Original Article

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Correlation between Acute Phase Symptoms with Neurological Long Covid Symptoms on COVID-19 Survivors

Ahmad Rizal Ganiem, Siuliyanty, Anam Ong, Uni Gamayani, Lisda Amalia, Yusuf Wibisono

Department of Neurology, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

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Correspondence:
Ahmad Rizal Ganiem,
Department of Neurology
Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.
Email: rizalbdg@gmail.com

Abstract

Objective: To investigate prolonged neurological impacts of COVID-19 and establish a connection between initial COVID-19 symptom severity and chronic fatigue syndrome (CFS) development, poor sleep quality (PSQ), and cognitive impairment (CI) in individuals recovered from COVID-19.

Methods: This cross-sectional study recruited COVID-19 survivors at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, between June and December 2021. All participants gave informed consent and underwent interviews on demography, clinical features, long-COVID questionnaire, and neurological examination. Participants underwent cognitive examination (MOCA-INA), Chalder Fatigue Scale and Pittsburgh Sleep Quality Index (PSQI) to assess CI, CFS, and PSQ variables. Chi-Square analysis was performed to determine the probability of neurological long COVID-19 syndrome manifestations using SPSS 24.0.

Results: Of the 127 participants recruited, 67.7% were women, median (IQR) age of 33 (21–65) years, and time from hospitalization to examination of nine months (1–13). The most common neurological Long COVID symptoms were PSQ (59.8. %), CFS (51.2%), and CI (33.9%). Participants with more than five acute phase COVID-19 symptoms had a higher probability of CFS and CI (OR 2.38 (1, 16-4.9, CI 95%); OR 2.20 (1.01-4.79, CI 95%)) than those with less than five symptoms. The study did not find a significant correlation between sleep quality and number of acute-phase COVID-19 symptoms (OR 1.56 (0.76-3.20, CI 95%)).

Conclusion: Almost two-thirds of the COVID-19 survivors experienced PSQ, more than half had CFS, and almost one-third had CI. The study revealed an increasing likelihood of CFS and CI in COVID-19 survivors as the number of acute COVID-19 symptoms increases.

Keywords: Chronic fatigue syndrome, cognitive impairment, long covid, poor sleep quality

Introduction

The COVID-19, also known as Coronavirus Disease-19, is an illness caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Initially identified in Wuhan, China, in 2019, it rapidly spread to numerous countries, leading the need for the World Health Organization (WHO) to declare a pandemic in early 2020. While the respiratory tract is primarily affected by this disease, it can also have an impact on various other organs, including both the central and peripheral nervous systems.[1] According to the World Health Organization (WHO) data available until May 2021, the global number of confirmed COVID-19 cases stood at 159 million, with a reported death toll of 3.3 million, resulting in a fatality rate of 2.1%. In the case of Indonesia, the COVID-19 death rate

was higher than the global average, reaching 2.7%.[2,3] The full range of health outcomes related to COVID-19 is still not completely understood. However, approximately 35% of individuals who have recovered from COVID-19 report not fully returning to their pre-illness state within 2–3 weeks after being declared cured. In cases where individuals have experienced severe pneumonia as a result of COVID-19, it may take six months or even longer for their breathing to return to normal. Furthermore, this prolonged disability can also affect the functioning of the heart and brain.[1,4] In neurology, many COVID-19 survivors report fatigue, sleep disturbances, and cognitive impairment symptoms. Patients with cognitive impairment tend to describe complaints of "brain fog," causing behavioural fluctuations that can be frustrating for patients and healthcare professionals and fatigue. This situation is called "Long COVID." An additional factor to consider is whether, in the long term, chronic subclinical inflammation can lead to accelerated aging both peripherally and as a neurodegenerative process. [4]

The exact cause of "Long COVID" is still not fully understood, but it is believed to involve potential cellular damage caused by the virus itself and the ongoing production of inflammatory cytokines by the immune system, even after the virus is no longer present. Emerging evidence has suggested that COVID-19 patients with Long COVID may experience brain injury, which aligns with the virus's ability to infect the central nervous system (CNS). However, the clinical manifestations, frequency of CNS effects, and specific mechanisms underlying the neurological damage caused by SARS-CoV-2 infection are not well-established and require further research. Therefore, the objective of this study was to provide an overview of the long-term neurological effects and explore the relationship between the number of acute-phase COVID symptoms and Long COVID symptoms in survivors of COVID-19.

