A study of neuropsychiatric manifestations in COVID-19 infection in inpatients and its long-term outcomes in Malaysia

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ABSTRACT

Introduction: This study aimed to determine the prevalence and association between the severity of COVID-19 and short and long-term neuropsychiatric symptoms, as well as the risk factors for the development of these symptoms.

Materials and Methods: A prospective observational study was conducted between 1st October 2021 till September 2022 in the state of Johor, Malaysia. 300 patients with confirmed SARS-CoV-2 infection were randomly selected and followed up for six months. Data were analysed by using Chi-square test, Fisher's Exact test, Paired t test and Multiple logistic regression.

Results: The prevalence of short-term neuropsychiatric symptoms was 78%, with anosmia being the most prevalent symptom. Long-term symptoms were found in 22.75% of patients, with headache being the most prevalent (p= 0.001). COVID-19 Stage 2 and 3 infections were associated with a higher risk of short-term neuropsychiatric symptoms, OR for Stage 2 infection was 5.18 (95% CI: 1.48-16.97; p=0.009) and for Stage 3 infection was 4.52 (95% CI: 1.76-11.59; p=0.002). Complete vaccination was a significant predictor of long-term symptoms with adjusted OR 3.65 (95% CI 1.22-10.91; p=0.021).

Conclusion: This study demonstrated that neuropsychiatric symptoms were common among COVID-19 patients in Johor, Malaysia and the risk of these symptoms was associated with the severity of the infection. Additionally, complete vaccination does not completely protect against long-term neuropsychiatric deficits. This is crucial for continuous monitoring and addressing neuropsychiatric symptoms in COVID-19 survivors.

KEYWORDS:
COVID-19; neuropsychiatric; vaccine

INTRODUCTION

In December 2019, a cluster of atypical 'viral pneumonia' like cases broke out in Wuhan, China, and this unravelled the pandemic to the whole world. This new disease, named COVID-19, is caused by a novel coronavirus called SARS-CoV-2. Up to 1st April 2023, WHO have reported 762,791,152 confirmed cases of COVID-19, including 6,897,025 deaths, while locally in Malaysia, our numbers stand at 5,052,337 confirmed cases with 36,982 deaths.[1] SARS-CoV-2 virus changes over time. This may affect the virus's properties, transmission rate, performances of vaccines, severity of the disease, detection rate by the diagnostic tools and effectiveness of treatment. Omicron as an example of Variant of Concern (VOC), which requires more meticulous public health actions, e.g. notify to local authority, enhancing preventive measures, and more studies on therapeutic medicine and vaccine effectiveness.

Studies have shown that COVID-19 does not solely affect the respiratory system but is multi-systemic as well. The most common central nervous system (CNS) symptoms include hyposmia or anosmia, ageusia, headache and myalgia, while symptoms indicating encephalopathy (e.g. delirium) are less common.[2,3,4] Even patients who have recovered from COVID-19 can develop long-term sequelae or persistent symptomatology (SPS). The CNS SPS made up 20.8%, and the most prevalent SPS is persistent anosmia or dysgeusia (7.2%) followed by headache (5.3%).[5] Patients may also experience psychological issues such as increased stress, anxiety or depression.[6] Thus, neuropsychiatric symptoms comprise neurological and psychiatric symptoms. Heneka et al.[7] suggested that patients recovered from COVID-19 are at high risk for neurodegenerative disease, e.g. Alzheimer's disease.

There are several postulations regarding the mechanism of SARS-CoV-2 invading the nervous system. Direct effect of SARS-CoV-2 such as its high binding affinity to human receptor angiotensin-converting enzyme 2 (ACE2) found in lung, interstitial epithelium and endothelium tissues of blood–brain barrier, haematogenous dissemination and invades into CNS via olfactory nerve. Other routes of infection are reportedly through the peripheral nervous system via retrograde neuronal routes. Apart from that, SARS-CoV-2 also can affect the nervous system indirectly. For instance, it can cause cytokine release syndrome which is due

This article was accepted: 13 December 2023
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to over-activity of the body's immune system, in which there is torrential release of cytokines leading to a harmful level of inflammation which can interfere with organ function. Moreover, SARS-CoV-2 also causes prothrombotic conditions, which may lead to debilitating complications, e.g. acute ischaemic stroke. On top of that, sepsis may be a catastrophic complication of COVID-19 infection, which may lead to multi-organ failure.[8,9]

The effects of COVID-19 infection can be devastating and long lasting. Therefore, this study aimed to determine the prevalence and association between the severity of COVID-19 and short and long-term neuropsychiatric symptoms, as well as the risk factor for the development of these symptoms. This, in turn, can aid medical practitioners and caretakers in managing these symptoms.

