Stroke in Patients with COVID-19 Infection in a Tertiary Hospital: A Retrospective Study

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ABSTRACT

Introduction. Stroke can be a complication and/or a presenting sign of COVID-19 infection. Although there is growing evidence on stroke in COVID-19 infection, only a few of these studies were done in Asia and there is very scarce evidence in the local setting.

Objective. This study aimed to characterize the clinical profile, management, and functional outcome of patients with acute stroke and COVID-19 infection.

Methods. This was a single-center retrospective study from March 30 to October 20, 2020. The demographic characteristics, respiratory symptoms, risk factors, neuroimaging, stroke characteristics, ancillary test results, treatment given, and functional outcome were obtained through a review of medical records. Computation of the mean, standard deviation, median, interquartile range, total count, and percentage was done for data analysis.

Results. Out of 2,018 patients with COVID-19 infection, 41 (2%) developed an acute stroke. The mean age of patients was 59.05 ± 14.04 years. Majority were men (n=24, 59%). Ischemic stroke (n=28, 68%) was the most common stroke with the anterior circulation commonly involved (n=21, 72%). The most common risk factors were hypertension (n=31, n=76%), cigarette smoking (n=18, 44%), dyslipidemia (n=16, 39%), and ethanol use (n=16, 39%). Among those with stroke and COVID-19 infection, 42% had mild infection and 29% had critical disease. The inflammatory markers were elevated in these patients. Upon discharge, 83% had a poor functional outcome (mRS 3–6). The overall mortality rate was high (n=24, 59%) with pulmonary cause as the most common cause of death.

Conclusion. Ischemic stroke was the most common stroke type in patients infected with COVID-19. The common risk factors were hypertension, dyslipidemia, smoking, ethanol use, and diabetes mellitus. The functional outcome was generally poor and the mortality rate was high. More studies are needed that compare these subsets of patients with a control group, including a longer follow up.

Keywords: Cerebrovascular disease, COVID-19, stroke

INTRODUCTION

COVID-19 infection is a disease with the most common symptoms being cough, myalgia, and fatigue.[1,2] It can be classified as mild, moderate, severe, or critical based on the WHO classification. Mild disease consists of patients meeting the case definition for COVID-19 without viral pneumonia or hypoxia, while moderate disease consists of clinical signs of non-severe pneumonia with SpO_2 ≥90%. Severe disease consists of severe respiratory distress or SpO_2 <90% on room air. Patients have critical disease if they have acute respiratory distress syndrome, sepsis, septic shock, or if they require life-sustaining treatment.[3]

COVID-19 infection may present with non-respiratory symptoms. Stroke has been reported in COVID-19, both

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as a presenting sign and as a complication of the disease.[4–13] This includes ischemic stroke (87.4% to 87.8%), intracerebral hemorrhage (5.2% to 11.6%), cerebral venous thrombosis (1.6% to 2.6%), and subarachnoid hemorrhage (1.7%).[9,14,15] The proposed mechanisms for ischemic stroke in COVID-19 infection include hypercoagulable state, vasculitis, and cardiomyopathy.[14] Because of this, the recommendations for the prevention and treatment of stroke in COVID-19 may be different from the usual etiologies of stroke.[5,6,14]

COVID-19 is a huge threat not only to the patients and communities but also to the economy worldwide. Although there is a growing number of researches about stroke in COVID-19 infection, many of these studies were done in Europe and North America. Antiplatelet medication, anticoagulation, intravenous thrombolysis, and mechanical thrombectomy were given in patients with ischemic stroke. Only a few of these studies were done in Asia and there is very scarce evidence in the local setting. Thus, there may be an issue with the applicability of these researches in our local setting as there are differences in terms of race, risk factors, and health care delivery system.

Since there are only very limited data on acute stroke in COVID-19 infection in the Philippines, the researchers formulated this study to help clinicians understand the association of COVID-19 and stroke. This study aims to look at the clinical profile, management, and outcome of this subset of patients.

