Neuroimmunomodulation

Review Article

Neuroimmunomodulation 2023;30:237–249
DOI: 10.1159/000533722

Received: April 12, 2023
Accepted: August 21, 2023
Published online: September 27, 2023

Neuropsychiatric Outcomes and Sleep Dysfunction in COVID-19 Patients: Risk Factors and Mechanisms

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Keywords
COVID-19 · SARS-CoV-2 · Psychological distress · Sleep dysfunction · Risk factors

Abstract
The ongoing global health crisis due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted all aspects of life. While the majority of early research following the coronavirus disease caused by SARS-CoV-2 (COVID-19) has focused on the physiological effects of the virus, a substantial body of subsequent studies has shown that the psychological burden of the infection is also considerable. Patients, even without mental illness history, were at increased susceptibility to developing mental health and sleep disturbances during or after the COVID-19 infection. Viral neurotropism and inflammatory storm damaging the blood-brain barrier have been proposed as possible mechanisms for mental health manifestations, along with stressful psychological factors and indirect consequences such as thrombosis and hypoxia. The virus has been found to infect peripheral olfactory neurons and exploit axonal migration pathways, exhibiting metabolic changes in astrocytes that are detrimental to fueling neurons and building neurotransmitters. Patients with COVID-19 present dysregulated and overactive immune responses, resulting in impaired neuronal function and viability, adversely affecting sleep and emotion regulation. Additionally, several risk factors have been associated with the neuropsychiatric sequelae of the infection, such as female sex, age, preexisting neuropathologies, severity of initial disease and sociological status. This review aimed to provide an overview of mental health symptoms and sleep disturbances developed during COVID-19 and to analyze the underlying mechanisms and risk factors of psychological distress and sleep dysfunction.

Introduction

The global health crisis due to the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted all aspects of life. Initially, symptoms from the respiratory system received most of the medical attention. However, there is evidence from both observational studies regarding SARS-CoV-2

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infection (COVID-19) and from previous coronavirus outbreaks that infected patients are at risk to experience symptoms of psychological distress and mental health disorders [1]. The psychological implications of the COVID-19 pandemic may exceed those of previous outbreaks, as COVID-19 has been found to increase the susceptibility of developing mental, cognitive, and sleep disturbances, not only during its acute phase but even after discharge [2]. Psychological distress and sleep dysfunction appear to be caused by a variety of stressors and psychosocial factors, such as isolation and socio-economic difficulties, the often-required hospitalization, and also by the direct bio-immunologic effects of the virus itself [3].

SARS-CoV-2 virus has been found to have greater neurotropic activity and damaging effects on the central nervous system (CNS), with the development of mental disorders being two times more common compared with influenza or other acute respiratory infections [4]. For that, much attention has been paid to the neurological and/or psychopathological mechanisms of this disease. Viral neurotropism and inflammatory storm damaging the blood-brain barrier (BBB) have been proposed as possible mechanisms for mental health manifestations [5]. In addition, stressful psychological factors and the indirect consequences of COVID-19, such as thrombosis and hypoxia [6], have been considered important. Several studies assessed the levels of distress and associated factors for inpatients infected with SARS-CoV-2, along with sleep disorders. A meta-analysis of 19 studies on COVID-19 patients [7] reported a pooled prevalence of anxiety symptoms of 38%, with similar rates for depressive symptoms. Moreover, in the same study, difficulty falling asleep and maintaining sleep and dissatisfaction with sleep quality were the most prevalent symptoms in acutely infected patients, with a pooled prevalence of 48% [7]. In addition, a variety of risk factors for mental distress and sleep disturbances during COVID-19 have been pointed out, with female sex [8], psychological vulnerability [9], socio-economical [8], and virus-related factors – such as viral strain [10] or the course of disease [11] – being the most relevant.

The present review aimed to provide a general overview of mental health symptoms and sleep disturbances during SARS-CoV-2 infection and to analyze the underlying mechanisms and risk factors. Only original research, reviews, and meta-analyses that included patients with COVID-19 and were published in English and passed the international peer-review process were included.