MATERIALS AND METHODS

We conducted a prospective observational study at the Hospital Enche' Besar Hajjah Khalsom, Kluang, Johor (government-assigned hospital for treatment of COVID-19) between 1st October 2021 till September 2022. This study was registered at National Medical Research Register with registration number NMRR-21-1720-61044. In addition, ethical approval was obtained from the Malaysia Medical Research and Ethics Committee (MREC).

We included patients admitted to the hospital and diagnosed with COVID-19 based on clinical data, epidemiological history and nasopharyngeal swab or sputum for polymerase chain reaction (PCR) to SARS-CoV-2. Patients were categorised into five severity stages according to Malaysia Ministry of Health COVID-19 protocol.[10] Clinical stage of COVID-19 are as follow: stage 1 is asymptomatic; stage 2 is symptomatic but no pneumonic changes on chest X-ray (CXR); stage 3 is symptomatic and has pneumonic changes on CXR; stage 4 is symptomatic, has pneumonic changes on CXR and required supplemental oxygen; stage 5 is critically ill with multiorgan involvement. Stage 1, 2 and 3 were categorized as mild severity, whereas stages 4 and 5 were categorised as severe stage. Upon admission, all patients underwent a full history taking, physical examination, blood sampling for tests and CXR.

Considering 90% confidence interval, margin of error 0.05, detectable difference of 35% based on previous study7 and a potential dropout rate of 20%, a sample size of 300 patients was randomly selected by using a random number generator application. They were assessed in the ward and then followed up at 6 months via telephone consultation (video call or phone call). Subjects' contacts were kept confidential and only used for study purposes. Telecommunication benefitted patients by eliminating the hassle of travelling and reducing the exposure risk to COVID-19 in the community.

Cognitive function in patients was evaluated by using the six-items screener.[11] A score of 2 or 3 indicates a need for further screening and diagnostic testing. Patient Health Question-9 (PHQ-9)[12] was used to evaluate depression while General Anxiety Disorder-7 (GAD 7)[13] for assessing anxiety. Patients with moderate to severe depression or anxiety disorder were informed and with their permissions, referred to a psychiatrist for further evaluation.[14] Apart from that, Confusion Assessment Method (CAM-S) short-form worksheets was used to assess delirious patients.[15] Permission to use these neuropsychiatric evaluation tools (PHQ-9, GAD-7, six-item screener and CAM-S) in this study was granted by the respective authors.

Subjects' personal information in this study would be handled confidentially. They would not be informed about the individual study findings. However, they would be informed about the study findings collectively if they opted to.

Inclusion criteria included hospitalised patients aged 18 years old and above with confirmed PCR to SARS-CoV-2 (confirmed cases according to the Malaysia Ministry of Health). Thus, patients with compatible clinical symptoms and imaging tests (suspected cases) but negative PCR tests were excluded. Other exclusion criteria were patients who did not require hospitalisation, passed away during the study period, defaulted on post-COVID-19 follow up and those declined to participate in the study. Apart from that, patients with severe neurological disorders which impede participation in the study, e.g. stroke with impaired cognitive functions, severe dementia, chronic headache prior to COVID-19 infection and those with psychiatric disorders prior to COVID-19 infection, e.g. major depression disorder, generalised anxiety disorder, bipolar disorder and schizophrenia were excluded.

Ethical considerations

The ethical implications of the study adhered to the principles of the Declaration of Helsinki Declaration. The database was anonymized, and no identification data was used in the analyses. Informed consent was taken for each patient enrolled in the study. Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia and other relevant approvals prior to the start of any study-related activities.

