

Advances in research on sleep disorders promoting the deterioration of novel coronaviruses

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Abstract. Novel coronavirus pneumonia (Corona Virus Disease 2019, COVID-19) is a disease with fever, dry cough and progressive dyspnea as the main manifestations. 2019 novel coronavirus (2019-nCoV) is transmitted by contact transmission. Sleep disorders are linked to novel coronavirus, it not only reduces the life motivation of patients with COVID-19, but increases the burden on the family members who care for patients. Sleep disorder is related to the aggravation of COVID-19 to some extent. Sleep disorders are a significant factor in advance of COVID-19 into the severe disease, and the pathophysiological changes in COVID-19 also contribute to the problem of it. Sleep disorders exacerbate the body's psychological stress promoting decreased immune function, while interfering with the normal exercise of physiological functions of reactive T cells, which have specific defenses against 2019-nCoV can prevent 2019-nCoV from entering the body, so people with sleep disorders infected with 2019-nCoV will have more severe symptoms than those who do not suffer from sleep disorders. Because the link between COVID-19 and sleep disorders is poorly understood by clinicians, this article describes recent research advances on sleep disorders that exacerbate COVID-19 disease, patient sleep status, and treatment options.

Keywords: Novel coronavirus pneumonia, Sleep disorders, Immune system, Influencing factors.

1. Introduction

Sleep plays a vital role in human beings, as adequate sleep can remove oxygen free radicals and metabolic wastes from the body and enhance the immune function [1]. There are many kinds of sleep disorders such as Sleep-Disorder Breathing (SDB), circadian rhythm disorders, Sundown Syndrome (SS), restless leg syndrome (RLS), Rapid Eye Movement Sleep Behavior Disorder and sleep disorders. REM Sleep Behavior Disorder (RBD), Obstructive Sleep Apnea (OSA), etc. Long-term sleep deprivation or sleep disorders can prevent the immune system from functioning properly, cause cardiovascular diseases, tumors, depression and other diseases, and even reduce cognitive ability to induce Alzheimer's disease in advance. It can lead to health problems in the human body [2].

Severe COVID-19 infection in some cases can cause pneumonia and lead to death of the patient. According to statistics, 36.5 million people have been infected by 2019-nCoV as of October 8, 2020, and it has killed more than 1 million people from all around the world, it is spreading rapidly in China and has spread to 213 countries worldwide [3].

Sleep disorders may make COVID-19 infection more likely to occur, sleep disorders can lead to changes the structures of T cells, CD4 and CD8 cells decreased number can also make type 1 T cells immune shift, and T cells and CD4 and other cells have a specific immune response to 2019-nCoV, after the onset of sleep disorders in because of the reduction in the number of T cells abnormal function makes the invasion of the body's 2019-nCoV cannot be rapidly cleared, thus aggravating COVID-19.

In the first part of this passage, I introduce the contemporary sleep status of COVID-19 patients, and then I describe the mechanisms by which sleep disorders promote COVID-19 exacerbation, and in the last part, we present a summary of the existing treatment modalities for COVID-19 exacerbation caused by sleep disorders. By summarizing the link between sleep disorders and COVID-19, this paper has clinical implications for future research. Most of the current studies are on sleep disorders after 2019-nCoV infection, but there are data suggesting that there is senescent apoptosis of immune cells in COVID-19, which have a corresponding link with type 1 T cell immune transfer due to sleep

disorders [4]. Therefore, the impact of sleep disturbance on with 2019-nCoV could be investigated in the future, and this paper reviews the latest research available on sleep disturbance affecting the severity of novel coronaviruses.

