Chapter 4: COVID-19 and Mental Health

Lindokuhle Thela
[Department of Psychiatry, University of Kwazulu Natal, King Edward VIII Hospital]
ltthela@gmail.com
Reviewed by:
John A. Joska
[HIV Mental Health Research Unit, Division of Neuropsychiatry, Groote Schuur Hospital and the University of Cape Town. John.Joska@uct.ac.za]

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is one of the most significant global pandemics of the twenty-first century. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-19). According to World Health Organization (WHO), the virus has infected over 625 million people and resulted in the deaths of over 6.5 million people (as of October 2022) (WHO, 2022).

SARS-CoV-2 is highly infectious and is transmitted via respiratory droplets. Infection occurs via direct or indirect contact with the nasal, conjunctival, or oral mucosa when respiratory particles are inhaled or deposited on these mucous membranes (Cevik et al., 2020). SARS-CoV-19 has a high affinity for the angiotensin-converting enzyme-2 receptors, which are highly expressed in the cells of the respiratory mucosa and vascular endothelium (Cevik et al., 2020).

The fundamental pathophysiology of COVID-19 is via an increase in the pro-inflammatory markers, also known as a “cytokine storm” (Stefanou et al., 2022). Hypoxia and vasculopathy are some of the complications of COVID-19.

The disease has been categorized into five clinical spectra based on severity: asymptomatic, mild, moderate, severe and critical illness. Most people infected with SARS-CoV-2 develop the either asymptomatic or mild disease (CDC, 2022).

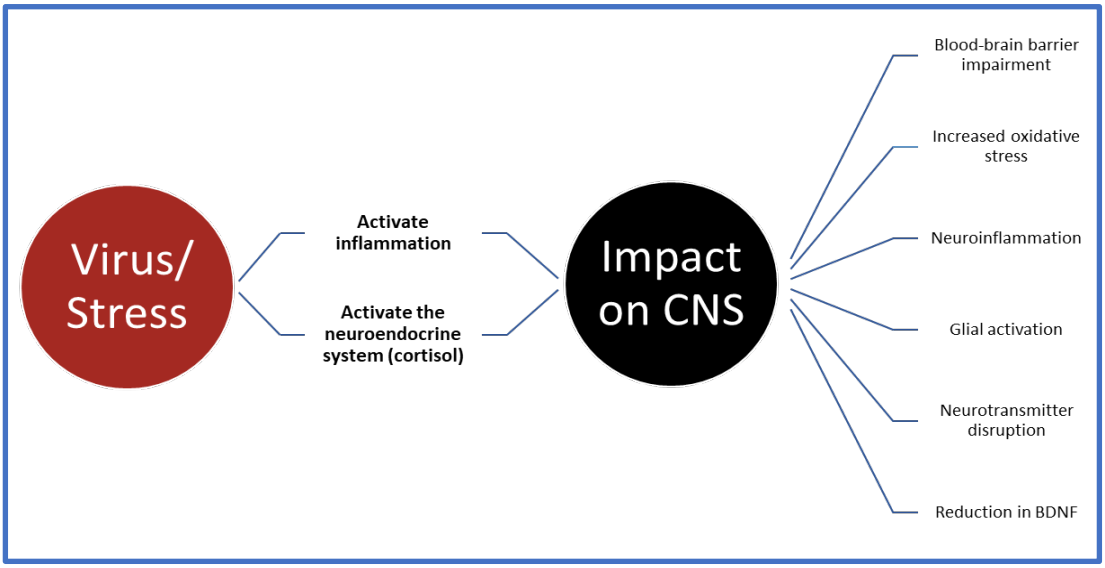
The impact of the disease on mental health follows either a direct route: caused by systemic inflammation that can lead to the development of neuropsychiatric symptoms/disorders, or an indirect route, due to the negative economic and psychosocial impact the disease has caused globally.

MECHANISM OF COVID-19 RELATED NEUROPSYCHIATRIC SYMPTOMS

(Stefanou et al., 2022)

The SARS-CoV-2 virus is neither highly neurotropic nor neurovirulent. It is rare to isolate SARS-CoV-2 in the central nervous system (CNS).