Statistical Analysis

Data were analysed as descriptive and analytical statistics. In this study, patients were grouped as experiencing short-term or long-term neuropsychiatric symptoms, if they experienced any of the neuropsychiatric symptoms upon admission or in the post 6 months. Chi-square test, Fisher's Exact test or Paired t-test were applied to evaluate the association between patients' social demographic background, the severity of COVID-19 infection, the development of early neuropsychological symptoms and the persistence of these symptoms 6 months post COVID-19 infection, where appropriate. Multiple logistic regression was used to predict the development of early neuropsychological symptoms and the persistence of these symptoms 6 months later.

RESULTS

Baseline Characteristics

From October 2021 until June 2022, 300 patients with confirmed COVID-19 infection were enrolled into the study and followed up after 6 months. 255 (85%) patients were

Table I: Baseline characteristic of study cohort (n=300)

Baseline characteristic	Number of patients, n (%)
Gender	
Male	122 (40.7)
Female	178 (50.3)
Age, mean (+SD)	47.09 (+16.57)
Race	
Malay	247 (82.3)
Chinese	26 (8.7)
Indian	21 (7.0)
Others	6 (2.0)
Risk factors	
No	93 (31.0)
Yes	207 (69.0)
Types of risk factor	
Cardiovascular	53 (17.7)
Respiratory	49 (16.3)
Endocrinology	16 (5.3)
Obstetrics and Gynecology	14 (4.7)
Renal	10 (3.3)
Oncology	4 (1.3)
Multiple comorbid[a]	61 (20.3)
Covid-19 severity	
Stage 1	23 (7.7)
Stage 2	152 (50.7)
Stage 3	34 (11.3)
Stage 4	62 (20.7)
Stage 5	29 (9.7)
Oxygen requirement	
No	212 (70.7)
Yes	88 (29.3)
Steroid use	
No	209 (69.7)
Yes	91 (30.3)
Intensive Care Unit admission	
No	294 (98.0)
Yes	6 (6.0)
Covid-19 vaccination status	
Incomplete	59 (19.7)
Complete	241 (80.3)

Data are given as number (percentage) unless otherwise indicated. [a]Multiple comorbid defined as patients suffered from two or more types of risk factors (cardiovascular, respiratory, endocrinology, obstetrics and gynecology, renal or oncology).

Table II: Prevalence of short-term and long-term neuropsychiatric symptoms

Neuropsychiatric characteristics	Short term (n = 300)	Long term (n = 255)	p value*
Number of patients with neuropsychiatric symptoms, n (%)	234 (78.00)	58 (22.75)	0.001[a]
Average number of neuropsychiatric symptoms per patients, mean (+ SD)	3.40 (+1.930)	2.09 (+1.218)	<0.001c
Neuropsychiatric symptoms, n (%)			
Ageusia	115 (38.33)	3 (1.18)	0.054[b]
Anosmia	137 (45.67)	5 (1.96)	0.178[b]
Myalgia	109 (36.33)	19 (7.45)	<0.001[a]
Headache	109 (36.33)	20 (7.84)	<0.001[a]
Delirium, mean (+SD) (assessed using CAM-S scores)	0 (+0.130)	0 (+0.000)	0.318[c]
Stroke	2 (0.67)	2 (0.78)	0.016[b]
Paresthesia	18 (6.00)	12 (4.71)	<0.001[b]
Movement disorder	0 (0.00)	1 (0.39)	-
Seizure	1 (0.33)	1 (0.39)	0.004[b]
Depressive severity (assessed using PHQ-9 scores)			
Mild	220 (73.33)	56 (21.96)	0.884[b]
Moderate to severe	14 (4.66)	2 (0.78)	
Anxiety severity (assessed using GAD-7)			
Mild	230 (76.66)	56 (21.96)	0.504[b]
Moderate to severe	4 (1.71)	2 (0.78)	
Sleep disturbance	56 (18.67)	17 (6.67)	<0.001[b]
Loss of concentration	15 (5.00)	5 (1.96)	<0.001[b]
Memory disturbance	13 (4.33)	12 (4.71)	0.001[b]
Cognitive impairment (assessed using six-item screener)	27 (9.00)	6 (2.35)	0.375[b]

Data are presented as number (percentage) unless otherwise indicated. *p-value <0.05 considered statistically significant. aChi-square test. bFisher's exact test. cPaired t test. SD, standard deviation, CAM-S, Confusion Assessment Method, PHQ-9, Patient Health Question-9, GAD-7, General Anxiety Disorder-7.

