

Original Research Article

Factors affecting death in COVID-19 patients with neurological disease manifestations

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) can also attack the nervous system besides the respiratory system. It is recorded that 25% of all COVID-19 cases are accompanied by neurological disorders with a higher death rate. The study aimed to determine the neurological manifestations of COVID-19 and analyse the factors that contribute to death in COVID-19 with neurological disorders.

Methods: This was an analytical cross-sectional study that included 183 patients with COVID-19 and neurological disorders at the Department of Neurology Dr. Mohammad Hoesin Central General Hospital, Palembang, Indonesia from March 2020 to June 2021. We evaluated the risk factor for mortality in COVID-19 patients with neurological disorders.

Results: In this study, 78.1% of patients were under 65 years old, and 89% were male with hypertension (51.4%) as the most comorbid disease. A total of 66.1% of the study subjects had peripheral leukocytes $10,000/\text{mm}^3$, with 82% having an NLR value of 3.3. The mortality rate of COVID-19 patients with neurological disorders is 30.1%. Neurological manifestations recorded were CVD (71.3%), encephalitis meningitis, seizures, exacerbation of myasthenia gravis, GBS, and myelitis. The bivariate analysis found no risk factors associated with death in COVID-19 patients with neurological disorders. Multivariate regression analysis obtained that male sex and diabetes mellitus have a correlation with death in COVID-19 accompanied by neurological disorders.

Conclusions: Male COVID-19 patients with neurological manifestations and diabetes mellitus have a higher risk for death.

Keywords: COVID-19, Neurological manifestations, Risk factors for death, SARS-COV-2

INTRODUCTION

In December 2019 there was an increase in pneumonia cases in Wuhan, China's Hubei province which was later called coronavirus disease-2019 (COVID-19). This disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) which can be transmitted

from human to human through coughing or sneezing droplets.¹

Clinical manifestation of COVID-19 patients can be asymptomatic, with mild to severe symptoms. To date, the disease exceeds two and a half million infections worldwide with a mortality rate of more than 7.08%.

This virus attacks the respiratory tract, diagnosis depends on clinical manifestations such as fever, fatigue, dry cough, dyspnea, and gastrointestinal symptoms. In Indonesia, the first positive case was recorded on March 2, 2020. Until March 14, 2021, positive cases in Indonesia reached 1,419,455 cases, with deaths reaching 38,426 people.²

The main manifestation of SARS-CoV-2 infection is respiratory system disorders, but neurologic findings have been reported in several kinds of literature. Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is noted to be able to manifest in the nervous system, both the central nervous system (CNS) and the peripheral nervous system. Neurological manifestations often occur in patients with severe COVID-19.

Since being declared a pandemic in March 2019, neurological manifestations have been recorded in 25% of all cases in the form of headache (13.6%) and myalgia (14.9%) followed by anosmia (5.1%). Some patients are also noted to have neuropathic symptoms such as paraesthesia and urinary and defecation disturbances and seizures. Seizures occur in 0.7-1.0% of COVID-19 cases with neurologic manifestations. Meanwhile, neurological diseases that can occur in COVID-19 are encephalitis, meningitis, stroke, and Guillain Barre syndrome.³⁻⁶ Research on neurological manifestations of COVID-19 in Indonesia is still limited.

Research at the Tangerang city hospital 2020 noted that from 494 confirmed cases of COVID-19 patients who were treated during the study period, 5% (25 cases) experienced neurological manifestations, with neurological manifestations in the form of cerebrovascular disease (50%), meningoencephalitis (7.7%), vertigo (23%), anosmia (15.4%) and myalgia (3.8%), with a mortality rate of 28%.⁷

Several studies have shown that several factors are associated with the severity and mortality of COVID-19 patients.

The study by Li et al found that old age, comorbid hypertension, high levels of cytokines, and lactate dehydrogenase were associated with the onset of severe COVID-19 manifestations, and male sex, leukocytosis, heart damage, hyperglycemia, and high-dose steroid use were associated with mortality in COVID-19 patients in Wuhan.⁸

Hu's study noted that male gender, age over 65 years, obesity, and comorbid disease were risk factors for severe COVID-19.

Meanwhile, significant laboratory values as predictors of severe cases in Hu's study were an increase in CRP, a

decrease in lymphocytes, and an increase in lactate dehydrogenase.⁹

Data on neurological manifestations of COVID-19 at Central General Hospital Dr. Mohammad Hoesin Palembang is not yet available, so preliminary research needs to be done.

This study aimed to determine the neurological manifestations of COVID-19 and identify the factors that contribute to the occurrence of death in COVID-19 patients with neurological manifestations at RSUP Dr. Mohammad Hoesin Palembang so that intervention efforts can be made on the factors that influence the death.

