

# Neuropsychiatric Effects of COVID and Long COVID in South East Asia a Systematic Review

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## ABSTRACT

**Objective:** This systematic review aimed to determine the prevalence of neuropsychiatric symptoms in COVID-19 and post-COVID-19 patients in Southeast Asia and explore associated factors.

**Methods:** Following PRISMA guidelines, a comprehensive literature search was conducted in relevant databases. Studies reporting on the prevalence of neuropsychiatric symptoms such as fatigue, anxiety, depression, sleep disturbances, cognitive impairment, and post-traumatic depression in COVID-19 and post-COVID-19 patients in Southeast Asia were included. Data were extracted and analysed to determine the prevalence rates and associated factors.

**Results:** A total of 7 studies met the inclusion criteria. The findings revealed a high prevalence of neuropsychiatric symptoms among COVID-19 patients in Southeast Asia. Fatigue was reported by approximately 43.3% of patients during active COVID-19 infection and 45.1-54% in the post-COVID-19 phase. Anxiety affected 14.3-28.1% of COVID-19 patients, with comorbidities and severity being closely associated. Depression was prevalent in 3.6-38.7% of COVID-19 patients, with healthcare workers showing a higher prevalence. Sleep disturbances were reported in approximately 16.1% of post-COVID-19 individuals. Various factors such as age, gender, quarantine duration, and socioeconomic status were identified as potential contributors to these symptoms.

**Conclusion:** Neuropsychiatric symptoms, including fatigue, anxiety, depression, sleep disturbances, cognitive impairment, and post-traumatic depression, are prevalent among COVID-19 and post-COVID-19 patients in Southeast Asia. These symptoms have a significant impact on patients' lives and warrant attention in clinical management. Further research is needed, particularly in the ASEAN region, to better understand these symptoms, explore gender differences, and develop effective management strategies. The findings of this study emphasize the importance of early detection and holistic treatment that addresses both physical and psychological symptoms in COVID-19 patients.

**Funding:** This research is supported by the International Medical University Joint Committee on Ethics and Research (IMU-JC).

**Conflicts of Interest:** No conflicts of interest.

**Keywords:** COVID-19, post-COVID-19, neuropsychiatric symptoms, fatigue, anxiety, depression, sleep disturbances, cognitive impairment, Southeast Asia.

## INTRODUCTION

The outbreak of pandemic associated with novel coronavirus (SARS-CoV-2): coronavirus disease 2019 (COVID-19) is identified as an infectious respiratory illness. However, individuals with COVID-19 also have been associated with a range of neuropsychiatric effects. Several studies have reported that at least 35% of the COVID-19 patients develop psychiatric symptoms, such as anxiety and depression in the acute phase of the disease.(1)

Although the underlying mechanism of COVID-19 causes neuropsychiatric effects is still largely unknown, but it is thought that the persistent inflammation, direct effects of the virus to the brain, immune dysregulation or psychological stress are closely linked to the aetiology.(1)

Long term effects of SARS-CoV-2 infection have been increasingly reported, particularly a high frequency of neuropsychiatric symptoms after COVID-19 infection. These persistent symptoms beyond the acute phase of COVID-19 are referred to as “Long COVID”.(2) Neuropsychiatric effects lasting for months after infection significantly impact the quality of life of those affected, which raised the concern to the healthcare system. There are several studies that suggest that previous history of mental illness are associated with increased risk of Long Covid.(3) Though, the prevalence of neuropsychiatric symptoms may differ in each country due to sociodemographic factors.

In line with extensive research carried out on a global scale, we believe that there is a vast avenue and utmost importance in exploring the neuropsychiatric symptoms specifically in South East Asia. There is a lack in collection and compilation of data specifically in this region, and we believe that the nature and extent of persistent neuropsychiatric symptoms after COVID-19 is an important study for the pandemic recovery phase. In this systematic review, cross-sectional study is generally the gold standard used for investigating the prevalence of neuropsychiatric symptoms in COVID and Long COVID patients. It will significantly enable us to promote the value of our research in contributing to scientific evidence.

## METHODOLOGY

A systematic literature search was performed on Google Scholar, Pubmed, EMBASE, MEDLINE, Proquest, and Science Direct to identify studies within the remit of the study.

