Incidence and risk factors of cognitive impairment in COVID-19 survivors within the first six months and its association with functional outcome

^{1,2}Darwinus LAJIM, ¹Mazlina MAZLAN, ³Sa'adah Muhamad AMIN, ¹Anwar SUHAIMI

¹Department of Rehabilitation Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia; ²Department of Rehabilitation Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia; ³Department of Rehabilitation Medicine, University Malaya Medical Center, Kuala Lumpur, Malaysia

Abstract

Background & Objective: There is growing evidence of cognitive decline post-COVID-19, even in mild infection. We aim to evaluate the incidence of cognitive impairment, domains affected, its risk factors and the effect on function during the subacute period when rehabilitation is crucial. *Methods:* In this study, the incidence of impaired cognition was assessed in patients at 3 and 6 months post-COVID-19 infection between August 2021 and July 2022 at University Malaya Medical Center, with Montreal Cognitive Assessment (MoCA). The most common cognitive domains affected were identified with descriptive analysis. Associated sociodemographic and clinical factors were analyzed with simple and multiple logistic regression models. The post-COVID-19 Functional Scale (PCFS) was used to assess functional status. The correlation between cognition (MoCA score) and functional status (PCFS scale) was performed using Spearman correlation test. *Results:* We recruited 100 patients and found that 44% had impaired cognition at three months and 43% at six months. Patients with secondary education level (p =0.001, OR 13.541), oxygen therapy (p=0.039, OR 7.811), and obesity (p=0.029, OR 4.764) were associated with a higher risk of impaired cognition. The most affected MoCA domains were language, executive function, attention and memory. Lower MoCA score was correlated with higher PCFS grade (lower functional status) (p <0.001, ρ -0.729).

Conclusion: Post-COVID-19 cognitive impairments were common up to 6 months of illness and affect function. Clinicians are advised to perform cognitive screening especially in higher risk patients and provide necessary interventions.

Keywords: COVID-19, cognitive dysfunction, functional status

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the COVID-19 pandemic. It primarily affects the respiratory system but also impacts other organs, including the central nervous system.^{1,2} Studies have linked COVID-19's inflammatory effects to neurological complications, notably cognitive impairment, necessitating further research on its long-term neurological consequences.³Mood disorders such as anxiety, depression, and sleep disturbances which are common among COVID-19 survivors, can further contribute to cognitive decline.⁴⁻⁷

Cognitive deficits post-COVID-19 include difficulties with executive functions, attention, processing speed, memory, and language.^{4,8,9} They can persist even after recovery from acute respiratory symptoms, with studies showing cognitive decline in both severe and mild COVID-19 cases.¹⁰⁻¹³ The timing of cognitive recovery also varies, with some patients showing improvement after four months, while others only after a year.^{14,15} These cognitive challenges significantly affect daily activities, work performance, and overall quality of life.⁴

There is a growing body of global research

Date of Submission: 7 January 2024; Date of Acceptance: 1 April 2024 https://doi.org/10.54029/2024wxa

Address correspondence to: Mazlian Mazlan MRehabMed, Department of Rehabilitation Medicine, Faculty of Medicine, Universiti Malaya, 59100 Kuala Lumpur, Malaysia. Tel: 03-79674766, email: drmazlina@gmail.com

on post-COVID-19 cognitive impairment, but local data, particularly in Malaysia, is sparse. The rise in COVID-19 cases recently raises concerns about cognitive impairments in the Malaysian population. A lack of understanding of the risk factors and progression of cognitive impairment may delay necessary rehabilitation interventions.

This study focuses on the incidence of cognitive impairment at 3 and 6 months post-COVID-19 infection. It aims to identify risk factors associated with cognitive impairment, determine the most affected cognitive domains, and assess the link between cognition and functional status in COVID-19 survivors. The findings could help identify at-risk individuals, facilitate early initiation of specific cognitive rehabilitation management, and prevent further functional decline.

METHODS

Study design, participants, and setting

This prospective cohort study was conducted at University Malaya Medical Center (UMMC) and included participants aged 18 and above, with confirmed COVID-19 infection via Reverse transcription polymerase chain reaction (rt-PCR) or Rapid test kit-Antigen (RTK-Ag) test, and consented to a six-month study duration. Exclusion criteria included pre-existing cognitive impairment and language barriers in either English or Malay language. Patients were recruited from August 2021 to July 2022 through convenience sampling from the COVID-19 Multidisciplinary Team Clinic (MDC) and Rehabilitation Medicine Specialist Clinic. Informed consent was obtained prior to study enrollment.

