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Cognitive Impairment and Risk Factors in Post-COVID-19 Hospitalized Patients

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Abstract

Introduction: Numerous reports regarding cognitive deficits after the coronavirus disease 2019 (COVID-19), described as "brain fog," have been published. However, the clinical presentations and risk factors of post-COVID-19 cognitive impairment are controversial. This study aimed to assess (a) the prevalence of cognitive impairment after COVID-19 hospitalization, (b) characteristics of the cognitive deficits, (c) risk factors of post-COVID-19 cognitive impairment, and (d) comparison of cognitive function between post-COVID-19 patients and healthy people. ***Methods:*** The study comprised 34 SARS-CoV-2-infected patients, admitted to the Neurological Institute of Thailand during the peak of COVID-19 pandemic in 2021–2022. These patients came for neuropsychological and clinical evaluations at 2-week follow-up visit. The cognitive impairment and characteristics were measured by TMSE and MoCA. Clinical risk factors and post-COVID-19 cognitive impairment were assessed. The comparison of cognitive function in post-acute COVID-19 patients and 22 healthy controls was also performed. ***Results:*** The prevalence of post-COVID-19 cognitive impairment defined by a total MoCA score below 25 points was 61.76%. Years of education were the only predictive factors related to cognitive impairment. Our multivariate analysis revealed no statistical difference in cognitive outcomes between post-acute COVID-19 patients and healthy controls. ***Conclusion:*** This study showed a moderate prevalence of cognitive dysfunction after COVID-19 hospitalization similar to previous reports. However, there was no significant difference in cognitive measurements between these patients and healthy people. Whether SARS-CoV-2 infection causes cognitive dysfunction is a myth or fact that still has a long way to prove via further longitudinal study.

Introduction

In December 2019, an outbreak of a new emerging disease called "coronavirus disease 2019" (COVID-19) from the infection of coronavirus SARS-CoV-2 occurred. The disease mainly affected the respiratory system, causing influenza-like symptoms and pneumonia. However, numerous studies indicate that it might also affect other systems, including central and peripheral nervous systems [1]. Acute phase of SARS-CoV-2 infection can cause many neurological presentations such as delirium, encephalopathy, and stroke [2, 3].

After acute COVID-19 infection, many reports of ongoing chronic neurological symptoms, especially fatigue, headache, dizziness, pain, and cognitive impairment, were

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released [4, 5]. Consequently, the recent meta-analyses suggested that the presence of cognitive impairment ranged from the acute phase to 7 months after infection [6]. Executive function, working memory, and attention were the most affected cognitive domains that likely exhibited symptoms called "brain fog" [6–11]. There were many hypotheses about the pathophysiology of cognitive impairment after SARS-CoV-2 infection, such as direct viral invasion, hypoxic encephalopathy, metabolic disturbances, systemic inflammation, hypercoagulable state, and abnormality of ACE2 receptor [2, 3, 5]. However, there were controversial findings about the risk factors of post-COVID-19 cognitive dysfunction, and not all studies report the association between hypoxia and the severity of acute COVID-19 with cognitive performance [6]. In addition, there is still a lack of data about inflammatory and hypercoagulable markers in these patients.

From 2020 to 2022, there were many clusters of pandemics in Thailand and overwhelming patients with moderate to severe COVID-19 who needed hospital admission. Then, the information concerning characteristics of post-COVID-19 syndromes is urgently required. Therefore, this study focused on the assessment of prevalence, clinical manifestations, and risk factors of cognitive impairment after COVID-19, which would fulfill a gap in this knowledge.

Materials and Methods

This prospective cohort study examined patients admitted for acute COVID-19 at the Neurological Institute of Thailand, Bangkok, Thailand, from August 2021 to May 2022. During that time, there were delta-variant and omicron-variant waves of COVID-19 epidemic in Thailand. This study included patients aged 18–75 years who were diagnosed with COVID-19 from positive RT-PCR for SARS-CoV-2 infection via nasopharyngeal swabs. Patients must have been admitted to the cohort ward at the Neurological Institute of Thailand, had complete treatment, and were fully recovered from acute COVID-19. Because of the pandemic expansion and local lockdown policy during that time, only patients who could attend on-site follow-up visits after discharge for at least 14 days were enrolled in this study.

