







Psychiatric Complications in Patients with COVID-19: A Narrative Review


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Received: 30 June 2021 Accepted: 24 Sep 2021
Published 2021 Volume 2, Issue 2,

Abstract

Coronavirus disease 2019 (COVID-19) is associated with severe multiorgan clinical manifestations. Although respiratory involvement is the predominant manifestation in patients infected with COVID-19, involvement of other organs, such as the nervous system, has also been identified; which highlights the virus' ability to disrupt the organs' function. There is ample evidence of a nervous system susceptibility to the COVID-19. In this regard, the COVID-19 pandemic effect on psychological health, including insomnia, anxiety, obsessive-compulsive disorder, and depression among health care workers and other high-risk groups has been identified. So far, many studies have examined the psychiatric manifestations in infected patients with COVID-19. Undoubtedly, awareness of these findings can help in the prevention and timely treatment of these patients. This study aimed to review the possible mechanisms of COVID-19 neuroinvasive potential, psychiatric manifestations, and the management of mental disorders in infected patients.

Keywords: COVID-19, Mental Disorders, Nervous System

 **How to Cite:** Hashemi SM, Nobakht M, Ghazaloo A, Ghadamgah AH, Kargar-Abarghouei E, Arab Firouzjaei M. Psychiatric Complications in Patients with COVID-19: A Narrative Review. 2021; 2(2): e1014.

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Introduction

In late 2019, a large number of unexplained pneumonia cases were reported in Wuhan, China, and quickly extended to other parts of the world, which caused global concerns. Ultimately, this outbreak was confirmed to be caused by a novel coronavirus [1]. It was renamed by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) and announced as pandemic on 11th March 2020 [2, 3]. Severe acute respiratory syndrome (SARS CoV-2) is known as an enveloped and single-stranded RNA virus that can enter human



host cells through binding to the angiotensin-converting enzyme (ACE2) receptor [4, 5]. Acute respiratory distress syndrome (ARDS) is one of the major manifestations of COVID-19 and is associated with systemic inflammation which can result in death by respiratory failure [6]. Neurological manifestations have been reported in patients with COVID-19. It has been observed that more than one third of infected patients experience various neurological complications, such as headache, taste and smell impairment, disturbed consciousness, and acute cerebrovascular disease [7-9]. The virus affects physical health as well as the psychological health as well as social and economic development [10].

There is a neuropsychiatric relation between the mental disorders and the prevalence of acute respiratory infection which is related to the prevalence of influenza and SARS occurred in the past. During lockdowns for COVID-19 prevalence, people may suffer from malaise, anger, and loneliness; also manifestations of viral infections, such as cough and fever, may also worsen cognitive impairment and anxiety in people due to the fear of COVID-19 infection [11].

A recent study conducted on 214 cases of severe coronavirus disease in Wuhan during the early phase of the outbreak, claimed that about 36% of patients experienced neurological symptoms [7]. The effect of the COVID-19 pandemic on psychological health has been established. The disease increases the risk of anxiety, insomnia and depression among healthcare workers and other endangered groups [3, 12-23]. The prevalence of depression, anxiety, insomnia, and acute stress symptoms in general population was 27.9%, 31.6%, 29.2%, and 24.4%, respectively [20].

It is reported that psychological complications persist in SARS patients; as a quarter of them had posttraumatic stress disorder (PTSD) and 15.6% of patients were diagnosed with depression in about 2 years after experiencing SARS [24]. The evidences suggest that infection with novel coronavirus could

also increase the risk for the development of neuropsychiatric diseases. Therefore, it is of interest to suggest the monitoring and examinations of patients with COVID-19 for investigating associative relationships between COVID-19 infection and the development of disorders. The current review discussed the psychological manifestations as well as possible mechanisms by which COVID-19 is able to invade the central nervous system (CNS), and finally the management of psychiatric symptoms in patients with COVID-19.

Mechanisms for the effect of COVID-19 infections on the central nervous system damage

Generally, the virus can reach to CNS through two routes, neural pathways, and body fluids (such as blood, lymph, and cerebral spinal fluid) [19].

Neuronal pathway

The neurotropic viruses spread to CNS through neuronal pathway as the main pathway. Viruses can reach retrograde or anterograde neuronal transport via the motor proteins and move by infecting motor or sensory nerve fibers [25]. Transmission through olfactory neuron is an example of a neuronal pathway. The unique anatomical structure of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain effectively create the channel between the nasal epithelium and the CNS [25, 26]. A potential route of viral spread into the brain is the olfactory epithelium and therefore cause hyposmia [27]. The results of genetic and histological studies of various cells in the olfactory tract showed that ACE-2 and TMPRSS2 are expressed on olfactory epithelial cells (especially supporting cells), but are not expressed on olfactory sensory nerves [28-30].

The virus may enter through sensory neurons of the tongue, which transmit the sense of taste, and then via cranial nerves (CN) VII, IX, and X, it reaches the nucleus of the tractus solitarius, thalamus, and finally the brain [31]. The virus could access to CNS from either the buccal epithelium via trigeminal nociceptors and then CN V [31].