A sample size calculator (Raosoft) was used to determine the recommended sample size with a confidence level of 95% in a population portion of 300. This study required a sample size of 143, with selected response distribution at 23% based on the response distribution from Rass et al.7 Our aim was to recruit an equal distribution of mild, moderate, and severe COVID-19 cases. Assessments were conducted at 3 and 6 months, including cognitive evaluation with the Montreal Cognitive Assessment (MoCA) and self-administered questionnaires (Patient Health Questionnaire-9 (PHQ-9), 7-item Generalized Anxiety Disorder (GAD-7), and Post COVID-19 Functional Scale (PCFS)). Sociodemographic and clinical data were collected from interviews and medical records.

Study instruments

Montreal Cognitive Assessment (MoCA)

We choose MoCA as it is a sensitive tool for detecting mild cognitive impairment, evaluates various cognitive domains and the most frequently used cognitive screening post-COVID-19.¹⁶ The total score is 30 points and a score of less than 26 is considered impaired cognition. The English and Malay versions of MoCA were used, administered by trained certified occupational therapists and rehabilitation medicine doctors.

Post COVID-19 Functional Scale (PCFS)

PCFS is a simple tool to monitor the course of symptoms and the impact of symptoms on the functional status of post-COVID-19 survivors.¹⁷ It is an ordinal scale with five statements assessing the full spectrum of functional outcomes, and focuses on limitations in everyday work or activities and lifestyle changes. PCFS was chosen for its simplicity and reproducibility. The post-COVID-19 management protocol produced by Ministry of Health Malaysia recommended the application of PCFS to monitor the patients' outcome.¹⁸

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a self-report measure consisting of nine questions based on the nine DSM-IV criteria for major depression. It is used to determine the presence or absence of depression. For severity measure, PHQ-9 scores range from 0 to 27, and each of the nine items scored from 0 (not at all) to 3 (nearly every day). PHQ-9 scores 5, 10, 15, and 20 represented mild, moderate, severe, and severe depression, respectively. For this study, we used the Malay and English versions. A score of 10 and above was categorized as participants having depression.¹⁹ PHQ-9 in Malay and English versions had shown to have good reliability and validity for patients with depression.^{20,21}

Generalized Anxiety Disorder (GAD-7)

GAD-7 is a screening tool for generalized anxiety disorder, which consists of seven items. Each item is scored on a four-point Likert scale (0-3), with scores ranging from 0 to 21. A higher score reflects greater anxiety severity. GAD-7 were employed in both Malay and English versions to rule out psychological issues affecting cognitive performance. It is a valid and reliable tool for screening generalized anxiety disorder.^{22,23}

Statistical analyses

Statistical analyses were performed using IBM SPSS, with a p-value of ≤ 0.05 indicating significance. Cognitive impairment incidence and affected cognitive domains were presented as frequency and percentage. Descriptive analysis identified sociodemographic and clinical characteristics. Continuous data were reported as mean and standard deviation, and categorical data as frequency and percentage. McNemar and Wilcoxon sign rank tests evaluated differences in outcomes between three and six months, while Spearman's correlation coefficient analyzed the relationship between MoCA scores and continuous variables. Logistic regression analysis determined associations between cognitive impairment and various variables. From the simple logistic regression analysis table, we identified variables with significant values (p < 0.05) at six months, and included them in multiple logistic regression analysis.

RESULTS

One hundred and sixteen eligible patients were recruited from the MDC and Rehabilitation Medicine Specialist Clinic. However, 16 patients dropped out due to logistic issues, busy with work, and uncontactable. One hundred patients completed the assessment at three- and six-months review.

Socio-demographic and COVID-19-related clinical data

The average age of the patients was 45.3 ± 11.9 years; There were more men compared to women, with the majority of them being Malay, married, employed, and reached tertiary education. (Table 1)

The COVID-19 clinical staging is classified as follows: Stage 1: asymptomatic; Stage 2: symptomatic without radiological pneumonia changes; Stage 3: symptomatic with radiological pneumonia changes; Stage 4: symptomatic, pneumonia, and supplemental oxygen required; and Stage 5: critically ill with multi-organ failure.²⁴ In this study, almost half of the patients had severe infections in Category(stage) 4 and 5. The mean length of hospital stay was 13.7 days and duration of oxygen dependency was 16.7 days. 24% of the patients were admitted to ICU and 19% were ventilated (Table 1).