The exclusion criteria were patients who (1) had a previous history of central nervous system diseases that may affect cognition such as cerebrovascular diseases, traumatic brain injuries, infectious or inflammatory encephalopathies, and brain tumors; (2) had a previous history of cognitive problems, mild cognitive impairment, or dementia before COVID-19 infection; (3) had severe psychiatric illnesses including major depressive disorders and schizophrenia; (4) had severe visual and hearing impairments that may affect cognitive tests; (5) were unable to communicate in Thai language; and (6) had severe COVID-19 with respiratory failure (because all patients who needed endotracheal intubation and invasive mechanical ventilation would be referred to other hospitals that had respiratory intensive care units).

Patients who were enrolled in this study visited the outpatient neurological clinic at 2 weeks post-hospitalization for clinical and neuropsychological evaluations. Two clinical psychologists (P.S. and T.W.) performed neuropsychological tests, including Thai Mental State Examination (TMSE) [12] and Montreal Cognitive Assessment (MoCA) Thai version [13], which were widely used as standard instruments to measure cognitive function in Thai people. Patients were also evaluated for symptoms and severities of depression and anxiety by Hamilton Depression Rating Scale (HAM-D) [14] and Hamilton Anxiety Rating Scale (HAM-A) [15], respectively. Then, neurologists (J.K.) examined these patients for clinical signs and symptoms of post-acute COVID-19 and provided appropriate management for these conditions.

TMSE is one of the standard cognitive screening tools in Thailand. The test has a total score of 30 points and composes of the following six cognitive domains: orientation (6 points); registration by 3-item encoding (3 points); attention by days recitation backward (5 points); calculation by serial-7 subtraction (3 points); language including 2-item naming, one-sentence repetition, 3-step verbal comprehension, reading comprehension, house copying, and abstract-thinking tests (10 points); and recall of the memory of 3 items (3 points). The total cut-off score for cognitive impairment is below 24 points [12].

MoCA Thai version is a one-page 30-point test and composes of the following 6 cognitive domain tasks: executive function including modified trail making part B, phonemic fluency, and 2-item verbal abstraction (4 points); visuospatial abilities including clock drawing and cube copying (4 points); short-term memory that is the recall of 5 nouns after 5 min (5 points); language including three animal naming and two sentence repetition (5 points); attention and working memory including tapping vigilance, serial-7 subtraction, digit span forward, and digit span backward (6 points); and orientation to time and place (6 points). A total score below 25 points is considered abnormal [13].

The prevalence of post-COVID-19 cognitive impairment was retrieved from these tests. Since sensitivity to detect mild cognitive impairment of MoCA was higher than TMSE, this study would specify patients with cognitive impairment by total MoCA score below 25 points at 2-week follow-up visits.

Later, the comparison between clinical risk factors and post-COVID-19 cognitive impairment was assessed. The patients' baseline characteristics were retrieved from in-patient admission data, including gender, age, years of education, occupation, body mass index, underlying diseases, history of alcohol and smoking, and family history of dementia. Then, the clinical manifestations, treatments, and investigations were assessed from medical records as follows: initial symptoms of COVID-19, vital signs, lowest oxygen saturation, respiratory and neurological signs, initial chest film, onset and duration of hospital admission, data about oxygen therapy (high-flow nasal cannula [HFNC] or normal nasal cannula), medications, initial investigation results (CBC, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, glucose, hemoglobin A1C, uric acid), and highest inflammatory and coagulation markers (D-dimer, INR, high-sensitivity C-reactive protein, lactate dehydrogenase, and procalcitonin levels).

Eventually, the comparison of cognitive function between post-acute COVID-19 patients and normal healthy patients was performed. Healthy volunteers without a history of COVID-19 infection were recruited between January 2022 and June 2022. The healthy controls were patients who visited the Neurological Institute of Thailand for peripheral neurological problems, such as peripheral neuropathies, compressive neuropathies, and degenerative spine diseases. People with a history of baseline cognitive impairment or central nervous system diseases would be excluded from the control groups. All enrolled patients would be tested with TMSE, MoCA, HAM-D, and HAM-A tests as same as post-COVID-19 patients.

Demographics, clinical characteristics, and prevalence of cognitive impairment were evaluated using descriptive statistics. For the evaluation of risk factors and cognitive dysfunction, all post-COVID-19 patients were dichotomized into two groups (cognitive-impaired and cognitive-unimpaired groups) using MoCA total score below 25 as a cut-off. The baseline demographic, COVID-19 clinical characteristics, oxygen treatment, medications, and laboratory data were then compared between these groups in the univariate analysis. Then, the multivariate analysis would be performed with a binary logistic regression model to adjust the associated factors with gender, age, and education levels (three factors that normally affected the cognitive measurement) as covariates. For the assessment of cognitive functions between post-COVID-19 patients and healthy controls, the univariate comparison of total score and sub-score of TMSE, MOCA, HAM-D, and HAM-A was measured. Lastly, the multivariate analysis with a binary logistic regression model would be calculated with gender, age, and education as covariates.