Blood circulation pathway

Studies have shown that other pathways, including transmission via the blood circulation or disruption of the blood-brain barrier (BBB), can cause the virus to enter the CNS [31]. The virus may enter the cerebral circulation through the general circulation, where it damages the capillary endothelium and eventually spreads to brain tissue [31]. A virus may cross the BBB through three main mechanisms: paracellular migration, transcellular migration, and the “Trojan horse” strategy [32]. In intracellular migration, the virus attacks host endothelial cells to penetrate the BBB. During paracellular migration, viruses attack the tight

junctions made by BBB endothelial cells [33]. During the Trojan horse strategy, the virus enters host cells through the host phagocytic cells, such as neutrophils and macrophages. The COVID-19 may use one or a combination of these three mechanisms to enter the host cell [33]. Studies have suggested that after accessing the BBB, COVID-19 can attack the host endothelial cells via binding to the ACE2 receptor, altering tight junction proteins made by BBB endothelial cells, or phagocytosis by immune phagocytic cells [33]. In either pathway, type I interferons (INFs) are released by cells infected with COVID-19, which call immune and adjacent cells to the presence of the pathogen (Fig. 1) [33].

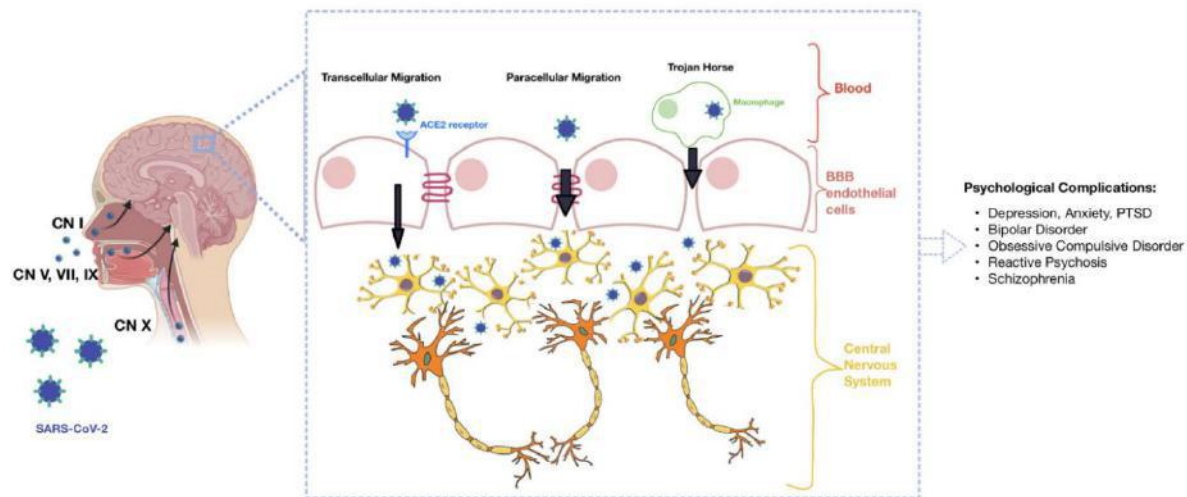


Figure 1: possible entry routes for SARS- COV-2 into central nervous system and psychological manifestations

Pathophysiology of neuropsychiatric manifestations in COVID-19

Angiotensin-converting enzyme 2

Angiotensin-converting enzyme 2 acts as a protecting factor in a variety of organs and plays an important role in blood pressure regulation and anti-atherosclerotic mechanisms [34]. It is clear that ACE2 receptor is also an important mediator for the majority of coronaviruses and influenza viruses [35-37]. The binding of virus to ACE2 receptors, may elevate abnormally blood pressure and increase

the risk of cerebrovascular complications. In addition, the virus may also enter the CNS by the interruption of the BBB and due to the interaction between ACE2 expressed in the capillary endothelium and SARS-CoV-2 spike protein, it can attack the blood vessels [38].

SARS-CoV-2 can cause endothelial damage and enter the blood circulation by binding to the ACE2 receptor on the alveolar epithelial cells. Virus infection can be very fast, due to the large surface area of pulmonary alveoli [39].

Hypoxia injury

Viral proliferation in alveolar epithelial cells can cause many manifestations, including diffusing alveolar inflammatory secretion, swelling, and formation of transparent membrane. Impaired alveolar gas exchange leads to hypoxia of the nervous system and as a result, increases anaerobic metabolism in the mitochondria of brain cells [40]. In addition, acid accumulation in the brain following respiratory involvement can cause dilation of cerebral arteries, swelling of brain cells, interstitial edema, and even obstruction of cerebral blood flow, so that headaches in infected patients may be due to ischemia and congestion [40].

Impact of cytokine storm on the BBB function

Damage to the CNS caused through viral infection may be mediated via the immune system [41]. Severe viral infection pathology is tightly associated with the development of systemic inflammatory response syndrome (SIRS). The SIRS could be present in severe pneumonia due to coronavirus infection, while the early intervention with anti-inflammatory agents could effectively inhibit immune damage and decrease the risk of nervous system impairment [42, 43]. In addition, most of the deaths due to SARS and COVID-19 have been linked to multiorgan failure (MOF) due to virus-induced SIRS or SIRS-like immune disorders [44, 45].