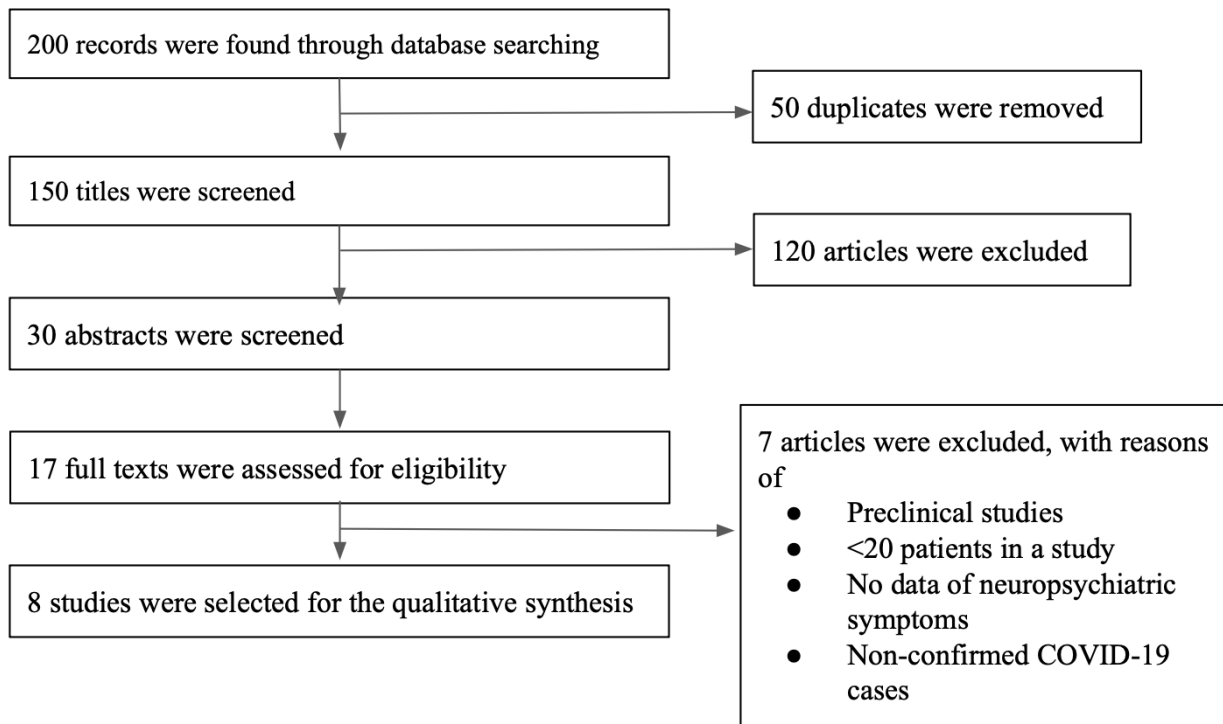


Figure 1

200 records were found (Figure 1). A group of key terms regarding the factors of investigations were used to attain relevant articles: (1) COVID-19; (2) Long COVID; (3) South-East Asia and (4) Neuropsychiatric symptoms. The search was devised to identify studies that portrayed the neuropsychiatric effects of covid and long covid amongst patients in South East Asia. Inclusion Criteria were (1) Studies on population of interest i.e. Current and recovered COVID-19 patients of all age groups from South East Asian region; (2) Studies relevant to the area of focus i.e. neuropsychiatric symptoms in COVID-19 and recovered COVID-19 patients; (3) Studies with patients with a positive PCR for COVID-19 and previously positive PCR patients; (4) Studies published in English and (5) Studies published after 1st January 2019. Exclusion criteria were (1) Publications in other languages and (2) Non-clinical studies i.e. economics, hazards or effect on corporations. This review was focused on recognition of the neuropsychiatric effect of COVID-19 and Long COVID on patients. Exclusion criteria was set to ensure studies that represent a broader population were identified. Systemic analysis was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

The 7 studies included a total population of  $n = 2481$  (sample size range 142-778). The gender population in this research was overall balanced, with 54.1% ( $n=1341$ ) being male. Some studies recorded symptoms during acute infection and after infection, so there is an overlap in numbers. Most studies originated from Malaysia (4).

**RESULTS**

<b>COVID-19 symptoms</b>				
<b>Study</b>	<b>n subjects</b>	<b>Symptoms</b>	<b>Prevalence</b>	<b>p-value</b>
Muhammad Azri Adam bin Adnan, et. al., Malaysia, 29 December 2022.	401	Anxiety	7.0%	<0.05
Kim Sui Wan, et. Al., Malaysia, March 8 202	452	Fatigue	43.3 %	<0.05
		Headache	36.7%	
Michael Austin Pradipta Lusida, et. al., East Java province, Indonesia	608	Anxiety	14.3%	0.014
		Depression	3.6%	
		Stress	7.9%	0.028
Ketut Suryana, et. al. Bali, Indonesia	292	Anxiety	28.1%	<0.001
Ye Minn Htun et. al., Myanmar, 4 June 2021	142	Depression	38.7%	<0.01

*Table 1*

<b>Long COVID</b>				
<b>Study</b>	<b>n Subjects</b>	<b>Symptoms</b>	<b>Prevalence</b>	<b>p-value</b>
Kim Sui Wan, et. Al., Malaysia, March 8 2023	452	Fatigue	54.00%	<0.05
		Sleep disturbances	16.10%	
		Memory disturbance	12.90%	
		Loss of concentration	10.50%	
		Anxiety	6.50%	
		Depression	2.4%	
		Stress	4.00%	
	215	Lethargy	45.1%	0.030

Hana Maizuliana Solehan, et. al., Malaysia , 16 August 2022.	Difficulty concentrating	22.1%
	Anxiety	0.50%
	Depression	5.1%

Table 2

Apart from the respiratory and other physical manifestations, the COVID-19 infection also brings mental health issues, especially neuropsychiatric symptoms that should not be discounted by the public and healthcare workers. A cross sectional study which studied the prevalence of anxiety as well as its associated factors among 401 stable inpatient COVID-19 patients conducted in 4 hospital settings in Malaysia has shown a prevalence of 7% among the respondents, evidenced by a mean Generalised Anxiety Disorder 7-item (GAD-7) score of 2.58. In this study, anxiety was more likely to be seen in single/ widow, male, Chinese group of respondents, as well as those whose age group was between 18 to 34. Despite the low prevalence in mental health symptoms, a cross sectional study instrumented by the Depression Anxiety Stress Scale-21 (DASS-21) from East Jawa Province, Indonesia that aimed to access the prevalence and risk factors of mental health symptoms among 608 asymptomatic non-hospitalized or mild COVID-19 patient proved the presence of depression (3.6%), anxiety (14.3%) and stress (7.9%) mental health symptoms among the respondents. Another similar study instrumented by Generalised Anxiety Disorder 7-item (GAD-7) in Bali also showed a prevalence of 28.1% among 292 participants to have anxiety symptoms. In Yangon City of Myanmar, a single-centre cross sectional study which assessed the prevalence and the associated factors of depressive symptoms in COVID-19 patients using the Center for Epidemiologic studies Depression Scale (CES-D)-based questionnaire showed 38.7% of 142 participants had depressive symptoms. It was found out that the patients 40 years and older, less than 4 of household size, low monthly family income (not more than 400,000 kyats) and infection to family members were strongly associated with the depressive symptoms.

