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Clinical Symptoms and Treatment Outcomes of COVID-19 Patients with Stroke

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Abstract

Background: COVID-19 patients who come to the emergency room often suffer from stroke. This study aimed to examine clinical symptoms and treatment outcomes of COVID-19 patients with stroke.

Methods: This study was a retrospective study using secondary data from medical records of COVID-19 patients with stroke, hospitalized at the Universitas Kristen Indonesia Hospital, Jakarta, Indonesia for the period 2020–2022. Patients with PCR test positive for COVID-19 who had clinical symptoms of stroke, confirmed by CT scan showing brain ischemic or hemorrhage were included. Data on gender, age, Glasgow coma scale (GCS), subtype of stroke, severity of COVID-19, and outcome were recorded and analyzed using paired t-test and the Spearman correlation.

Results: Of the 49 patients included, 91.8% were over 45 years old and suffered from severe COVID-19. Men were slightly more (51.1%) than women and 93.9% of patients suffered from ischemic stroke. The GCS scores of 46.9% of patients decreased significantly during hospitalization (p=0.02). Most of patients (65.3%) had used non-rebreathing mask (NRM), 10.2% ventilators, and others used nasal cannulas. As many as 46.9% of patients died, 44.9% recovered with neurological deficits, and only 8.2% recovered completely. Interestingly, oxygen delivery devices were significantly correlated with outcome (p=0.00). Patients receiving the antiviral favipiravir had better outcomes compared with those taking remdesivir (p=0.021).

Conclusions: The mortality rate for stroke patients with severe COVID-19 is high, and the outcome of patients using NRM or ventilator is worse than patients using nasal cannulas. The antiviral favipiravir has better outcomes for stroke patients with severe COVID-19.

Keywords: COVID-19, favipiravir, outcome, stroke, treatment

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Introduction

Stroke patients with COVID-19 infection were reported in many journals during this pandemic. One study reported that 1.02% of all COVID-19 patients who came to the emergency department and were treated at the hospital also suffered from stroke.[1]

Stroke attacks in patients with COVID-19 have hypothesized due to several mechanisms including hypercoagulation, vasculitis, disseminated intravascular coagulation (DIC), necrotizing-encephalopathy, and cardiomyopathy.[2] Hypercoagulation is characterized by increasing of D-dimer and prothrombin time values, thrombositopenia, and decreasing fibrinogen. Vasculitis in COVID-19 occurs due to direct infection by the viruses and the systemic impact of the cytokine storm.[2,3] Meanwhile, cardiomyopathy in COVID-19 was because by myocarditis as an influence of cytokine release and stress cardiomyopathy due to increased sympathetic stimulation.[4]

According to several reports, the severity of stroke in COVID-19 patients is generally more severe than stroke patients without COVID-19. This is indicated by a higher National Institutes of Health Stroke Scale (NIHSS) score in patients with COVID-19.[5–7] Mortality rate of stroke

patients with COVID-19 was also higher than without COVID-19. The rate was 39.3% for ischemic strokes with COVID-19 and 16.1% for stroke without COVID-19. It was 40.3% versus 19.0% in hemorrhagic stroke.[8]

These outcomes indicate that COVID-19 infection is proven to make the outcome of stroke patients worse. Therefore, the current management of stroke patients with COVID-19 needs to be evaluated. The results of the evaluation can be used as feedback to improve patient management in reducing mortality and morbidity.

At our teaching hospital, Universitas Kristen Indonesia General Hospital and its affiliates also treated stroke patients with COVID-19 infection. All patients have been treated in the isolation room and the COVID-19 intensive care unit. The patients were managed according to stroke and COVID-19 disease treatment. This study evaluated clinical symptoms, treatment, and outcomes of stroke patients with COVID-19.

Methods

This study was a retrospective study evaluating data of stroke patients with COVID-19 infection from 2020 to 2022. Data was taken from the medical record after the ethical clearance of the study was approved by the Ethics Review Committee of the Faculty Medicine Universitas Kristen Indonesia, number: 09/Etik Penelitian/FKUKI/2022. The inclusion criteria for this study were patients who had clinical symptoms of stroke with CT scan results of brain ischemia or hemorrhage and patients who also had clinical symptoms of COVID-19 with PCR positive. Exclusion criteria were patients who required neurological surgery to save the patient's life.

Data on the patient's gender, age, clinical symptoms, and subtype of stroke based on brain CT scan, the severity of COVID-19 clinical symptoms, Glasgow coma scale (GCS) of patients, the type of breathing apparatus, and the drugs were recorded and tabulated. Severity COVID-19 was classified clinically as mild, moderate, and severe. The patients who had a fever, cough, and without pneumonia were classified as mild. Moderate patients had a fever, and cough with mild pneumonia; and severe patients had a fever, and cough with severe pneumonia. Patients' outcomes were classified into three categories: full recovery (without neurological deficits), recovery with one or more neurological deficits, or death during treatment in the hospital.