The persistence of coronavirus infection can lead to damage to microglia, macrophages, and astrocytes in the brain. A neurotropic virus could stimulate a pro-inflammatory state by activating glial cells [46]. Interleukin (IL)-6 a main mediator of the cytokine storm, is strongly linked to the severity of COVID-19 signs [47]. Furthermore, a recent study showed the secretion of a wide range of inflammatory factors, such as IL-6, IL-12, IL-15, and tumor necrosis factor alpha (TNF- α) from primary glial cells cultured in-vitro after being infected with the coronavirus [48]. Also, immune

cell activation in the nervous system will cause brain injury due to chronic inflammation.

Multiple studies have claimed elevated levels of inflammatory factors associated with COVID-19 infection; for instance, high levels of pro-inflammatory cytokines IFN- γ , TNF- α , and IL-6, as well as low levels of anti-inflammatory cytokines IL-2, IL-4, and IL-10 have been detected in infected patients with COVID-19 compared to healthy individuals [49]. These studies have suggested that cytokine upregulation and systemic inflammation may be associated with the severity of the disease [50-52].

Psychiatric complications

Depression, anxiety, and PTSD

Previous studies have shown that respiratory viral disease can be associated with acute and chronic mental health problems in people who have experienced the infection. These people reported psychiatric complications, including depression and post-traumatic stress disorder (PTSD) at 1 to 50 months of follow up [53-55]. A recent report examining the pathology of psychology disorders in a group of people surviving from COVID-19 within one month after discharge from hospital, reported high degrees of anxiety, depression, and PTSD [56].

It is well known that coronaviruses have neurotropic properties and can therefore cause neuronal damage [57]. Coronaviruses could cause psychopathological impact either directly through CNS involvement or indirectly mediated with immune response [55]. In spite of possible invasion of the brain, "cytokines storm" due to immune response to coronaviruses can also cause psychological symptoms through neuroinflammation [58, 59].

Increased levels of interleukin (IL)-1 β , IL-6, IFN- γ , C-X-C chemokine ligand 10 (CXCL10), and chemokine (C-C motif) ligand 2 (CCL2) suggest activation of T-helper-1 detected in infected patients with COVID-19. Unlike other SARS viruses, the

levels of secretory T-helper-2 cell cytokines (such as IL-4 and IL-10) increased in COVID-19 patients [60, 61]. With higher concentrations of these cytokines, a more severe clinical course is expected [50]. The dysregulation of cytokines [especially IL-1 β , IL-6, IL-10, IFN- γ , TNF- α , and transforming growth factor- β (TGF- β)] are known as important factors that can cause mental disorders [62-65]. In addition to the damage caused by immune responses, many psychological stressors that patients experience during the pandemic, including fear of disease and social isolation and stigma could worsen the psychological outcomes [14, 66].

To date, many mechanisms have been proposed for the relationship between immune responses and mental disorders, including neuroinflammation, increased permeability of the BBB due to its dysfunction, invasion of peripheral inflammatory factors into the brain, and hypothalamic-pituitary adrenal (HPA) axis dysfunction [58, 67, 68].

INFs are important factors in innate immunity. Type I INFs (alpha and beta) are released via cells infected with viral pathogens and are known to have antiviral effects against coronaviruses, such as SARS-CoV-1 [69]. In two separate clinical trials, INFs (beta-1b and alpha-2b with or without combination with other drugs) administration seems to reduce viral shedding, symptom alleviation and hospital stay in patients with mild to moderately severe COVID-19 [50, 70].

A study suggested that treatment with different INFs alone or in combination with other antiviral drugs could improve drug-induced depression [71]. Tryptophan (TRP) is an essential amino acid and a precursor to the synthesis of serotonin. This amino acid is needed for the synthesis of serotonin (5-hydroxytryptamine) or kynurenine. Any factor that directs TRP to kynurenine production can cause depression due to reduced serotonin synthesis. TRP is mostly synthesized via the kynurenine pathway. The two isoforms of indoleamine 2–3- dioxigenase

(IDO) and TRP 2,3-dioxygenase play important roles in this pathway; since IDOs are regulated by IFN, so IFNs can change the catabolism of TRP from serotonin to kynurenine [72]. Interferon-induced reductions in serotonin may cause depression [7, 73]. Also, the limited amount of TRP received through diet can cause depression in some people and can even aggravate depression in the patient [74-76].

Bipolar disorder

Probably, high levels of pro-inflammatory factors and chemokines in patients infected with SARS-CoV-2, lead to activated T-helper-1 cell responses [50]. Previous studies have suggested, infection-associated immune reactions and cytokine release, as a potential mechanism for bipolar disorder (BD) [77, 78]. Also a recent study showed that inflammatory changes are happened particularly during acute episodes of mania in BD patients [79]. Furthermore, a recent study detected high plasma levels of IL-6, IL-10, and C-reactive protein (CRP) in the acute phase of the disease in a patient infected with SARS-CoV-2 that presented with manic-like symptoms [51]. In addition, there is a potential risk of relapses in patients presented with acute SARS-CoV-2 infection and a past psychiatric history [80].