All categorical variables were analyzed with a Fisher's exact test. Two-sample continuous variables were analyzed using an independent sample *t* test and Mann-Whitney U test for parametric and nonparametric variables, respectively. The cut-off for statistical significance was a p value <0.05. Statistical analysis was performed using SPSS software for Windows version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic Data

As shown in Table 1, a total number of 34 patients were enrolled from August 2021 to May 2022. There were 13 male and 21 female patients with a mean age of 50.18 ± 14.40 years. The median length of education was 12 years (IQR 10). There was no family history of dementia in these patients. From the admission data, variable symptoms of COVID-19 were found, in which upper respiratory symptoms (cough and rhinorrhea) and unspecific viral syndrome (fever, myalgia, and headache) were the most common presentations. Pneumonia was found in the chest film of 13 patients (38.24%). Only 8 patients (23.53%) had a history of hypoxemia (oxygen saturation in room air <95%) requiring additional oxygen supplementation (4 patients with HFNC and 4 patients with only normal nasal cannula). At the follow-up visits, the most common post-COVID-19 somatic symptom was dyspnea (30.30%), and the most common neuropsychiatric symptoms were memory problems (27.27%) and concentration impairment (18.18%). However, most patients did not complain about neuropsychological symptoms (60.60%).

Prevalence and Clinical Characteristics of Cognitive Impairment

Post-acute COVID-19 neuropsychological test results are described in Table 2. The median time of cognitive measurement at the first follow-up visit was 18.5 days (IQR 12) after hospital discharge. The median total TMSE score was 28 points (IQR 3), and only 1 patient had a TMSE score below 24 points. The median total MoCA score was 23 points (IQR 6). When using the cut-off with a total MoCA score below 25 points, 21 patients (61.76%) would have cognitive impairment at follow-up visits. The most affected cognitive domains were executive function, short-term memory, and visuospatial function, whereas language, attention, and orientation had relatively normal scores.

Risk Factors of Post-Acute COVID-19 Cognitive Impairment

As shown in Table 1, a comparison of clinical factors was performed between the cognitive-impaired group (21 patients) and the cognitive-unimpaired group (13 patients). There were equal genders and underlying metabolic diseases between both groups. However, the cognitive-impaired group was older (means 55.24 ± 12.32 vs. 42.00 ± 14.16 years; p value = 0.007) and had a lower year of education (median 7 years (IQR 8) versus 16 (IQR 3) years; p value <0.001) than the normal cognitive group. Loss of taste seemed to be found more on the cognitive-unimpaired side (p value = 0.048) but with a small number of patients. Two cognitively impaired patients had acute confusion in their first COVID presentation, but it did not reach statistical significance (p value = 0.513). Other manifestations were the same for both groups. All laboratory data, including inflammatory and coagulation markers, were also similar except for higher direct bilirubin levels in impaired patients (median: 0.115 [IQR 0.0550] versus 0.075 (IQR 0.0625) mg/dL; p value = 0.027). Notably, there was no difference in treatment modalities between these patients. Although 4 patients with severe hypoxemia who required oxygen therapy with HFNC belonged to the cognitive-deficit group, the association did not reach statistical significance (p value = 0.144).

Table 1. Demographic data and comparison of risk factors and post-COVID-19 cognitive impairment