Mechanisms of COVID-Related Neuropsychiatric Pathology and Sleep Disorders

Neuropsychiatric symptomatology associated with COVID-19 has been well established in the international literature, as patients with no history of mental illness were more likely to receive a diagnosis of anxiety or depression for the first time during or after COVID-19 [12]. Furthermore, the development of neuropsychiatric symptoms was directly associated with SARS-CoV-2, as these symptoms were more prevalent in COVID-19 patients compared to patients hospitalized due to other respiratory disease [10]. The underlying pathophysiologic mechanisms of the neuropsychiatric symptomatology associated with COVID-19 are not fully understood. Nevertheless, several mechanisms have been proposed, such as the direct effect of the neurotropic properties of the virus itself and the potential viral damage manifested as thrombosis, inflammation, hypoxia, and dysregulation of blood pressure [6, 13]. The mediators of COVID-19-related psychopathology are shown in Figure 1.

A. CNS Neuroinvasion

Many authors have suggested that SARS-CoV-2 inflicts direct damage to the CNS through both neuronal and endothelial cell infection [14]. The virus can infect peripheral olfactory neurons and exploit axonal migration pathways [15], reaching other CNS regions through retrograde neuronal transmission [16, 17]. It has been found that angiotensin converting enzyme 2 receptor (ACE2), that plays a crucial role in the manner SARS-CoV-2 penetrates cells [18], is widely present in multiple human organs including the nervous system and also the epithelial cells of the oral cavity [19]. ACE2-positive neurons are affected by binding with the SARS-CoV-2 virus, especially those in the paraventricular hypothalamic nucleus, that reduces the modulation of stress/anxiety and disturbs sleep cycles in COVID-19 patients [20]. The viral neuroinvasion has also been associated with astrogliosis, microgliosis, and immune cell accumulation [21]. Astrocytes are the main sites of viral infection and replication within the CNS, exhibiting metabolic changes detrimental to fueling neurons and building neurotransmitters, despite their lack of ACE2 expression [22]. These cells exhibit an elevated expression of the receptor NRP1, another SARS-CoV-2 spike target [23]. This receptor is abundantly expressed in the CNS but particularly in astrocytes [23]. Another explanation for SARS-CoV-2 preferably affecting astrocytes could be their proximity to the virus entry points, such as the brain vasculature and pericytes, which are in direct contact with