Atypical antipsychotics (AA) are known as common drug treatments for the treatment of BD, schizophrenia and severe depression. A recent study showed a highly inflammatory and adaptive immune responses dysregulation through AA (specifically risperidone (RIS)) that can potentially lead to sudden death in infected patients with COVID-19 [81]. During normal Toll-like receptor 4 (TLR4)-mediated signaling, levels of cytokines and chemokines, including TNF- α , IL-6, IL-1 β , IL-12, IL-8, CCL5, macrophage inflammatory protein (MIP)1- α , MIP1- β , CxCL10, CxCL9, and CxCL11 are increased [82]. Risperidone also significantly decreased TNF- α , IL-6, IFN γ , CxCL10, and CCL2 and dysregulated IL-1ra, IL-1 α , IL-4, and MIP1- β

[81]. Therefore, the dysregulation of immune response to SARS-CoV-2 in BD patients via AA is highly suspected.

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is a chronic intolerable disease that is characterized by obsessive stressful behaviors and makes individuals to do repetitive mental or physical actions in order to reduce anxiety or avoid dreadful events [83]. According to psychologic findings, stressful incidents could establish OCD pattern [84]. Obsessive compulsive disorder as a serious consequence of preventive cares against COVID-19 could harm patients with preexisting anxiety disorders [85, 86]. The increased number of OCD have been reported as a result of pandemics. In addition, fear of contamination is a very common issue in OCD patients [87]. The COVID-19 pandemic have led general population to allocated symptoms of OCD and other similar anxiety disorders, such as obsessive hand hygiene and overreact to infection [88]. Other behaviors, such as the tendency to hoarding, increased during the pandemic [89]. Anxiety and fear can cause people to buy mask, soap, antiseptis, and antiviral drugs more than their needs [87] and these attitudes could induce OCD symptoms [90].

Reactive psychosis

Reactive psychosis, also known as psychogenic psychosis, involves a series of acute and short-term states of psychosis resulted from a psychological trauma. Emotional reaction to stress is the main basis for the formation of reactive psychosis [91]. The COVID-19 epidemic has had negative effects on health and the occurrence of stress and anxiety in the community, not only due to the fear of contracting the disease, but also due to the policies of the health care systems in different countries [14]. These policies can lead to mental disorders, such as reactive psychosis in the community due to the burden of stress on individuals. Although stress studies have limited the direct impact of the COVID-19

pandemic on the increase in reactive psychosis [92], in this disease, the risk of suicidal behavior is high among patients [93]. For example, in a case-report, a 33-year-old married man without any history of mental disorder was hospitalized due to a sudden period of psychotic suicide behavior. This person has suffered from paranoid psychosis due to home quarantine and worries about losing his job, and he believed in the imminent end of the world. Suicide was seen in the patient for reacting to this reactive psychosis. This patient completely passed all symptoms of psychosis and suicidal ideation by receiving 10 mg of olanzapine daily during 48 hours [93]. As a result, COVID-19 epidemics and forced quarantine are a risk factor for reactive psychosis, and close clinical monitoring in the acute stages of the disease is essential [93].

Schizophrenia

Immune-response triggers have long been studied in various studies on the pathogenesis of psychiatric illnesses, including schizophrenia [94, 95]. Increased CRP levels as a marker of immune activation can play as a factor or triggering role in schizophreniform psychosis [96]. Various inflammatory mediators increase in the body of patients suffering from COVID-19; one of them is IL-6 [21, 22]. Increase in serum IL-6 levels of individuals is one of the most important factors proving immunological risk factors in the development of schizophrenia [97].

Other clinical studies have reported that patients suffering from COVID-19, who have recently shown symptoms of psychosis, have higher levels of antibodies for various strains of the coronavirus than control group. Particularly in patients with symptoms of schizophrenia, anti NL-63 strain antibody were measured to be above the average [98].

Management

In order to relieve psychological impacts of COVID-19 pandemic in general population, more attention should be paid to mostly affected groups, such as people ≤ 40 , students, and those with

preexisting psychiatric illnesses. In addition, governments should continuously provide true pandemic-related information, to prevent panic from false information. Also, governments must provide easy access to mental health services for individuals to relieve long-term impacts of quarantine [99, 100]. Due to limited in-person and delayed health services as a result of quarantine, services could be provided through online services [101].

Government intervention in various forms, such as new employment opportunities, financial support, housing support, and encouragement of healthy behaviors can affect suicide risk associated with economic reasons [24].

Individuals efforts is crucial to initially prevent and then relieve their complications of psychological distress, for example regular exercising or having a healthy diet can significantly reduce depression and stress [102-104]. Also keeping in touch with family and friends via video calls and social media can alleviate social separation distress [105].

Yoga and meditation have been shown to be beneficial in managing mental health issues [106, 107]. A recent study claimed that performing progressive muscle relaxation has a positive and strong effect on improving sleep quality and anxiety reduction in patients infected with COVID-19 [108].