METHODS

Study design and participants

This was a cross-sectional analytic study, in the Neurology Department of Dr. Mohammad Hoesin Central General Hospital, Palembang city of South Sumatera province, Indonesia.

We screened all adult patients (over 18 years old) using a consecutive sampling method diagnosed with confirmed COVID-19 with neurological manifestation between March 2020 to June 2021.

Diagnosed confirmed COVID-19 based on the positive polymerase chain reaction (PCR) for SARS-CoV2 of the nasopharyngeal swab.

Inclusion and exclusion criteria

Inclusion criteria were all department of neurology patients and confirmed cases of COVID-19 during treatment, and the participants were excluded if they are infected with COVID-19 after being hospitalized and had incomplete medical data.

Statistical analysis

The dependent variable in this study was the incidence of death in COVID-19 patients with neurological manifestations with independent variables including age, gender, neurological manifestations (CVD, meningitis-encephalitis, GBS, myelitis, others), hypertension, diabetes, COPD, cardiovascular disease, peripheral blood leukocytes, NLR values.

Data were analyzed using SPSS 28 for Windows. Univariate analysis was used to describe the characteristics of respondents by presenting the frequency distribution of each variable studied, and bivariate analysis to obtain the odds ratio value, 95% confidence interval of odds ratio, and significance level using the chi-square test on each risk factor.

Multivariate analysis with multiple logistic regression on the eligible variables in the bivariate analysis (chi-square and Mann-Whitney/Wilcoxon were selected as significant for $p < 0.25$) to determine the effect of several variables on mortality in COVID-19 with neurological manifestations.

Ethical approval

This study has been reviewed and approved by the Health Research Ethics Committee Dr. Mohammad Hoesin Central General Hospital, Palembang city of South Sumatera province, Indonesia.

RESULTS

Characteristics of subjects

During the study period, the number of COVID-19 patients with neurological manifestations was 256 patients.

A total of 73 patients were excluded from the study because the data obtained were incomplete, so the number of patients who were the subjects of this study was 183 patients.

In this study, most of the patients (78.1%) were under 65 years old, with the sex of most subjects being male (89%).

The most common comorbidities suffered by the subjects were hypertension (51.4%) followed by diabetes mellitus (36.1%). A total of 66.1% of the study subjects had a peripheral leukocyte count above $10,000/\text{mm}^3$.

The NLR values of the majority (82%) of the study subjects were above 3.3, and 30.1% of the subjects in this study were recorded as having died.

The distribution of the characteristics of the research subjects is shown in Table 1.

Table 1: Distribution of COVID-19 with neurological manifestation.

Variables	Frequency	% (n=183)
Age (years)		
<65	143	78.1
≥65	40	21.9
Sex		
Male	89	48.6
Female	94	51.4
Comorbid		
Hypertension	94	51.4
Diabetes mellitus	66	36.1
Cardiovascular diseases	36	19.7
COPD	10	5.5
Peripheral leukocyte count		
< $10,000/\text{mm}^3$	62	33.9
> $10,000/\text{mm}^3$	121	66.1
NLR values		
<3.3	33	18.0
≥3.3	150	82.0
Outcome		
Died	55	30.1
Survived	128	69.9

Neurological manifestations of COVID-19

In this study, out of 183 study subjects, 40 subjects had neurological diseases that did not include neurological manifestations due to COVID-19 infection.

In 143 study subjects with neurological manifestations due to COVID-19 infection, CVD was the most common

neurological manifestation, namely in 102 subjects (71.3%), followed by meningitis encephalitis (18.9%).

Other noted manifestations were seizures (3.5%), exacerbation of myasthenia gravis (4.1%), GBS (1.4%), and myelitis (0.7%). The distribution of neurological manifestations due to COVID-19 infection can be seen in Table 2.

Table 2: Neurological Manifestations due to COVID-19 infection (n=143).

Neurological manifestations	Frequency	%
CVD	102	71.3

Continued.

Neurological manifestations	Frequency	%
Meningitis encephalitis	27	18.9
Seizure	5	3.5
Myasthenia gravis exacerbation	6	4.1
SGB	2	1.4
Myelitis	1	0.7

There were 40 patients with a diagnosis of other neurological diseases that did not include neurological manifestations of COVID-19, namely intracranial tumors (primary and secondary) in many as 30 patients, vascular dementia in 1 patient, cerebral toxoplasmosis in 2 patients, cerebral abscess in 1 patient, tetanus in 2 patients, compression myelopathy in 1 patient, metabolic encephalopathy in 3 patients.