Based on a cross-sectional study identifying the long-term clinical symptoms found in COVID-19 infection and the risk factors associated within the Malaysian population, it was found that out of the 215 post COVID-19 survivors, lethargy(45.1%) followed by difficulty in concentration(22.1%) were the two most prevalent neuropsychiatric symptoms found in patients. A retrospective analysis study done in Malaysia on determining the proportion and factors tied to long COVID-19 among COVID-19 patients in Port Dickson Malaysia showed that among the 452 patients fatigue(54.0%), experiences of sleep disturbances(16.1%), loss of concentration(10.5%) and memory impairment(12.9%) were neuropsychiatric symptoms exhibited by the patients. Another cross-sectional study done in Malaysia to compare the severity of psychological distress as well as determining associations among COVID-19 survivors in two varied cohorts at two different points of time showed that among the 371 patient group of COVID-19 survivors, both the one and six months post-hospitalization groups had higher psychological distress reported by those that have a past psychiatric illness history.

The analysis findings of study in Vietnam shows that people with suspected Covid-19 symptoms had a lower health-related quality of life (HROoL). In comparison with different sociodemographic factors, older people had a lower HRQoL score compared to the younger age groups. Meanwhile, the HRQoL score was significantly higher in men and in people with higher education attainment, with better ability

to pay for medication, with middle or high social status, who did more physical activity, and who had higher health literacy as compared to their counterparts. Quality of life regarding emotional well-being & social functioning domain, a study from Indonesia found that Covid-19 patients were slightly better than Non-Covid patients (38.1% vs 20.6% and 55.3% vs 36.2%, respectively). Factors include unemployment and having non-health-related work were also associated with poor quality of life in COVID-19 patients.

## DISCUSSION

In this systematic review, we find that there is a high prevalence for neuropsychiatric symptoms during COVID-19 and post-COVID 19 infection.

### Fatigue

Based on the results we gathered, about 43.3% of patients experienced fatigue during active COVID-19 infection and 45.1-54% listed fatigue as a symptom post COVID-19. In active COVID-19 patients, fatigue is commonly reported and is characterised by weakness, lacking of energy as well as feelings of exhaustion. A study conducted by Tenforde et al. shows that fatigue was reported by 53% of patients suffering from symptomatic COVID-19.(4) Ladds et al was also another study which showed 58.3% of actively infected COVID-19 patients reporting fatigue.(5) These studies further imply fatigue as a significant symptom amongst patients with active COVID-19 infections. Factors that contribute to the development of this symptom include infection from the virus itself when inflammatory responses and the immune system is activated,(6) physical manifestations of COVID-19 like cough, fever and dyspnoea,(4) stress and anxiety that come along with the infection also contribute to fatigue.(5)

Based on Tansley et al. 18% of post COVID-19 individuals within a sample size of 117 were reported to have fatigue after a year from infection. Fatigue has been noted to be one out of the many symptoms attributing to long COVID.(21) A systematic review done encompassing 5,629 participants showed that the risk factors for post-COVID-19 fatigue included advancing age, female gender, severe clinical status during patients acute phase of infection, patients with numerous comorbidities, a pre-diagnosis of depression/anxiety and autoimmune cause.(7) Current knowledge on the emergence of fatigue in patients is linked to numerous biological or physical dysfunctions. Cytokines released during the COVID-19 infection are noted to impair psychological defence reactions in the body. A prospective cohort study done in Bangladesh showed post viral fatigue as the most common symptom with 70% of the cases manifesting this symptom in 46% of the total sample of patients(n = 400) with long COVID.Those of females gender, with a prolonged duration of the disease, lethargy and respiratory distress were more prone to developing post-COVID syndromes. (8)

### Anxiety

From our systematic review, studies show that (14.3% -28.1%) of COVID-19 patients suffer from anxiety. There is a significant association between comorbidities and the severity of anxiety. (7) There is increasing evidence in literature that show increased mortality rates, prolonged hospital stay and composite adverse events in COVID-19 patients with comorbidities. (11)

Anxiety is reported differently in different countries due to the difference in cultural and societal factors, lifestyle and work. 2 studies done in Italy and Iran, which found that the fear of COVID-19 was correlated with anxiety. (9,10) A longer quarantine duration and hospitalisation increases the severity of anxiety (12).

Our study found that COVID-19 patients who were healthcare workers had more severe anxiety symptoms than the general public. This is in line with a study done in Egypt which found that 90.5% of healthcare workers suffered from anxiety while working in the COVID-19 pandemic. (13)

We did not manage to find articles on long COVID in ASEAN countries, but there is an overall trend of anxiety in patients with long-COVID. A study in University of Campinas found brain changes in patients with long COVID. 40.2% of patients who had mild COVID-19 symptoms 3 months after COVID-19 reported anxiety symptoms. Researchers did a brain scan which found that patients with long COVID had a shrunken brain limbic area than people who had never had a COVID-19 infection prior. This is a preliminary study that will be presented at the American Academy of Neurology (AAN) (15) However, a systematic review and meta-analysis done in the United Kingdom through the COVID-19 Symptom Study app found a weak correlation between COVID-19 infection and anxiety / depressive symptoms. (14) More evidence and literature is required.