Methods

This cross-sectional study was conducted at the Neurology Outpatient Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between January – June 2022. We invited survivors of COVID-19 infection who had been hospitalized in this hospital during the period of June–December 2021. Inclusion criteria were (1) aged 18 to 65 years, (2) had confirmed COVID-19 infection based on the result of the reverse transcription real-time polymerase chain reaction (RT-PCR) from nasal swabs, (3) had recovered from COVID-19, either confirmed negative by RT-PCR from nasal swabs, or had undergone mandated isolation period for a minimum of 14 days, (4) had undergone at least grade 3 Elementary School, (5) domiciled in the city of Bandung and its surroundings and (6) willing to complete questionnaires. Subjects with previous medical history (stroke, diabetes, cardiovascular disease, sleep disorder, and psychological disorders) were excluded from the study. The research ethical approval was obtained from the ethics committee of Hasan Sadikin Hospital (ethical clearance number: LB.02.01/X.6.5/231/2021). Global function examination with the Montreal Cognitive Assessment Indonesia (MoCA-Ina) is the value obtained by adding up all existing domains with a score range of 0-30, then grouped based on cognitive scores.[5] The questions examined the followings: visuospatial, executive function, naming, memory, attention, delayed recall, language, abstraction, and orientation, and the measurement scale obtained is in the form of a categorical (ordinal) scale. Value of 24 or more is considered normal. Fatigue was evaluated by utilizing the Chalder Fatigue Scale (CFQ-11) survey, which consisted of 11 questions rated on a scale of 0 to 3.[6] The responses from these questions were combined to calculate a comprehensive score ranging from 0 to 33, with higher scores indicating more severe symptoms. The questionnaire also included two subcategories of physical exhaustion that comprised of seven items with a potential score range of 0 to 21 and mental exhaustion, consisting of four items with a possible score range of 0 to 12. The Chalder Fatigue Scale (CFQ-11) offers an alternative scoring method called the bimodal score, where each item response is divided into two categories: 0 (0–1) or 1 (2–3). These scores are then summed up to create a scale ranging from 0 to 11. Typically, the fatigue case status, distinguishing between feeling tired or not tired, was determined using this scale. The conventional threshold for categorization was set at a score of <4 for not tired and 4 or above for feeling tired. Each participant fulfilled the Indonesian Version of Pittsburgh Sleep Quality Index (PSQI, Cronbach's alpha of 0.79) to assess the sleep quality in patients over a 1-month period. PSQI consists of 19 questions, which include sleep latency, duration, efficiency, disturbances, use of sleeping medication, and daytime dysfunction.[7] The questionnaire requires the