Risk factors for death of patients with COVID-19 with manifestations of neurological disease

In a bivariate analysis to reach for risk factors for death in patients with COVID-19 with neurological disease manifestations, it was found that the variables of age, gender, hypertension, diabetes mellitus, COPD, cardiovascular disease, peripheral blood leukocyte count, and NLR values were not statistically significant for death in COVID patients.

The age variable has a p value =0.70 with a PR of 0.864 (95% CI; 0.407-1.834), but the mortality rate in the age group 65 years was higher at 32.5% while in the <65 years group it was 29.4%. The gender variable had p=0.09 with PR 1.733 (95% CI; 0.915-3.284) where the male sex had a higher mortality rate of 35.9% and women had a mortality rate of 24.5%.

The hypertension variable had p=0.69 with a PR of 0.878 (95% CI; 0.467-1.652) where subjects with hypertension had a lower mortality rate of 28.7% and in subjects who did not have hypertension, the mortality rate was 31.5%. The diabetes mellitus variable had p=0.19 with PR 0.640 (95% CI; 0.324-1.265) with a mortality rate in subjects with diabetes mellitus of 24.3% and mortality in subjects without diabetes of 33.3%. The COPD variable had

p=0.99 with a PR of 0.997 (95% CI; 0.248-4.008) with a mortality rate of 30% in subjects with COPD and 30.1% in subjects without COPD.

The cardiovascular disease variable had p=0.38 with a PR of 1.413 (CI 95%; 0.655-3.047) with a mortality rate of 37.1% in subjects with cardiovascular disease and 28.6% in subjects without cardiovascular disease.

Variable peripheral leukocyte count had p=0.37 with PR 0.731 (CI95%; 0.369 1.450) with mortality in subjects with peripheral blood leukocyte count <10,000/mm³ of 25.8% and mortality in the group of subjects with peripheral blood leukocytes 10,000/mm³ of 29.7%. The variable NLR value has p=0.42 with PR 0.701 (CI 95%; 0.294-1.670) with mortality in the group of subjects with NLR<3.3 by 24.2% and in the group with NLR 3.3 by 31.3%.

Multivariate analysis of risk factors for death in COVID-19 with neurologic manifestations

In this study, a multivariate analysis was conducted to look for risk factors for death in COVID-19 with neurological manifestations. Although the bivariate analysis did not find a variable with a p value <0.05, a variable with a p value <0.2 was selected to proceed to multivariate analysis, namely gender and diabetes mellitus.

From the multivariate analysis, it was concluded that patients with neurological manifestations were at risk of death 1.7 times in males with moderate correlation strength (r=0.573) and 1.6 times in diabetics with strong correlation strength (r=0.735).

Table 3: Bivariate analysis of risk factors for death of COVID-19 patients with neurological manifestations.

Risk factor	Outcome		P	PR (CI 95%)	
	Died	Survived			
Age (years)	≥65	13	27	0.70	0.864 (0.407-1.834)
	<65	42	101		
Sex	Male	32	57	0.09	1.733 (0.915-3.284)
	Women	23	71		
Hypertension	Yes	27	67	0.69	0.878 (0.467-1.652)
	No	28	61		
Diabetes mellitus	Yes	16	50	0.19	0.640 (0.324-1.265)
	No	39	78		
COPD	Yes	3	7	0.99	0.997 (0.248-4.008)
	No	52	121		

Continued.

Risk factor		Outcome		P	PR (CI 95%)
Cardiovascular diseases	Yes	13	22	0.38	1.413 (0.655-3.047)
	No	42	105		
Peripheral leukocyte count	<10,000/mm ³	16	46	0.37	0.731 (0.369 1.450)
	≥10,000/m ³	39	82		
NLR value	<3.3	8	25	0.42	0.701
	≥3.3	47	103		

Table 4: Multivariate analysis of COVID-19 death risk factors with neurological manifestations.

Comorbid factors and sociodemography	B	P value	r	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
Sex	0.587	0.075	0.573	1.798	0.943	3.428
Diabetes mellitus	0.495	0.060	0.735	1.610	0.306	1.216
Constant	1.794	0.087		2.213		

DISCUSSION

In this study, there were 183 COVID-19 patients with manifestations of neurological disease with a mortality rate of 30.1%. This mortality rate is not much different from the mortality rate in the research at the Tangerang city hospital 2020, which was 28%.⁷

The global mortality rate due to COVID-19 infection is quite low at 3.8%, and this study supports scientific evidence that COVID-19 with neurological manifestations has a higher mortality rate.

This study noted the neurological manifestations due to COVID-19, including CVD, meningitis encephalitis, seizures, exacerbation of myasthenia gravis, GBS, and myelitis.

