu XB, Qi TK, Zhao JJ, Xiao L, Xu ST, Liu Y, Shen YN, Liu YJ, Lu HZ, Shan CL. Guidance and suggestions on rehabilitation training of integrated traditional Chinese and western medicine for functional recovery of patients with COVID-19. *Shanghai J Traditional Chin Med* 2020;54:9–13.
- [39] Lovell N, Maddocks M, Etkind SN, Taylor K, Carey I, Vora V, Marsh L, Higginson IJ, Prentice W, Edmonds P, Sleeman KE. Characteristics, symptom management, and outcomes of 101 patients with COVID-19 referred for hospital palliative care. *J Pain Symptom Manage* 2020;60:e77-81.
- [40] Ma J, Huo XQ, Chen X, Zhu WX, Yao MC, Qiao YJ, Zhang YL. Study on screening potential traditional Chinese medicines against 2019-nCoV based on Mpro and PLP [in Chinese]. *Zhongguo Zhong Yao Za Zhi* 2020;45:1219–24.
- [41] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China. *JAMA Neurol* 2020;77:683–90.
- [42] 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:e273-83.
- [43] Motta-Santos D, Dos Santos RA, Oliveira M, Qadri F, Poglitsch M, Mosienko V, Kappes Becker L, Campagnole-Santos MJ, Alenina N, Bader M. Effects of ACE2 deficiency on physical performance and physiological adaptations of cardiac and skeletal muscle to exercise. *Hypertens Res* 2016;39:506–12.
- [44] National Health Commission of China. General Office of National Health Commission of the People's Republic of China, Office of National Administration of Traditional Chinese Medicine. Diagnosis and treatment of corona virus disease-19 (8th trial edition). *China Medicine* 2020;15:1494–99.
- [45] National Health Commission of China. Notice on strengthening the establishment of fever clinics in primary medical and health institutions. Primary Health Department. Available at: <http://www.nhc.gov.cn/jws/s3581/202012/20049f0fe43a4d1588acf7088255048a.shtml>, 2020. Accessed December 7, 2020.
- [46] Ouyang XY, Yang C, Zhu Z, Li J, Sun YH, Ding G, Ji YH, Jiang F. Cancer pain, a serious threat to patients. *Sheng Li Xue Bao* 2019;71:343–9.
- [47] Ouyang XY, Zhu Z, Yang C, Wang L, Ding G, Jiang F. Epinephrine increases malignancy of breast cancer through p38 MAPK signaling pathway in depressive disorders. *Int J Clin Exp Pathol* 2019;12:1932–46.
- [48] Pang WT, Jin XY, Pang B, Yang FW, Wang H, Liu CX, Zheng WK, Zhang JH. Analysis on pattern of prescriptions and syndromes of traditional Chinese medicine for prevention and treatment of COVID-19 [in Chinese]. *Zhongguo Zhong Yao Za Zhi* 2020;45:1242–7.
- [49] Pinho-Ribeiro FA, Verri WA, Jr, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends Immunol* 2017;38:5–19.
- [50] Puntillo KA, Max A, Chaize M, Chanques G, Azoulay E. Patient recollection of ICU procedural pain and post ICU burden: the memory study. *Crit Care Med* 2016;44:1988–95.
- [51] Qu JM, Cao B, Chen RC. COVID-19: The Essentials of prevention and treatment. Amsterdam, the Netherlands: Elsevier Inc., 2020.
- [52] Research Group of New Coronavirus Epidemic Prevention and Control NIODS, Wuhan University. China's experience in fighting the new crown virus epidemic. *Study Pract* 2020;434:23–35.
- [53] Riquelme C, Acuna MJ, Torrejon J, Rebolledo D, Cabrera D, Santos RA, Brandan E. ACE2 is augmented in dystrophic skeletal muscle and plays a role in decreasing associated fibrosis. *PLoS One* 2014;9:e93449.
- [54] Saeed U, Sellevoll HB, Young VS, Sandbaek G, Glomsaker T, Mala T. Covid-19 may present with acute abdominal pain. *Br J Surg* 2020;107:e186-7.

- [55] Song XJ, Xiong DL, Wang ZY, Yang D, Zhou L, Li RC. Pain management during the COVID-19 pandemic in China: lessons learned. *Pain Med* 2020;21:1319–23.
- [56] Soung A, Klein RS. Viral encephalitis and neurologic diseases: focus on astrocytes. *Trends Mol Med* 2018;24:950–62.
- [57] Swanson PA, II, McGavern DB. Viral diseases of the central nervous system. *Curr Opin Virol* 2015;11:44–54.
- [58] Tolebeyan AS, Zhang N, Cooper V, Kuruvilla DE. Headache in patients with severe acute respiratory syndrome coronavirus 2 infection: a narrative review. *Headache* 2020;60:2131–38.
- [59] Vachon-Preseau E. Effects of stress on the corticolimbic system: implications for chronic pain. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;87:216–23.
- [60] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. *JAMA* 2020;323:1061–9.
- [61] Wen R. Research on the phenomenon of “COVID-19 shelter hospital Dance” and dance medical health. *J Beijing Dance Acad* 2020;2:16–21.
- [62] Wilson M, Finlay M, Orr M, Barbosa-Leiker C, Sherazi N, Roberts MLA, Layton M, Roll JM. Engagement in online pain self-management improves pain in adults on medication-assisted behavioral treatment for opioid use disorders. *Addict Behav* 2018;86:130–7.
- [63] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420–2.
- [64] Yang C, Sun Y, Ouyang X, Li J, Zhu Z, Yu R, Wang L, Jia L, Ding G, Wang Y, Jiang F. Pain may promote tumor progression via substance P-dependent modulation of toll-like receptor-4. *Pain Med* 2020;21:3443–50.
- [65] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–81.
- [66] Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, Wei J, Gong Z, Zhou C, Yu H, Yu M, Lei H, Cheng F, Zhang B, Xu Y, Wang G, Dong W. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect* 2020;26:767–72.
- [67] Zhang YD, Lin CH, Zhao LJ, Xu B, Zang WD, Cao J. Pain: one of the challenges of COVID-19 infection. *Chin J Pain Med* 2020;26:565–70.
- [68] Zouikr I, Bartholomeusz MD, Hodgson DM. Early life programming of pain: focus on neuroimmune to endocrine communication. *J Transl Med* 2016;14:123.