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Long-COVID neurological symptoms are associated with D-dimer levels in COVID-19 patients

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a disease designated as a global pandemic by the WHO that can manifest clinically as neurological disorders that can occur in the acute phase or after the acute phase (long COVID-19), such as headache, myalgia, anosmia, and cognitive impairment. These neurological disorders as symptoms of long COVID-19 are presumably caused by hypercoagulable conditions characterized by an increase in D-dimer level. This study aims to determine the correlation of long COVID-19 neurological symptoms with hypercoagulable conditions and the role of D-dimer as a biomarker of long COVID-19 neurological symptoms.

METHODS

This was a cross-sectional study involving 31 patients with long COVID-19 symptoms. Admitted long COVID-19 cases with recorded D-dimer levels and definitive outcomes were included consecutively. Long COVID-19 neurological symptoms were collected. D-dimer level was measured using immunofluorescence assay and reported in fibrinogen equivalent units (μg/mL). The correlation between D-dimer levels and neurological clinical manifestations was assessed by using ordinal regression analysis. The p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the subjects was 38.81 ± 11.58 years and 18 (58.06%) were female. Long COVID neurological symptoms comprised myalgia, anosmia and cephalgia, and most subjects complained of myalgia (80.65%). On multivariable analysis, long-COVID-19 neurological symptoms were significantly correlated with D-dimer [odds ratio (OR) = 1.05; p=0.020].

CONCLUSION

The number of neurological long COVID symptoms were significantly correlated with level of D-Dimer. Ultimately, more clarity is needed on the neurological impact of COVID-19, its diagnosis, and its treatment.

Keywords: COVID-19, D-dimer, long COVID neurological symptoms

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] As of January 25, 2021, there were 99,851,223 confirmed cases and 2,140,684 deaths from this infection worldwide. In Indonesia, there were 999,256 confirmed cases with a death toll of 28,132.[2]

Severe acute respiratory syndrome coronavirus 2 enters target cells through the angiotensin-converting enzyme 2 (ACE2) receptor with an incubation period of 2-14 days.[3,4] Common symptoms include fever, dry cough, fatigue, dyspnea, pneumonia, and even respiratory failure.[5] Other manifestations of neurological disorders also frequently appear, such as headache, myalgia, or anosmia. These manifestations can be considered as a direct effect of the virus on the central nervous system (CNS), or as a neurological complication in the para-infectious or post-COVID-19 phase.[6,7] Similar to SARS-CoV, the SARS-CoV-2 virus uses the angiotensin 2 (ACE2) receptors to enter the cells.[3,8] Angiotensin-converting enzyme 2 receptors in the central nervous system are located on the cell surface, namely on neurons and on endothelial and smooth muscle cells in cerebral blood vessels. The SARS-CoV virus will stimulate the emergence of a cytokine storm which causes disruption of tight junctions in the blood-brain barrier resulting in its impaired permeability. Through this scheme, the SARS-CoV virus is able to enter the central nervous system and cause neurological symptoms.[9,10]

Long COVID-19 symptoms are symptoms that appear persistently for more than 3 weeks after a patient is infected with COVID-19.[11] It can appear in the form of neurological or non-neurological symptoms. The most common symptoms are fatigue (87%) and shortness of breath (71%) that appear within 79 days after infection with COVID-19.[12] Other symptoms include cognitive and memory disorders, headache, myalgia, pain in the chest and joints, disturbances of smell and taste, coughing, hair loss, sleep disturbances, wheezing, rhinorrhea, excess mucus production and disturbances in the heart and digestive system. The symptoms may persist for 6 months after the patient is discharged from the hospital [13] and can interfere with the patient's activities of daily living and quality of life.