The findings of the study reveal certain major characteristics related with anxiety in COVID-19 patients. Anxiety has been demonstrated to be substantially associated with the female gender, fear of infection, lack of information, and negative coping mechanisms such as behavioural disengagement and self-blame. A significant proportion of patients, particularly females, had persistent anxiety and depression symptoms even after a month of recovery.

### **Depression**

From the data pooled, 3.6%- 38.7% of COVID-19 patients suffer from depression. Similar to anxiety, there is a higher prevalence of depression symptoms in health care workers compared to non-healthcare workers.

However, a study in China found that being a healthcare worker was a protective barrier to depression and anxiety. (16) Yet another study from Italy found that there was no difference between the risk of developing depression and anxiety between frontline health care workers and the general public. (17) We propose that the differences in results are due to the different degree of severity of COVID-19 outbreaks in various countries, country health regulations and how the COVID-19 outbreaks were managed. This is lower than the range of other regions and countries outside Southeast Asia.

In long COVID, we find that depressive symptoms are prevalent in 3.6%-38.7% of survivors.

Patients who are older than 40 years old, of a lower family income (<400, 000 kyats per month), healthcare workers, a recent history of self quarantine and have a family member who had infection, were associated with depressive symptoms. Low household income is a COVID-19 stressor, which had a negative impact on the mental health of adults during the pandemic. (18)

Beyond COVID-19 stressors, we propose that the alteration of COVID-19 on the brain - shrinking of the limbic brain also increases the risk of depression. (15) Quarantine has a negative effect on one's health, as research from previous pandemics show an increase in psychological effects like anxiety, low mood, depression, anger and stress. (19) A meta-analysis also found that there is a strong correlation between mass quarantine and neuropsychiatric symptoms during the COVID-19 pandemic. (20)

## Sleep Disturbances

A study done in Port Dickson, Malaysia reported about 16.1% of the patients having sleep disturbances post COVID-19. This is one of the common neurological symptoms presented in COVID-19 patients which is induced by the neuroinflammatory response affecting the brain. The sleep disturbances generally cause adverse effects on mood and behaviour including mental distress, depression, anxiety and even to a greater extent that altering cognitive and motor functions. (2) It is interesting to note that females, asthmatic patients and those with an underlying cardiovascular disease have the highest risk of developing long COVID symptoms, including sleep disturbances. This is lower than a published study done at the Cleveland clinic which found that 34-50% of COVID survivors suffer with this. (21)

Interestingly, this systematic review discovered that several somatic symptoms, such as headache and myalgia, were substantially linked with depression and anxiety in patients, suggesting that these symptoms could serve as early indications of neuropsychiatric effects in COVID-19 patients.

The findings imply that while treating patients with COVID-19, it is of the utmost importance to address both the physical as well as psychological symptoms. This systematic review also discovered that, although females had a higher predisposition to anxiety, males experienced a greater degree of severity of anxiety symptoms than females.

However, there was no statistically significant gender difference in the proportion of patients suffering from depression. While the male gender reported a lower overall incidence of depression and anxiety symptoms, the proportion of males with severe anxiety was much higher. The findings imply that gender may have a role in the expression of anxiety in COVID-19 patients. However, more research is needed to investigate the underlying causes that contribute to this disparity.

It is also worth noting that, while the study discovered substantial connections, this does not always imply causation.

Finally, the data imply that addressing psychological problems in addition to physical symptoms is critical in the treatment of COVID-19 patients. The study also emphasises the significance of early detection and therapy of physical symptoms, which might be early markers of psychological distress in patients. More literature and research is needed to investigate gender differences in neuropsychiatric symptoms and to develop effective management strategies in COVID-19 and long-COVID-19 patients.

## CONCLUSION

We find that neuropsychiatric symptoms are common and increasingly prevalent in COVID and long-COVID patients in SouthEast Asia. Anxiety, depression, brain fog, cognitive impairment, sleep disturbances and post-traumatic depression are some of the symptoms which can potentially implicate COVID-19 patients during acute infection and the quality of their lives following infection for as long as 1 year. This includes their social, daily activities and function of life. Symptoms can persist up to 1 year and beyond.



Future research is essential, particularly in SouthEast Asia, as we did not manage to find a lot of studies done in this region. Our findings suggest that there is a significant impact on COVID-19 survivors and patients in ASEAN countries. More research is required, as established data can empower ASEAN countries to dedicate more resources and funding towards the psychiatric and cognitive management of COVID and long-COVID survivors here.

## FUNDING

This research is supported by the International Medical University Joint Committee on Ethics and Research (IMU-JC).

## CONFLICT OF INTEREST

There are no conflicts of interest.