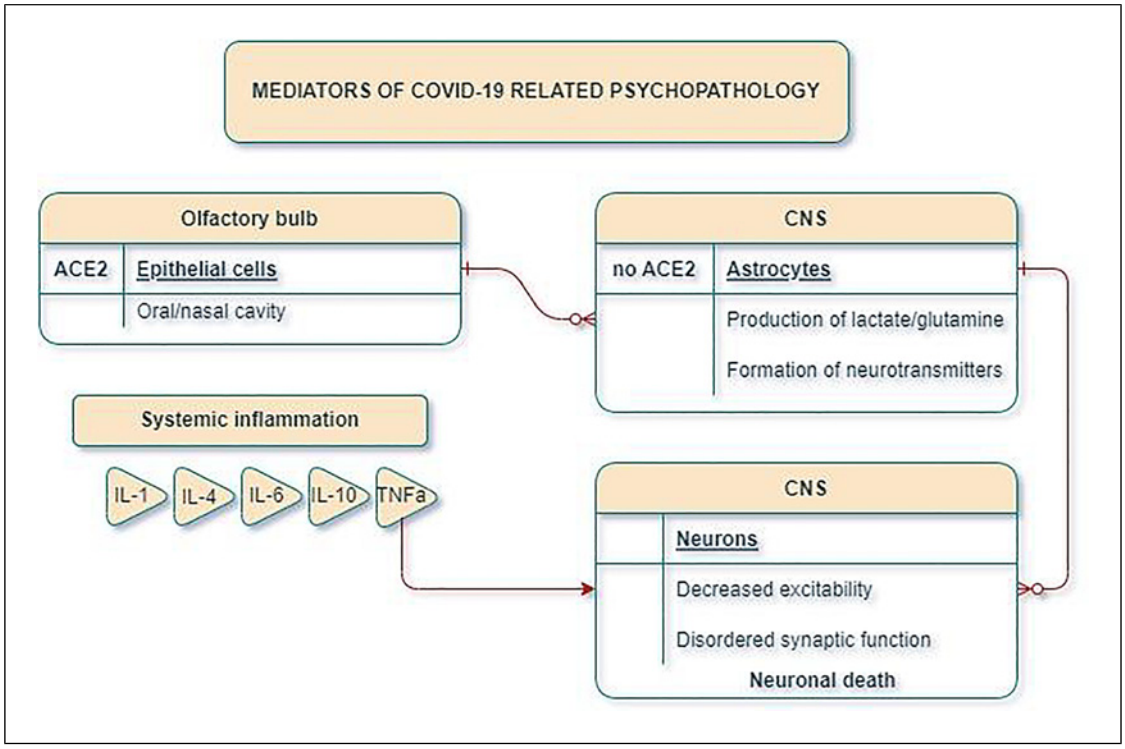

Fig. 1. Mediators of COVID-19-related psychopathology. Neuronal and astrocyte infection with SARS-CoV-2 have been proposed as underlying pathophysiologic mechanisms of the neuropsychiatric symptomatology associated with COVID-19. One potential route includes infection of the endothelial cells through binding to ACE2 receptor in the oral and nasal cavity, and then, migration to the CNS through the olfactory bulb. CNS astrocytes have been proposed as a main site of viral infection and replication within the CNS, despite their lack of ACE2 expression. Their proximity to the virus entry points, such as the brain vasculature and pericytes, that are in direct contact with astrocytes, could support the aforementioned theory of viral migration that starts at the endothelial cells and further progresses reaching the brains astrocytes, as shown in the top two blocks of this figure. The detrimental effects of the virus to the CNS could be both due to neuronal and astrocyte infection and as a consequence of systemic inflammation. In the first case, as astrocytes metabolically support the brain's neurons, synaptic function, plasticity, and neuronal excitability could be compromised. In the second, release of inflammatory mediators could alter the activation of brain areas that regulate sleep patterns as well as emotion, manifesting as psychiatric symptoms and sleep disturbances.

astrocytes [23]. Neurons are supported metabolically by astrocytes, as astrocyte-derived lactate and glutamine are required for neuronal metabolism [24], neurotransmitter formation, and recycling [25]. These processes are vital for the maintenance of synaptic function, plasticity, and neuronal excitability [26]. In combination with neuronal death, a decrease in intermediates of glutamine metabolism, such as glutamate and GABA, and a decrease in pyruvate and lactate levels (as seen in SARS-CoV-2-infected astrocytes), have been considered responsible for the neuropsychiatric symptoms of COVID-19 patients [27]. These important neurotransmitters, besides neuronal function, are also linked to encoding emotional and fear memory, perhaps rendering patients more vulnerable to acute post-traumatic stress disorder [PTSD] [28] and anxiety [29]. Furthermore, the sleep-wake regulatory system mainly depends on these fast neurotransmitters, and GABA depletion has been associated with poorer sleep quality [30] and primary insomnia [31]. This raises the debate about whether clinical psychopathology is a consequence of peripheral changes or of the potential ability of the virus to invade the CNS.

B. Systemic Inflammatory Responses, Immune Cell Infiltration, and Neuronal Death

In addition to the metabolic changes observed in SARS-CoV-2-infected astrocytes, the secretion of neurotoxic factors resulting in increased neuronal death has been pointed out as another pathophysiologic mechanism. These patients often present with dysregulated and overactive immune responses [32], that may indirectly affect the CNS [33]. COVID-19-induced immune

responses are characterized by a hyperinflammatory state with elevated serum levels of pro-inflammatory cytokines such as interleukin (IL) 1, IL-6, tumor necrosis factor (TNF)-α, CXCL10, and CCL2, and deregulation of IL-4 and IL-10 [34, 35]. It is known that inflammation is associated with depression by inducing BBB disruption, microglia activation, neurotransmission alteration, oxidative stress, and indoleamine 2,3-dioxygenase 1 activation [36]. Numerous neuroimaging studies have shown that elevated pro-inflammatory factors alter the activation of the medial prefrontal and dorsal anterior cingulate cortices and their projections, as well as the microglia of the amygdala and hippocampus, manifesting symptoms such as depression and anxiety [37]. As pro-inflammatory cytokines increase the BBB permeability via cyclooxygenase-2 upregulation, they enter the CNS [38], activating astrocytes and microglia. This activation leads to the release of inflammatory mediators (glutamate, interleukins, complement, and acute-phase proteins). Furthermore, activated neuroinflammatory microglia secretes inflammatory markers that induce reactive astrocytes, leading to neuronal death [39]. This cascade resulting in neuroinflammation and pruning of the synapses [40], has been observed in severe psychiatric disorders [41], such as major depressive disorder [42, 43]. Furthermore, areas of the brain that regulate sleep, such as the hypothalamus, hippocampus, and brain stem, are abundant with immunoreactive neurons for IL-1β and TNF-α and their receptors. During the acute phase of the immune response, sleep patterns are altered. These alterations include protracting of the duration of slow-wave sleep and a decrease in wakefulness and REM sleep. This mechanism may be in favor of metabolic devotion to the immune system, in order to clear the infection [44]. Increased levels of cytokines, peripherally as well as centrally in the CNS, have been related not only to lung inflammation and dysfunction [45, 46] but also to the development of psychiatric disease [47] and have been suggested as a mechanism of the development of depression and anxiety in COVID-19 patients [48, 49].