The paired t-test was used to assess the difference in GCS before and after treatment. Additionally, the Spearman correlation tests were conducted to examine the correlation between clinical symptoms and patient outcomes; between oxygen delivery device and outcome, and between antiviral drugs and outcomes.

Results

As many as 49 patients met the criteria for this study. They suffered from stroke and COVID-19. Twenty-five (51.1%) patients were male and 24 (48.9%) were female. There were 28 (57.1%) patients between 46-65 years old, and 17 (34.7%) patients were more than 65 years old. Forty-six (93.9%) patients suffered from ischemic stroke and only three patients suffered from hemorrhagic stroke. The severity of COVID-19 clinical symptoms and stroke clinical symptoms were presented. There were 33 (67.4%) patients had left or right hemiparesis, and 26 (53.1%) patients were unconscious. Forty-five (91.8%) patients were classified as severe COVID-19, and there was no patient with mild COVID-19. The outcome of stroke patients with severe degrees COVID-19 was 22 (44.9%) out of 45 patients died (Table 1). However, the correlation test between the severity of COVID-19 illness and the outcome of the patient was not significant ($p>0.05$).

Table 2 shows the patients' level of consciousness. GCS score of 26 (53.1%) patients at admission ranged from 7 to 14, and 23 (46.9%) patients had GCS 15. After treatment, there were 23 (46.9%) patients deteriorated to GCS 3 and died. The results of the paired t-test on the patient's level of consciousness at the time of discharge compared to the time of admission showed a significant worsening of GCS ($p <0.021$).

There were 32 (65.3%) patients required non-rebreathing mask oxygen delivery, 5 (10.2%) patients used ventilators, and the other used nasal cannula. Patients' mortality rate was high. Twenty-three (46.9%) out of 49 patients were dead, and only 4 (8.2%) patients had full recovery. The correlation between oxygen delivery device and the outcome of patients was significant ($p=0.00$) (Table 3). The outcome of the patient who used NRM or ventilator was worse than patients who used nasal cannula.

There were 20 out of 31 (64.5%) patients who received antiviral favipiravir were survived (fully recovered or disabled), and 11

Table 1 Characteristics of COVID-19 Patients with Stroke

Variable	n	%
Sex		
Male	25	51.1
Female	24	48.9
Age (year)		
<45	4	8.2
46–65	28	57.1
>65	17	34.7
Stroke subtype		
Ischemic	46	93.9
Hemorrhage	3	6.1
Stroke symptoms		
Hemiparesis	33	67.4
Unconscious	26	53.1
Aphasia	10	20.4
Seizure	4	8.2
Severity of COVID-19		
Mild	0	0.0
Moderate	4	8.2
Severe	45	91.8

(35.5%) patients who died. Moreover, 12 out of 20 (66.7%) patients who received remdesivir were dead. The correlation between antiviral drugs and outcomes of stroke patients with COVID-19 was significant (p<0.021). The outcome was better in the patients who received favipiravir drugs.

Discussion

This study proves some patients come to the emergency room with symptoms of COVID-19 also suffer from stroke. The incidence rate between men and women is not different. This is in accordance with the prevalence rate of stroke according to Indonesian Ministry of Health survey reports in 2018.[9] The difference between men and women was not significant, 11.0 per mil for men and 10.9 per mil for women. The prevalence of stroke in Indonesia at the age of 35–44 years old was less than 4 per 1000 people, but at the age of 45–54 years old the rate was 14.2 per 1000 people, increasing to 50.2 per 1,000 for the people over 75 years old.[9]

In this study, there are 6.1% of patients

Table 2 Differences in Patient GCS at Admission and Discharge

GCS	Admission	Discharge	p*
3	0	23	
4	0	0	
5	0	0	
6	0	0	
7	1	0	
8	5	0	
9	5	0	0.021
10	3	0	
11	2	0	
12	4	0	
13	3	0	
14	3	0	
15	23	26	

Note: GCS= Glasgow coma scale, *Paired t-test, significance: p<0.05

Table 3 Outcome of the Patients

Treatment	Outcomes			p*
	Full Recovery	Recovered with Diasibility	Died	
Oxygen delivery device				0.000
Nasal cannula	1	11	0	
NRM	3	11	18	
Ventilator	0	0	5	
Antiviral drugs				0.021
Favipiravir	4	16	11	
Remdesivir	0	6	12	

Note: *Spearman correlation test, significance: p<0.05, NRM= non-rebreathing mask

suffered from hemorrhagic stroke. It is lower than the number of hemorrhagic stroke patients in the world which reached 27.05% of all stroke patients without COVID-19 as reported by the World Stroke Organization (WSO).[10] Another study reports about 11.6% to 28.42% of stroke patients accompanied by COVID-19 are hemorrhagic strokes.[1,11] This study could not explain why the incidence of hemorrhagic stroke subtype was less than the results of previous reports.