2. Sleep status of patients with novel coronavirus pneumonia

2.1. Current status of patients with OSA COVID-19

Sleep disorders include a variety, but the majority of current studies have examined the current sleep status of patients with OSAS/COVID-19. The prevalence of COVID have an important influence on the general population, also especially on patients with OSA. OSA has multiple characteristics, and during sleep patients with OSA experience continuous upper airway collapse and intermittent hypoxia and reoxygenation, so that the body's heart rate and blood pressure during normal sleep decreases are offset by the body's oxygenation cycle, negatively affecting cardiovascular and other systems [5]. In the study by Satu Strausz et al., severe COVID-19 patients were defined by him as patients with COVID-19 who needed to be hospitalized, by extracting hospital discharges, the reason of death and the diseases which have some infectious from the population participating in FinnGen (A large biological sample bank), including two types of biospecimen repositories) registries of people with OSA prevalence and COVID-19 infection using multivariate regression models to examine the association between the two concluded that the risk of developing COVID-19 was essentially the same for healthy people and people with OSA, but the OSA was a separate risk factor for those who have severe COVID-19 people [6]. On the one hand, the pathogenesis of COVID-19 and OSA are similar in the sense that both are pro-inflammatory states. On the other hand, angiotensin 2 receptor can bind to 2019-nCoV in human body, promoting novel coronavirus to enter human cells, and the expression of this receptor in obese people will be higher than that in healthy people. This suggests that obese OSA patients may be more likely to promote the aggravation of COVID-19. Some symptoms of COVID-19 related cardiac disease include heart failure, myocardial infarction, and myocarditis, and OSA is a significant factor for arrhythmia, heart failure, and hypertension. Therefore, those patients who are infected with COVID-19 and have OSA may have more serious symptoms than those who are infected with COVID-19 but do not have OSA. The occurrence of OSA is accompanied by hypoxemia and altered hemodynamics, both of which can increase blood viscosity in humans and aggravate the hypercoagulable state of blood in COVID-19 patients [5]. Based on these two studies, it can be inferred that OSA is one of the important causes of COVID-19 from light to heavy, so treating OSA may help the recovery process of COVID-19 patients.

2.2. Status of patients with other sleep disorders COVID-19

The study by Mo Saying et al. evaluated and analyzed the patients' sleep status by taking 183 cases of COVID-19 light patients from February 10-February 28, 2020, by using a questionnaire, Pittsburgh Sleep Quality Interview (PSQI), and Self-Assessment Scale of Anxiety (SAS) from the Fangcao Hospital in Wuhan, Hubei Province. The results of this study showed that COVID-19 patients had some sleep problems (e.g., poor sleep quality and inefficient sleep) and psychological problems (e.g., fear of family infection and excessive worry about prognosis) during isolation, and that the PSQI was lower in those who exercised regularly and never smoked, and the SAS was lower in those who never exercised and former smokers. Also, this study found a positive correlation between patients' exercise habits and sleep quality, and a negative correlation between smoking and sleep quality [7]. Based on this study, it can be concluded that there is often a link between the decrease in sleep quality and the surrounding environment, self-factors, and psychological state.

3. Contribution of sleep disorders to the development of novel coronavirus pneumonia

Sleep is an important physiological process for the human body. Sleep disorders lead to immune problems in the human body, where sleep disorders lead to immune transfer of type 1 T helper cells, which have a corresponding immune effect on 2019-nCoV, and research has shown that the levels of reactive immune cells are lower than normal in patients with novel coronaviruses, and the level of cytotoxic somatic cells is even lower in patients with concomitant sleep disorders [8]. Therefore, there is a link between sleep disorders, the immune system, and novel coronaviruses.

3.1. Modulation of immunity by sleep

Sleep has a significant character in the maintenance of immunity. At social settings, likes during the COVID-19 pandemics, psychological stress increases significantly and promotes the development of anxiety, and therefore sleep is affected, leading to inflammation and a decrease in the immune response to the virus [9]. Normal sleep and circadian rhythms are required for the maintenance of many immune functions. Sleep disorders promote immune diversion of type 1 T cells (TH1) and suppress the functioning of immune cells, especially T lymphocytes [1, 8]. A study in healthy adult men showed that after two nights of total sleep deprivation CD4⁺ T cells and neutrophils were increased, and after three nights of sleep recovery time, CD4⁺ levels still did not return to normal levels, and a similar condition was found in OSA patients [10, 11]. Sleep regulates the immune system as well as the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. During SWS sleep, lower levels of cortisol promote the immune response to viruses, and when the binding of glucocorticoid receptors to the former is blocked, the secretion of both CD4 and CD8T cells is increased. In case of chronic sleep disorders, it leads to prolonged activation of HPA and consequently to glucocorticoid resistance of immune cells [1]. The above-mentioned elements can be represented by Figure 1.