Conclusion

Evidence from previous pandemics strongly suggests that infection, particularly with viral respiratory pathogens, is a risk factor for psychiatric manifestations. So far, limited studies have been performed on neuropsychiatric symptoms in patients with COVID-19. However, based on the results of previous respiratory virus epidemics, psychiatric disorders can be considered a serious complication for respiratory viral diseases. In addition to the fact that SARS-COV-2 can cause damage to brain by direct invasion, the experience of COVID19 as a potentially incurable disease can cause severe distress,

which may lead to long-term behavioral changes, or exacerbate a previous mental disorder. The possible psychiatric complications are described that can occur in patients infected with SARS-COV-2. As discussed, patients with COVID-19 can experience a wide range of psychiatric complications, which can be due to the direct involvement of neurons with COVID-19, systemic inflammation, the effects of inflammatory factors and cytokines on nervous system, neuroinflammation, glial dysfunction, and abnormal epigenetic modifications in stress-related genes.

Acknowledgements

The authors greatly acknowledge the clinician and healthcare staff at Hormozgan University of Medical Sciences for their hard work and endless hours with COVID-19 patients.

Authors' contribution

Study concept and design: M. Arab Firouzjahi and SM. Hashemi; Drafting of the manuscript: M. Arab Firouzjahi and SM. Hashemi, M. Nobakht, A. Ghazalgoo, AH. Ghadamgah; Critical revision of the manuscript for important intellectual content: E. Kargar-Abarghouei.

Funding source

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors of this manuscript declare no conflicts of interest related to this article.

References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. **A novel coronavirus from patients with pneumonia in China, 2019.** *N Engl J Med.* 2020;382:727-33
- [2] Cai W, Lian B, Song X, Hou T, Deng G, Li H. **A cross-sectional study on mental health among health care workers during the outbreak of Corona Virus Disease 2019.** *Asian journal of psychiatry.* 2020;51:102111

- [3] Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. **Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study.** *Brain, Behavior, and Immunity*. 2020;88:17-27
- [4] Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. **Features, evaluation and treatment coronavirus (COVID-19).** Statpearls [internet]: StatPearls Publishing; 2020
- [5] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. **The trinity of COVID-19: immunity, inflammation and intervention.** *Nature Reviews Immunology*. 2020;20:363-74
- [6] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. **Pathological findings of COVID-19 associated with acute respiratory distress syndrome.** *The Lancet respiratory medicine*. 2020;8:420-2
- [7] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. **Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China.** *JAMA neurology*. 2020;77:683-90
- [8] Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. **Clinical characteristics of coronavirus disease 2019 in China.** *New England journal of medicine*. 2020;382:1708-20
- [9] Davoodian N, Arab Firouzjaei M, Negahi A. **Neurological Involvement of Patients with COVID-19: Proposed Neuroinvasive Mechanisms and Management.** *Hormozgan medical journal*. 2020;24:107977-10.5812/hmj.107977.
- [10] Pulla P. **Covid-19: India imposes lockdown for 21 days and cases rise.** *British Medical Journal Publishing Group*. 2020;368:m1251
- [11] Xiang Y-T, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. **Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed.** *The Lancet Psychiatry*. 2020;7:228-9
- [12] Que J, Le Shi JD, Liu J, Zhang L, Wu S, Gong Y, et al. **Psychological impact of the COVID-19 pandemic on healthcare workers: a cross-sectional study in China.** *General psychiatry*. 2020;33:e100259
- [13] Tang W, Hu T, Hu B, Jin C, Wang G, Xie C, et al. **Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students.** *Journal of affective disorders*. 2020;274:1-7
- [14] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. **The psychological impact of quarantine and how to reduce it: rapid review of the evidence.** *The Lancet*. 2020;395:912-920
- [15] Cao W, Fang Z, Hou G, Han M, Xu X, Dong J, et al. **The psychological impact of the COVID-19 epidemic on college students in China.** *Psychiatry research*. 2020;287:112934
- [16] González-Sanguino C, Ausín B, ÁngelCastellanos M, Saiz J, López-Gómez A, Ugidos C, et al. **Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain.** *Brain, Behavior, and Immunity*. 2020;87:172-6
- [17] Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, et al. **Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science.** *The Lancet Psychiatry*. 2020;7:547-60
- [18] King DL, Delfabbro PH, Billieux J, Potenza MN. **Problematic online gaming and the COVID-19 pandemic.** *Journal of Behavioral Addictions*. 2020;29:184-6
- [19] Li Z, Liu T, Yang N, Han D, Mi X, Li Y, et al. **Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain.** *Frontiers of Medicine*. 2020:1-9
- [20] Shi L, Lu Z-A, Que J-Y, Huang X-L, Liu L, Ran M-S, et al. **Prevalence of and risk factors associated with mental health symptoms among the general population in China during the coronavirus disease 2019 pandemic.** *JAMA network open*. 2020;3:e2014053
- [21] Wang C, Pan R, Wan X, Tan Y, Xu L, McIntyre RS, et al. **A longitudinal study on the mental health of general population during the COVID-19 epidemic in China.** *Brain, behavior, and immunity*. 2020;87:40-8
- [22] Wang H, Li T, Gauthier S, Yu E, Tang Y, Barbarino P, et al. **Coronavirus epidemic and geriatric mental healthcare in China: how a coordinated response by professional organizations helped older adults during an unprecedented crisis.** *International Psychogeriatrics*. 2020;32:1117-20
- [23] Xiao H, Zhang Y, Kong D, Li S, Yang N. **Social capital and sleep quality in individuals who self-isolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China.** *Medical science monitor: international medical journal of experimental and clinical research*. 2020;26:e923921
- [24] Mak IWC, Chu CM, Pan PC, Yiu MGC, Chan VL. **Long-term psychiatric morbidities among SARS survivors.** *General hospital psychiatry*. 2009;31:318-26
- [25] Swanson II PA, McGavern DB. **Viral diseases of the central nervous system.** *Current opinion in virology*. 2015;11:44-54
- [26] Koyuncu OO, Hogue IB, Enquist LW. **Virus infections in the nervous system.** *Cell host & microbe*. 2013;13:379-93
- [27] Yazdanpanah N, Saghadzadeh A, Rezaei N. **Anosmia: a missing link in the neuroimmunology of**