## REFERENCE

1. Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, Zhang Z, Ding L. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. *Brain Behav Immun*. 2020 Oct;89:587-593. doi: 10.1016/j.bbi.2020.07.016. Epub 2020 Jul 15. PMID: 32681866; PMCID: PMC7362867.
2. Long COVID: let patients help define long-lasting COVID symptoms. *Nature*. 2020 Oct;586(7828):170. doi: 10.1038/d41586-020-02796-2. PMID: 33029005.
3. Ahmed GK, Khedr EM, Hamad DA, Meshref TS, Hashem MM, Aly MM. Long term impact of Covid-19 infection on sleep and mental health: A cross-sectional study. *Psychiatry Res*. 2021 Nov;305:114243. doi: 10.1016/j.psychres.2021.114243. Epub 2021 Oct 12. PMID: 34673325; PMCID: PMC8507572.
4. Tenforde, M. W., Kim, S. S., Lindsell, C. J., Billig Rose, E., Shapiro, N. I., Files, D. C., ... & Self, W. H. (2020). Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. *MMWR. Morbidity and mortality weekly report*, 69(30), 993.
5. Ladds, E., Rushforth, A., Wieringa, S., Taylor, S., Rayner, C., Husain, L., ... & Greenhalgh, T. (2021). Persistent symptoms after Covid-19: qualitative study of 114 “long Covid” patients and draft clinical case definition. *medRxiv*.
6. Huang, Y., Pinto, M. D., Borelli, J. L., Mehrabadi, M. A., Abrihim, H., & Salem, N. M. (2020). COVID symptoms, symptom clusters, and predictors for becoming a long hauler: looking for clarity in the haze of the pandemic. *medRxiv*.
7. Joli J, Buck P, Zipfel S, Stengel A. Post-COVID-19 fatigue: A systematic review. *Front Psychiatry*. 2022 Aug 11;13:947973. doi: 10.3389/fpsyt.2022.947973. PMID: 36032234; PMCID: PMC9403611.
8. Bansal R, Gubbi S, Koch CA. COVID-19 and chronic fatigue syndrome: An endocrine perspective. *J Clin Transl Endocrinol*. 2022 Mar;27:100284. doi: 10.1016/j.jcte.2021.100284. Epub 2021 Dec 3. PMID: 34877261; PMCID: PMC8641402.
9. Soraci P, Ferrari A, Abbiati FA, Del Fante E, De Pace R, Urso A, et al. Validation and Psychometric Evaluation of the Italian Version of the Fear of Covid-19 Scale. *Int J Ment Health Addict* 2020; 4; 1-10. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. *Int J Ment Health Addict* 2020; 1-9.

10. Sanyaolu, A., Okorie, C., Marinkovic, A. *et al.* Comorbidity and its Impact on Patients with COVID-19. *SN Compr. Clin. Med.* 2, 1069–1076 (2020). <https://doi.org/10.1007/s42399-020-00363-4>
11. Mario Gennaro Mazza, Rebecca De Lorenzo, Caterina Conte, Sara Poletti, Benedetta Vai, Irene Bollettini, Elisa Maria Teresa Melloni, Roberto Furlan, Fabio Ciceri, Patrizia Rovere-Querini, Francesco Benedetti, Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors, *Brain, Behavior, and Immunity*, Volume 89, 2020, Pages 594-600, ISSN 0889-1591, <https://doi.org/10.1016/j.bbi.2020.07.037>.
12. Aly HM, Nemr NA, Kishk RM, *et al* Stress, anxiety and depression among healthcare workers facing COVID-19 pandemic in Egypt: a cross-sectional online-based study *BMJ Open* 2021;11:e045281. doi: 10.1136/bmjopen-2020-045281
13. Klaser K, Thompson EJ, Nguyen LH, Sudre CH, Antonelli M, Murray B, Canas LS, Molteni E, Graham MS, Kerfoot E, Chen L, Deng J, May A, Hu C, Guest A, Selvachandran S, Drew DA, Modat M, Chan AT, Wolf J, Spector TD, Hammers A, Duncan EL, Ourselin S, Steves CJ. Anxiety and depression symptoms after COVID-19 infection: results from the COVID Symptom Study app. medRxiv [Preprint]. 2021 Jul 8:2021.07.07.21260137. doi: 10.1101/2021.07.07.21260137. Update in: *J Neurol Neurosurg Psychiatry*. 2021 Sep 28;: PMID: 34268526; PMCID: PMC8282115.
14. American Academy of Neurology's 75th Annual Meeting [https://www.newswise.com/coronavirus/can-the-lingering-effects-of-a-mild-case-of-covid-19-change-your-brain/?article\\_id=787215&sc=mwhr&xy=10048578](https://www.newswise.com/coronavirus/can-the-lingering-effects-of-a-mild-case-of-covid-19-change-your-brain/?article_id=787215&sc=mwhr&xy=10048578) [Last reviewed, 13 April 2023]
15. He Q, Fan B, Xie B, Liao Y, Han X, Chen Y, Li L, Iacobucci M, Lee Y, Lui LMW, Guo L, Lu C, McIntyre RS. Mental health conditions among the general population, healthcare workers and quarantined population during the coronavirus disease 2019 (COVID-19) pandemic. *Psychol Health Med.* 2022 Jan;27(1):186-198. doi: 10.1080/13548506.2020.1867320. Epub 2020 Dec 30. PMID: 33378219.
16. Rossi R, Soggi V, Pacitti F, Mensi S, Di Marco A, Siracusano A, Di Lorenzo G. Mental Health Outcomes Among Healthcare Workers and the General Population During the COVID-19 in Italy. *Front Psychol.* 2020 Dec 8;11:608986. doi: 10.3389/fpsyg.2020.608986. PMID: 33363500; PMCID: PMC7753010.
17. Anne N. Thorndike, Vicki Fung, Jessica L. McCurley, Cheryl R. Clark, Sydney Howard, Douglas E. Levy, COVID-19 stressors and one-year changes in depression and anxiety in a longitudinal cohort of low-income adults in the United States, *Preventive Medicine Reports*, Volume 26, 2022, 101730, ISSN 2211-3355, <https://doi.org/10.1016/j.pmedr.2022.101730>.
18. 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. *Lancet.* 2020;395(10227):912–20. Epub 2020/03/01. pmid:32112714; PubMed Central PMCID: PMC7158942.
19. Jin Y, Sun T, Zheng P, An J. Mass quarantine and mental health during COVID-19: A meta-analysis. *J Affect Disord.* 2021;295:1335–46. Epub 2021/10/29. pmid:34706447; PubMed Central PMCID: PMC8674683.
20. Tansey C.M. One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome. *Arch Intern Med.* 2007;167(12):1312. doi: 10.1001/archinte.167.12.1312.
21. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur. Heart J.* 2022;43:1157–1172. doi: 10.1093/eurheartj/ehac031