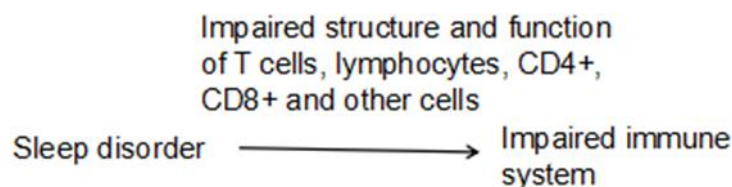


Figure 1. Regulation of the immune system by sleep

3.2. Role of immune cells for 2019-nCoV

As we all know, the immune system plays an immeasurable role in preventing viruses from entering the human body, and it can also protect people's healthy growth, and Jun Chen et al. showed that in old BALB/c mice, the slow clearance of 2019-nCoV upon entry into BALB/c mice due to T-cell depletion led to an increased prevalence of COVID-19, and in healthy mice when 2019-nCoV invaded In healthy mice, 2019-nCoV is cleared in a timely manner to prevent infection, while in BALB/c mice, infection and disease increase because of abnormal immune cell function that does not clear 2019-nCoV in a timely manner, Compared with the immune cells in healthy people, the proportion of T cells and neutrophils in total immune cells in suffering from severe COVID-19 increased [12]. The research of Sara De Biasi et al suggests that a controlled trial with a healthy population resulted in structural changes in T cells, and lymphocytes in COVID-19 patients, with a significant increase in activated T cells and a significant increase in the production of interleukin IL-17 in vitro by CD4⁺ or CD8⁺, and such changes activate neutrophils. In addition, studies have found that many changes have taken place in T cells of patients with COVID-19, such as the increase in the production of aging, activation and failure markers, at the same time, the distinguish subtype of T cells has changed, the number of circulating cells in the lung and other organs has decreased, and the number of neutrophils has decreased [4].The study by Min Kyung Jung and Eui-Cheol Shin also showed that in COVID-19 patients body the 2019-nCoV-specific T cells were fully activated and

also showed that in animal models T cells are contributing to host defense against 2019-nCoV and CD4+ cells promote to virus elimination. CD4+ and CD8+ cells can exert their cytotoxic activity by producing effector cytokines to neutralize antibodies, and this way they directly interfere with viral invasion of host cells [13]. What was described above can be represented by Figure 2.

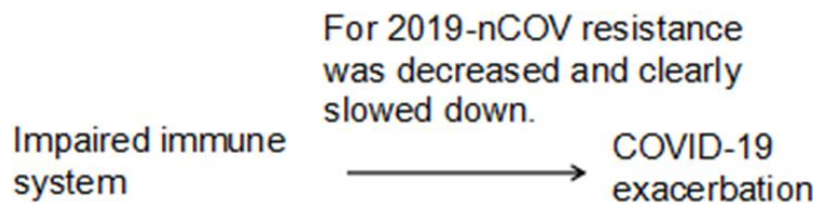


Figure 2. Modulation of COVID-19 by the immune system.

3.3. Modulation of COVID-19 by sleep

According to statistics, the combined prevalence of all patients suffering from sleep disorders is 35.7% worldwide, while the prevalence of COVID-19 patients suffering from sleep disorders is 74.8% [14]. Beatrice Ragnoli et al. reported that there is a link between sleep, COVID-19 infection and the immune system. One of the important reasons for novel coronavirus to develop into severe disease is the occurrence of sleep disorder, which has been proposed. Reduced sleep problem can promote viral infection has been demonstrated in mice, and reduced sleep affects immune cells leading to dysfunctional T-lymphocytes, CD4+ and CD8+ T-lymphocytes with diminished defense against 2019-nCoV, mechanisms that have been observed in partial sleep deprivation (SD) [15]. Also, by the introduction of the first and second sections, it can be understood that sleep disorders affect some specific immune cells, which are structurally or functionally altered in COVID-19 patients. In summary, it can be clearly seen from the second paragraph that sleep disorder can promote the aggravation of COVID-19 by affecting the immune cells of the immune system. The above-mentioned elements can be represented by Figure 3.