Nearly half of the patients (48%) did not require oxygen. The oxygen support methods for the other

half of the patients are listed in Table 1. The three most common comorbidities are hyperlipidemia, hypertension, and diabetes mellitus.

Incidence and risk factors of impaired cognition post COVID-19

In this study (Table 2), we found that 44% of the patients had impaired cognition at three months and 43% at six months. The difference after three months was not significant (McNemar test P=1.000). We found that at three months, 22% had depression and 18% had anxiety, but the incidence for both dropped to 11% at six months. The changes were significant (McNemar test P=0.003 and P=0.039, respectively).

PCFS grading at three months (Table 2) showed that by ascending order, most of the patients had grade 2(35%), followed by grade 3(27%)and grade 0(25%), and the last one was grade 4(5%). However, later, at six months, there were significant changes (Wilcoxon sign rank test P <0.001). Most of the patients had grade 2(45%)and grade 0(32%), and the least grade was still grade 4 but became lesser (2%).

The simple logistic regression model of our study found that (Table 3) at three and/or six months: older patients, Chinese, unemployment, lower education level, history of ICU admission, history of ventilation, history of oxygen therapy, severe COVID-19 category, duration of oxygen therapy, hypertension, diabetes mellitus, obesity had a significant (P < 0.05) higher chance of impaired cognition than their counterparts.

Those variables with significant results using simple logistic regression were chosen to be further analyzed with Multiple Logistic Regression. Our study found that at six months (Table 4), patients with secondary education level had fifteen times higher chance of impaired cognition than those with tertiary education (P <0.001, OR 15.312), patients with oxygen therapy had seven times higher chance of impaired cognition than patients without oxygen therapy (P=0.012, OR 7.795), and obese patients had three times higher chance of impaired cognition than patients (P=0.046, OR 3.752).

Cognitive domains affected mainly by COVID-19

The most affected domains from descending order were language, memory, executive function, visuospatial, and attention. The least affected domain was orientation (Figure 1). The number of patients with affected language, memory, and orientation decreased after three months.

Independent variables	n(%)	Mean ± SD
Gender:		
Male	60(60.0)	
Female	40(40.0)	
Race:		
Malay	74(74)	
Chinese	16(16)	
Indian	10(10)	
Marital status:		
Married	81(81)	
Single/Divorced /Widowed	19(19)	
Employment:		
Employed	83(83)	
Unemployed	17(17)	
Education level:		
Tertiary	72(72)	
Secondary	24(24)	
Primary	4(4)	
COVID-19 Category:		
1	1(1)	
2	32(32)	
3	12(12)	
4	34(34)	
5	21(21)	
Age (years):		
18 - 39	37(37)	45.3 ± 11.9 years
40 - 59	52(52)	
60 – 74	11(11)	
Length of hospital stay (days)		13.7 ± 23.6 days
Duration of oxygen dependency (days)		16.7 ± 33.4 days
Ventilation history:		
Yes	19(19)	
No	81(81)	
Type of oxygen support:		
Intubation	16(16)	
Noninvasive ventilation	3(3)	
High-flow nasal cannula	12(12)	
High flow mask	1(1)	
Face mask	4(4)	
Nasal Prong	16(16)	
None	48(48)	
Comorbidities:		
Hypertension	35(35)	
Diabetes Mellitus	30(30)	
Hyperlipidemia	41(41)	
DIOIICHIAI ASINMA	11(11) 10(10)	
Obstructive sleep appea	7(7)	
Obesity	23(23)	
Thyroid disease	6(6)	
Chronic kidney disease	7(7)	

Notes: n(%) = number(percentage); SD = standard deviation

Outcome Measures	three months, n(%)	six months, n(%)	McNemar p-value
MoCA:			
Impaired	44(44.0)	43(43.0)	>0.999
Normal	56(56.0)	57(57.0)	
PHQ-9			
Depression	22(22.0)	11(11.0)	0.003
Normal	78(78.0)	89(89.0)	
GAD-7			
Anxiety	18(18.0)	11(11.0)	0.039
Normal	82(82.0)	89(89.0)	
PCFS grade:	25(25.0)	32(32.0)	Wilcoxon sign rank
0	8(8.0)	14(14.0)	p-value
1	35(35.0)	45(45.0)	-
2	27(27.0)	7(7.0)	<0.001
3	5(5.0)	2(2.0)	
4			

Table 2: The outcome measures of patients with COVID-19 at 3 and 6 months.