22. Pena-Orbea, C., Lapin, B., Li, Y. *et al.* Sleep Disturbance Severity and Correlates in Post-acute Sequelae of COVID-19 (PASC). *J GEN INTERN MED* (2023). <https://doi.org/10.1007/s11606-023-08187-3>

## APPENDIX A: STUDY PROPOSAL

### NEUROPSYCHIATRIC SYMPTOMS IN COVID AND LONG COVID IN SOUTHEAST ASIA, A SYSTEMIC REVIEW

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#### Background

There have been increasing studies of neuropsychiatric symptoms in COVID-19 and Long COVID patients. According to the NICE guidelines, Long COVID syndrome is defined as symptoms persisting more than 12 weeks after the onset of acute symptoms. (2) Neuropsychiatric symptoms are prevalent amongst patients with COVID-19. Delirium, depression and anxiety are the more common symptoms which have been extensively documented amongst COVID patients (1,6). A recent study in Istanbul, Turkey found that psychiatric morbidity (20-56%), PTSD (10-26%) and depression (9-27%) were most prevalent amongst COVID-19 patients in Istanbul. [9] Another study found that COVID-19 had a strong correlation toward the development of dementia in older patients, be it through the infection itself and/or through social isolation. Viral infection of COVID-19 does indeed have a negative impact on neuropsychiatric symptoms in patients above 60 years old. Other studies have also shown that mere social isolation (without infection) causes a negative impact on the cognitive abilities of the elderly. (3) Research has proven that a significant proportion of patients with COVID-19-pneumonia suffer from neurological disorders like stroke or encephalopathy, as well as psychiatric disorders like depression, PTSD, anxiety and insomnia. (5,6)

A fascinating study done in the UK showed a strong correlation between COVID-19 patients and cerebrovascular events (acute ischaemic, haemorrhagic, thrombotic vascular events) and peripheral neuropathology. Amongst the 153 patients in which the trial had, (43%) 23 patients with neuropsychiatric disorders had new-onset psychosis, six (26%) had a neurocognitive (dementia-like) syndrome, and four (17%) had an affective disorder. 18 (49%) of 37 patients with altered mental status were younger than 60 years and 19 (51%) were older than 60 years, whereas 13 (18%) of 74 patients with cerebrovascular events were younger than 60 years versus 61 (82%) patients older than 60 years. (7)

Neuropsychiatric symptoms in Long-COVID syndrome are also now being extensively documented. A meta-analysis encompassing 10,530 patients (both hospitalised and non-hospitalised) 3 months after COVID-infection found that patients experienced symptoms such as fatigue (37%), brain fog (32%), memory issues (28%), attention disorder (22%), myalgia (17%), anosmia (12%), dysgeusia (10%), and headache (15%). The prevalence of neuropsychiatric symptoms was sleep disturbances (31%), anxiety (23%), and depression (17%). (11)

COVID-19 has impacted the quality of life of COVID and Long COVID patients, and this may progress without a clear end. In line with extensive research carried out on a global scale, we believe that there is a vast avenue and utmost importance in exploring the neuropsychiatric symptoms specifically in South East Asia. There is a lack in collection and compilation of data specifically in this region, and we believe that the nature and extent of persistent neuropsychiatric symptoms after COVID-19 is an important study for the pandemic recovery phase. In this systemic review, cross-sectional study is generally the gold standard used for investigating the prevalence of neuropsychiatric symptoms in COVID and Long COVID patients. It will significantly enable us to promote the value of our research in contributing to scientific evidence.

### Study objectives

1. To compare the types and degree of severity of neuropsychiatric symptoms between COVID and Long Covid patients in Southeast Asia
2. To compare the prevalence of neuropsychiatric symptoms among COVID patients in Southeast Asia
3. To compare the prevalence of neuropsychiatric symptoms among Long COVID patients in Southeast Asia

### Research hypothesis

1. Alternate hypothesis: Long COVID and COVID both have neuropsychological symptoms on South East Asian patients.
2. Null hypothesis: Both Long COVID and COVID do not have neuropsychological symptoms on South East Asian patients.

### Research questions

1. Is there a difference between the types and degree of severity of neuropsychiatric symptoms between COVID and Long Covid patients in Southeast Asia?
2. Is there a difference between the prevalence of neuropsychiatric symptoms among COVID patients in Southeast Asia?
3. Is there a difference between the prevalence of neuropsychiatric symptoms among Long COVID patients in Southeast Asia?

### Methodology

1. Databases: PubMed, EMBASE, MEDLINE, ProQuest, Science Direct
2. Keywords: (1) "COVID-19", (2) "Long COVID-19", (3) "Neuropsychiatric symptoms", (4) "Southeast Asia"
3. Date of publication of published papers: 1st January 2020 to 31st December 2021

4. Inclusion criteria: (1) Publications in English, (2) Studies relevant to the area of focus (Neuropsychiatric symptoms), (3) Studies on population of interest (recovered COVID-19 patients of all age groups from Southeast Asian Region)
5. Exclusion criteria: (1) Publications not in English, (2) Non-clinical studies (Eg, economics, hazards, or effect of COVID-19 on corporates), (3) Have less than 50 patients included in the research.