Data	Cognitive impairment (n = 21)	Cognitive normal (n = 13)	Total (n = 34)	p value
Male gender, n (%)	8 (38.10)	5 (38.46)	13 (38.24)	1.00
Age, years, mean ± SD	55.24±12.32	42.00±14.16	50.18±14.40	0.007#
Education, years, median (IQR)	7 (8)	16 (3)	12 (10)	<0.001*
BMI, kg/m^2, mean ± SD	24.11±4.40	23.60±2.62	23.91±3.78	0.707
Underlying diseases, n (%)				
Hypertensio	10 (47.62)	4 (30.77)	14 (41.18)	0.477
Diabetes mellitus type 2	4 (19.05)	1 (7.69)	5 (14.71)	0.627
Dyslipidemia	6 (28.57)	4 (30.77)	10 (29.41)	1.00
Presenting symptoms of COVID-19, n (%)				
Unspecific viral syndrome	12 (57.14)	9 (69.23)	21 (61.76)	0.718
Cough and rhinorrhea	20 (95.24)	11 (84.62)	31 (91.18)	0.544
Dyspnea and chest pain	5 (23.81)	3 (23.08)	8 (23.53)	1.00
Anosmia	3 (14.29)	5 (38.46)	8 (23.53)	0.211
Ageusia	0 (0)	3 (23.08)	3 (8.82)	0.048#
Gastrointestinal symptoms	4 (19.05)	1 (7.69)	5 (14.71)	0.627
Clinical information in admission				
Dyspnea at presentation, n (%)	5 (23.81)	1 (7.69)	6 (17.65)	0.370
Confusion, n (%)	2 (9.52)	0 (0)	2 (5.88)	0.513
Pneumonia in chest film, n (%)	9 (42.86)	4 (30.77)	13 (38.24)	0.718
Duration of symptom, days, median (IQR)	4 (4)	3 (4)	3.5 (4)	0.727
Length of stay, days, median (IQR)	15 (5)	14 (6)	15 (5)	0.148
Hypoxemia (SpO_2 < 95%), n (%)	5 (23.81)	3 (23.08)	8 (23.53)	1.00
Laboratory investigations				
Complete blood count (initial)				
WBC, 1,000 cell/cu.mm, median (IQR)	6.035 (1.420)	5.705 (1.725)	6.000 (1.650)	0.291
Hemoglobin, g/dL, median (IQR)	12.55 (2.70)	13.80 (2.55)	13.05 (2.75)	0.058
Hematocrit, %, mean±SD	38.36±5.42	40.82±4.79	39.28±5.26	0.164
Platelet, 1,000 cell/cu.mm, mean±SD	244.40±76.70	217.17±65.51	234.19±72.86	0.314
Clinical chemistry (initial)				
BUN, mg/dL, mean±SD	12.55±3.79	10.92±2.81	11.94±3.50	0.206
Cr, mg/dL, median (IQR)	0.730 (0.4350)	0.755 (0.1625)	0.745 (0.2700)	0.954
AST, U/L, median (IQR)	30.50 (10)	31.00 (24)	30.50 (18)	0.803
ALT, U/L, median (IQR)	32.50 (29)	24.50 (37)	30.00 (31)	0.307
Total bilirubin, mg/dL, median (IQR)	0.430 (0.29)	0.455 (0.21)	0.430 (0.23)	0.365
Direct bilirubin, mg/dL, median (IQR)	0.115 (0.0550)	0.075 (0.0625)	0.100 (0.0700)	0.027#
Glucose, mg/dL, median (IQR)	103.50 (26)	96.00 (16)	104 (25)	0.985
HbA1C, %, mean±SD	6.07±0.72	6.26±0.61	6.13±0.68	0.507
Uric acid, mean±SD	5.41±1.58	4.40±1.39	5.12±1.52	0.078
Inflammatory and coagulation markers (highest)				
D-dimer, ng/mL	453 (2069)	492 (336)	473 (775)	0.578
High-sensitivity C-reactive protein, mg/dL	19.26 (34.5000)	21.59 (28.5625)	21.24 (28.9000)	0.927
LDH, U/L	183 (54)	210 (106)	200 (61)	0.269
Procalcitonin, ng/mL	0.040 (0.05)	0.025 (0.02)	0.030 (0.04)	0.255
Treatment of COVID-19				
Oxygen HFNC, n (%)	4 (19.05)	0 (0)	4 (11.76)	0.144
Duration of HFNC, days, median (IQR)	11.5 (13)	–	11.5 (13)	–
Maximum FiO_2, median (IQR)	0.575 (0.26)	–	0.575 (0.26)	–
Maximum airflow, LPM, median (IQR)	50 (15)	–	50 (15)	–
Titrate to nasal cannula, days, median (IQR)	9 (10)	–	9 (10)	–
Nasal cannula, n (%)	1 (4.76)	3 (23.08)	4 (11.76)	0.274
Duration of nasal cannula, days, median (IQR)	4 (0)	4 (0)	4 (5)	1
Maximum airflow, LPM, median (IQR)	3 (0)	3 (0)	3 (1)	1

Table 1 (continued)