Notes: n(%) = number(percentage); MoCA = Montreal Cognitive Assessment; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = 7-item Generalized Anxiety Disorder; PCFS = Post COVID-19 Functional Scale

The significant difference after three months was memory and orientation (McNemar test P=0.007 and P=0.022, respectively), while the difference after three months in language was not significant (McNemar test P=0.607). The number of patients with affected visuospatial and attention increased after three months, but the difference was insignificant (McNemar test P=0.084 and P=0.860, respectively).

Correlation between cognition and functional status among COVID-19 patients

We found that a lower score of MoCA (poorer cognitive function) correlates with a higher grade of PCFS (worse function). $\varrho = -0.526$, p-value <0.001 at three months; $\varrho = -0.729$, p-value <0.001 at 6 months. The strength of the correlation between MoCA score and PCFS grading was moderate at three months, but strong at six months.



Figure 1. The number of patients with COVID-19 who had cognitive impairments at 3 and 6 months, in the different cognitive domains according to MoCA.

Neurology Asia

September 2024

Table 3. continued												
Oxygen therapy: No O2 Therapy O2 Therapy	12(27.3) 22(50)	33(58.9) 17(30.4)	Ref 3.559	1.425	8.885	0.007	9(20.9) 23(53.5)	36(63.2) 16(28.1)	Ref 5.750	2.180	15.166	<0.001
Intubated & ventilated	10(22.7)	6(10.7)	4.583	1.365	15.350	0.014	11(25.6)	5(8.8)	8.800	2.435	31.807	0.001
COVID-19	(2) (1) 2		بو ت				5/11 6					
severuy Mild	0(13.0) 23(52.3)	21(48.2) 23(41.1)	ter 4.500	1.564	12.946	0.005	(0.11.0) 22(51.2)	28(49.1) 24(42.1)	rei 5.133	1.686	15.633	0.004
Moderate Severe	15(34.1)	6(10.7)	11.250	3.079	41.103	<0.001	16(37.2)	5(8.8)	17.920	4.493	71.475	<0.001
Length of hospital stay			1.007	066.0	1.025	0.426			1.016	0.994	1.038	0.162
Duration of oxygen therapy			1.008	0.996	1.020	0.208			1.015	1.001	1.029	0.037
Hypertension: Present Absent	24(54.5) 20(45.5)	11(19.6) 45(80.4)	4.909 Ref	2.022	11.918	<0.001	24(55.8) 19(44.2)	11(19.3) 46(80.7)	5.282 ref	2.166	12.884	<0.001
Diabetes Mellitus: Present Absent	19(43.2) 25(56.8)	11(19.6) 45(80.4)	3.109 Ref	1.278	7.564	0.012	20(46.5) 23(53.5)	10(17.5) 47(82.5)	4.087 Ref	1.648	10.136	0.002
Hyperlipidemia: Present Absent	25(56.8) 19(43.2)	16(28.6) 40(71.4)	0.304 ref	0.132	0.698	0.005	26(60.5) 17(39.5)	15(26.3) 42(73.7)	0.234 ref	0.100	0.546	0.001
Obesity: Present Absent	15(34.1) 29(65.9)	8(14.3) 48(85.7)	3.103 ref	1.172	8.220	0.023	15(34.9) 28(65.1)	8(14.0) 49(86.0)	3.281 ref	1.237	8.705	0.017
Heart disease: Present Absent	6(13.6) 38(86.4)	4(7.1) 52(92.9)	2.053 ref	0.542	7.781	0.290	7(16.3) 36(83.7)	3(5.3) 54(94.7)	3.500 ref	0.849	14.433	0.083
Bronchial Asthma: Present Absent	4(9.1) 40(90.9)	7(87.5) 49(87.5)	0.700 Ref	0.191	2.562	0.590	4(9.3) 39(90.7)	7(12.3) 50(87.7)	0.733 Ref	0.200	2.682	0.638
Depression: Present Absent	9(20.5) 35(79.5)	13(23.2) 43(76.8)	0.851 ref	0.326	2.221	0.741	7(16.3) 36(83.7)	4(7) 53(93)	2.576 ref	0.703	9.447	0.153
Anxiety: Present Absent	7(15.9) 37(84.1)	11(19.6) 45(80.4)	0.774 Ref	0.273	2.196	0.630	6(14) 37(86)	5(8.8) 52(91.2)	1.686 Ref	0.479	5.942	0.416
Notes: $ICU = Intensive$	care unit, O2 =	= oxygen										