- coronavirus disease 2019 (COVID-19).** *Reviews in the Neurosciences.* 2020;31:691-701
- [28] Schaller T, Hirschtbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. **Postmortem examination of patients with COVID-19.** *JAMA.* 2020;323:2518-20
- [29] Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. **SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes.** *Nature medicine.* 2020;26:681-7
- [30] Chen M, Shen W, Rowan NR, Kulaga H, Hillel A, Ramanathan Jr M, et al. **Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication.** *bioRxiv.* 2020;56:2001948
- [31] Stafstrom CE, Jantzie LL. **COVID-19: neurological considerations in neonates and children.** *Children.* 2020;7:133
- [32] Dahm T, Rudolph H, Schwerk C, Schrotten H, Tenenbaum T. **Neuroinvasion and inflammation in viral central nervous system infections.** *Mediators of inflammation.* 2016;2016: 8562805
- [33] Robinson CP, Busl KM. **Neurologic manifestations of severe respiratory viral contagions.** *Critical Care Explorations.* 2020;2:e0107
- [34] Miller AJ, Arnold AC. **The renin–angiotensin system in cardiovascular autonomic control: recent developments and clinical implications.** *Clinical Autonomic Research.* 2019;29:231-43
- [35] Turner AJ, Hiscox JA, Hooper NM. **ACE2: from vasopeptidase to SARS virus receptor.** *Trends in pharmacological sciences.* 2004;25:291-4
- [36] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. **Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation.** *Science.* 2020;367:1260-3
- [37] Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, et al. **Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury.** *Scientific reports.* 2014;4:1-6
- [38] 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 chemical neuroscience.* 2020;11:995-8
- [39] Corman V, Lienau J, Witzernath M. **Coronaviruses as the cause of respiratory infections.** *Der Internist.* 2019;60:1136-45
- [40] Abdennour L, Zeghal C, Deme M, Puybasset L. **Interaction brain-lungs.** *Annales francaises d'anesthesie et de reanimation.* 2012;31:e101-7
- [41] Klein RS, Garber C, Howard N. **Infectious immunity in the central nervous system and brain function.** *Nature immunology.* 2017;18:132-41
- [42] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. **COVID-19: consider cytokine storm syndromes and immunosuppression.** *Lancet (London, England).* 2020;395:1033-4
- [43] Fu Y, Cheng Y, Wu Y. **Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools.** *Virologica Sinica.* 2020;35:266-71
- [44] Yin C, Wang C, Tang Z, Wen Y, Zhang S, Wang B. **Clinical analysis of multiple organ dysfunction syndrome in patients suffering from SARS.** *Zhongguo wei zhong bing ji jiu yi xue= Chinese critical care medicine= Zhongguo weizhongbing jijiuyixue.* 2004;16:646-50
- [45] Chen C, Zhang X, Ju Z, He W. **Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies.** *Zhonghua shao shang za zhi= Zhonghua shaoshang zazhi= Chinese journal of burns.* 2020;36:471-5
- [46] Li Y, Fu L, Gonzales DM, Lavi E. **Coronavirus neurovirulence correlates with the ability of the virus to induce proinflammatory cytokine signals from astrocytes and microglia.** *Journal of virology.* 2004;78:3398-406
- [47] Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. **Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP).** *MedRxiv.* 2020
- [48] Bohmwald K, Galvez N, Ríos M, Kalergis AM. **Neurologic alterations due to respiratory virus infections.** *Frontiers in cellular neuroscience.* 2018;12:1-15
- [49] Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. **Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors.** *Emerging Microbes & Infections.* 2020;9:1123-30
- [50] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.** *The lancet.* 2020;395:497-506
- [51] Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. **Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients.** *EBioMedicine.* 2020;55:102763
- [52] Del Valle DM, Kim-Schulze S, Hsin-hui H, Beckmann ND, Nirenberg S, Wang B, et al. **An inflammatory cytokine signature helps predict COVID-19 severity and death.** *medRxiv.* 2020
- [53] Cheng SK, Wong C, Tsang J, Wong K. **Psychological distress and negative appraisals in survivors of severe acute respiratory syndrome (SARS).** *Psychological Medicine.* 2004;34:1187-95