Figure 1. Mechanisms of COVID-19 neuropsychiatric effects



This figure illustrates the synergistic effects of viral factors and psychosocial stress in COVID-19. Anxiety and COVID-19 share some pathways in activating inflammation and the neuroendocrine system, which can ultimately negatively impact the central nervous system.

Viral factors

- Systemic pro-inflammatory surge, also known as the cytokine storm.
- Hypoxic brain injury due to severe respiratory compromise.
- Vasculopathy, such as cerebrovascular accidents.
- Iatrogenic factors, such as the use of medications used in the treatment of COVID-19 (e.g., corticosteroids)

Stress factors

- High stress levels during the pandemic include loss of loved ones, loss of income and loneliness.

Acute Illness Phase Various factors can contribute to neuropsychiatric symptoms during the early phase of the disease. These factors include hypoxia, systemic inflammation, oxidative stress, microglial activation, demyelination, vasculopathy and impaired

neurotransmission. In addition, individuals with severe or critical illnesses must endure the stress of hospitalisation and the fear of dying.

Post-Acute / Long Covid

This can result from persisting neuroinflammation and brain injury sustained during the acute phase. Persisting or established neuronal pathology may be a potential catalyst for neurodegenerative pathologies, such as beta-amyloid plaques.

Risk factors for developing neuropsychiatric illness

The risk factors for developing chronic or longer-term neuropsychiatric symptoms following COVID-19 are not unique but similar to other systemic diseases.

a. COVID-19 may lead to social isolation and job losses due to strategies implemented to curb the spread. Other risk factors include sociodemographic factors such as female gender and advanced age.

b. The role of an existing or previous history of mental illness has been shown to increase the risk of developing neuropsychiatric symptoms during COVID-19.

c. The severity of COVID-19 is also linked with an increased risk of developing neuropsychiatric symptoms/disorders during the acute and post-acute phases.

Neuropsychiatric symptoms in COVID-19

Common psychiatric/mental disorders (CMD) such as depressive disorder, anxiety and trauma-related disorders were significantly increased compared to the pre-pandemic time (Nochaiwong et al., 2021; Santomauro et al., 2021). Increased rates of substance use during the pandemic could be attributed to isolation and trying to cope with stress. Severe psychiatric syndromes such as psychosis, delirium and dementia (neurocognitive disorders) have also been reported in people with COVID-19. Unlike CMD, severe psychiatric disorders are more likely to result from viral and iatrogenic factors rather than psycho-social stressors.

COVID-19 NEUROPSYCHIATRIC DISORDERS

Neuropsychiatric symptoms can appear at different stages of COVID-19. The symptoms may begin in the acute phase and remit, persist into the post-acute phase, or manifest for the first time in the post-acute period (Nalbandian et al., 2021)

Acute COVID-19

A range of neuropsychiatric disorders and symptoms can develop during this period.

- Patients with mild-moderate disease frequently complain of excessive fatigue and insomnia over and above the common psychiatric disorders such as anxiety and depression.
- Neurocognitive impairment, known as brain fog, is commonly reported by people during and after COVID-19. This syndrome manifests as an inability to think clearly, poor concentration and word-finding difficulties.
- Severe COVID-19 illness and certain medications used to treat COVID-19 (e.g., steroids) can increase the likelihood of developing severe neuropsychiatric manifestations such as delirium and psychosis. Patients in the hospital may suffer from acute stress/distress, anxiety and panic, fear of dying and express treatment refusal.

Post-acute COVID-19

Acute diseases last up to four weeks. It is common for some patients to continue to experience symptoms after this period (acute) is over or to develop new symptoms related to COVID-19 (during the subacute and post-COVID-19 period) (Nalbandian et al., 2021).

- Sub-acute (ongoing) COVID-19 - lasts up to 12 weeks
- Post-COVID -19 – symptoms are present beyond 12 weeks

Post-COVID-19 neuropsychiatric symptoms

In the case definition for post-COVID-19 conditions, it is recommended that this diagnosis be considered when the patient presents with symptoms beyond three months that other possible causes cannot explain in the presence of a probable or confirmed prior infection. (Soriano et al., 2022).