Variables	95% C. I for OR			
	Adjusted OR	Lower	Upper	p-value
Age:				
18 – 39				ref
40 – 59	0.876	0.224	3.429	0.850
60 - 75	0.517	0.051	5.281	0.578
Education level:				
Tertiary				ref
Secondary	15.312	3.593	65.256	<0.001
Primary	6.627	0.500	87.751	0.151
Unemployed	6.041	0.798	45.743	0.082
Ventilation history (Yes)	0.127	0.001	17.268	0.410
ICU admission (Yes)	1.595	0.117	21.747	0.726
Oxygen therapy:				
No oxygen Therapy				ref
Oxygen Therapy	7.795	1.558	38.984	0.012
Intubated & ventilated	62.193	0.493	7845.470	0.094
Hypertension (Present)	4.414	0.893	21.815	0.069
Diabetes Mellitus (Present)	5.207	0.651	41.635	0.120
Obesity (Present)	3.752	1.023	13.763	0.046
Hyperlipidemia (Present)	0.124	0.013	1.212	0.073
Duration of oxygen dependency	0.991	0.967	1.016	0.465

Table 4: Multiple	logistic re	egression of	the significa	nt risk factors	s for impaired	cognition pos	st-COVID-19
1		0				0 1	

Notes: OR = Odd ratio; C.I = Confidence interval; ICU = Intensive care unit

DISCUSSION

This study found nearly half of the participants had impaired cognition at both time points. The choice and time of cognitive assessments play a role to the different incidence in previous studies. Rass et al.⁷ examined 135 patients at three months after disease onset using MoCA and found that 23% had impaired cognition, which is lower than our study. Notably, their participants constitute more patients with less severe COVID-19 patients (77%). In contrast, Ferruci et al.²⁵ used 10 neuropsychological batteries and reported a higher incidence of cognitive impairment at 5 months (65%). The use of more extensive assessment batteries may be more sensitive to detect milder cognitive impairments. However, in clinical practice, not all centers have sufficient resources and time to perform the assessment batteries to all patients with COVID-19.

Most extensive neuropsychological batteries are conducted by trained neuropsychologists and Malaysia has a handful of neuropsychologists serving the public and private sector.²⁶ Therefore, the choice of MoCA, which is simpler and reliable to detect mild cognitive impairment were chosen, as in most other studies. In our study, MoCA was administered by doctors and occupational therapists after appropriate training and certification.

While we do not find a reducing trend in our patients with cognitive impairment from three to six months follow-up, other longer-term studies showed otherwise. Hartung *et al.* examined 969 patients between 8 to 12 months after COVID-19 infection and reported a lower incidence of cognitive impairment.²⁷ Ferrucci *et al.* also found that the prevalence of cognitive impairment decreased at one year.²⁵ Since our study is only assessing up till 6 months, we could not ascertain if there is any further improvement beyond that.

In terms of affected cognitive domains, our study found that language was the most impacted, followed by memory and executive function. Sentence repetition was most affected, which also requires good attention function. This is followed by verbal fluency, in which executive function plays a significant role too.²⁸ Although participants could communicate normally, the demands on attention and executive function for the language component of the MoCA might explain the patients' challenges. Cognitive fatigue, which is often seen in post-COVID-19 patients may also add as a contributing factor.²⁹ After three months, there was a significant decrease in the

number of patients with memory and language impairment which is in line with other studies.^{25,28}

In our study, three factors were found to be significantly associated with cognitive impairment which are: history of oxygen therapy (hypoxemia), lower education, and obesity. These factors are in accordance with other studies.^{25,30,31} Respiratory distress in moderate to severe COVID-19 infection leads to hypoxia, especially at the susceptible area of the brain, the hippocampus. This leads to the direct consequence of hypoxic damage to the brain and causes long-lasting cognitive impairment.³²⁻³⁴ Lower education, on the other hand, has an inverse dose-response relation with dementia.³⁵ Thus, a high education level may protect against cognitive decline in COVID-19 patients. The high leptin level in obesity promotes B cell maturation and inhibits antiviral CD8+ T cell response, thus possibly reducing the effective immune response against viral infections.31

We also examined the effect of cognitive impairment with functional outcome. A lower MoCA score was correlated with higher PCFS grade (poorer functional status) at both time periods. This may be the first study to examine the correlation between MoCA and PCFS. Other study has used Functional Independence Measure Cognitive as the functional outcome measure.³⁶ The results from this study highlight the importance of early cognitive impairment detection in COVID-19 patients as it can negatively affect the functional status of the patients.