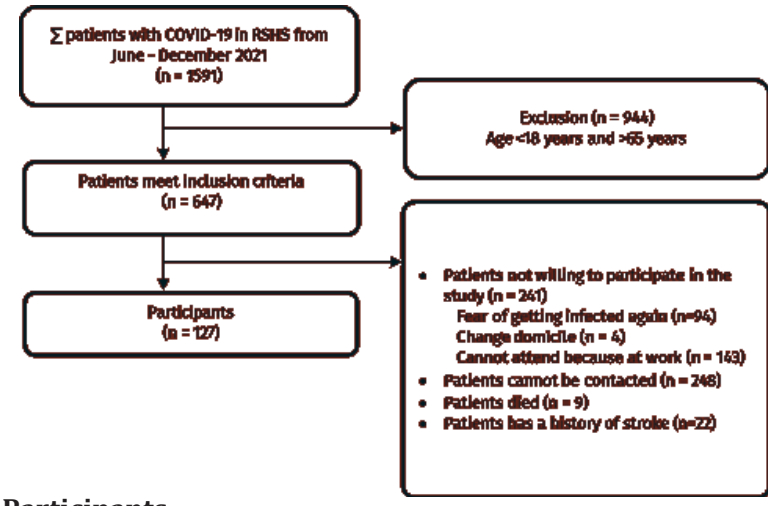

Fig. 1 Flow Chart of Participants

Table 1 Demographic Characteristics of Participants

Variable	(n=127) (%)	Median
Gender		
Male	41 (32.3)	
Female	86 (67.7)	
Age (years)		33 (21–65)
Body Mass Index (kg/m^2)		24.8 (16.2–43.5)
Underweight	4 (3.1)	
Normal	45 (35.4)	
Overweight	15 (11.8)	
Obesities	63 (49.6)	
Comorbidity		
Hypertension	11 (8.7)	
Diabetes	2 (1.6)	
Cardiovascular disease	4 (3.1)	
Chronic Obstructive Pulmonary Disorder	5 (3.9)	
Hypertension and Cardiovascular disease	3 (2.4)	
No comorbid	102 (80.3)	
Length of hospital stay (days)		14 (0–40)
ICU admission	5 (3.9)	
Length of ICU stay (days)		14 (7–20)
Time from discharge to follow-up (months)		9 (1–13)
CT Value		24 (11–38)
Number of acute phases of COVID symptoms		
≤5	54 (42.5)	
>5	73 (57.5)	

Note: Categorical characteristic data is displayed in terms of frequency and percentage, while numerical characteristics are displayed in the form of mean, standard deviation (SD), and range

patient to describe sleep patterns, such as typical bedtime and wake time, length of time taken to fall asleep, and actual sleep duration. The patient then answers a series of questions relating to sleep habits and quality. Component scores ranges from 0-3. The possible total score is within the range of 0-21 with cut-off point for poor sleep quality is higher than 5. Statistical analysis was performed with SPSS version 24.0. The normally distributed variables were expressed as mean ± standard deviation and were compared by t-test. The skewed variables were expressed as medians (IQR) and were compared by using the Mann–Whitney U-test. The Chi Square test was used to determine the relationship between long COVID symptoms and the number of acute phases of COVID symptoms.

Results

From existing records, there were 1,591 patients with COVID-19 who were treated at RSHS from June to December 2021. 944 subjects did not fulfil age criterion, leaving 647 subjects eligible for the study. Of these 647 subjects, nine people had died, 22 had a history of stroke, 248 people could not be contacted/did not give an answer, and 241 people were not willing to take part in the study for the following reasons: (1) fear of re-infection (n=94); (2) change of domicile (n=4); and (3) unable to attend due to work (n=143), so that 127 patients were available for this study (Fig. 1).

The characteristics of the research subjects comprised 32.3% men and 67.7% women, with a median age of 33 years (range: 21 – 65 years), and almost 50% were obese. Most had no comorbidity (80.3%), and the most comorbid was hypertension (8.7%). The median length of stay was 14 days (range: 0 – 40 days); 3.9% were admitted to the ICU, with the median length of stay in the ICU being 14 days. The median CT-value is 24 (range (11 –38)). Based on the number of symptoms of the acute phase of COVID, subjects who had symptoms >5 were 57.5%, and 5 were 42.5%. The basic characteristics of the research subjects can be seen in Table 1.

The median time to go home or be declared cured until the examination was nine months (range 1–13 months). All subjects completed the Long COVID questionnaire and obtained the most neurological symptoms, namely fatigue (53.9%), sleep disturbances (26.8%), muscle weakness (22.8%). Other symptoms such as joint pain, headache, myalgia, dizziness, olfactory disturbances, and taste disturbances were found in less than 10% of the subjects (Table 2).