Neurocognitive impairment has been commonly reported in patients with viral infections such as SARS and MERS [50, 51]. In COVID-19, dysexecutive syndrome [52] and general cognitive dysfunction have been reported and may be linked to the underlying inflammatory processes [53]. Many studies have implied a link between inflammation activation, cognitive dysfunction, and the presence of psychopathology, suggesting the primary role of cytokines [54]. Furthermore, in patients presenting with depressive episodes, an association of peripheral IL-8, TNF-α, CCL2, CCL4 with cortical thickness has been reported [55]. In addition, associations of IL-1β, IL-9, CCL5 with brain glutamate, N-acetylaspartate, and myo-inositol levels [56] and of IL-8, IL-10, TNF-α, IFN-γ with white matter microstructure have been found. The levels of inflammatory cytokines have been inversely related to measures of white matter integrity [57]. Subtle structural and functional brain connectivity impairments could mediate the detrimental effects of COVID-19 on neurocognition, as information processing is closely associated with white matter microstructure in humans and in animal models [58]. Recent studies also highlighted brain abnormalities in both hospitalized and mildly affected patients, showing gray matter alterations with increased volumes [59] and cortical thickness [22] in some brain areas. Some of these alterations were correlated with the severity of anxiety symptoms, consistent with findings from pre-pandemic studies [60, 61] that have linked orbitofrontal cortical thickness to anxiety disorders. It is worth noting that trans-ethmoidally accessed post-mortem samples of COVID-19 patients with histopathological alterations due to infection were proximal to these same brain regions. These findings could potentially support the model in which SARS-CoV-2 reaches the CNS through neuroinvasion of the olfactory nerves [62], infects astrocytes, and impairs neuronal function and viability, resulting in neuropsychiatric symptomatology.

C. Damage of Cerebral Vessels-Coagulopathies

In the context of a pre-existing oxygen-deprived state in severe COVID-19, local brain hypoxia and lowering of the threshold for tissue damage have also been suggested as possible consequences of SARS-CoV-2 infection leading to direct neuronal damage [63]. Furthermore, infection of endothelial cells of the brain's vascular system and activation of neutrophils, thrombin production, and complement pathways promote micro-thrombi disposition [17]. This is also supported by post-mortem tissue-based studies, that reported micro-hypoxic and ischemic brain injuries in fatal COVID-19 cases [64, 65]. Some authors found percentages as high as 34% of micro-hemorrhages, infarcts [66, 67] and cerebrovascular disorders as ischemic strokes in COVID-19 patients, further cautioning that delirium without a focal deficit could be an unusual first stroke presentation [68]. These microvascular disturbances, along with the aforementioned immune-mediated damages leading in neuronal loss, have been frequently described as representators of the biological underpinning of the neuropsychiatric symptoms described in COVID-19 [65, 69]. Especially for depressive and post-traumatic symptoms, it is difficult to differentiate between the direct or indirect biological effects of the virus, the

psychological trauma related to the infection itself, and the iatrogenic effects related to aggressive life-saving treatments in intensive-care units [69].

Sleep Disturbance Pathologies

There is great heterogeneity in the international literature regarding the prevalence of sleep disturbances in patients with COVID-19. The variability in the rates of poor sleep across studies could be attributed to the different psychometric scales utilized, with Insomnia Severity Index and Pittsburgh Sleep Quality Index [70] being the most commonly used. In general, COVID-19 patients seem to be severely affected by sleep disturbances [71]. A systematic review found a global pooled prevalence rate of poor sleep quality of 35.7% among all populations, with COVID-19 patients being the most affected with a prevalence rate of around 75% [71]. This is far from unexpected, as the respiratory distress that characterizes COVID includes core symptomatology, such as difficulty breathing, coughing, and fever, that are associated with worsened sleep quality [72, 73]. Poor sleep was related to lymphopenia in hospitalized COVID-19 patients, a finding that was absent in good sleepers [74] and associated with a slower recovery rate. An increased neutrophil/lymphocyte ratio has been correlated with obstructive sleep apnea syndrome severity, although a clear causal relationship of the aforementioned factors with sleep disturbances still remains unclear [74, 75].