METHOD

Study Design

This was a single-center cross-sectional study done at the Philippine General Hospital, one of the designated COVID-19 centers in the country since March 2020.

Study Population

The study population included all adult patients with COVID-19 infection who developed acute stroke from March 30 to October 15, 2020. The sudden onset of neurologic deficits in these patients either followed or preceded the respiratory symptoms of COVID-19 infection. The patients were included in the study if they were 19 years old and above with confirmed COVID-19 infection by reverse transcription-polymerase chain reaction of nasopharyngeal swab or endotracheal aspirate and stroke documented radiographically within 15 days of the onset of respiratory symptoms or 15 days after the patient is declared free of COVID-19 infection.[9,15] Those with a history of recent head trauma, intracranial tumor, and central nervous system infection were excluded.

Data Collection

This study was approved by the institutional ethics review board. Data were collected using a standardized data collection form. The charts for data collection were identified based on the stroke database and ICD-11 (International Classification of Diseases, 11th Revision). The severity of the COVID-19 infection was based on the World Health Organization (WHO) guidelines.[3] The study obtained the demographic characteristics, respiratory symptoms, interval between the respiratory manifestations and stroke, neurologic deficits, vascular risk factors, neuroimaging, stroke characteristics, ancillary test results, and treatment given (medical and/or surgical). The primary outcome was death, while the secondary outcome was functional disability measured using the modified Rankin score. The modified Rankin scale (mRS) is a measure of functional outcome and a score of 0–2 is considered good and 3–6 is considered poor.

Data Analysis

We computed mean and standard deviation, and median and interquartile range for continuous data while total counts and percentages were computed for the categorical data using the STATA/IC version 16.1.

RESULTS

Out of 2,018 patients with confirmed COVID-19 infection, 41 (2%) developed acute stroke. The mean age of patients was 59.05 ± 14.04 and the majority of these patients were men (n=24, 59%). Ischemic stroke (n=28, 68%) was the most common stroke type followed by intracranial hemorrhage (n=10, 24%), subarachnoid hemorrhage (n=1, 2%), cerebral venous thrombosis (n=1, 2%), and infarct with subarachnoid hemorrhage (n=1, 2%). One case of non-aneurysmal subarachnoid hemorrhage had a concomitant left occipital lobe infarct. The most common risk factors were hypertension (n=31, 76%), cigarette smoking (n=18, 44%), dyslipidemia (n=16, 39%), and ethanol use (n=16, 39%). Five (12.2%) patients had no identified risk factor. The most common neurologic manifestations were motor weakness (n=35, 85%), decreased sensorium (n=21, 51%), sensory deficits (n=20, 49%), visual disturbances (n=19, 46%), and dysarthria (n=25, 37%). The median initial National Institute of Health Stroke Scale (NIHSS) was 22.

In terms of COVID-19 related variables, majority had mild infection (n=17, 42%) and critical disease (n=12, 29%). The mean PaO_2/FiO_2 ratio of these patients was 295.80 ± 123.09. Many of the COVID-19 infected patients with stroke had no respiratory symptoms (n=17, 42%). In those who developed respiratory symptoms, the interval for the development of stroke from the onset of respiratory symptoms was a median of 5 days. The most common inflammatory markers that were elevated were the white blood cell count (95%), high sensitivity C-reactive protein (88%), D-dimer (83%) and lactate dehydrogenase (78%) (Table 1).