Data	Cognitive impairment (n = 21)	Cognitive normal (n = 13)	Total (n = 34)	p value
Medications, n (%)				
Favipiravir	21 (100)	12 (92.31)	33 (97.06)	0.382
Remdesivir	1 (4.76)	0 (0)	1 (2.94)	1.00
Lopinavir/ritoniavir	6 (28.57)	2 (15.38)	8 (23.53)	0.444
Oral steroid	6 (28.57)	4 (30.77)	10 (29.41)	1.00
Intravenous high dose steroid	5 (23.81)	4 (30.77)	9 (26.47)	0.704
Antibiotics	5 (23.81)	2 (15.38)	7 (20.59)	0.682
Tocilizumab	1 (4.76)	0 (0)	1 (2.94)	1.00
Infliximab	1 (4.76)	0 (0)	1 (2.94)	1.00
Clinical assessment at follow-up (33 patients)[b]				
Post-COVID general symptoms, n (%)				
Fatigue	3 (15)	1 (7.69)	4 (12.12)	1.00
Dyspnea	9 (45)	1 (7.69)	10 (30.30)	0.054
Cough	3 (15)	3 (23.08)	6 (18.18)	0.643
Chest pain	1 (5)	0 (0)	1 (3.03)	1.00
Pain and paresthesia	5 (25)	2 (15.38)	7 (21.21)	1.00
Dizziness	0 (0)	1 (7.69)	1 (3.03)	0.364
Insomnia	4 (20)	2 (15.38)	6 (18.18)	1.00
Others	3 (15)	5 (38.46)	8 (24.24)	0.106
No symptoms	4 (20)	4 (30.77)	8 (24.24)	0.420
Post-COVID neuropsychological symptoms, n (%)				
Memory impairment	7 (35)	2 (15.38)	9 (27.27)	0.429
Attention deficit	2 (10)	4 (30.77)	6 (18.18)	0.159
Executive dysfunction	0 (0)	2 (15.38)	2 (6.06)	0.125
Language dysfunction	1 (5)	0 (0)	1 (3.03)	1.00
Impaired social cognition	0 (0)	1 (7.69)	1 (3.03)	0.364
Anxiety	1 (5)	3 (23.08)	4 (12.12)	0.125
Depression	1 (5)	1 (7.69)	2 (6.06)	1.00
Apathy	1 (5)	0 (0)	1 (3.03)	1.00
Agitation and aggression	0 (0)	2 (15.38)	2 (6.06)	0.125
Others, n (%)	2 (10)	0 (0)	2 (6.06)	0.523
No symptom, n (%)	13 (65)	7 (53.85)	20 (60.6)	1.00
HAM-A (points), median (IQR)	2 (3)	8 (8)	3 (6)	0.007[a]
HAM-D (points), median (IQR)	2 (4)	2 (4)	2 (4)	1.00

Frequency data are expressed as number (%), continuous data with normal distribution are expressed as mean ± SD, continuous data with non-normal distribution are expressed as median (IQR), and p value indicates probability in a comparison between the cognitive-impairment group and the cognitive-normal group. BMI, body mass index; HFNC, high-flow nasal cannula; LPM, liters per minute; FiO_2, fraction of inspired oxygen; SpO_2, oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; HAM-D, Hamilton Dementia Rating Scale; HAM-A, Hamilton Anxiety Rating Scale. *Statistically significant difference at p value <0.05 in both univariate and multivariate analyses. [a]Statistically significant difference at p value <0.05 in only univariate analysis. [b]Clinical assessment at follow-up had 1 missing patient's data from cognitively normal group.

During the patients' first visit after hospitalization, those with cognitive deficits demonstrated a tendency to report dyspnea symptoms more frequently, even if this difference did not reach statistical significance (p value = 0.054). Both groups displayed similar rates of neuropsychological symptoms. While higher levels of anxiety were frequently found more in normal cognitive patients measured by HAM-A (median of cognitive impaired group 2 (IQR 3) versus cognitive unimpaired group 8 (IQR 8) points; p value = 0.007), depression rates were