Table 2 Characteristics of Long COVID Symptoms in Participants

Variables	Total (n=127)
Long COVID symptoms, n (%)	
Fatigue	68 (53.9)
Headache	9 (7.1)
Myalgia	4 (3.1)
Chest pain	2 (1.6)
Joint pain	10 (7.9)
Sore throat	5 (3.9)
Difficult to swallow	2 (1.6)
Low grade fever	5 (3.9)
Palpitations	8 (6.3)
Dizziness	6 (4.7)
Nasal congestion	5 (3.9)
Skin rash	5 (3.9)
Diarrhea or vomiting	6 (4.7)
Nausea	6 (4.7)
Smell disorder	11 (8.7)
Taste disorder	6 (4.7)
Decreased appetite	4 (3.1)
Sleep difficulties	34 (26.8)
Muscle weakness	29 (22.8)
Hair loss	41 (32.3)

Note: Categorical variables of Long COVID symptoms are displayed in the form of frequency (%)

The analysis results in Table 3 showed that subjects who had > 5 symptoms of acute phases COVID symptoms had more cognitive impairment than thos who had < 5 symptoms (41.1% vs 24.1%, OR: 2.20; 95% CI: 1.01–4.79; p=0.045). Chronic fatigue syndrome was also more frequently found in subjects with >5 symptoms in the acute phase of COVID-19 (60.3 vs 38.9%, OR: 2.38; 95% CI: 1.16–4.90; p=0.017). there were no significant statistical difference between those two groups with regard to sleep disturbance (Table 3).

Discussion

The study's results on 127 patients showed that COVID-19 was more common in women,

Table 3 Correlation between Cognitive Disorders, Chronic Fatigue Syndrome, and Sleep Disorders (categorical) based on the Number of Symptoms of COVID-19 in the Acute Phase

Long COVID	Total n=127	Number of Symptoms of COVID-19 in Acute Phase		p-value	OR (95% CI)
		>5 n=73	≤5 n=54		
MOCA-INA					
Cognitive impairment	43 (33.9)	30 (41.1)	13 (24.1)	0.045*	2.20 (1.01 – 4.79)
Normal	84 (66.1)	43 (58.9)	41 (75.9)		
Chalder Fatigue Scale,					
Chronic Fatigue Syndrome	65 (51.2)	44 (60.3)	21 (38.9)	0.017*	2.38 (1.16 – 4.90)
Normal	62 (48.8)	29 (39.7)	33 (61.1)		
PSQI					
Poor Sleep Quality	76 (59.8)	47 (64.4)	29 (53.7)	0.225	1.56 (0.76 – 3.20)
Normal	51 (40.2)	26 (35.6)	25 (46.3)		

Note: analysis using Chi-Square test, *p<0.05

which was 67.7%. This result is supported by similar results obtained in several other studies, which show that more women suffer from COVID-19 than men, with a relatively small percentage of 69%, 63%, and 52%.[8,9],[10] The study of Francesca Bai *et al*.[11] also revealed that women have a 3-fold higher risk of being diagnosed with Long COVID. Hormones may play a role in maintaining a hyperinflammatory state during the acute phase even after recovery, and more robust IgG antibody production in women in the early stages of the disease has been reported; this may result in a more favorable outcome in women, but may also play a role in prolonging the manifestations of the disease.The patients in this study had a median of 33 years. Several similar studies showed variations in the median age of patients suffering from Long COVID-19, namely 33, 36.5, and 39.35 years.[8],[12,13] Nearly 50% of the patients in this study were obese. Obesity is associated with chronic inflammatory conditions and a reduced immune system, increasing a person's susceptibility to infection. Therefore, obesity is an independent risk factor for the poor progression of COVID-19 disease. The mechanisms associated with disease severity in obesity are thought to occur through higher ACE-2 concentrations, chronic inflammation, and the restrictive functional capacity of the obese lung.[14] The comorbidity most often accompanies patients with COVID-19 is hypertension, which is 8.7%. Meanwhile, Huang *et al*.[16] in their study showed a higher percentage (29%) of hypertension, and research by Sanyaolu *et al*.[15] proved that hypertension was the most common comorbid (15%) in patients diagnosed with COVID-19. The investigators agree that subjects with comorbidities were associated with more severe disease outcomes when infected with SARS-CoV-2 compared to patients without previous comorbidities.[16]