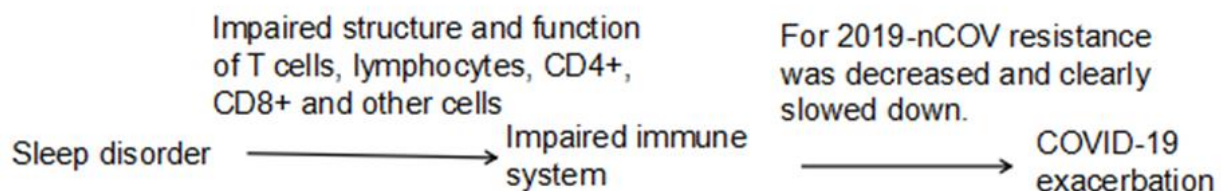


Figure 3. Modulation of COVID-19 by sleep

4. Treatment of sleep disorders in patients with COVID-19

With the increase of patients not only suffering from sleep disorders but also from COVID-19, how to treat them has become an important problem. Since COVID-19 patients often have sleep disorders, COVID-19 can be attenuated by regulating T-cell abnormalities due to sleep disorders, indirectly by regulating sleep-related melatonin, or by reducing the severity of COVID-19 through other therapies such as humane care.

4.1. Treatments for sleep disorders causing T-cell damage

Since sleep disorders cause immune cell damage leading to exacerbation in COVID-19 patients, the severe disease can be reduced by enhancing immune function. Salman M. Toor et al. showed that the immune response of T cells is highly specific and also has an essential role in fighting against viral invasion. T cells can recognize 2019-n-COV, because the interaction between T cells and 2019-nCoV has been described above, and will not be described in detail here. The first therapeutic approach is to cure COVID-19 patients who accompanied with sleep disorders by extracting T cells specific for 2019-nCoV from recovered COVID-19 patients. A second approach to treating patients

with COVID-19 is to inject a small amount of recombinant IL-2 to mitigate lymphopenia and normalize the recovery of the t-cell count. Because T cell senescence in COVID-19 patients leads to the loss of T cell function and the failure of viral clearance, and also 2019-nCoV may increase suppressive immune checkpoints (IC) so the third treatment is targeting IC, which may be effective in COVID-19 patients [16].

4.2. Melatonin treatment of the immune system

Melatonin is a derivative of tryptophan, mostly synthesized in the pineal gland, which is synthesized with regularity and its concentration reaches a maximum in the plasma during the night. Melatonin has unique efficacy in the treatment of sleep disorders. In a report by Adam Wichniak et al. it is noted that melatonin has the potential to inhibit the developmental process of COVID-19 and that melatonin can inhibit the risk of 2019-nCoV entry into cells. It may also reduce the activation of immune cells and the occurrence of uncontrolled excessive inflammation, because free radicals can attack human organs and some tissues while melatonin inhibiting its activity suppresses multiple organ failure and tissue cell damage, and increase the preventive function of COVID-19 vaccine. Because melatonin has some degree of anti-inflammatory capacity, melatonin may reduce inflammation triggered by 2019-nCoV infection. In addition, treating COVID-19 patients with melatonin is still a safe treatment with no side effects. In the current study, clinicians are using melatonin not only as an important treatment for sleep disorders, but also as an important adjunct to COVID-19 treatment. As mentioned above, the angiotensin receptor (ACE2) can bind to the 2019-nCoV to facilitate its entry into the host cells, which would explain why 2019-nCoV would damage organs with high ACE2 content (e.g., liver, cardiovascular system, etc.) and melatonin happens to interact with the renin-angiotensin system, where melatonin the expression of ACE2 will be limited by melatonin, thus reducing the risk of 2019-nCoV entry into cells. Because 2019-nCoV can promote free radical production by promoting inflammation, melatonin as an antioxidant can scavenge some free radicals, and therefore melatonin can also have a therapeutic effect on COVID-19 [17,18]. By elaborating above, it can be understood that melatonin is a significant treatment to COVID-19 patients.