Table 2. Neuropsychological test result in post-acute COVID-19 patients

Cognitive data	Cognitive impairment (n = 21)	Cognitive normal (n = 13)	Total (n = 34)
Length after COVID-19, days, median (IQR)	18 (10)	19 (14)	18.5 (12)
TMSE total score (points), median (IQR)	27 (4)	28 (2)	28 (3)
Cognitive deficit by TMSE (<24), *n* (%)	1 (4.76)	–	1 (2.94)
Orientation (points), median (IQR)	6 (0)	6 (0)	6 (0)
Registration (points), median (IQR)	3 (0)	3 (0)	3 (0)
Attention (points), median (IQR)	5 (0)	5 (0)	5 (0)
Calculation (points), median (IQR)	2 (2)	3 (1)	2.5 (1)
Language (points), median (IQR)	9 (2)	9 (1)	9 (2)
Naming (points), median (IQR)	2 (0)	2 (0)	2 (0)
Sentence repetition (points), median (IQR)	1 (0)	1 (0)	1 (0)
Comprehension (points), median (IQR)	3 (1)	3 (0)	3 (0)
Reading (points), median (IQR)	1 (0)	1 (0)	1 (0)
Figure copying (points), median (IQR)	1 (1)	1 (1)	1 (1)
Abstract (points), median (IQR)	1 (1)	1 (0)	1 (0)
Recall (points), median (IQR)	2 (3)	3 (1)	2 (2)
MoCA total score (points), median (IQR)	20 (4)	26 (2)	23 (6)
Cognitive deficit by MoCA (<25), *n* (%)	21 (100)	-	21 (61.76)
Executive functions (points), median (IQR)	1 (2)	2 (2)	2 (2)
Verbal fluency (words), median (IQR)	6 (5)	10 (7)	8 (6)
Visuospatial functions (points), median (IQR)	2 (2)	4 (1)	2.5 (3)
Short-term memory (points), median (IQR)	3 (2)	4 (2)	3 (2)
Language (points), median (IQR)	3 (1)	5 (1)	4 (2)
Attention and working memory (points), median (IQR)	5 (2)	6 (0)	6 (1)
Orientation (points), median (IQR)	6 (0)	6 (0)	6 (0)
HAM-A (points), median (IQR)	2 (3)	8 (8)	3 (6)
Normal (0–13), *n*	20	12	32
Mild anxiety (14–17), *n*	1	0	1
Moderate anxiety (18–24), *n*	0	1	1
Severe anxiety (>24), *n*	–	–	0
HAM-D (points), median (IQR)	2 (4)	2 (4)	2 (4)
Normal (0–7), *n*	21	12	33
Mild depression (8–17), *n*	0	1	1
Moderate depression (18–24), *n*	–	–	0
Severe depression (>24), *n*	–	–	0

Frequency data are expressed as number (%); continuous data are expressed as median (IQR). TMSE, Thai Mental State Examination; MoCA, Montreal Cognitive Assessment; HAM-D, Hamilton Dementia Rating Scale; HAM-A, Hamilton Anxiety Rating Scale.

similar for both sides from HAM-D scores (median 2 (IQR 4) versus 2 (IQR 4) points; p value = 1.000).

Finally, multivariate analysis was performed using a binary logistic regression model, comparing between significant factors and cognitive impairment after COVID-19. The covariates included gender, age, education, ageusia at first presentation, direct bilirubin level at admission, and HAM-A score in follow-up visits. Only years of education were related to the cognitive deficit (OR: 0.654, 95% CI: 0.434–0.985; p value = 0.042). Clinical characteristics, inflammatory and coagulation markers, oxygen therapy, and medications did not correlate with post-acute COVID-19 cognitive impairment. Age and HAM-A scores also did not associate with cognitively impaired patients (p value = 0.543 and p value = 0.429, respectively).

Comparison of Cognitive Status between COVID-19 Patients and Healthy Controls

As shown in Table 3, between January 2022 and June 2022, 22 healthy volunteers without prior history of COVID-19 infection were recruited. There were seven

Table 3. Comparison of cognitive impairment between COVID-19 patients and healthy controls

Data	COVID-19 patients (n = 34)	Healthy controls (n = 22)	p value
Male gender, n (%)	13 (38.24)	7 (31.82)	0.777
Age, years, median (IQR)	54.5 (21)	52.5 (29)	0.913
Education, years, median (IQR)	12 (10)	16 (5)	0.008*
Cognitive measurement			
TMSE total score (points), median (IQR)	28 (3)	28 (2)	0.221
Orientation (points), median (IQR)	6 (0)	6 (0)	0.707
Registration (points), median (IQR)	3 (0)	3 (0)	0.754
Attention (points), median (IQR)	5 (0)	5 (0)	0.251
Calculation (points), median (IQR)	2.5 (1)	3 (1)	0.34
Language (points), median (IQR)	9 (2)	9 (1)	0.73
Recall (points), median (IQR)	2 (2)	3 (1)	0.245
MoCA total score (points), median (IQR)	23 (6)	25.5 (4)	0.036*
Cognitive deficit by MoCA (<25), n (%)	21 (61.76)	8 (36.36)	0.100
Executive functions (points), median (IQR)	2 (2)	2 (2)	0.132
Verbal fluency (words), median (IQR)	8 (6)	8.5 (5)	0.458
Visuospatial functions (points), median (IQR)	2.5 (3)	3 (2)	0.258
Short-term memory (points), median (IQR)	3 (2)	3.5 (2)	0.413
Language (points), median (IQR)	4 (2)	5 (1)	0.024*
Attention and working memory (points), median (IQR)	6 (1)	6 (1)	0.617
Orientation (points), median (IQR)	6 (0)	6 (0)	0.251
HAM-A (points), median (IQR)	3 (6)	6 (3)	0.105
HAM-D (points), median (IQR)	2 (4)	2 (3)	0.706