The coagulopathy in COVID-19 is caused by the induction of proinflammatory cytokines known as cytokine storms which can cause vasoconstriction resulting in increased deposition of fibrin and D-dimer.[9,14] The increase in D-dimer levels can last up to 2 months in patients who have been infected with COVID -19.[15] This is in line with other studies which claim that long COVID-19 symptoms can last up to 2-3 months.[12] Interestingly, in long-COVID-19 patients, it is possible to detect a prolonged elevation of D-dimer, regardless of the inflammatory indices and the severity of the acute phase.[15]

One of the indicators of a condition induced by hypercoagulative infection is the increase in D-dimer that can cause various clinical manifestations. The commonest lung function abnormality (16.36%) is a decline in diffusion capacity for carbon monoxide (DLCO) in patients after 30 days discharge for acute COVID-19. A higher level of D-dimer at admission is significantly associated with DLCO%<80% suggesting that D-dimer might be a potential biomarker for the prediction of DLCO decline in patients with COVID-19.[15] A study involving 30 long COVID-19 patients and 20 non-COVID-19 subjects, showed that long COVID-19 is independently and significantly correlated with D-dimer (standardized coefficient =0.259; p=0.047). However, these long-COVID-19 patients had no evidence of hypofibrinogenemia or thrombocytopenia.[16]

Because of the high incidence of COVID-19 in the pandemic and inconsistent results of previous studies, the researchers were interested

in conducting a study to determine the role of D-dimer as a biomarker of long neurological COVID symptoms in COVID-19 patients.

METHODS

Research design

This cross-sectional study was conducted at the Neurology Outpatient Clinic and Clinical Pathology Laboratory of dr. Moewardi General Hospital of Surakarta from January to August 2021.

Study subjects

A total of 31 patients aged at least 18 years with long COVID symptoms who came to the neurology outpatient clinic of dr. Moewardi General Hospital of Surakarta from January to August 2021 were included as subjects of the study. Exclusion criteria were (1) having no data on D-dimer examination when initially infected with COVID, (2) pregnant patients, and (3) possessing a history of symptoms and disorders related to hypercoagulation such as stroke infarct, deep vein thrombosis (DVT), and pulmonary embolism (PE). Consecutive non-random sampling was used to select the subjects.

Data collection

Demographic characteristics of patients (age, sex, comorbidity), D-dimer on admission, neurological symptoms, length of stay, and D-dimer outcome were recorded for each patient. All data were recorded on a standardized data collection form using standard units of measurement and were verified by the principal investigator.

Laboratory testing

Blood samples for D-dimer assessment were collected within 24 hours of admission and sent to the clinical pathology laboratory of dr. Moewardi General Hospital of Surakarta. All measurements were done in the laboratory within 2 hours of sample collection. D-dimer was measured by immunofluorescence using the Mispa-i2 analyzer (Agappe Diagnostics Ltd., India). The kit used had a biological reference range of<0.5 μg/mL and the results were reported in Fibrinogen Equivalent Units [FEU (μg/mL)]. The results of laboratory testing were verified by a certified clinical pathologist.

Statistical analysis

By using the normality test, the age data for the initial and final D-dimer levels in this study were not normally distributed. A multivariate ordinal logistic regression was used to assess the correlation between the D-dimer levels and the long COVID-19 neurological symptoms. The software used for statistical analysis was Statistical Package for Social Sciences (SPSS) 22.0 version. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance

The subjects who met the inclusion and exclusion criteria and agreed to participate in this study were asked to fill out an informed consent form. This research has been declared ethically compliant by the Health Research Ethics Committee of Universitas Sebelas Maret through the Ethics Eligibility Certificate No. 118/UN27.06/KEPK/2019.

RESULTS

There were more female than male patients, with a mean age of 35 ± 11.58 years. The most common initial symptom complained of by the patients was fever, followed by anosmia, headache, myalgia, cough, and shortness of breath, while the least common symptom was diarrhea. The length of stay in hospital ranged from 8 to 21 days. There were 7 subjects with a history of comorbid diseases, the most common of which was hypertension followed by diabetes mellitus (DM), obesity, and asthma. The highest initial D-dimer levels of the patients (the D-dimer levels obtained when they were initially infected with COVID and undergoing hospitalization) was 2740 μg/mL, while the lowest was 245 μg/mL.