4.3. Other

Many patients with COVID-19 patients are placed in ICU, and they are often accompanied by sleep disorders, which has become a problem that cannot be ignored, so it is especially important for the therapists of patients with severe COVID-19. Humanized care is a special type of clinical care, Ma Qingyun by collecting a total of 33 cases of ICU COVID-19 with sleep disorders in Wuhan Xinzhou District People's Hospital in Hubei Province from January 2020 to March 2020, a controlled trial was taken to divide the patients into two parts, the observation group used conventional care and humanized care including psychological care, discomfort relief, environmental care and The observation group used conventional care and humanized care including psychological care, discomfort relief, environmental care and medication guidance, while control group used only conventional care and evaluated and analyzed the patients' sleep through the Sleep Quality Inventory and PSQI. The results of his study showed that humanized care measures given to patients with COVID-19 sleep disorder in ICU could enhance the sleep quality of patients [19]. According to this study, a good psychological state and appropriate medication can be given to patients in the therapy of COVID sleep disorders, which could enhance the mental health and relieve pain of the disease. Also, good dietary nutrition can enhance the quality of sleep to reduce the degree of sleep disorders [20].

5. Conclusion

In summary, the regulatory mechanism of sleep disorder for COVID-19 is complex, because sleep has an important regulatory role for immunity, sleep disorder will lead to type 1 T-cell immune

proliferation, abnormal CD4 and CD8 T-cell function, T-cell content and function changes will cause damage to the human immune system, and because T cells have an important defense role for 2019-nCoV, so sleep disorder may cause the body to fail to respond normally to 2019-nCoV invasion, causing immune dysfunction, which further may make COVID-19 patients' symptoms more severe, and sleep disorders and COVID-19 together affect the daily life of COVID-19 patients and increase the burden of caregivers. Numerous data suggest that sleep disorders and COVID-19 are interlinked. What can be concluded is that the immune system's defense against COVID-19 is weakened due to sleep disorders. Secondly, factors such as temperature, feeding, light, socialization, and medications also contribute to the development of sleep disorders.

Most of the current studies have focused on the development of sleep disorders after COVID-19 illness, and future studies need to further define the relationship between COVID-19 and sleep disorders, because sleep has some relationship with nerves, thus the relationship both sleep disorders and nervous system can be inquired into determine the severity of COVID-19 and sleep disorders, or to explore whether it is possible to enhance the immune system by reducing the degree of sleep disturbance and thus the probability of reducing the severity of COVID-19. Thus, professionals studying sleep and COVID-19 can investigate preventive measures for sleep disorders, which can help prevent and treat both diseases, and further understand the relationship between the two, which can promote the mental health of patients and reduce the burden on caregivers. In an era of high-tech precision medicine that strives for full personalization, a deeper understanding of the relationship between sleep disorders and COVID-19 can help provide more effective and safe ways to treat COVID-19, as well as explore new drug and non-drug therapeutic targets.