This study collected data on the number of symptoms experienced by patients suffering from acute COVID-19 and the symptoms experienced by patients after being declared cured of COVID-19, including those involving neurological sequelae, with the most common symptoms being excessive fatigue, cognitive impairment, and sleep disorders.

This study results are in line with several previous studies, including those from the United States, Europe, and China, which reported the outcome of patients who had completed hospitalization in the acute phase of COVID-19. COVID-19 survivors are reported to have some persistent symptoms. In a study in the United States, 32.6% of patients still had symptoms, 55% in Europe and 76% in China. The most frequently reported symptoms were fatigue (98%), shortness of breath (93%), and headache (91%). However, many symptoms still affect other systems in the body and fluctuate from time to time. A review article of 27 studies on the post-COVID-19 syndrome showed that the most common symptoms were fatigue (47%), shortness of breath (32%), and muscle aches (25%). The study

of Graziella Orru *et al*. on the persistence of neurological and psychological symptoms also showed similar results, where the main symptoms associated with Long COVID were headache (90%), fatigue (80%), muscle pain/ myalgia (70%), articular pain (55%), cognitive impairment (59%), loss of smell (55%), and sleep disturbances such as insomnia (26%).[17,18,19] Long COVID-19 syndrome is a complication with persistent symptoms after recovery from SARS-CoV-2 infection. Guidelines published by the National Institute for Health and Care Excellence (NICE), The Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners define long COVID-19 as signs and symptoms that develop during or after COVID-19-related illness and persist for more than four weeks without being supported by another diagnosis. Two main symptom groups of long COVID have been identified: (1) a group consisting only of fatigue, headache, and upper respiratory tract complaints; and (2) the group with multi-system complaints including fever and gastroenterological symptoms.[20,21] Studies linking the number of symptoms experienced during acute conditions with long COVID-19 have been carried out previously. According to Sudre *et al*.,[21] more than five symptoms in the first week of acute infection were significantly associated with the development of long COVID-19 regardless of age or gender. In this study, long COVID symptom indicators were expressed by several scoring systems for cognitive impairment, CFS, and sleep disorders.