Our study has a few limitations. Despite the surge of COVID-19 infections, patient recruitment was hampered due to high clinic load and the extended period which the patients had to wait to be seen for cognitive assessment. Therefore, our study sample was slightly less than recommended, which was 100/143. This is also a single-center study and in an urban setting, which may not reflect the Malaysian population. We were also unable to recruit the healthy control group during the pandemic due to the strict Movement Control Order at that time. Despite the limitations, we believe that this study is important as it is the first to establish the incidence of cognitive impairment in our local population, the risk factors, the domains most affected, and the relationship with functional outcome.

In conclusion, post-COVID-19 cognitive impairments were common up to 6 months of illness with the most common domains affected of language, executive function, attention and memory. This study can guide clinicians to perform cognitive screening within the first six months and refer for cognitive rehabilitation, especially in higher-risk patients. Future studies with larger sample sizes are needed to confirm our results and a follow-up of longer than six months to assess the progression of cognitive impairment.

ACKNOWLEDGMENTS

We would like to acknowledge the MDC team and the clinic staff who assisted in the research. We also thank Ms Nurhafida Mohd Daud for her assistance in the MoCA scoring.

DISCLOSURE

Ethics: This study was approved by the University Malaya Medical Center (UMMC) Medical Research Ethics Committee, identification number: 20200831-9030

Financial support: None

Conflict of interest: None

REFERENCES

- Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol* 2020;16(11):636-44. doi:10.1038/s41582-020-0398-3
- Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology* 2020;95(8):e1060-e1070. doi:10.1212/ WNL.000000000009937
- Ermis U, Rust MI, Bungenberg J, et al. Neurological symptoms in COVID-19: a cross-sectional monocentric study of hospitalized patients. Neurol Res Pract 2021;3(1):17. doi:10.1186/s42466-021-00116-1
- Miskowiak KW, Johnsen S, Sattler SM, et al. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. Eur Neuropsychopharmacol 2021;46:39-48. doi:10.1016/j.euroneuro.2021.03.019
- Lindert J, Paul KC, Lachman ME, Ritz B, Seeman TE. Depression-, Anxiety-, and anger and cognitive functions: Findings from a longitudinal prospective study. *Front Psychiatry* 2021;12:665742. doi:10.3389/ fpsyt.2021.665742
- Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry* 2014;27(6):478-83. doi:10.1097/YCO.00000000000106
- Rass V, Beer R, Schiefecker AJ, et al. Neurological outcome and quality of life 3 months after COVID-19: A prospective observational cohort study. Eur J Neurol 2021;28(10):3348-59. doi:10.1111/ene.14803.
- 8. Ferrucci R, Dini M, Groppo E, et al. Long-Lasting

Cognitive Abnormalities after COVID-19. *Brain Sci* 2021;11(2):235. doi:10.3390/brainsci11020235

- Zhou H, Lu S, Chen J, et al. The landscape of cognitive function in recovered COVID-19 patients. J Psychiatr Res 2020;129:98-102. doi:10.1016/j. jpsychires.2020.06.022
- Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort. *Eur J Neurol* 2021; 28(10):3245-53. doi:10.1111/ene.14775
- Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. Brain 2021;144(4):1263-76. doi:10.1093/brain/awab009
- 12. Alemanno F, Houdayer E, Parma A, *et al*. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. *PLoS One* 2021;16(2):e0246590. doi:10.1371/journal.pone.0246590
- Woo MS, Malsy J, Pottgen J, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. Brain Commun 2020;2(2):fcaa205. doi:10.1093/braincomms/fcaa205
- Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G. Neurological and cognitive sequelae of COVID-19: a four month follow-up. *J Neurol* 2021;268(12):4422-8. doi:10.1007/s00415-021-10579-6
- Frontera JA, Yang D, Lewis A, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. J Neurol Sci 2021;426:117486. doi:10.1016/j.jns.2021.117486
- Tavares-Júnior JWL, de Souza ACC, Borges JWP, et al. COVID-19 associated cognitive impairment: A systematic review. *Cortex* 2022;152:77-97. doi:10.1016/j.cortex.2022.04.006
- Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J 2020;56(1):2001494. doi:10.1183/13993003.01494-2020
- Ministry of Health Malaysia. Post COVID-19 management protocol.1st ed. Malaysia. 2021. Available at: https://covid-19.moh.gov.my/garis-panduan/garispanduan-kkm/ANNEX_50_POST_COVID-19_ MANAGEMENT PROTOCOL 12JULY2021.pdf
- Levis B, Benedetti A, Thombs BD. DEPRESsion Screening Data (DEPRESSD) Collaboration. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis [correction in *BMJ* 2019;365:11781]. *BMJ* 2019;365:11476. doi:10.1136/ bmj.11476
- Sherina MS, Arroll B, Goodyear-Smith F. Criterion validity of the PHQ-9 (Malay version) in a primary care clinic in Malaysia. *Med J Malaysia* 2012;67(3):309-15.
- Sun Y, Fu Z, Bo Q, Mao Z, Ma X, Wang C. The reliability and validity of PHQ-9 in patients with major depressive disorder in psychiatric hospital.