Approximately 20% of people who have survived COVID-19 experience some disabling symptoms in the post-COVID-19 period. The frequent neuropsychiatric symptoms are sleep difficulties (27%), fatigue (24%), cognitive impairment (20%), anxiety (19%) and post-traumatic stress disorder (16%) (Badenoch et al., 2022).

1. Insomnia

Insomnia is regarded as the most common COVID-19-related neuropsychiatric symptom. Insomnia is also one of the symptoms that continues to be present in the post-COVID-19 period. Insomnia can be attributed to COVID-19-related psychological distress and the neurological manifestations of COVID-19, such as neuroinflammation (Pataka et al., 2021). Sleep dysfunction is also a common symptom in people presenting with other COVID-19-related psychiatric disorders, such as anxiety, depression and post-traumatic stress disorder. As part of managing insomnia, it is critical to document the duration and pattern of the

symptoms. Additionally, it is essential to screen for substances such as caffeine and stimulants, as well as psychiatric disorders. A sleep study may be recommended if necessary.

Treatment should be tailored to the patient based on the assessment findings.
Ideally, insomnia should be treated according to the **American Academy of Sleep Medicine guidelines.** The guidelines recommend cognitive behavioural therapy (CBT) as the first treatment for insomnia. Medication should be considered if CBT fails or the insomnia is chronic. The use of sleep hygiene and progressive muscle relaxation are also effective treatment strategies.

Pharmacological strategies
There is not much evidence to support pharmacological treatment for post-COVID-19 insomnia. Therefore, it is imperative to assess each case independently. In a patient with anxiety or depression, antidepressants that treat insomnia may be beneficial.

2. Fatigue

Fatigue is one of the most common complaints in survivors of COVID-19. It is characterised by decreased physical and mental performance (resulting from changes in central, psychological, and peripheral factors). Although fatigue often occurs early in the illness course, the symptoms often persist, leading to significant dysfunction in most COVID-19 survivors.

Post-COVID-19 fatigue is diagnosed when symptoms persist for more than six months.
The symptoms often begin acutely manifesting and may vary from symptoms such as incapacitating fatigue, muscle aches, joint pains, weakness after exercise, headaches, swollen glands, digestive disorders, inability to concentrate, memory loss, recurring minor infections or low-grade fevers, depression, an increasing sense of being unable to function, sleep disturbance, light sensitivity and food intolerance.

To diagnose post-COVID-19 fatigue conducting a comprehensive assessment and excluding all possible causes, including endocrinopathies and primary psychiatric disorders, is necessary.
The exact mechanism of COVID-19 fatigue is not well understood, but the role of infection and inflammation (including the multi-organ involvement) is a plausible mechanism behind

the syndrome. Psychosocial factors such as, such as low socioeconomic status, and psychological factors, such as emotional stress, are also implicated.

The risk factors for developing post-COVID-19 fatigue are severe COVID-19 disease, pre-existing psychiatric disorders such as depression and anxiety, advanced age, female gender, and multiple co-morbidities (Joli et al., 2022).

Treatment

Even though fatigue is sometimes not seen as a disease or disorder entity (as opposed to a "symptom"), there is clear evidence that it can cause significant dysfunction in functioning (Komaroff & Lipkin, 2021). Therefore, a non-judgemental person-centred holistic treatment approach will likely enhance positive outcomes (however, clinicians should always be mindful of secondary gains).

Showing empathy and validating the patient's symptoms may also enhance treatment outcomes. Management of post-COVID-19 fatigue should include multidisciplinary team members such as physicians, psychiatrists, neurologists, psychologists, and occupational therapists.

Persistent illnesses such as poor respiratory sufficiency and other organ damage may contribute to fatigue; therefore, treatment for any comorbid condition should be undertaken to minimise symptoms burden. Treatment often requires symptoms using biological and psychological intervention.

Psychological interventions

a. Cognitive behavioural therapy

Feeling fatigued, anxious, or depressed may be relieved by this treatment.
During treatment, the therapist focuses on the patient's thinking process and how it affects their actions and feelings. The fatigue-causing behaviours and thoughts are identified and altered.

b. Graded exercise therapy (GET)

A physiotherapist often offers this. The underlying theory is that physiological dysfunction perpetuates chronic fatigue. Treatment, therefore, aims to improve the patient's physical activity and conditioning levels. In addition to graded exercise, graded exposure involves viewing exercise and overexertion as feared stimuli.