As assessed by the Chalder Fatigue Scale, the number of acute phase COVID-19 symptoms was significantly associated with CFS. A study by Stavem *et al*. also demonstrated that CFS rates were higher in patients with severe symptoms during acute COVID-19 based on three different scoring systems. The study's results by Goertz *et al*.[22] also support this finding by suggesting that the number of symptoms present during initial infection was the most potent factor in predicting the number of symptoms at three months.[23] Chronic fatigue syndrome is defined as fatigue, post-activity malaise, sleep disturbance, cognitive impairment, as well as persistent unprovoked pain lasting six months or more of sufficient intensity, not fully explained by any medical condition. This condition can be observed after some viral and bacterial infections. There is also an association between CFS and depression, although it remains unclear whether one diagnosis precedes the onset of another.[24] Symptoms of CFS can be caused by damage to multiple organ systems during the acute phase of COVID-19, causing impaired heart, lung, or kidney function. The overall inflammatory state increased inflammatory mediators, and activation of cell-mediated immunity may contribute to a CFS-like state. Disruption of routine activities due to ongoing post-COVID-19 draining symptoms, social isolation, and post-traumatic syndrome due to severe illness requiring mechanical ventilation can lead to depression, which can sometimes trigger CFS. Endocrine dysfunction leading to hypocortisolism, hypothyroidism, or disruption of the hypothalamus-pituitary-adrenal (HPA) axis may also be another potential explanation for CFS.[24] In this study, it was found that there was a significant relationship between the number of acute phase COVID-19 symptoms and cognitive impairment as measured by MoCA-Ina. This result is similar to that was observed by Jessica *et al*., who did a follow-up of up to 12 months on 96 COVID-19 survivors and found that only 22.9% of patients were completely symptom-free, and one of the symptoms persisted until the 12th month was neurocognitive symptoms. The cause of some patients experiencing long-term symptoms after COVID-19 remains unclear, but a potential cause for differences in post-infection outcome is viral load and host factors such as genetic susceptibility or induction of anti-inflammatory cells. The development of IgA ANA autoantibodies and high titers of serum IgG antibodies targeting the GD1b ganglioside have been found in certain neurologic affected patients. A study by Miskowiak *et al*.[25] observed the trajectory of cognitive functions from 3 months to 1 year after hospitalization with COVID-19, indicating that patients with impaired cognition three months after hospitalization do not improve after one year, while patients with no impairments after three months remain cognitively normal. This is consistent with meta-analytic analysis by Ceban *et al*. that suggested that patients' cognitive impairments after COVID-19 persist over time. However, this is contradicted by the results of a study conducted by Alemanno *et al*., who reported a high prevalence of cognitive impairment during the acute phase of COVID-19; examination at follow-up one month after discharge found that the total MoCA and Mini-Mental Status Examination (MMSE) scores were significantly higher than at admission. This indicates that cognitive impairment is more severe during the acute phase of

COVID-19 than in the acute post-COVID-19 phase.[26] This study discovered that COVID-19 survivors with some acute phase COVID symptoms >5 experienced sleep disturbances but were not statistically significant. Several previous studies have shown that the number of symptoms of the acute phase of COVID is associated with decreased sleep quality in COVID-19 survivors. The increased number of symptoms of the acute phase of COVID is closely related to the severity of COVID. The severity of COVID-19 is related to a cytokine storm mediated by IL-6, thereby increasing the permeability of the blood-brain barrier causing activation of glial cells, producing inflammatory cytokines, and resulting in sleep disturbances. In this study, the results were not statistically significant, possibly because the cutoff score for the PSQI was too low. The study of Fernández-de-las-Peñas *et al*.[26] in Spain with a Caucasian population getting a PSQI cut of 8 showed a statistically significant difference in sleep quality in Long COVID patients. Vitale *et al*.[28] conducted a study on four COVID-19 survivors that aimed to objectively assess the consequences of the severity of COVID-19 on sleep quality using actigraphy. Research subjects who experience severe COVID-19 degrees and require extended ICU care have the potential to affect sleep quality results, so it is concluded that there is a relationship between ICU care and poor sleep quality. On the other hand, the administration of necessary sedation during mechanical ventilation may play a role in decreasing sleep quality and disrupting sleep habits. Meanwhile, COVID-19 survivors treated in the ICU in this study were only 3.9%, so it did not produce a significant relationship.[23,24,25]

There are some limitation in this study. First, PSQI is a subjective questionnaire, so objective sleep measures are necessary to make a definite diagnosis and to clarify the presence or absence of other sleep disorders causative for the participants' subjective disturbance in sleep maintenance. Second, this study assessed cognitive impairment using MOCA-INA as a screening tools that could not describe the specific cognitive subdomain in Long COVID. Third, this study did not collect laboratory data (cytokines, d-dimer, CRP, fibrinogen, procalcitonin) for patients during the acute phase of COVID. This study shows that almost two-thirds of COVID-19 survivors at this hospital experienced sleep quality disorders, more than half experienced chronic fatigue syndrome, and almost a third experienced cognitive disorders. There is a significant relationship between the number of symptoms of more than five during the acute phase of COVID-19 with chronic fatigue syndrome and cognitive impairment. Sleep disturbances were more common in COVID-19 survivors with more than five acute-phase COVID symptoms but were not statistically significant.

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