Table 1. Characteristics of study subjects

Characteristics	Mean ± SD	Median (Min – Max)	n (%)
Sex			
Male			13 (41.94%)
Female			18 (58.06%)
Age	38.81 ± 11.58		
Initial COVID symptoms			
Fever			21 (67.74%)
Anosmia			16 (51.61%)
Cough			12 (38.71%)
Myalgia			7 (22.58%)
Shortness of breath			4 (12.90%)
Diarrhea			3 (9.68%)
Long COVID neurological symptoms			
Myalgia			25 (80.65%)
Anosmia			13 (41.94%)
Cephalgia			6 (19.35%)
Number of long COVID neurological symptoms			
0			1 (3.23%)
1			16 (51.61%)
2			14 (45.16%)
Comorbidity			
Diabetes Mellitus			2 (6.45%)
Hypertension			5 (16.13%)
Obesity			1 (3.23%)
Asthma			1 (3.23%)
D-dimer level (µg/mL)			
Initial D-dimer		460 (245 – 2740)	
Final D-dimer		283 (147 – 871)	
Difference D-dimer		198 (-2540 – 272)	
Length of stay (days)	12.32 ± 2.91		

The final D-dimer levels (D-dimer levels checked at the polyclinic) ranged from 147 µg/mL to 871 µg/mL. There were 8 subjects whose final D-dimer levels were higher than the initial. The lowest increase in D-dimer levels was 20 µg/mL, while the highest was 272 µg/mL (Table 1).

Based on the multivariate ordinal regression analysis, there was a significant correlation between the D-dimer levels and the number of long COVID-19 neurological symptoms (OR=1.05; p=0.020) (Table 2).

DISCUSSION

COVID-19 infection has a very wide range of clinical manifestations. The most frequent symptoms complained of by the subjects of this study were fever (67.74%), followed by anosmia (67.74%), and cough (38.71%). This result was in line with the findings of other researchers. Based on several studies summarized by Iser et al.[17] symptoms such as fever, cough, and dyspnea are the most frequent indicators/

Table 2. Ordinal logistic regression analysis of D-dimer level in COVID-19 patients

	Variable	OR	p-value	aOR	95 % CI
Early model	Age	0.787	0.040*	1.53	0.89-1.97
	Neurological symptoms	0.637	0.288	1.19	0.91-1.74
Final model	Neurological symptoms	0.841	0.020*	1.05	0.96-1.15

OR: Odds Ratio, aOR: adjusted Odds ratio; CI: confidence interval
*Statistically significant

symptoms of COVID-19. Gastrointestinal symptoms and loss of taste (ageusia) or loss of smell (anosmia/hyposmia) are frequently reported in mild cases, while shortness of breath or dyspnea is common in severe and fatal cases. According to Lechien et al.,[18] anosmia is a specific symptom of COVID-19 infection, so it can serve as a diagnostic tool for developing countries in the current pandemic. The mechanism of anosmia in COVID-19 does not appear to directly involve nasal obstruction but is more associated with the damage to the olfactory neuroepithelium. The long COVID neurological symptoms complained by our study subjects were myalgia (80.65%), anosmia (41.9%) and cephalgia (19.35%). This result is in accordance with the study conducted by Stefanou et al.[9] who found that after 6 months following acute COVID-19 infection, the patients complained of at least one of the symptoms of fatigue or muscle weakness, sleep disturbances, smell or taste impairment, myalgia and headache. In this study, the subjects' D-dimer levels during admission were 245 μg/mL at the lowest and 2740 μg/mL at the highest. Meanwhile, the D-dimer levels examined after COVID-19 infection were 147 μg/mL at the lowest and 871 μg/mL at the highest. This finding is in accordance with those of the studies conducted by Yao et al.[19] and Poudel et al.[20] who showed D-dimer to be a biomarker of the severity of COVID-19 cases.