Sleep Disturbance due to Neuroinvasion

On the other hand, a decrease in the $CD56^{+}CD16^{-}$ natural killer cell population in patients with major depressive disorder seems to be associated with sleep disturbances [76]. Since CD56+CD16– cells are a major producer of IFNγ, the decrease in this cellular subset could partly explain the results of other studies which have reported that sleep disturbance and/or sleep deprivation is associated with a shift away from T_h1 immunity and increased vulnerability to viral infection [77]. The neuronal injury caused by COVID-19 could also contribute to sleep disturbance by invasion of specific brain areas, like the thalamus and brain stem, which play essential roles in sleep control and respiratory regulation. Neuronal injury secondary to COVID-19, due to aberrant innate immune response, could also lead to chronic neurological sequelae that adversely affect sleep and emotion regulation [78]. This indicates a possible long-lasting impact of COVID-19 on sleep. However, a definite causal relationship remains to be established, as well as the association of poor sleep with a specific virus.

Quarantine-Inflicted Sleep Pathologies

As humans are social entities, sleep problems and other health risks seem to increase when they are isolated from human contact [79]. Worsening of sleep quality, increasing sleep problems, or increasing problems with insomnia during quarantine conditions or even delays in sleep timing were commonly found across many countries. Social support, that seemed to be diminished during quarantine, has been suggested to serve as a "buffer" for the isolation's period detrimental effect on sleep [80]. On the opposite end, lack of social support could worsen sleep quality by inflicting poorer decisions regarding sleep habits [80]. Moreover, sleep onset, sleep maintenance, and early morning awakening insomnia all seemed to increase during lockdown for the general population. Likewise, a greater use of hypnotics during the pandemic with respect to the precedent period has also been found [81]. Confinement was associated with poor sleep quality and problems falling asleep, a problem exaggerated by the psychological impact of the disease. At the same time, exposure to artificial lighting of electronic devices may have worsened symptoms of insomnia and reduced sleep duration through desynchronization of the circadian clock [81].

Along with psychological impacts of the disease, social isolation and quarantine have also imposed sedentary behavior, manifested as reduced physical activity and poor sleep hygiene [82]. Restricted mobility and irregularity of the sleep-wake cycle hours, along with overall psychological distress and worry about the future, have affected the amount and quality of sleep in the general population. Physical exercise is well supported by the literature as a nonpharmacological treatment method for sleep disorders; however, COVID-19 patients, either bedridden or simply quarantined, lack the required exercise to maintain healthy sleep [82], and even incidents of dream-enactment behaviors and other parasomnias have been reported and have been attributed to physical restriction during quarantine that may potentially alter their physical activity pattern [83]. Furthermore, they are at risk of developing circadian rhythm problems due to changes in daytime routine, possible daytime naps, and insufficient exposure to natural light [82]. Finally, regardless of SARS-CoV-2 infection, little to non-existent social contact, concern about financial resources and infection of loved ones, or even uncertainty about the duration of self-quarantine period have been described as major contributing variables of clinical insomnia and changes of sleep patterns [84].

Psychosocial Mechanisms of Mental Pathologies

It is interesting to notice that all patients with COVID-19 do not develop mental health symptomatology, and that COVID-19 infection and course of disease severity do not contribute equally to experiencing mood symptoms [85]. This indicates that a variety of psychosocial factors may play a role in developing COVID-19-related anxiety or depression [86]. In non-hospitalized COVID-positive individuals increased levels of depression were found, as they were required to self-isolate. These patients consistently reported increased feelings of loneliness, frustration, and boredom due to confinement, time away from loved ones, and a general disruption of daily routine [87]. In addition, fear of COVID implications regarding the course of the disease, as well as self-blame and fear of infection of other family members, were also associated with anxiety [87]. Additionally, the stigma, either toward the infected or toward specific demographic groups, has been related to psychological distress [88]. A recent cross-sectional study of patients who recovered from SARS-CoV-2 infection in Qatar showed a prevalence of 26.4% of moderate-to-highly perceived stigma related to COVID-19. Isolation in a non-home setting was found to be the primary risk factor of increased likelihood of perceived stigma [89]. These findings are aligned with other qualitative studies showing that COVID-19 patients isolated far from their homes have higher COVID-19 perceived stigma [90].