Among those patients who developed ischemic stroke, the anterior circulation was the most commonly involved (n=21/29, 72%). Among those who developed intracranial hemorrhage, the most common location was subcortical

Table 1. Demographic and clinical characteristics of acute stroke patients with COVD-19 infection (n=41)

Characteristic	n (%)
Age in years (mean, SD)	59.05 ± 14.04
Sex	
Male	24 (59)
Female	17 (42)
Type of Stroke	
Ischemic stroke	28 (68)
Intracranial hemorrhage	10 (24)
Subarachnoid hemorrhage	1 (2)
Cerebral venous thrombosis	1 (2)
Subarachnoid hemorrhage + infarct	1 (2)
Risk Factors	
Hypertension	31 (76)
Cigarette smoking	18 (44)
Dyslipidemia	16 (39)
Ethanol use	16 (39)
Diabetes mellitus	13 (32)
Chronic kidney disease	11 (27)
Coronary artery disease	6 (15)
Heart Failure	5 (12)
Obesity	5 (12)
Chronic stroke	4 (10)
Atrial fibrillation	4 (10)
Methamphetamine use	3 (7)
Rheumatic heart disease	2 (5)
Cancer (Multiple myeloma)	1 (2)
None	5 (12)
Admission NIHSS (Median, IQR)	22 (0–34)
Baseline Glasgow coma score	
3–6	4 (10)
7–11	18 (44)
12–15	19 (46)
Admission mRS	
0	0 (0)
1	6 (15)
2	2 (5)
3	0 (0)
4	14 (34)
5	19 (46)
Duration of hospitalization (Median, IQR)	14 (2–67)
COVID-19-related variables	
Mild infection	17 (42)
Moderate infection	8 (20)
Severe	4 (10)
Critical	12 (29)
Respiratory symptoms preceded stroke	23 (56)
Respiratory symptoms followed stroke	1 (2)
Interval between stroke and respiratory symptoms in days (Median, IQR)	5 (0–15)
Elevated inflammatory markers	
White blood cell	39 (95)
High-sensitivity C-reactive protein	30/34 (88)
D-dimer	30/36 (83)
Lactate dehydrogenase	32 (78)
Procalcitonin	20/36 (56)
Interleukin-6	7/13 (54)
Ferritin	20 (49)

mRS, Modified Rankin Score
NIHSS, National Institute of Health Stroke Score
IQR, Interquartile range
SD, Standard deviation

(n=9/10) and the mean amount of blood was 26.17 ± 21.70 mL. Throughout their hospital course, a total of 17.1% (n=7) developed pulmonary embolism and 10% developed acute coronary syndrome (n=4). In terms of medical management, majority received anti-platelet medications (n=22, 54%) and therapeutic dose anticoagulation (n=17, 42%). Therapeutic dose anticoagulation was given primarily to those who developed acute coronary syndrome and pulmonary embolism and to those who were deemed high risk for thrombotic events based on the inflammatory markers and COVID-19 infection severity. Two patients with a smaller intracranial hemorrhage volume received antiplatelet and anticoagulation within 3–16 days of the stroke onset. Medical decompression (n=14, 34%) was done on those with larger infarct and larger hemorrhage volume. Only two patients were given intravenous thrombolysis (n=2/29, 7%). This is because most of the patients were brought to the hospital beyond 4.5 hours from the onset of symptoms. Thrombectomy was not offered since this procedure is not yet available in our institution. In terms of surgical management, one patient with ischemic stroke underwent decompressive hemicraniectomy (n=1, 2%). Three patients with intracranial hemorrhage underwent surgical decompression, one for evacuation of hematoma and two for tube ventriculostomy (Table 2).

One patient with cerebral venous thrombosis and mild COVID-19 infection was a 28-year-old woman who had no co-morbid conditions. She was discharged with an mRS of 0 and maintained on oral anticoagulant and anti-seizure medications.

Two patients developed subarachnoid hemorrhage. The first patient was a 54-year-old woman who had critical COVID-19 disease, hypertension, dyslipidemia, and chronic kidney disease maintained on hemodialysis. The other patient was a 64-year-old hypertensive and dyslipidemic man with mild COVID-19 infection and concomitant left occipital infarct. Both patients had no ruptured aneurysm or structural vascular lesion on angiography.