Table III: Association and predictors of short-term neuropsychiatric symptoms (n = 300) in logistic regression models

Characteristics	Short term Neuropsychiatric symptoms		Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
	Yes (n = 234)	No (n = 66)				
Socio-demographic data						
Age, mean (+SD)	46.58 (+16.343)	48.91 (+17.358)	0.99 (0.98–1.01)	0.313	0.99 (0.97–1.01)	0.330
Race, n (%)						
Malay	197 (81.88)	50 (75.76)	1		1	
Non-Malay	37 (15.81)	16 (24.24)	0.59 (0.30–1.14)	0.115	0.58 (0.29–1.19)	0.139
Risk factors, n (%)						
No	72 (30.77)	21 (31.82)	1		1	
Yes	162 (69.23)	45 (68.18)	1.05 (0.58–1.89)	0.871	0.79 (0.41–1.54)	0.487
Clinical data						
COVID-19 severity, n (%)						
Stage 1	11 (4.70)	12 (18.18)	1		1	
Stage 2	120 (51.28)	32 (48.48)	4.09 (1.65–10.13)	0.002*	4.52 (1.76–11.59)	0.002*
Stage 3	27 (11.54)	7 (10.61)	4.21 (1.31–13.51)	0.016*	5.18 (1.48–16.98)	0.009*
Stage 4	52 (22.22)	10 (15.15)	5.67 (1.96–16.40)	0.001*	2.75 (0.45–16.87)	0.274
Stage 5	24 (10.26)	5 (7.58)	5.24 (1.48–18.53)	0.010*	2.20 (0.24–20.18)	0.486
Oxygen requirement, n (%)						
No	159 (67.95)	53 (80.30)	1		1	
Yes	75 (32.05)	13 (19.70)	1.92 (0.99–3.74)	0.054	3.28 (0.60–17.94)	0.170
Intensive Care Unit admission, n (%)						
No	229 (97.86)	65 (98.48)	1		1	
Yes	5 (2.14)	1 (1.52)	1.42 (0.16–12.36)	0.751	1.08 (0.10–12.50)	0.946
COVID-19 vaccination status+, n (%)						
Incomplete	45 (19.23)	14 (21.21)	1		1	
Complete	189 (80.77)	52 (78.78)	1.13 (0.58–2.22)	0.721	1.52 (0.72–3.26)	0.270

CI, confidence interval; OR, odds ratio. *p value <0.05 considered statistically significant. +Complete COVID-19 vaccination status defined as individual who received complete primary dose vaccination series (2 doses for CoronaVac®, Comirnaty®, COVID-19 AstraZeneca®) at least 14 days before SARS-CoV-2 virus infection.

Table IV: Association and predictors of long-term neuropsychiatric symptoms (n= 255) in logistic regression models

Characteristics	Long term neuropsychiatric symptoms		Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
	Yes (n=58)	No (n=197)				
Sociodemographic Data						
Age, Mean (+SD)	43.67 (+14.867)	47.86 (+16.916)	0.99 (0.97–1.00)	0.091	0.98 (0.96–1.00)	0.073
Race, n (%)						
Malay	48 (82.76)	159 (80.71)	1		1	
Non-Malay	10 (17.24)	38 (19.29)	0.87 (0.41–1.88)	0.726	1.30 (0.55–3.05)	0.548
Risk Factors, n (%)						
No	23 (39.66)	61 (30.96)	1		1	
Yes	35 (60.34)	136 (69.04)	0.68 (0.37– 1.25)	0.217	0.76 (0.39–1.47)	0.415
Clinical Data						
COVID-19 Severity, n (%)						
Stage 1	5 (8.62)	18 (9.14)	1		1	
Stage 2	35 (60.34)	99 (50.25)	1.27 (0.44–3.69)	0.657	1.35 (0.45–4.07)	0.592
Stage 3	2 (3.45)	28 (14.21)	0.28 (0.05–1.47)	0.127	0.27 (0.04–1.59)	0.144
Stage 4	14 (24.14)	32 (16.24)	1.58 (0.49–5.09)	0.448	0.78 (0.07–8.91)	0.842
Stage 5	2 (3.45)	20 (10.15)	0.36 (0.06– 2.09)	0.255	0.11 (0.01–2.61)	0.171
Oxygen Requirement, n (%)						
No	42 (72.41)	145 (73.60)	1		1	
Yes	16 (27.59)	52 (26.40)	1.06 (0.55–2.05)	0.857	2.98 (0.32–28.09)	0.340
Intensive Care Unit Admission, n (%)						
No	57 (98.28)	194 (98.48)	1		1	
Yes	1 (1.72)	3 (1.52)	1.14 (0.12–11.12)	0.914	6.18 (0.28–135.88)	0.248
COVID-19 vaccination status+, n (%)						
Incomplete	5 (8.62)	36 (18.27)	1		1	
Complete	53 (91.38)	161 (81.73)	2.37 (0.89–6.35)	0.086	3.65 (1.22–10.91)	0.021*