Frequency data are expressed as number (%); continuous data are expressed as median (IQR). TMSE, Thai Mental State Examination; MoCA, Montreal Cognitive Assessment; HAM-D, Hamilton Dementia Rating Scale; HAM-A, Hamilton Anxiety Rating Scale. *Statistically significant difference at p value <0.05 in univariate analysis.

males (31.82%) with a median age of 52.5 years (IQR 29) and a median of 16 years of education (IQR 5). The education levels were different between patients and healthy controls (p value = 0.008), whereas gender (p value = 0.777) and age (p value = 0.913) were the same. The total TMSE score was even in both groups (median 28 [IQR 3] versus 28 [IQR 2] points; p value = 0.221). However, the total MoCA score seemed to be lower in COVID-19 patients compared to healthy persons (median 23 [IQR 6] versus 25.5 [IQR 4]; p value = 0.036). The prevalence of cognitive impairment was higher in patients than normal controls but did not reach statistical significance (61.76% vs. 36.36%; p value = 0.100). Regarding cognitive subtests, language was the only distinct domain between both groups (median score 4 (IQR 2) versus 5 (IQR 1); p value = 0.024). Anxiety and depression rates were also nearly equal in HAM-A and HAM-D scores.

A binary logistic regression model was used to conduct multivariate analysis. The outcomes were classified into cognitive-impaired and cognitive-unimpaired groups based on MoCA total score <25 points. The association between the history of COVID-19 and cognitive impairment was examined while accounting for gender, age, and education as covariates. In summary, there was no statistically significant correlation between post-acute COVID-19 and cognition (p value = 0.583).

Discussion

This study determined that the prevalence of cognitive impairment assessed in patients evaluated after COVID-19 was 61.76%. The only predictive factor related to cognitive impairment was years of education. Furthermore, when compared between post-acute COVID-19 patients and healthy controls, there was no significant difference in cognitive outcome at a median of 18.5 days after SARS-CoV-2 infection.

The recent meta-analysis, including many cohort studies, showed a high prevalence of cognitive impairment in post-COVID-19 patients, ranging from 54% in patients with moderate illness to 65% in moderate-to-severe

patients [6]. There are also some considerations regarding the instruments used for cognitive assessment. The utilization of TMSE and MoCA, which are easy to perform and appropriate for clinical practice, are the most encouraged tools for cognitive screening in post-COVID-19 follow-up visits. However, previous studies have shown that MoCA may be a better tool to detect mild cognitive impairment, especially in executive function, while TMSE might be more helpful in identifying severe impairment [16]. The prevalence of post-COVID-19 cognitive dysfunction in our study is approximate to other studies when using the MoCA Thai version.

The pathophysiology underlying the cognitive impairment after COVID-19 remains unclear. In non-COVID-19 critically ill patients, there is a higher prevalence of delirium in the hospital and a subsequent higher prevalence of cognitive dysfunction among survivors of acute respiratory distress syndrome [8]. Therefore, the finding assumes that hypoxemia may be crucial in this event. However, not all studies report the association between the severity of respiratory symptoms and hypoxia with post-COVID-19 cognitive function [6]. In our study, only 8 patients had hypoxemia and needed oxygen supplementation, but there was no correlation with cognitive impairment. The limitation of a small number of hypoxemic patients may be considered in this result.

Other mechanisms that may relate to cognitive dysfunction are inflammation and a hypercoagulable state. The first report of COVID-19 related to neurological manifestations found that many patients with neurological complications had higher C-reactive protein and D-dimer [1]. The study from a mouse model found that SARS-CoV-2 could lead to neuroinflammation and subsequent brain damage through microglia activation [17]. The study from UK Biobank also identified a greater reduction in global brain size among SARS-CoV-2 cases [18]. However, previous studies reported conflicted results regarding the association between these clinical biomarkers and cognitive symptoms [6–9, 11]. Our study did not find any laboratory markers related to post-COVID-19 cognitive impairment in multivariate analysis.