Table 2. Clinical profile of patients with acute stroke and COVID-19 infection

	n/N (%)
Vascular territory involved in ischemic stroke	
Anterior circulation	21/29 (72)
Large vessel disease	14/21 (67)
Small vessel disease	7/21 (33)
Posterior circulation	8/29 (28)
Large vessel disease	6/8 (75)
Small vessel disease	2/8 (25)
Location of intracerebral hemorrhage	
Subcortical	9/10 (90)
Pontine	1/10 (10)
Amount of hemorrhage in ml (mean, SD)	26.17 ± 21.70
Complications	
Pulmonary embolism	7/41 (17)
Acute coronary syndrome	4/41 (10)
Medical Management	
Anti-platelet medication	22/41 (54)
Anti-coagulation (therapeutic)	17/41 (42)
Medical decompression	14/41 (34)
Anti-coagulation (prophylactic)	9/41 (22)
Intravenous thrombolysis	2/29 (7)
Anti-seizure medications	1/41 (2)
Surgical Management	
Tube ventriculostomy	2/41 (5)
Evacuation of hematoma	1/41 (2)
Decompressive hemicraniectomy	1/41 (2)

SD, Standard deviation

Table 3. Outcome among acute stroke patients with COVID-19 infection

	n, %
Primary outcome: All-cause mortality	24/41 (59)
Pulmonary	17/24 (71)
Pneumonia	15/24 (63)
Pulmonary embolism	1/24 (4)
Pneumothorax	1/24 (4)
Neurologic	4/24 (17)
Brain herniation	3/24 (13)
Brainstem failure	1/24 (4)
Cardiac	3/24 (13)
Acute coronary syndrome	2/24 (8)
Fata arrhythmia	1/24 (4)
Secondary outcome: Functional disability	
mRS 0–2	7/41 (17)
mRS 3–6	34/41 (83)

mRS, Modified Rankin Score

The overall mortality rate was high at 58.5%. These patients had critical or severe infection and developed in-hospital complications such as pulmonary embolism, acute coronary syndrome, or hospital-acquired pneumonia. The leading cause of death was pulmonary (n=17/24, 71%). The majority of these patients had a poor functional outcome (mRS 3-6) upon discharge (n=34/41, 83%) (Table 3). Among those with mild COVID-19 infection, more stroke patients had a poor functional outcome (n=11/17, 65%).

DISCUSSION

This study explored the clinical profile of acute stroke in relation to COVID-19 infection. This study showed that 2% of patients infected with COVID-19 had acute stroke. The mean age was 59.05 ± 14.04 years. The majority of these patients were men, and ischemic stroke was the most common stroke type. The most common risk factors were hypertension, cigarette smoking, and dyslipidemia. The functional outcome on discharge was generally poor in the majority. These patients had a high mortality rate with pulmonary cause as the leading cause of death. To the best of our knowledge, this study was the first in the Philippines and Southeast Asia to delve into this topic.

The percentage of COVID-19 patients developing stroke in this study was similar to published studies, which is 0.5 to 2% of the patients infected with COVID-19.[8,9,11,16] The patients in this study were relatively younger as compared to the other studies about stroke in COVID-19 patients (mean age=59.05 years vs. 65.3 to 73.5 years).[4,9–11,17,18] The sex predilection and risk factors were similar in the other COVID-19 studies.[4,8–12,15,17] We had patients who had no identified risk factors for stroke other than being infected with COVID-19. This may suggest that COVID-19 can be a risk factor for stroke.[7] Interestingly, many of our stroke patients with COVID-19 infection (41.46%) did not have any respiratory symptoms at all, suggesting that stroke can be a presenting symptom of COVID-19 infection. Our patients had the traditional risk factors for stroke.[19–21]