CI, confidence interval; OR, odds ratio. *p value <0.05 considered statistically significant. +Complete COVID-19 vaccination status defined as individual who received complete primary dose vaccination series (2 doses for CoronaVac®, Comirnaty®, COVID-19 AstraZeneca®) at least 14 days before SARS-CoV-2 virus infection

reassessed after 6 months. Table I shows the baseline sociodemographic and clinical characteristics of the entire cohort. The mean age of the study population was 47.09 (+16.57) with females (178, 50.3%) and Malay (247, 82.3%) predominance. Majority of them were admitted as Stage 2 Covid-19 infection (152, 50.7%) and have completed their COVID-19 vaccination (241, 80.3%).

Prevalence of Short-Term and Long-Term Neuropsychiatric Symptoms

In this study, the prevalence of the short-term neuropsychiatric symptoms in the study cohort was 78% (n = 234). Among those with short-term symptoms, the mean number of neuropsychiatric symptoms suffered per patient was 3.40 +1.930. In contrast, a majority of those suffering from short-term neuropsychiatric symptoms improved post 6 months of study follow-up with only 58 (22.75%) of the patients showing persistence with long-term symptoms (p = 0.001). From those post 6 months cohort with long-term neuropsychiatric symptoms, the mean number of symptoms suffered per patients was 2.09+1.218. After 6 months post COVID-19 infection, the mean number of persistent neuropsychiatric symptoms suffered per patient was statistically significantly reduced (p < 0.001).

The most prevalent short-term neurological symptoms were anosmia (46%), ageusia (38%), headache and myalgia (36%). On the other hand, the most prevalent long-term neurological symptoms were headache (7.8%), myalgia (7.6%) and sleep disturbance (6.7%). From a psychological aspect, about 73% and 76% have mild depressive and anxiety symptoms respectively during both initial and subsequent assessments (Table II). Besides, ageusia, anosmia, delirium, anxiety, depressive and cognitive impairment were among those neuropsychiatric symptoms that were found to be persistent post 6 months of evaluation (p>0.05) while movement disorder cannot be assessed in this study due to the small sample size (n = 1).

Associations and Predictors of Short- and Long-Term Neuropsychiatric Symptoms

The univariate analysis (Table III) demonstrated no statistically significant association between sociodemographic characteristics (age, race) and clinical characteristics (risk factors, oxygen requirements, ICU admission, COVID-19 vaccination status) with the manifestation of short-term neuropsychiatric symptoms (p > 0.05). COVID-19 disease severity was reported to be the only influencing predictor that affected the development of short-term symptoms. After adjusting and controlling all the possible confounding variables under the multivariate logistic regression, patients presented with COVID-19 Stage 2 and 3 infections appeared to have 4 to 5 times higher risk of suffering from short-term neuropsychiatric symptoms compared to other stages of infections. The reported adjusted OR for Stage 2 infection was 5.18 (95% CI: 1.48– 16.98; p = 0.009) and for Stage 3 infection was 4.52 (95% CI: 1.76–11.59; p = 0.002).