Peripheral Organ Dysfunction

Peripheral organ dysfunction secondary to respiratory insufficiency or acute respiratory distress syndrome (ARDS) has also been associated with adverse mental health effects and sleep disturbances. About a third of ARDS survivors, who participated in a 5-year longitudinal study, presented with a prolonged (i.e., continuous or recurring) course of substantial anxiety, depression, and PTSD symptoms, while half of them suffered from any prolonged, post-infection symptomatology [91]. Hypoxia itself may trigger stress-related diseases [92]. Impaired mitochondrial aerobic respiration disrupts the cerebral energy metabolism, leading to reduced oxygen-dependent brain processes, including tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis [92]. Increased sympathetic activity and hypothalamic-pituitary-adrenal axis activation result in cortisol release dysregulation and, therefore, increased glycogenolysis and glycolysis in response to oxygen insufficiency for oxidative phosphorylation. This leads to brain hyperglycemia, which has been referred as a risk factor for depression and anxiety [93]. In addition, central release of oxytocin, known for its anxiolytic effects, and vasopressin are affected by oxygen levels. As vasopressin release is increased under hypoxic conditions, potential opposite regulation of oxytocin and vasopressin release in the bed nucleus of the stria terminalis and amygdala contribute to anxiety and fear responses due to hypoxia in COVID-19 patients [92]. In addition, hypercapnia also seems to be a significant factor in the case of mental distress [94]. Finally, respiratory or even cardiovascular consequences of COVID-19, manifesting as inflammation of the airways and hypoxia, could worsen existing sleep apnea symptomatology or even lead to new cases that could also be exacerbated by the psychological effects of the isolation and the disease as a whole [82].

Risk Factors Associated with Mental Symptoms and Sleep Disturbances

Psychological consequences of respiratory infections have historically been reported in the international literature, dating back to the influenza pandemic in 1918 [95] and later in the SARS and MERS pandemics [27]. In a meta-analysis of hospitalized patients due to SARS or MERS, the prevalence of depression, anxiety, and insomnia exceeded 30%. Loneliness and frustration from isolation, as well as concern of dying and spreading the virus to family members, were all prominent features of patient experiences [27]. Studies during the early phases of the COVID-19 pandemic yielded similar results, with one-third of patients exhibiting neuropsychiatric distress and most fulfilling the clinical definitions of psychiatric diagnoses. In an early UK study of COVID-19 patients, nearly all psychiatric diagnoses were new-onset psychosis, and more than half of them occurred in patients younger than 60 years [96]. A following study of electronic health records for almost 70 million patients from 54 healthcare organizations in the USA found that 18.1% of patients hospitalized for COVID-19 were diagnosed with a psychiatric condition [11]. An increased incidence of first-time psychiatric diagnoses was found compared to patients hospitalized for other reasons, with the highest increase in anxiety and insomnia [11]. In an Italian university hospital, almost 50% of hospitalized COVID-19 patients complained of sleep disturbance with symptoms appearing immediately after admission and with the frequency increasing with prolongation of hospitalization [97]. This may indicate

that sleep disturbance cannot be simply explained by acute psychological response to the disease. Sleep disturbance, experienced as insomnia, was also found even in mild patients in mobile cabin hospitals [98]. Several risk factors have been associated with the neuropsychiatric sequelae of COVID-19 infection.

1. Disease Severity, Hospitalization, and ICU Stay

Disease severity has been suggested to be a risk factor for adverse mental health defects with several studies reporting that anxiety and/or depression, as well as sleep disturbances, significantly affect patients recovering from severe COVID-19. Except for the neuronal pathology caused by the virus, the physical manifestations, including respiratory symptoms, fever, and pain, may also negatively affect sleep quality. Pittsburgh Sleep Quality Index (PSQI) scores were shown to be associated with the severity of pneumonia [99] as well as the subjective perception of the disease severity in COVID-19 patients [100]. On the other hand, medications routinely used in hospitalized COVID-19 patients such as corticosteroids, sedatives, beta-blockers, and non-steroidal anti-inflammatory drugs (NSAID) also create and exacerbate sleep problems [101]. On the notion of hospitalization, environmental factors, especially during ICU stay, including noise, abnormal light exposure, patient care activities, diagnostic and treatment procedures, seem to be detrimental to sleep quality [74, 102]. Sleep disturbance is a predominant feature in ICU patients, that presents with decreased sleep efficiency, a shift toward light sleep stages, increased arousals, and abnormal circadian rhythmicity [74]. Furthermore, duration of hospitalization has been correlated with depressive symptomatology and sleep disturbances, independently of acute COVID-19 severity [103]. Finally, it is worth mentioning that the relation between sleep disturbances and symptom quantity can be bidirectional, as patients with COVID-19 exhibiting poor sleep quality also present with higher depression rates, sense of fatigue, and duration of hospitalization, especially in the ICU [84, 86].