GET protocol example: Exercise duration is usually set between 5 and 15 minutes at first. It is then gradually increased to 30 minutes for 4 to 5 days a week, depending on the patient's physical condition.

Other nonpharmacological interventions

- Sleep hygiene
- Deep breathing, muscle relaxation, and mindfulness.

Biological treatments

No specific drugs have been developed explicitly for fatigue. Treatment should therefore target enduring symptoms. Severe symptoms in the acute phase may benefit from short-term use of medication.

For pain: anti-inflammatory drugs can be used effectively

There are case reports of patients who improved following hyperbaric oxygen therapy (Bhaiyat et al., 2022).

Regular follow-up is essential for monitoring functional status and promoting a return to normal activity.

3. Neurocognitive impairments or "brain fog."

Individuals with persistent cognitive impairment following COVID-19 frequently report that their thinking feels dull and their mind feels slow and foggy. The term "brain fog" is now used to describe these subjective experiences, which may also include a constellation of symptoms, including inattention, short-term memory, and reduced mental acuity. This condition is often viewed as the result of neuroinflammation.

A multidisciplinary team should assess and treat brain fog. A comprehensive psychiatric assessment should include a bedside neurocognitive assessment such as the Montreal Cognitive Assessment (MoCA). Neuropsychological assessment of cognitive impairment is essential to establish the domains most affected and the severity of impairments.

For functional impairments and cognitive rehabilitation, an occupational therapist is needed.

An assessment should include exploring possible causes of the impairment, such as looking for infections like syphilis and excluding vitamin B12 deficiency. The treatment interventions should be tailored to the patients with consideration of other risk factors such as pre-existing medical or psychiatric illnesses, age, and occupation.

Treatment strategies

a. Cognitive rehabilitation (CR)

This is a systematised functional-oriented therapeutic approach with the aim of improving and restoring cognitive function. For example, domain-specific strategies can be used during CR: **Learning and memory**

- Strategies include task-specific learning, mnemonics structuring, external cueing and associations.

b. Pharmacological strategies

There is no evidence to support pharmacological strategies in post-COVID-19 brain fog.

4. Post-traumatic Stress Disorder

There have been increased rates of psychological trauma exposure because of the COVID-19 pandemic. People around the world were exposed to death threats and unexpected deaths. Acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) develop in response to psychological trauma. The two disorders only differ in the duration of symptoms and impairment.

Global pandemics, like COVID-19, do not cause PTSD as readily as individual traumas like sexual assault (Bryant, 2019). However, large-scale infectious disease outbreaks (or global pandemics) such as COVID-19 are linked with higher rates of PTSD compared to natural disasters such as floods (Yuan et al., 2021).

The global pooled prevalence of PTSD symptoms in the general population during the COVID-19 pandemic was slightly higher (16%) compared to a lifetime prevalence of 13 – 20% for women and 6 – 8% for men (Bryant, 2019). The highest rates were observed in health professionals (17%) and survivors of COVID-19 (16%) (Yunitri et al., 2022).

Delayed onset of PTSD (beyond 6 months after exposure to trauma) occurs in approximately 25%. Previous exposure to traumas such as childhood trauma and adverse childhood events, neurotic personality and pre-existing psychiatric illness is linked with an increased risk of developing PTSD in people exposed to COVID-19 psychological trauma. Other risk factors include sociodemographic factors such as female, younger, low income, and low level of education; pandemic-related factors such as being infected, stigma, social isolation, and quarantine experience; and occupational factors such as being frontline worker frontline workers such as nurses and doctors.

Management

Treatment can be achieved for both disorders by using psychosocial strategies such as providing a psychologically supportive environment through emotional support and Trauma-focused Cognitive behavioural therapy.
Pharmacotherapy in the form of antidepressants is only indicated in managing PTSD.

Special investigations for covid-19 neuropsychiatric symptoms

There are no specific investigations available to confirm that COVID-19 is the cause of neuropsychiatric symptoms. However, investigating the brain is prudent when COVID-19 is considered the possible cause of symptoms. Since COVID-19 is a systemic disease that may affect the brain in various ways, it is expected that the pathology will vary depending on the severity of the disease.