### Ethical issues

We do not anticipate ethical concerns.

### Statistical analysis

Preferred Reporting Items for Systemic Reviews, Meta-Analyses (PRISMA) guidelines

### References

1. Şenol Turan, Burç Çağrı Poyraz, Cana Aksoy Poyraz, Ömer Faruk Demirel, Ezgi Tanrıöver Aydın, Büşra Uçar Bostan, Öznur Demirel, Ritvan Kara Ali, Characteristics and outcomes of COVID-19 inpatients who underwent psychiatric consultations, *Asian Journal of Psychiatry*, Volume 57, 2021, 102563, ISSN 1876-2018, <https://doi.org/10.1016/j.ajp.2021.102563>.
2. P. Venkatesan, NICE guideline on long COVID, *Lancet Respir. Med.*, 9 (2) (2021), p. 129
3. Manca R, De Marco M and Venneri A (2020) The Impact of COVID-19 Infection and Enforced Prolonged Social Isolation on Neuropsychiatric Symptoms in Older Adults With and Without Dementia: A Review *Front. Psychiatry* 11:585540. doi:10.3389/fpsy.2020.
4. Stephen J. Ferrando, Lidia Klepacz, Sean Lynch, Mohammad Tavakkoli, Rhea Dornbush, Reena Baharani, Yvette Smolin, Abraham Bartell, COVID-19 Psychosis: A Potential New Neuropsychiatric Condition Triggered by Novel Coronavirus Infection and the Inflammatory Response, *Psychosomatics*, Volume 61, Issue 5, 2020, Pages 551-555, ISSN 0033-3182, <https://doi.org/10.1016/j.psym.2020.05.012>
2. Han, Y., Yuan, K., Wang, Z. *et al.* Neuropsychiatric manifestations of COVID-19, potential neurotropic mechanisms, and therapeutic interventions. *Transl Psychiatry* 11, 499 (2021). <https://doi.org/10.1038/s41398-021-01629-8>
3. Matt Boden, Nichole Cohen, Jessilyn M. Froelich, Katherine J. Hoggatt, Hoda S. Abdel Magid, Swapandeep S. Mushiana, Mental disorder prevalence among populations impacted by coronavirus pandemics: A multilevel meta-analytic study of COVID-19, MERS & SARS, *General Hospital Psychiatry*, Volume 70, 2021, Pages 124-133, ISSN 0163-8343, <https://doi.org/10.1016/j.genhosppsy.2021.03.006>
4. Aravinthan Varatharaj, MRCP Naomi Thomas, MRCPCH Mark A Ellul, MRCP Nicholas W S Davies, PhD Thomas A Pollak, MRCP Elizabeth L Tenorio, PhD Mustafa Sultan Ava Easton, PhD Prof Gerome Breen, PhD Michael Zandi, PhD Prof Jonathan P Coles, PhD Hadi Manji, FRCP Prof Rustam Al-Shahi Salman, PhD Prof David K Menon, PhD Timothy R Nicholson, PhD Laura A Benjamin, PhD Prof Alan Carson, PhD Prof Craig Smith, MD Prof Martin R Turner, PhD Prof Tom Solomon, PhD Rachel Kneen, MRCPCH Prof Sarah L Pett, PhD Ian Galea, PhD \* Rhys H Thomas, PhD Benedict D Michael. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study [Internet]. VOLUME 7, ISSUE 10, P875-882, OCTOBER 01, 2020. 2020 [cited 2022 Dec 1]. Available from: [http://dx.doi.org/10.1016/S2215-0366\(20\)30287-X](http://dx.doi.org/10.1016/S2215-0366(20)30287-X)

5. James B. Badenoch, Emma R. Rengasamy, Cameron J. Watson, Katrin Jansen, & Stuti Chakraborty. (2021, May 4). Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. medRxiv. Retrieved January 12, 2022, from [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X)
6. Sheng Hong, S., Oh Lean Hooi, J., Shu Sing, L., Zhi Hao, T., & Sheikh, S. (2020). *Psychological Wellbeing And Coping Strategies During Covid-19 Pandemic In Malaysia*. [IMU] Retrieved January 26, 2022.
7. Laviendraj Premraj, Nivedha V. Kannapadi, Jack Briggs, Stella M. Seal, Denise Battaglini, Jonathon Fanning, Jacky Suen, Chiara Robba, John Fraser, Sung-Min Cho, Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis, *Journal of the Neurological Sciences*, Volume 434, 2022, 120162, ISSN 0022-510X, <https://doi.org/10.1016/j.jns.2022.120162>.
8. James B. Badenoch, Emma R. Rengasamy, Cameron J. Watson, Katrin Jansen, & Stuti Chakraborty. (2021, May 4). Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. medRxiv. Retrieved January 12, 2022, from [https://doi.org/10.1016/S2215-0366\(20\)30287-X](https://doi.org/10.1016/S2215-0366(20)30287-X).