Numerous studies have shown the correlation between the D-dimer levels and the severity of COVID-19 cases, but no studies have presented the correlation between the D-dimer levels and the type of clinical manifestations in patients. The higher the final D-dimer levels were, the higher would be the number of long COVID symptoms experienced by the patient. In our study, the long COVID symptoms consisted of cephalgia, anosmia, and myalgia. This may be because the subjects in this study were limited to patients with mild to moderate COVID-19 symptoms, such that the clinical manifestations of COVID-19 and long COVID symptoms were less diverse.

Camargo-Martínez et al.[21] concluded that the common cephalgia symptoms experienced by COVID-19 patients tend to occur together with gastrointestinal symptoms related to the brain-gut axis. Activation of the brain-gut axis is mediated by the release of inflammatory cytokines such as TNF- α, interleukins, and peptides linked to the calcitonin and neuropeptides genes that are significantly associated with trigeminovascular activation leading to cephalgia.

Osawa et al.[22] revealed that COVID-19 infection is usually associated with coagulopathy resulting in elevated D-dimer levels. The increase in D-dimer levels during admission is associated with thromboembolic events.[15] The increase also indicates an increase in fibrinolysis, the occurrence of coagulation in blood vessels, the incidence of vascular thrombus, and tissue damage which can be the cause of the appearance of severe clinical symptoms in COVID-19 patients.

At this moment, there is no consensus regarding the limit for D-dimer levels to predict the prognosis of COVID-19 patients. However, other studies stated that COVID-19 is associated with an increased incidence of thrombosis, although its correlation with an increase in D-dimer is still unclear.[23] There is significant heterogeneity among studies on D-dimer and COVID-19. Different laboratories use different kits for measurement (such as STANDARD F200 analyzer from SD Biosensor,Korea; POCT Axceed P200 from Bioscience (Tianjin) Diagnostic Technology Co., Ltd; Getein 1100 Immunofluorescence Quantitative Analyzer from Getein Biotech Inc., China; and Mispa-i2 from Agappe Diagnostics Ltd., India) and the accuracy and reliability of measurement can vary according to the kit manufacturer. Furthermore, there is variation in reporting units. Favaloro and Thachil [24] analyzed 20 papers on COVID-19 and D-dimer and found that most papers did not report which manufacturer and reagent kit was used and whether D-dimer values were reported in D-dimer units (DDU) or Fibrinogen equivalent units (FEU). They also found that nearly half of the studies did not report normal cutoff values. This lack of standardization leads to chances of

pitfalls in the analysis and interpretation of D-dimer values in COVID-19.

A major limitation of our study is selection bias because only patients admitted to the hospital were included, which meant that asymptomatic patients with high oxygen saturation, who were not admitted according to hospital guidelines, were not included in the study. In addition, the time from the onset of the illness to hospital presentation may affect the D-dimer values. The D-dimer assay is a widely available, relatively inexpensive, and easy to perform laboratory test. Finally, the findings of this study supported the potential benefit of measuring D-dimer as biomarkers in the prevention of long-COVID neurological symptoms and provided an indication for further research. Apart from the need of COVID-19 treatment options, there is actually an urgent need for the discovery of new biomarkers of early long-COVID neurological symptoms as well as biomarkers for monitoring the severity of COVID-19 which may also be useful as new treatment targets.

CONCLUSION

This study demonstrated that there was a significant correlation between the final D-Dimer levels and the number of long COVID neurological symptoms in COVD-19 subjects. It can be concluded that the neurological long COVID symptoms were significantly correlated with the hypercoagulable condition, and that the D-dimer level could be a predictor of this condition.

CONFLICT OF INTEREST

Competing interests: No relevant disclosures.

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CONTRIBUTORS

Conceptualization, manuscript writer, and guarantor: DKM. Data collecting, analysis, and manuscript writer: PB, S,RD, NAS. Writing, review and editing the final manuscript: HRP, IR, SNZ. All authors have read and approved the final manuscript.

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