According to the severity of COVID-19 illness, almost all of the patients are categorized as severe. It is because the patients of COVID-19 with mild symptoms carried out independent isolation or treated at home according to the instructions from the Ministry of Health of the Republic of Indonesia due to the limited of hospital capacity.

The level of consciousness of the patients' decreases during treatment and the result is worse than stroke patients without COVID-19.[12] Patients with COVID-19 will experience more hypoxia due to the patient's lung problem or pneumonia. This study supports that the presence of comorbid diseases including cardiovascular disease could impact the outcome of patients' COVID-19.[13,14]

The patient outcomes in this study are poor and no different from the results of a meta-analytic study which revealed the mortality rate for hemorrhagic stroke patients accompanied by COVID-19 is 44.72%, and 36.23% for ischemic stroke patients.[11] This mortality rate was greater than the in-hospital mortality rate of stroke patients without COVID-19. It was 5–15%.[15]

The outcome of the patients who have been treated with antiretroviral favipiravir is better than the patients treated with remdesivir (p<0.05). This is consistent with a previous study that compared 70 patients with COVID-19 treated with favipiravir and 70 patients who received remdesivir. The recovery rate was 68.67% in the favipiravir group, while it was only 51.43% in the remdesivir group.[16]

Likewise, one study conducted in Bali[17] compared the effect of favipiravir and remdesivir treatments on 192 patients divided into two groups. The study evaluated the impact of these drugs on improving clinical symptoms, such as freedom from fever and respiratory problems, after 14 days of treatments. The results showed a clinical improvement rate of approximately 79.2% in the favipiravir group and 56.3% in the remdesivir group. The difference was found to be statistically significant (p<0.05).

Favipiravir is a selective inhibitor of RNA-dependent RNA-Polymerase (RdRP) located on the nsp12 protein. RdRp plays an important role in the replication of the coronavirus. Therefore, favipiravir can disrupt the chain of viral replication and mutation, leading to rapid clearance of the virus from the blood and clinical improvement in patients.[18]

In this study, almost all of the patients needed non-rebreathing mask oxygen delivery because the majority of the patients suffered from severe COVID-19 symptoms. They required a higher oxygen therapy level, and 5 patients needed a ventilator. Sadly, all of the patients who used ventilators could not survive. There are 3 types of oxygen delivery that can be used in COVID-19 therapy: high-flow nasal cannula (HFNC), continuous positive air pressure (CPAP), and non-invasive ventilation. It has been proven that the use of oxygen therapy with HFNC and CPAP shows a better result than using the non-invasive ventilation type. Oxygen therapy with HFNC and CPAP can reduce the risk of COVID-19 patients being intubated, and also reduces the risk of patient death during 28 daily period of

care.19 Therefore, oxygen therapy with the HFNC or CPAP types is highly recommended for COVID-19 patient treatment.

Stroke patients with severe COVID-19 symptoms will need NRM or a ventilator device. The morbidity and mortality of these patients is high. This result is convincing evidence that COVID-19 significantly worsens the outcome of stroke. This effect is likely related to hypoxia resulting from lung destruction caused by COVID-19 infection. It is also proven that the higher the viral load of COVID-19 exposure for patients, the greater the risk of requiring intubation and ventilators.[20] The viral load can be recognized from the cycle threshold value (CT value) of PCR examination of patients' oropharynx and nasopharyngeal swabs. The risk of patients requiring intubation and ventilator if the CT value >30 (low) is 14.9%; CT value 25–30 (medium) is 20.8%; and CT value is <25 (high) is 29.1%. The mortality rate is also higher in patients with a higher viral load. It is 35% if the CT value is <25; 17.6% if the CT value is 25–30, and 6.2% if the CT value is >30.[20]

This study has the limitation of not being able to evaluate patient NIHSS because most patient medical records do not contain this information. This may be due to limited time for doctors to examine patients due to the increasing number of COVID-19 cases and the high risk of transmitting COVID-19 to health workers. Additionally, this study did not evaluate the CT value of PCR results or follow up on long-term results.

In conclusion, the morbidity and mortality rates of stroke patients with severe COVID-19 are high, and the outcomes of patients who require NRM or mechanical ventilation are worse compared to those using nasal cannula. Correlation between antiviral drugs and patient outcomes is significant with favipiravir showing superiority over remdesivir.

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