**APPENDIX B: CHARTS AND TABLES**

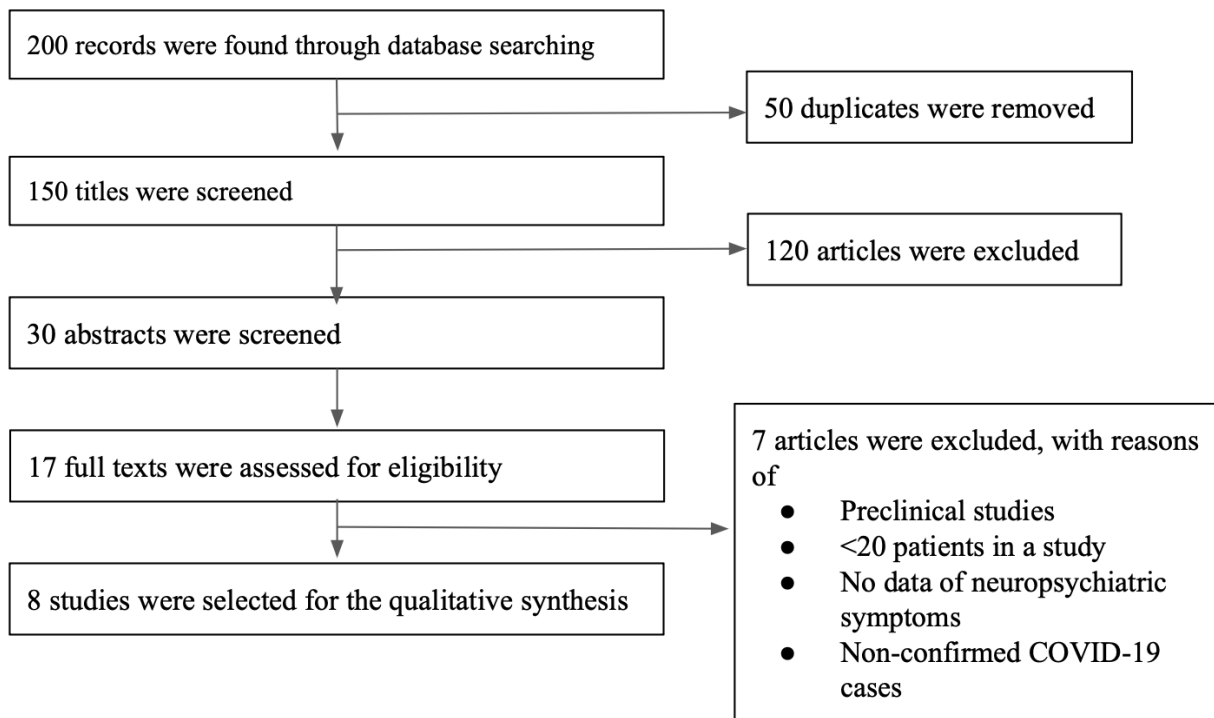


Figure 1

<b>COVID-19</b>			
<b>Study</b>	<b>n Subjects</b>	<b>Symptoms</b>	<b>Prevalence</b>
Muhammad Azri Adam bin Adnan, et. al., Malaysia, 29 December 2022.	401	Anxiety	7.0%
Hana Maizuliana Solehan, et. al., Malaysia , 16 August 2022.	215	Anxiety	0.50%
		Depression	11%
Michael Austin Pradipta Lusida, et. al., East Java province, Indonesia	608	Anxiety	14.40%
		Depression	3.60%
		Stress	7.90%
Ketut Suryana, et. al. Bali, Indonesia	292	Anxiety	28.10%
		Others	19.20%
Ye Minn Htun et. al., Myanmar, 4 June 2021	142	Depression	38.70%

Table 1

<b>Long COVID</b>			
<b>Study</b>	<b>n Subjects</b>	<b>Symptoms</b>	<b>Prevalence</b>
Kim Sui Wan, et. al., Malaysia, March 8 2023	452	Anxiety	6.50%
		Depression	2.40%
		Sleep disturbances	16.10%
		Stress	4.00%
		Others	2.00%

Table 2

## APPENDIX C: RESEARCH APPROVAL



INTERNATIONAL MEDICAL UNIVERSITY  
MALAYSIA

No. 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia.  
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Date: 4 July 2022

Ms. Lilian Tan Teng Ming  
Senior Manager  
Finance Department  
International Medical University

Dear Ms Lilian,


### Request for Approval of Research Fund and Issuance of Project Identification Number

**Project Title:** Neuropsychiatric Symptoms In Covid And Long Covid in Southeast Asia, A Systematic Review

**Principal Investigator:** Dr Shane Varman a/l Pannir Selvam

**Co-Investigators:** Hong Khye Yi; Heng Seng Kiat; Gaurangkumar Dharmendrakumar Patel; Isabella Barie anak Peter Nyaarok; Fan Shi Yi Phoebe

**Grant Amount:** RM 2000

**Duration:** 26 May 2022 to 19 April 2023 

The attached proposal for research on "**Neuropsychiatric Symptoms In Covid And Long Covid in Southeast Asia, A Systematic Review**" was submitted to the Secretariat for funding of RM 2000 on 5 May 2022. It was presented at the IMU Joint-Committee on Research and Ethics on 23 June 2022, 248th IMU-JC and was given a Recommended With Amendments. It was revised and resubmitted on 30 June 2022.

Please allocate the stipulated amount for use by the Principal Investigator for the project.

Please let us know the **COA** for this new project.

Thank you.

Yours sincerely,



**Associate Professor Dr Tan Eng Lai**  
Secretary, IMU Joint-Committee on Research and Ethics

cc: Research Management Centre  
**Dr Shane Varman a/l Pannir Selvam** - Principal Investigator / Supervisor  
Project File

Let\_CSs-Sem6(18)2022 / (**Non-Contract Research** / Contract Research)  
IMU/SOP/IRDI/02 [Appendix 5]  
Revised as of 16 November 2021 (19th Edition)  
File – Appen 5 - Letter to Finance Dept on ID&COA Number