- [54] Lam MH-B, Wing Y-K, Yu MW-M, Leung C-M, Ma RC, Kong AP, et al. **Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up.** *Archives of internal medicine.* 2009;169:2142-7
- [55] Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. **Nervous system involvement after infection with COVID-19 and other coronaviruses.** *Brain, behavior, and immunity.* 2020;87:18-22
- [56] January S. **Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19.** *The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information.* 2020
- [57] Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. **Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system?** *Viruses.* 2020;12:14
- [58] Dantzer R. **Neuroimmune interactions: from the brain to the immune system and vice versa.** *Physiological reviews.* 2018;98:477-504
- [59] Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. **Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2.** *Journal of virology.* 2008;82:7264-75
- [60] Channappanavar R, Perlman S. **Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology.** *Seminars in immunopathology.* 2017;39:529-39
- [61] Ye Q, Wang B, Mao J. **The pathogenesis and treatment of the Cytokine Storm in COVID-19.** *Journal of infection.* 2020;80:607-13
- [62] Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, de Wit H, Wijkhuijs AJ, et al. **Higher baseline proinflammatory cytokines mark poor antidepressant response in bipolar disorder.** *The Journal of clinical psychiatry.* 2017;78:e986-93
- [63] Köhler C, Freitas T, Maes Md, De Andrade N, Liu C, Fernandes B, et al. **Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies.** *Acta Psychiatrica Scandinavica.* 2017;135:373-87
- [64] Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. **Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects.** *Biological psychiatry.* 2011;70:663-71
- [65] Renna ME, O'Toole MS, Spaeth PE, Lekander M, Mennin DS. **The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: A systematic review and meta-analysis.** *Depression and anxiety.* 2018;35:1081-94
- [66] Carvalho P. de M, Moreira MM, de Oliveira MNA, Landim JMM, Neto MLR. **The psychiatric impact of the novel coronavirus outbreak** *Psychiatr Res.* 2020;286:112902
- [67] Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. **Neuroinflammation in Bipolar Depression.** *Frontiers in Psychiatry.* 2020;11:71
- [68] Jones KA, Thomsen C. **The role of the innate immune system in psychiatric disorders.** *Molecular and Cellular Neuroscience.* 2013;53:52-62
- [69] Hensley LE, Fritz EA, Jahrling PB, Karp C, Huggins JW, Geisbert TW. **Interferon- β 1a and SARS coronavirus replication.** *Emerging infectious diseases.* 2004;10:317-19
- [70] Zhou Q, Wei X-S, Xiang X, Wang X, Wang Z-H, Chen V, et al. **Interferon- α 2b treatment for COVID-19.** *MedRxiv.* 2020;11:1-6
- [71] DR RIS. **COVID-19, Interferons, and Depression: A Commentary.** *Psychiatry Research.* 2020;291:113198
- [72] Wichers MC, Koek G, Robaey G, Verkerk R, Scharpe S, Maes M. **IDO and interferon- α -induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity.** *Molecular psychiatry.* 2005;10:538-44
- [73] Capuron L, Neumeister A, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. **Interferon- α -induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment.** *Biological psychiatry.* 2003;54:906-14
- [74] Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, et al. **Effects of tryptophan depletion in fully remitted patients with seasonal affective disorder during summer.** *Psychological Medicine.* 1998;28:257-64
- [75] Spillmann MK, Van der Does AW, Rankin MA, Vuolo RD, Alpert JE, Nierenberg AA, et al. **Tryptophan depletion in SSRI-recovered depressed outpatients.** *Psychopharmacology.* 2001;155:123-7
- [76] Lindseth G, Helland B, Caspers J. **The effects of dietary tryptophan on affective disorders.** *Archives of psychiatric nursing.* 2015;29:102-7
- [77] Benros ME, Waltoft BL, Nordentoft M, Østergaard SD, Eaton WW, Krogh J, et al. **Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study.** *JAMA psychiatry.* 2013;70:812-20
- [78] Réus GZ, Fries GR, Stertz L, Badawy M, Passos I, Barichello T, et al. **The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders.** *Neuroscience.* 2015;300:141-54
- [79] Mazza MG, Tringali AGM, Rossetti A, Botti RE, Clerici M. **Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-**