1. Cerebrospinal fluid analysis

CSF studies help evaluate whether or not COVID-19 pathology exists in the brain. Detecting markers of neuroinflammation is an invaluable aspect of investigating COVID-19.
In people with CNS involvement, CSF levels of Interleukin-6 are often elevated. Other markers of CNS involvement include:

1. SARS-CoV-2 antibodies
2. Markers of neuronal injury, such as neurofilament light chains

It is still uncertain whether the virus is neurotropic, as researchers have not found viral RNA in the CSF of people with CNS involvement (Jarius et al., 2022).

2. Brain imaging

Imaging the brain may be beneficial in a person who develops neuropsychiatric symptoms during the acute phase or in the post-acute phase.
The imaging serves two roles:

- Evaluation of COVID-19 related neuropathology
- Exclusion of other causes.

There are no specific structural brain abnormalities associated with NeuroCOVID-19.
Imaging findings include vasculopathy, cerebrovascular accidents, posterior reversible encephalopathy syndrome, and leukoencephalopathy.

Conclusion

Global pandemics such as COVID-19 are associated with a surge in neuropsychiatric symptoms.

Biological and socioeconomic dynamics resulting or perpetuated by the pandemic can contribute to the development of psychiatric symptoms.
The higher-than-normal transmission of SARS-CoV-19 resulted in a pandemic of unprecedented proportion resulting, affecting persons from various socioeconomic backgrounds.
The measures undertaken to curb the spread of the virus, such as isolation and quarantine, are psychologically traumatic experiences known to result in psychiatric disorders.
Many COVID-19 survivors experience lingering psychiatric symptoms beyond the acute phase, a condition called post-COVID-19 or long COVID-19.
The frequent symptoms are fatigue, insomnia, brain fog, anxiety, depression, and acute/post-traumatic stress disorders.
Risk factors include being female, having a low socioeconomic background, having severe acute COVID-19, and having a pre-existing psychiatric disorder.
Psychiatric disorders such as PTSD may have delayed onset.

REFERENCES

- Badenoch, J. B., Rengasamy, E. R., Watson, C., Jansen, K., Chakraborty, S., Sundaram, R. D., Hafeez, D., Burchill, E., Saini, A., Thomas, L., Cross, B., Hunt, C. K., Conti, I., Ralovska, S., Hussain, Z., Butler, M., Pollak, T. A., Koychev, I., Michael, B. D., Rooney, A. G. (2022). Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *Brain Communications, 4*(1), fcab297. 10.1093/braincomms/fcab297
- Bhaiyat, A. M., Sasson, E., Wang, Z., Khairy, S., Ginzarly, M., Qureshi, U., Fikree, M., & Efrati, S. (2022). Hyperbaric oxygen treatment for long coronavirus disease-19: a case report. Journal of Medical Case Reports, 16(1), 80. 10.1186/s13256-022-03287-w
- Bryant, R. A. (2019). Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. World Psychiatry, 18(3), 259-269. 10.1002/wps.20656
- Centers for disease control and prevention. (2022). *Clinical Spectrum of SARS-CoV-2 Infection.* Centre for disease control and prevention. Retrieved October, 27, 2022, from
- Centers for disease control and prevention. *Post-COVID Conditions: Healthcare Providers.* Centers for disease control and prevention. Retrieved 0ctober 27, 2022, from https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html
- Cevik, M., Kuppalli, K., Kindrachuk, J., & Peiris, M. (2020). Virology, transmission, and pathogenesis of SARS-CoV-2. *Bmj, 371*, m3862. 10.1136/bmj.m3862