This supports the evidence that although SARS-CoV-2 mainly affects the respiratory system, it can also show nervous system involvement in some patient groups, namely headache, dizziness, cerebrovascular disease, peripheral nerve, and muscle symptoms as well as olfactory and taste disturbances.

In this study, CVD was the most common neurological manifestation in 102 subjects (71.3%), followed by meningitis encephalitis (18.9%). Other noted manifestations were seizures (3.5%), exacerbation of myasthenia gravis (4.1%), GBS (1.4%), and myelitis (0.7%). This is comparable to previous studies which stated that CVD was the most common neurological manifestation of COVID-19.

In a retrospective cohort-based study in New York, 0.9% had an imaging-proven acute ischemic stroke and the majority (65%) of strokes were cryptogenic.

Mao et al found that two out of six patients with cerebrovascular disease presented to the emergency department with complaints of sudden onset of hemiplegia without the typical symptoms of COVID-19

(fever, cough, anorexia, and diarrhea), but positive results for SARS-CoV-2 PCR. Avula et al also reported 4 patients with an average age of 81 years who were confirmed positive for COVID-19 presenting with complaints of cerebrovascular disorders.^{10,11}

The virus can enter the CNS through blood vessels, neurons (olfactory and trigeminal nerves), cerebrospinal fluid, and the nervous system. lymphatic. A hematogenous spread involves the presence of a virus in the bloodstream and retrograde spread of the virus to the CNS occurs when the virus infects neurons and uses transport systems within cells to gain access to the CNS.

The spread of the virus in brain tissue may be accompanied by neuroinflammation and vascular endothelial dysfunction, which have been reported to contribute to cognitive enhancement, especially in debilitated or elderly patients.

The hematogenous route involves the presence of a virus in the blood where the virus can remain free for some time before infecting the endothelial cells of the blood-brain barrier, or infecting leukocytes that serve as reservoirs of the virus for spread to the CNS.

In this study, there were 2 cases of GBS with the AMSAN variant. This supports the evidence that SARS-CoV-2 infection can trigger GBS. The mechanism of GBS due to viral infection can be due to an immune mimicry reaction or as part of an inflammatory response syndrome.

Guillain-Barre syndrome both subtypes of acute motor and sensory axonal neuropathy and acute inflammatory demyelinating polyneuropathy can occur in patients after COVID-19 infection.

The Miller Fisher syndrome variant was reported in the case report of Gutierrez-Ortiz et al. Toscano et al reported that the first symptoms of GBS appeared between 5-10 days after the onset of COVID-19 symptoms in 5

patients. Three other studies found that patients experienced the first symptoms of GBS while the course of the COVID-19 illness was still ongoing.

In this study, no statistically significant variables were found as risk factors for death in COVID-19 with neurological manifestations, however, this study noted that the mortality rate in the group of subjects with age 65 years, male gender, cardiovascular disease, peripheral leukocyte count $10,000/\text{mm}^3$, NLR 3.3, without diabetes mellitus, hypertension and COPD had a higher mortality rate.

The findings of old age, cardiovascular disease, NLR count 3.3, and peripheral blood leukocytes had a higher mortality rate similar to the results of previous studies.

The findings in this study which noted that subjects without diabetes mellitus, hypertension, and COPD had higher mortality rates were not in line with previous studies. Research Hu's study noted that comorbid disease is a risk factor for severe COVID-19.⁹

Theodorus et al study on COVID-19 patients in Mexico had a comorbid disease, diabetes, chronic obstructive pulmonary disease, hypertension related to the length of stay, and poor outcome.¹²

This study requires further research to see the extent of the influence of comorbid disease as a risk factor for death in COVID-19 with neurological manifestations.

In this study, two variables could be included in the multivariate analysis, and from the multivariate analysis, it was concluded that patients with neurological manifestations were at risk of death 1.7 times in males with moderate correlation strength and 1.6 times in diabetics with correlation strength. strong.

Limitations

This study has several weaknesses, namely the collection of some data with secondary data causing quite a lot of incomplete research samples to be excluded from the study.

Data collection through medical records also cannot describe the clinical neurological symptoms suffered by the subject in detail.

CONCLUSION

The present study identified the neurological manifestation of COVID-19 as cerebrovascular disease (CVD), meningitis encephalitis, myasthenia gravis exacerbation, GBS, and myelitis.

The mortality rate for COVID-19 with neurological manifestations is recorded to be higher.

Patients who were male and had comorbid diabetes mellitus were noted to have a higher risk of death, but this study still cannot determine the risk factor for mortality in COVID-19 with neurological manifestation.

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