- lymphocyte ratios in mood disorders.** *General hospital psychiatry.* 2019;58:7-12
- [80] Iqbal Y, Al Abdulla MA, Albrahim S, Latoo J, Kumar R, Haddad PM. **Psychiatric presentation of patients with acute SARS-CoV-2 infection: a retrospective review of 50 consecutive patients seen by a consultation-liaison psychiatry team.** *BJPsych open.* 2020;6:e109
- [81] May M, Slitzky M, Rostama B, Barlow D, Houseknecht KL. **Antipsychotic-induced immune dysfunction: a consideration for COVID-19 risk.** *Brain, Behavior, & Immunity-Health.* 2020;6:100097
- [82] Kanehisa M, Sato Y, Furumichi M, Morishima K, Tanabe M. **New approach for understanding genome variations in KEGG.** *Nucleic acids research.* 2019;47:D590-D5
- [83] Gillan C, Fineberg N, Robbins T. **A trans-diagnostic perspective on obsessive-compulsive disorder.** *Psychological medicine.* 2017;47:1528-48
- [84] Del Casale A, Sorice S, Padovano A, Simmaco M, Ferracuti S, Lamis DA, et al. **Psychopharmacological treatment of obsessive-compulsive disorder (OCD).** *Current neuropharmacology.* 2019;17:710-36
- [85] Fineberg NA, Hengartner MP, Bergbaum C, Gale T, Rössler W, Angst J. **Lifetime comorbidity of obsessive-compulsive disorder and sub-threshold obsessive-compulsive symptomatology in the community: impact, prevalence, socio-demographic and clinical characteristics.** *International Journal of Psychiatry in Clinical Practice.* 2013;17:188-96
- [86] Kumar A, Somani A. **Dealing with Corona virus anxiety and OCD.** *Asian Journal of Psychiatry.* 2020;51:102053
- [87] French I, Lyne J. **Acute exacerbation of OCD symptoms precipitated by media reports of COVID-19.** *Irish Journal of Psychological Medicine.* 2020;37:1-4
- [88] Rivera RM, Carballea D. **Coronavirus: A trigger for OCD and illness anxiety disorder?** *Psychological Trauma: Theory, Research, Practice, and Policy.* 2020;12:s66
- [89] Seçer İ, Ulaş S. **An Investigation of the Effect of COVID-19 on OCD in Youth in the Context of Emotional Reactivity, Experiential Avoidance, Depression and Anxiety.** *International Journal of Mental Health and Addiction.* 2020;13:1-14
- [90] Cox RC, Olatunji BO. **Linking insomnia and OCD symptoms during the coronavirus pandemic: Examination of prospective associations.** *Journal of anxiety disorders.* 2020;77:102341
- [91] Castagnini A, Galeazzi GM. **Acute and transient psychoses: clinical and nosological issues.** *BJPsych Advances.* 2016;22:292-300
- [92] Zulkifli NA, Sivapatham S, Guan NC. **Brief psychotic disorder in relation to coronavirus, COVID-19 outbreaks: a case report.** *Malaysian Journal of Psychiatry.* 2020;29
- [93] Valdés-Flórida MJ, López-Díaz Á, Palermo-Zeballos FJ, Martínez-Molina I, Martín-Gil VE, Crespo-Facorro B, et al. **Reactive psychoses in the context of the COVID-19 pandemic: clinical perspectives from a case series.** *Revista de psiquiatria y salud mental.* 2020;13:90-4
- [94] Upthegrove R, Khandaker GM. **Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia.** *Neuroinflammation and Schizophrenia.* 2019;44:49-66
- [95] Munjal S, Ferrando SJ, Freyberg Z. **Neuropsychiatric aspects of infectious diseases: an update.** *Critical care clinics.* 2017;33:681-712
- [96] Miller BJ, Culpepper N, Rapaport MH. **C-reactive protein levels in schizophrenia: a review and meta-analysis.** *Clinical schizophrenia & related psychoses.* 2014;7:223-30
- [97] Feng Z, Zhang Y, You X, Zhang W, Ma Y, Long Q, et al. **Effects of risperidone on blood levels of interleukin-6 in schizophrenia: A meta-analysis.** *Medicine.* 2020;99:e19694
- [98] Severance EG, Dickerson FB, Viscidi RP, Bossis I, Stallings CR, Origoni AE, et al. **Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms.** *Schizophrenia bulletin.* 2011;37:101-7
- [99] Tran BX, Dang AK, Thai PK, Le HT, Le XTT, Do TTT, et al. **Coverage of health information by different sources in communities: Implication for COVID-19 epidemic response.** *International Journal of Environmental Research and Public Health.* 2020;17:3577
- [100] Tran BX, Phan HT, Nguyen TPT, Hoang MT, Vu GT, Lei HT, et al. **Reaching further by Village Health Collaborators: The informal health taskforce of Vietnam for COVID-19 responses.** *Journal of Global Health.* 2020;10:010354
- [101] Pisciotta M, Denneson LM, Williams HB, Woods S, Tuepker A, Dobscha SK. **Providing mental health care in the context of online mental health notes: advice from patients and mental health clinicians.** *Journal of Mental Health.* 2019;28:64-70
- [102] Carek PJ, Laibstain SE, Carek SM. **Exercise for the treatment of depression and anxiety.** *The International Journal of Psychiatry in Medicine.* 2011;41:15-28
- [103] Lassale C, Batty GD, Baghdadli A, Jacka F, Sánchez-Villegas A, Kivimäki M, et al. **Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of**

- observational studies.** *Molecular psychiatry.* 2019;24:965-86
- [104] Molendijk M, Molero P, Sánchez-Pedreño FO, Van der Does W, Martínez-González MA. **Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies.** *Journal of affective disorders.* 2018;226:346-54
- [105] Hwang T-J, Rabheru K, Peisah C, Reichman W, Ikeda M. **Loneliness and Social Isolation during the COVID-19 Pandemic.** *International Psychogeriatrics.* 2020:1-4
- [106] Harner H, Hanlon AL, Garfinkel M. **Effect of Iyengar yoga on mental health of incarcerated women: A feasibility study.** *Nursing research.* 2010;59:389-99
- [107] Kirkwood G, Rampes H, Tuffrey V, Richardson J, Pilkington K. **Yoga for anxiety: a systematic review of the research evidence.** *British journal of sports medicine.* 2005;39:884-91
- [108] Liu K, Chen Y, Wu D, Lin R, Wang Z, Pan L. **Effects of progressive muscle relaxation on anxiety and sleep quality in patients with COVID-19.** *Complementary Therapies in Clinical Practice.* 2020;39:101132