Ischemic stroke remained to be the most common type of stroke in those with or without SARS-CoV2 infection as seen in this study and other studies.[4,8,9,19–21] The anterior circulation was consistently the most commonly affected vascular territory.[10,11,17] There are three mechanisms for the development of ischemic stroke in COVID-19 infection. The first mechanism is a hypercoagulable state as evidenced by an elevated D-dimer level, thrombocytopenia, and decreased fibrinogen level. Antiphospholipid antibodies (anti-cardiolipin IgA, anti-ß2-glycoprotein I IgA ang IgG) have been reported in patients with COVID-19 who developed multiple cerebral infarctions. The second mechanism is vasculitis, which can be from a direct local effect of SARS CoV-2 on the angiotensin-converting enzyme-2 (ACE-2) receptors in the vascular endothelium and from the systemic immune response to the pathogen. The third mechanism is cardiomyopathy, which can lead to an intracardiac thrombus formation and then to cardioembolic stroke.[5,14,22] These mechanisms can be associated with elevated inflammatory markers seen in our patients.[4,8,9,12]

There were fewer cases of intracranial hemorrhage (ICH) in this study and in the literature.[8,13] Thus, there were fewer studies on ICH in COVID-19 infection compared to ischemic stroke. The proposed mechanisms for the development of ICH are different. One mechanism includes direct damage of the intracranial arteries by the SARS-CoV2, leading to vessel wall rupture and then bleeding. Another mechanism includes downregulation of the renin-angiotensin system, causing an elevated blood pressure that can predispose to ICH. The other mechanisms are consumptive coagulopathy and impairment of the blood-brain barrier that can lead to hemorrhagic conversion of the infarct.[9]

Many of the patients in this study had a poor functional outcome in terms of the mRS (mRS≥4), as seen in other COVID-19-related stroke studies. This may be attributed to the complications related to COVID-19 infection.[10,12,13] The overall mortality rate in this study was higher than the reported mortality rate in other studies (58.5% vs. 19.8% to 47.9%).[9,10,13,15] Majority of the cause of death of these patients were non-neurologic. The disproportionately high mortality rate among stroke patients with COVID-19 infection had severe to critical disease and this predisposed them to a dismal outcome. Risk factors that were associated with a higher mortality rate include intensive care unit admission, dyslipidemia, two or more vascular risk factors, and elevated ferritin, D-dimer, CRP and LDH.[15] These risk factors were present in our patients who died.

This study had several limitations. The vascular studies of stroke (echocardiogram, transcranial Doppler, cranial CT angiogram, magnetic resonance angiogram) were not performed in all patients so the exact subtype of their ischemic stroke could not be fully identified. Since this study did not compare the patients with stroke and COVID-19 with those with stroke and without COVID-19 infection, a definite causal relationship between acute stroke and COVID-19 cannot be firmly established. The outcomes presented in this study were limited to the outcome upon discharge only. Therefore, the functional outcome of these patients several months after their stroke was unknown.

The findings of this study can help contribute to the knowledge about stroke in the background of COVID-19 infection. It is recommended that routine testing for SARS-CoV-2 using RT-PCR should be done in all patients who present with stroke symptoms since stroke may be the only clinical manifestation of a patient infected with the virus. Some patients may not possess the traditional risk factors for stroke and COVID-19 infection may be their only risk factor. This study can encourage other researchers to conduct case control or cohort studies with a greater number of participants and longer duration of follow up to determine the long-term outcome of those patients who survived stroke and COVID-19 infection. The high mortality rate of stroke patients with COVID-19 infection calls for a more aggressive and proactive management plan for this group of patients. This study can also help the administrative bodies in sound health policy formulation and allocation of proper resources in preventing and treating this disease.

CONCLUSION

Ischemic stroke was the most common stroke type in patients infected with COVID-19. Majority of the patients were men and the common risk factors are hypertension, dyslipidemia, smoking, ethanol use, and diabetes mellitus. Inflammatory markers were elevated in these patients. The functional outcome in terms of mRS was generally poor and the mortality rate was high. More studies are needed that compare these subsets of patients with a control group, including a longer follow up.

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Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

Authors Disclosure

The authors declare that they have no competing interests. The views expressed in the submitted article are the authors' own views and not an official position of the institution.

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