- Chu, K. M., Smith, M., Steyn, E., Goldberg, P., Bougard, H., & Buccimazza, I. (2020). Changes in surgical practice in 85 South African hospitals during COVID-19 hard lockdown. *South African Medical Journal, 110*(9), 916-919. 10.7196/SAMJ.2020.v110i9.15014
- Jarius, S., Pache, F., Körtvelyessy, P., Jelčić, I., Stettner, M., Franciotta, D., Keller, E., Neumann, B., Ringelstein, M., Senel, M., Regeniter, A., Kalantzis, R., Willms, J. F., Berthele, A., Busch, M., Capobianco, M., Eisele, A., Reichen, I., Dersch, R., Wildemann, B. (2022). Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients. Journal of Neuroinflammation, 19(1), 19. 10.1186/s12974-021-02339-0
- Joli, J., Buck, P., Zipfel, S., & Stengel, A. (2022). Post-COVID-19 fatigue: A systematic review. Frontiers in Psychiatry, 13, 947973. 10.3389/fpsyt.2022.947973
- Komaroff, A. L., & Lipkin, W. I. (2021). Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. Trends in Molecular Medicine, 27(9), 895-906. 10.1016/j.molmed.2021.06.002
- Nalbandian et al., (2021) Post-Acute COVID-19 Syndrome. Naturemedicine 27:601 – 615. https://www.nature.com/articles/s41591-021-01283-z
- Nochaiwong, S., Ruengorn, C., Thavorn, K., Hutton, B., Awiphan, R., Phosuya, C., Ruanta, Y., Wongpakaran, N., & Wongpakaran, T. (2021). Global prevalence of mental health issues among the general population during the coronavirus disease-2019 pandemic: a systematic review and meta-analysis. *Scientific Reports, 11*(1), 10173. 10.1038/s41598-021-89700-8
- Pataka, A., Kotoulas, S., Sakka, E., Katsaounou, P., & Pappa, S. (2021). Sleep Dysfunction in COVID-19 Patients: Prevalence, Risk Factors, Mechanisms, and Management. Journal of Personalized Medicine, 11(11), 1203. 10.3390/jpm11111203
- Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., Abbafati, C., Adolph, C., Amlag, J. O., Aravkin, A. Y., Bang-Jensen, B. L., Bertolacci, G. J., Bloom, S. S., Castellano, R., Castro, E., Chakrabarti, S., Chattopadhyay, J., Cogen, R. M., Collins, J. K., Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet (British Edition), 398*(10312), 1700-1712. 10.1016/S0140-6736(21)02143-7
- Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P., & Diaz, J. V. (2022). A clinical case definition of post-COVID-19 condition by a Delphi consensus. *The Lancet Infectious Diseases, 22*(4), e102-e107. 10.1016/S1473-3099(21)00703-9

- Stefanou, M., Palaiodimou, L., Bakola, E., Smyrnis, N., Papadopoulou, M., Paraskevas, G. P., Rizos, E., Boutati, E., Grigoriadis, N., Krogias, C., Giannopoulos, S., Tsiodras, S., Gaga, M., & Tsivgoulis, G. (2022). Neurological manifestations of long-COVID syndrome: a narrative review. *Therapeutic Advances in Chronic Disease, 13*, 20406223221076890. 10.1177/20406223221076890
- WHO. (2020). *COVID-19 disrupting mental health services in most countries, WHO survey.* World Health Organization. Retrieved August 04, 2022, from https://www.who.int/news/item/05-10-2020-covid-19-disrupting-mental-health-services-in-most-countries-who-survey
- WHO. (2022). *WHO Coronavirus Dashboard.* World Health Organization. Retrieved 27 October 2022, from https://covid19.who.int/
- Yuan, K., Gong, Y., Liu, L., Sun, Y., Tian, S., Wang, Y., Zhong, Y., Zhang, A., Su, S., Liu, X., Zhang, Y., Lin, X., Shi, L., Yan, W., Fazel, S., Vitiello, M. V., Bryant, R. A., Zhou, X., Ran, M., . . . Lu, L. (2021). Prevalence of posttraumatic stress disorder after infectious disease pandemics in the twenty-first century, including COVID-19: a meta-analysis and systematic review.10.1038/s41380-021-01036-x
- Yunitri, N., Chu, H., Kang, X. L., Jen, H., Pien, L., Tsai, H., Kamil, A. R., & Chou, K. (2022). Global prevalence and associated risk factors of posttraumatic stress disorder during COVID-19 pandemic: A meta-analysis. International Journal of Nursing Studies, 126, 104136. 10.1016/j.ijnurstu.2021.104136