Following 6 months of study follow-up, COVID-19 vaccination status was found to be a significant predictor for long-term neuropsychiatric sequelae in multiple regression analysis. Interestingly, while vaccination status did not show to affect short-term symptoms, those with complete COVID-19 vaccination demonstrated approximately 3.6 times higher risk of long-term deficits with adjusted OR 3.65 (95% CI 1.22–10.91; p = 0.021). From another perspective, although COVID-19 disease severity was shown to be associated with short-term symptoms, it did not become an influencing predictor post 6 months of follow-up (p>0.05). Furthermore, our 6 months post-data implied that persistent neuropsychiatric deficits were independent from other socio-demographic characteristics (age, race) and clinical characteristics (risk factors, oxygen requirements, ICU admission) from the regression analysis with p > 0.05 (Table IV).

DISCUSSION

SARS-CoV-2 affects multiple systems acutely and also brings long-term effects to human health, known as long COVID. This study mainly focuses on the neurological and psychological impacts of COVID in acute infection and long-term effects later in life. We enrolled 300 patients who were diagnosed with COVID-19 infection and followed up in 6 months' time to assess for persistent neuropsychiatric symptoms. After 6 months, 255 patients were reassessed. We extensively outlined the neuropsychiatric symptoms, sociodemographic (age, gender, race, risk factors, comorbidities) and clinical variables (COVID stage, oxygen requirement, steroid use, ICU admission, vaccine status) observed within the cohort. This comprehensive list aimed to offer a detailed exploration of the cohort's clinical profile and contribute to a nuanced understanding of the study population.

Our mean age of expectancy was found to be lower compared to previous studies conducted in Mediterranean cohorts, specifically in Italy, Brazil and Spain.[5] This variance can be attributed to the overall lower life expectancy in Malaysia, a Southeast Asian country characterised by its diverse population comprising three main ethnic groups—Malays, Chinese and Indians. Despite the cultural and demographic differences, our study revealed no significant correlation between race and the occurrence of neuropsychiatric syndromes in both short and long-term period. Furthermore, it is a well-established fact that individuals with comorbidities often face heightened risks of severe illnesses or complications during acute illness. Consequently, our study was strategically designed to explore the potential relationship between comorbidities and neuropsychiatric symptoms. Interestingly, our findings defied expectations, as the study did not unveil a clear correlation between a patient's premorbid conditions and the subsequent development of neuropsychiatric symptoms.

From this study, we found that 78% of cohorts exhibited short-term neuropsychiatric symptoms while 22.75% experienced persistent symptoms. The number of patients with short-term symptoms was higher, whereas the number of patients with long-term symptoms fell between other studies.[5,6,7,16,17,18] This difference could be attributed to people being more anxious and paying closer attention to symptoms when experiencing less severe respiratory symptoms. Additionally, increased knowledge about the effects of COVID-19 on various systems may contribute to higher

awareness and education among the public, leading to more reported symptoms.

The most prevalent short-term neurological symptoms were anosmia (46%), ageusia (38%), headache and myalgia (36%). These results were similar to other studies.[17,18] The most prevalent long-term neuropsychiatric symptoms were headache (7.8%), myalgia (7.6%) and sleep disturbance (6.7%). All of these neuropsychiatric manifestations were the results of direct invasion of SARS-COV-2 virus into CNS via olfactory nerve or interaction with angiotensin-converting enzyme 2 (ACE2) receptors on the endothelial cells of the blood–brain barrier (BBB), systemic inflammation and massive cytokine release, cerebrovascular changes and complications of multi-organ dysfunction.[2,4,7] Additionally, there has been a hypothesis concerning the activation of the PYD domains-containing protein 3 (NLRP3) inflammasome and interleukin-1β, which causes the pathological accumulation of neurodegeneration-associated peptides. These peptides, such as fibrillar amyloid-β, induce or worsen neurodegenerative processes, ultimately leading to functional impairment in Alzheimer's Dementia. The heightened secretion of IL-1β through the activation of NLRP3 can induce neuroinflammation, neuronal death and cognitive impairments. This process might play a role in the pathogenesis of Alzheimer's Disease (AD).[19,20] In our study, 4.7% of patients suffer memory disturbance as a long-term sequelae ($p < 0.05$). This raises the concern of COVID-19-infected patients tending to suffer neurodegenerative disease in the future and further follow-up studies are warranted.