References

- [1] Wan Yahui, Xue Rong, Advances in sleep and immune correlation research [J] Chinese Journal of Neuroimmunology and Neurology. 2020, 27 (06).
- [2] Deng H. M. Yan N. Progress in the study of co-morbid mechanisms of Alzheimer's disease and sleep disorders [J] Using Chinese and Western medicine. 2019, 19 (01).
- [3] Anshika Sharma, Isra Ahmad Farouk, Sunil Kumar Lal, COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention[J]Viruses.2021 Jan 29; 13 (2): 202.
- [4] Sara De Biasi, Marianna Meschiari, et al. Marked T cell activation, senescence, exhaustionskewing towards TH17 in patients with COVID-19 pneumonia [J] Nat Commun 2020 Jul 6; 11 (1): 3434.
- [5] Hu K, Yang HZ, Yue F. Impact of the new coronavirus pneumonia epidemic on the diagnosis and treatment of obstructive sleep apnea and countermeasures [J] Theory and Practice. 2021, 16 (02).
- [6] Satu Strausz, Tuomo Kiiskinen, Martin Broberg, et al. Sleep apnoea is a risk factor for severe COVID-19 [J] BMJ Open Respir Res.2021 Jan; 8 (1): e000845.
- [7] Mo Suying, Deng Xianbing, et al. Analysis of the psychological and sleep status of patients with mild novel coronavirus pneumonia and its influencing factors in Fang Cabin Hospital [J] Journal of Clinical Nursing. 2021, 20 (01).
- [8] Hideo Suzuki, Jonathan Savitza, et al. Altered Populations of Natural Killer Cells, Cytotoxic T Lymphocytes, and Regulatory T Cells in Major Depressive Disorder: Association with Sleep Disturbance [J] Brain Behav Immun.2017 Nov;66:193 - 200.
- [9] Eduardo de, Sousa Martins e Silva1, et al. Sleep and immunity in times of COVID-19[J]Rev Assoc Med Bras (1992). 2020 Sep 21; 66Suppl 2 (Suppl 2): 143 - 147.
- [10] Christofferson G, Vagesjo E, Pettersson US, et al. Acute sleep deprivation in healthy young men: impact on population diversity and function of circulating neutrophils [J]. Brain Behav Immun, 2014, 41: 162 - 172.
- [11] Hui-Leng Tan, David Gozal, Yang Wang, et al. Alterations in Circulating T-Cell Lymphocyte Populations in Children with Obstructive [J]. Sleep ApneaSleep.2013 Jun 1; 36 (6): 913 - 22.

- [12] Jun Chen, Yuk Fai Lau, Elaine W. Lamirande, et al. Cellular Immune Responses to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection in Senescent BALB/c Mice: CD4 T Cells Are Important in Control of SARS-CoV Infection[J] J Virol.2010 Feb; 84 (3): 1289 - 301.
- [13] Min Kyung Jung, Eui-Cheol Shin¹, Phenotypes and Functions of SARS-CoV-2-Reactive T Cells [J] Mol Cells.2021 Jun 30; 44 (6): 401 - 407.
- [14] Haitham Jahrami, Ahmed S. BaHammam, Nicola Luigi Bragazzi, et al. Sleep problems during the COVID-19 pandemic by population: a systematic review and meta-analysis [J] J Clin Sleep Med. 2021 Feb 1; 17 (2): 299 - 313.
- [15] Beatrice Ragnoli, Patrizia Pochetti, Patrizia Pignatti, et al. Sleep Deprivation, Immune Suppression and SARS-CoV-2 Infection [J] Iny J Environ Res Public Health.2022 Jan 14; 19 (2): 904.
- [16] Salman M. Toor, Reem Saleh, Varun Sasidharan Nair, et al. T-cell responses and therapies against SARS-CoV-2 infection [J] Immunology.2021 Jan; 162 (1): 30 - 43.
- [17] Olivia G. Camp, David Bai, Damla C. Gonullu, et al. Melatonin interferes with COVID-19 at several distinct ROS-related steps [J]. J Inorg Biochem.2021 Oct; 223: 111546.
- [18] Adam Wichniak, Aleksander Kania, Mariusz Siemiński, et al. Melatonin as a Potential Adjuvant Treatment for COVID-19 beyond sleep disorders [J] Int J Mol Sci.2021 Aug 11; 22 (16): 8623.
- [19] Qinghai Red Cross Hospital (810000) Ma Qingyun ICU Analysis of the effect of sleep disorder intervention in patients with novel coronavirus pneumonia [J] Qinghai Journal of Medicine.2020, 50 (11).
- [20] Mingxia Zhao, Houzhen Tuo, Shuhui Wang, et al. The Effects of Dietary Nutrition on Sleep and Sleep Disorders [J] Mediators Inflamm.2020 Jun 25; 2020: 3142874.