2. Inflammation

Studies examining inflammatory markers found a correlation between elevated immune response and symptoms of anxiety and depression [104, 105], even predicting the development of depression during follow-ups [47, 106]. Prolonged exposure to proinflammatory mediators and innate immune molecules has been speculated to modulate neuroinflammation, causing clinical symptoms of insomnia, arousal, and diminished sleep efficiency [107]. It is also of particular interest that, while IL-6 has been generally linked to depressive symptomatology, in several studies [108, 109] that did not find an increased incidence of anxiety or depression [39, 53] blood levels of IL-6 were also not elevated.

3. Female Sex

A recent study of patients hospitalized in isolation wards due to COVID-19 found that perceived stress was significantly greater in women, who scored higher on questions about depression but not psychotic or compulsory behavior and addictions [8]. This finding is consistent with studies conducted earlier during the pandemic that associated female sex with a higher probability of reporting anxiety and depression [94, 110]. It has been proposed that such differences could be due to different immune system functions [111, 112] or to different hormone regulation [113], underlining the need of considering gender differences in order to promote more individualized care.

4. Age

Several studies have found age to be a factor associated with a higher prevalence rate of sleep difficulties during COVID-19 [71, 114]. Aging of the circadian network and reduction of the amplitude of melatonin, known for its immunoregulatory properties, could worsen sleep among the elderly [100]. Additionally, melatonin-related mechanisms have been speculated to partly contribute to increased susceptibility to SARS-CoV-2 infection [115]. While the aging population might have a better advantage of emotion-regulation capacities, they present with more severe morbidity and higher mortality from COVID-19 due to increased co-morbidities and compromised immune status [114]. Moreover, IL-6 also appears to be upregulated in normal aging and may be a key mediator of age-related neuroinflammation [116]. Despite the fact that older age has been associated with certain outcomes, individuals of younger age were also impacted in several studies. Children with COVID-19 and co-morbid physical or mental disorders may be vulnerable to exacerbations of neurotropic factors, as it has been already documented for other coronaviruses [117]. In addition, in patients between 12 and 13 years, a significant impact in cognitive and executive functioning has been observed, regarding those who were either hospitalized or non-hospitalized but symptomatic [118]. The level of serum granulocyte colony-stimulating factor (G-CSF) was significantly higher in children with coronavirus infections, consistent with

the fact that CNS viral infection might induce the proliferation of microglia and astrocytes. These results in the release of interleukin-8 (IL-8), that causes the migration of granulocytes toward the site of infection, playing an important role in the immune reaction and the damage to the CNS [117].

5. Co-Morbidities

It has been proposed that patients with underlying biological vulnerability might experience greater sleep disturbance and mental health problems from COVID-19. COVID-19 causes systemic inflammation known to influence sleep and mood. Individuals with a mental health diagnosis prior to COVID-19 were at higher risk for the development of depression or anxiety [86]. Furthermore, history of poor mental health has been characterized by infection-related symptoms of depression and anxiety, as well as higher hospital and ICU admission, longer hospital stays, mechanical ventilation, and sleep dysfunction [71, 119]. More specifically, hospitalized COVID-19 patients suffering from schizophrenia reported poorer sleep quality and greater incidents of depression and anxiety [120, 121]. Furthermore, as depression is a common co-morbidity among patients with autoimmune diseases, flares and elevated immune responses render this population more vulnerable to mental health defects [122]. Patients with other co-morbidities such as asthma, diabetes, and cardiovascular disease presented with higher odds of exhibiting symptoms of stress, anxiety, and depression than healthy individuals, during COVID-19. This highlights the need for additional mental health resources for patients with chronic diseases [123].

In addition, chronic inflammation, which accompanies obesity and metabolic syndrome, as well as the associated poor sleep quality and sleep apnea [100], may have an additional impact in obese patients suffering from COVID-19. The innate immune response in patients with obesity leads to an increased inflammatory state, that has been previously established as a predictor of poor outcomes in infections due to H1N1 [124]. Individuals with obesity have endorsed increased stress and loneliness during the COVID-19 pandemic and are at a greater risk for poor sleep outcomes; however, these disturbances cannot be directly attributed only to the SARS-CoV-2 infection per se.