The level of education seems to be the only predictive factor for post-acute COVID-19 cognitive symptoms in our research. Although education is well known to be one of the main confounding factors in neuropsychological assessment (other than gender and age) [19], on the other hand, it cannot be cut out that lower education might be the "real" risk factor of cognitive deterioration after COVID-19 infection. As we know that less education is one of the early life factors that negatively affect the cognitive reserve [20]. Therefore, people with a high cognitive reserve may cope with the cognitive decline better in the presence of degenerative neuropathology, while people with less education may not [21]. Therefore, this may suggest that patients with low education could be the main target for cognitive follow-up due to their potential risk of developing mental deterioration after COVID-19.

Although the total MoCA scores of post-COVID-19 patients were lower than normal controls in univariate analysis, the multivariate analysis did not find a statistically significant difference in cognitive function between both groups. The higher education level in the healthy control group might be the possible reason for our outcome. This finding may contrast with other large studies that found worsened cognitive function in post-COVID-19 patients, but there could be many explanations for the result. There have been many cohort studies and systematic reviews about post-COVID-19 cognitive problems since the start of the global pandemic in 2020. The meta-analysis by Crivelli et al. [6] from a subgroup of five studies with 290 participants showed a difference in MoCA score between post-COVID-19 patients versus controls. However, there were many variations in study designs, such as surveys in hospital or community settings. There were also scattered outcomes of the MoCA score in each study, and even the largest study did not find cognitive differences in MoCA total score. Several studies in the systematic review had no control group to compare and used scores below cut-off values to present a cognitive impairment. Subsequently, this might be disturbed by age and educational biases from the study population. The scant amount of longitudinal studies and the limited assessment of specific cognitive domains could also be considered [6, 16]. Many patients also had baseline psychiatric conditions that could mimic cognitive decline, especially attention and working memory [7–9]. Lastly, the lack of baseline neuropsychological assessment in most study populations makes it unable to conclude that COVID-19 is the main cause of cognitive impairment. Because many patients might have had preexisting dementia before the infection, in this situation, COVID-19 may be like any other infection or critical illness that could aggravate their old cognitive dysfunction. Whether SARS-CoV-2 infection causes neurodegenerative dementia is a myth or fact that still has a long way to prove via long-term studies for more than 5–10 years that are yet to come.

To our knowledge, this research is the first published study in Thailand about post-acute COVID-19 cognitive impairment and risk factors. The main strength of this study is that we performed the face-to-face follow-up visit after COVID-19 hospitalization with paper-and-pencil

neuropsychological assessment and clinical examinations. Therefore, we were able to assess many predictive factors from hospital data that may affect cognitive function after SARS-CoV-2 infection. We also had the comparison of cognitive tests between patients and healthy controls that not only used standard cut-off to measure. Lastly, we performed a multivariate analysis to reiterate that all confounding factors would be counted in the final analysis.

Our study has some limitations. First, due to the long pandemic period of COVID-19 in Thailand from 2021 to 2022, we can only include small numbers of patients for cognitive follow-up visits. Second, it was also inconvenient for patients during the lockdown period to visit the hospital frequently, then there was a lack of longitudinal data from these patient groups. Third, although TMSE and MoCA are the standard cognitive screening tests in clinical practice, they still miss the information about specific cognitive domains, which may need more formal neuropsychological batteries that are more time-consuming. Fourth, this information came from only a single neurological hospital and might need more data from multi-center studies in the future. Finally, patients with severe respiratory failure that required intubation were not included in this study, so we might not have enough assessment of patients with severe COVID-19 that tended to have more neurological complications.

Conclusion

This study found a moderate prevalence of cognitive dysfunction after COVID-19 hospitalization, like many other previous studies. The lower year of education is the main strong risk factor for cognitive impairment after COVID-19 infection. However, when compared between post-acute COVID-19 patients and healthy controls, there was no significant difference between cognitive outcomes in both groups. Further longitudinal studies with larger participants in Asian populations are needed to comprehensively assess the long-term neuropsychological functions after COVID-19.

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Statement of Ethics

The study was reviewed and approved by the Institutional Review Boards of the Neurological Institute of Thailand (Research No. 64051). All participants provided written informed consent before study participation. The study was conducted according to Thai and international ethical and privacy laws, which followed the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

All the authors contributed to the manuscript writing and revised and approved the final draft. The work was designed by J.K. Data were collected by J.K., P.S., and T.W. Statistics was performed by J.K. and S.A. The manuscript was supervised and edited by A.R. and S.A.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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