BMC Psychiatry 2020;20(1):474. doi:10.1186/ s12888-020-02885-6

- 22. Sidik SM, Arroll B, Goodyear-Smith F. Validation of the GAD-7 (Malay version) among women attending a primary care clinic in Malaysia. *J Prim Health Care* 2012;4(1):5-A1.
- Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-7. https://doi.org/10 .1001/ archinte.166.10.1092
- Ministry of Health Malaysia. Clinical management of confirmed COVID-19 case in adult and paediatric. In: Clinical staging of COVID-19. Malaysia. 2022. Available at: https://covid-19.moh.gov.my/ garis-panduan/garis-panduan-kkm/ANNEX-2E-CLINICAL-MANAGEMENT-OF-CONFIRMED-COVID-19-31052022.pdf
- Ferrucci R, Dini M, Rosci C, et al. One-year cognitive follow-up of COVID-19 hospitalized patients. Eur J Neurol 2022;29(7):2006-14. doi:10.1111/ene.15324
- Ke GN, Beevi Z, Khairudin R, Salem E. Employability of the psychology community in Malaysia. *Jurnal Psikologi Malaysia* 2022;36(1):79-9. Available at: http://journalarticle.ukm.my/19380/1/731-2664-1-PB.pdf
- Hartung TJ, Neumann C, Bahmer T, et al. Fatigue and cognitive impairment after COVID-19: A prospective multicentre study. *EClinicalMedicine* 2022;53:101651.doi:10.1016/j.eclinm.2022.101651
- Hadad R, Khoury J, Stanger C, et al. Cognitive dysfunction following COVID-19 infection. J Neurovirol 2022;28(3):430-7. doi:10.1007/s13365-022-01079-y
- 29. Ortelli P, Ferrazzoli D, Sebastianelli L, et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. J Neurol Sci 2021;420:117271. doi:10.1016/j.jns.2020.117271
- Liu YH, Wang YR, Wang QH, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol Neurodegener* 2021;16(1):48. doi:10.1186/s13024-021-00469-w
- Ho JSY, Fernando DI, Chan MY, Sia CH. Obesity in COVID-19: A systematic review and meta-analysis. *Ann Acad Med Singap* 2020;49(12):996-1008. doi:10.47102/annals-acadmedsg.2020299
- Daroische R, Hemminghyth MS, Eilertsen TH, Breitve MH, Chwiszczuk LJ. Cognitive impairment after COVID-19. A review on objective test data. *Front Neurol* 2021;12:699582. doi:10.3389/ fneur.2021.699582.
- Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care* 2019;23(1):352. doi:10.1186/ s13054-019-2626-z
- 34. Cervós-Navarro J, Sampaolo S, Hamdorf G. Brain changes in experimental chronic hypoxia. *Exp Pathol* 1991;42(4):205-212. doi:10.1016/s0232-1513(11)80067-8
- 35. Ott A, Breteler MM, van Harskamp F, et al.

Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. *BMJ* 1995;310(6985):970-3. doi:10.1136/ bmj.310.6985.970

 Zakharova-Luneva E, Cooke DM, Okano S, Hurst C, Geffen S, Eagles R. The relationship between cognition and functional outcomes in rehabilitation: FIMCog vs. MoCA. *Geriatr Gerontol Int* 2020;20(4):336-42. doi:10.1111/ggi.13884