Noteworthy, mild depression and mild anxiety were highly prevalent among acute infection and during long-term follow-up ($p > 0.5$). This could be due to multifactorial, e.g. worrying of one's own health, societal stigmatisation, isolation policy, financial restraint due to worldwide economic recession, post-traumatic stress disorder (PTSD) and fear of long-term impact on health. Prevalence of PTSD symptoms in COVID19-19 was 9%.[14] The intense stressors linked to COVID-19 encompassed experiences such as undergoing treatments during severe illness (fear of death in critical situations, pain resulting from medical interventions like endotracheal intubation and central line insertion, and dealing with any complications), as well as witnessing the severe illness or death of beloved family members. Depression and anxiety have been identified as potential contributors to a decline in concentration, with a 5% decrease in the short term and a 1.96% decrease in the long term. Additionally, these psychological factors are associated with sleep disturbances, manifesting as an 18.67% occurrence in the short term and a 6.67% occurrence in the long term ($p < 0.05$).

Our study showed that patients with mild COVID-19 were associated with short-term neuropsychiatric symptoms. COVID-19 Stage 2 and 3 infections appeared to have 4 to 5 times higher risk of suffering from short-term neuropsychiatric symptoms compared to other stages of infections. Misra S et al. reported that mild COVID-19 patients have a higher tendency to get alteration in smell and taste.[18] It could be due to our first line defense—nasal cavity which acts as mechanical protection to prevent spreading of COVID-19 virus to the whole body. Thus, those patients suffer less severe symptoms of the disease. Apart from that, those severe COVID-19 patients are more ill and may not be able to give clear history or attention to neuropsychiatric symptoms as they are suffering from more severe lung inflammation and/or other organ involvements. Hence, severity of COVID-19 may predict the development of neuropsychiatric symptoms in acute infection.

COVID-19 vaccine is generally safe and provides strong protection from detrimental effects of COVID-19 and greatly reduces the rate of hospitalisation. It has short, tolerable side effects after injection. Nonetheless, this study found that those who completed COVID-19 vaccination (received at least two doses of COVID-19 vaccine eg Pfizer, AstraZenaca and Sinovac) at least 14 days before infection with SARS-CoV-2 virus, demonstrated approximately 3.6 times higher risk of long-term neuropsychiatric symptoms. This is contrary to other studies, which showed favourable results of COVID-19 vaccine on long covid.[21,22] It could be explained by the difference in duration of follow-up, as this study has a longer cohort period of 6 months, different SARS-CoV-2 variants, and different socio-demographic background. Another possible reason could be due to the existence of other factors affecting neuropsychiatric symptoms, e.g. mild depression symptoms that might be affected by stress of daily living. Moreover, perception of patients is subjective, and belief or fear of vaccines will bring long-term side effects. Those non-specific symptoms may be over-reported by the cohort.

LIMITATIONS

The limitations of this study include a small sample size, particularly in the incomplete vaccinated group, which accounted for only 16% of the study population at the end of the study. Secondly, it is not possible to confirm that the long-term neuropsychiatric symptoms were solely caused by COVID-19 since there was no comparison group. Thirdly, those suffering severe COVID-19 infection may not be able to provide a clear history and under-report the neuropsychiatric symptoms.

CONCLUSION

This study highlighted that neuropsychiatric symptoms were common among COVID-19 patients in Johor, Malaysia and most of these symptoms improved after 6 months. The most prevalent short-term neurological symptoms were anosmia, ageusia, headache and myalgia whereas the most frequent long-term neurological symptoms were headache, myalgia and sleep disturbance. Additionally, the risk of these symptoms was associated with the severity of the infection. Nonetheless, socio-demographic and premorbid did not correlate with short and long-term neuropsychiatric symptoms. Moreover, complete vaccination did not fully protect against long-term neuropsychiatric deficits. These findings emphasise the importance of monitoring and addressing neuropsychiatric symptoms in COVID-19 patients. Further follow-up and monitoring for any potential neuropsychiatric symptoms or neurodegenerative disease is warranted.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia and Head of Department for permission to publish this article.

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