6. Social-Educational Factors

Several social factors have been correlated with the negative mental and sleep health outcomes of COVID-19. Married people and people belonging to a family seem to present more stress compared to singles, often due to financial insecurity and social responsibility towards their family [8]. Meanwhile, in hospitalized or home-isolated patients, the fear of infecting loved ones may act as an additional stressor [125]. Testing positive for COVID-19 and the following self-isolation requirement imposed increased feelings of loneliness and frustration, resulting in increased levels of depression [87]. Urban setup and higher educational status have also been associated with higher levels of mental distress, with this finding being attributed to the higher knowledge or awareness of COVID-19 than less educated individuals or those living in rural background [8, 126]. However, regarding the level of education the results were contradictory, as other studies rendered the less educated more prone to psychological distress [127, 128] possibly due to misperceptions with regard to COVID-19. Individuals with a higher education may understand better the disease and thus may be less prone to experience COVID-19-perceived stigma [129].

Post-COVID-19 Syndrome

Finally, despite it being beyond the scope of this review, it is worth mentioning that COVID-19 sequelae concerning mental and sleep health often persist after the end of the disease course, rendering post-COVID-19 syndrome a global public health burden. Most of the aforementioned risk factors have been identified as predictors of persisting symptomatology after hospital discharge or even at-home quarantine. Severity of disease course has been highlighted as a risk factor for post-traumatic stress disorder (PTSD) and sleep disorders [130, 131] at follow-up. Two studies reported an increased risk of PTSD in patients discharged from the ICU [132, 133]. It has also been reported that significantly more COVID-19 survivors suffered from insomnia 6 months after SARS-CoV-2 infection and a severe acute disease course was a risk factor for insomnia. Severity of initial disease [11, 134], as well as the duration of symptoms and hospitalization [103], despite the variations between reports, have been highlighted as risk factors of anxiety and depressive symptoms post-SARS-CoV-2 infection. Despite it being beyond the scope of this review, the presence of post-COVID-19 syndrome highlights the importance of persisting symptomatology after the end of the disease course.

Studies that examined baseline inflammatory markers regarding depression and anxiety at follow-up found that inflammation measured during acute infection was a predictor of severity of depressive psychopathology at 3-month follow-up [103, 104].

However, women and patients with a previous psychiatric diagnosis suffered more from both anxiety and depression without displaying elevated baseline inflammatory markers [9, 135]. Previous studies have pointed out that female sex is a risk factor for sleep disturbances after recovery from COVID-19 [136], as well as for anxiety, depression [137], and stress [114]. On the contrary, another study found no correlation between sex, co-morbidities, severity of initial infection, or initial illness duration with post-COVID depressive symptoms, but a rather elevated immune response as measured by increased white blood cell and neutrophil counts was found [138]. A cohort study of hospitalized patients reported that 22% of patients with co-morbidities at baseline suffered from anxiety or depression after COVID-19 recovery, whereas only 9% without baseline co-morbidities [139]. This finding is further supported by an array of work on the relationship between depression and neuroinflammation [47]. COVID-19 patients often report dyspnea post-infection, a fact that could exacerbate their symptomatology. More specifically, the continuous sensation of breathlessness, even at rest, could explain the higher levels of anxiety, depressive symptoms, and poorer sleep quality [140].

Conclusions

The majority of early research following COVID-19 has focused on the physiological effects of the virus, with a substantial body of subsequent studies [141] showing that the psychological burden of the infection is also considerable. Apart from a number of psychological factors, COVID-19 diagnosis is more likely to increase susceptibility to developing mood and sleep disturbances due to direct bio-immunologic or psychological pathways. These disorders should be diagnosed in time in order to improve prognosis and apply effective personalized interventions. It is also imperative to continue the recording of prevalence rates, especially in vulnerable populations such as women, elderly, and those with preexisting co-morbidities, to prevent the development of the long-term manifestations of the virus and to establish a multidisciplinary approach to patient care during both active infection and recovery.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

A.K. and A.T. contributed to the conception and writing of the review; A.P. contributed to drafting and revising the review critically; and A.K., S.K., E.S., and A.Z. participated in the acquisition, analysis, and interpretation of the work. All authors approved the manuscript.

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