Neurology Asia 2021; 26(1) : 15 – 25

Clinical characteristics of cerebrovascular disease with COVID-19: A single-center study in Manila, Philippines

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Abstract

Background: Among the morbid neurological complications, stroke has been frequently observed in COVID-19 but there are limited reports, especially in the Philippines. This study aims to determine the clinical characteristics of COVID-19 patients with cerebrovascular disease (CVD). *Methods:* We performed a single-center retrospective analysis of stroke patients with COVID-19 from March to August 2020. Results: Of the 584 COVID-19 cases, 27 patients have cerebrovascular disease, with rate of COVID-19 related CVD at 4.62%. COVID-19 with CVD were younger than those without COVID-19 (58.23 vs 61.53 years). The median admitting NIHSS was mild for both groups (4 vs 5) and the vascular risk factors of these groups were similar. The median time of onset of CVD at 7 days from onset of COVID-19. Deranged levels of procalcitonin, D-dimer, ferritin, CRP, and LDH were elevated and greater in the large artery atherothrombosis. Anti-platelet therapy was given in 4 (20%) while 16 (80%) received anticoagulation. For intracranial hemorrhage, 6 out of 7 (86 %) were admitted without prior COVID-19 symptom; hence, a causal relationship is difficult to establish.
Conclusion: Less than 5 % of the COVID-19 patients present with CVD. They are younger but share similar vascular risk factors with COVID-19 negative stroke patients. There is a possible association between COVID-19 and acute ischemic stroke. Large artery atherothrombosis are more common in patients with COVID-19 this type showed more deranged laboratory investigation. A causal relationship between intracranial hemorrhage and COVID-19 is difficult to establish; thus, further study regarding this is merited.

Keywords: COVID-19, cerebrovascular disease, stroke

INTRODUCTION

Historically, there have been several strains of coronavirus that cause respiratory and enteric infection in humans, and remarkably, neurotropic and neuroinvasive capabilities have been described.[1] Among the morbid neurological complications, acute cerebrovascular events have been mostly observed in patients with severe or critical COVID-19[2], but reports also show that patients with mild to moderate infection can develop stroke.[3] These increasing reports suggest an association between COVID-19 and stroke, but due to the presence of multiple vascular risk factors it is difficult to establish a direct causal relationship.[4]

Published studies of COVID and Stroke show that acute ischemic stroke (AIS) is the most common form of cerebrovascular disease (CVD), with an overall incidence of 1.2% based on 5 studies.[4-6] Intracerebral hemorrhage (ICH) and Subarachnoid hemorrhage (SAH), on the other hand, are scarce, and studies on them are limited to case reports.[6-8,18]

In the Philippines, we are still experiencing an increase of cases of COVID-19, with approximately 4,000 new patients added per day (total of 217,000 since August 31, 2020).[9] Reporting and determining the true local incidence of COVID-19 with CVD is extremely challenging; limited testing capabilities[10], social isolation policies, and fear to go to the hospital result in under-reporting of CVD in mild COVID-19 patients.[11] However, determining the incidence and clinical characteristics despite the limited population is essential.

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Date of Submission: 13 November 2020; Date of Acceptance: 16 December 2020

METHODS

Study Population

We performed a single-center retrospective analysis of all stroke patients diagnosed in our institution after an Institutional Review Board approval was obtained. Informed consent was waived due to the retrospective nature of the study. All stroke patients seen in the institution underwent reverse transcription-polymerase chain reaction (RT-PCR) assay of the oropharyngeal and nasopharyngeal swab. Twenty-seven patients admitted and/or seen in the Emergency Department with confirmed COVID-19 from March 1, 2020 to August 31, 2020 were included.

Procedures

Demographics, clinical, and stroke data were obtained through an electronic medical record review. All laboratory and radiologic assessments were performed as part of routine clinical care. The following data were taken from the subjects electronic medical records:

1. Demographic data: Age and sex.
2. Clinical data: History of vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, atrial fibrillation, congestive heart failure, myocardial infarction on the time of admission, previous stroke and transient ischemic attack; onset of neurologic deficit or stroke; time from onset of neurologic deficit to onset of COVID-19 symptoms; National Institute of Health Stroke Scale (NIHSS); and COVID-19 symptoms.
3. Laboratory data: Laboratories test results closest to the time after onset of neurologic deficits, including arterial blood gases (ABG), cardiac troponin level, serum ferritin, CRP, Procalcitonin, D-dimer, LDH and Creatinine. The highest value of these laboratories while the patient was admitted were also recorded.
4. Imaging/radiologic data: Chest radiograph closest to the time after stroke and subsequent chest radiograph while admitted; and cranial magnetic resonance imaging diffusion weighted imaging (Cranial MRI-DWI) or Cranial CT scan for infarct pattern or hemorrhage with MR angiography (MRA) to determine large artery atherosclerosis.
5. Treatments/management: IV recombinant tissue plasminogen activator (rtPa), mechanical thrombectomy, anticoagulation or antiplatelet therapy for ischemic stroke; medical or surgical decompression for non-traumatic intraparenchymal hemorrhage; and surgical intervention (clipping or coiling) for SAH.
6. Outcomes: discharge disposition and in-hospital mortality.

Statistical analysis

We used purposive sampling; hence, no sample size calculations were performed. Descriptive and frequency statistical analysis were utilized. Means and standard deviations (SD) were used for normally distributed data and medians and ranges for data that were not normally distributed. Categorical variables were expressed as absolute values and percentages.

RESULTS

Rate of cerebrovascular disease in relation to COVID-19

There were 584 patients with RT-PCR confirmed COVID-19 from March 2020 to August 2020. Of these, 27 had CVD based on clinical diagnosis by a neurologist and confirmed radiologically by either cranial CT scan or MRI-DWIS comprised of 27 patients, putting its rate at 4.62%. Rate based on stroke type showed 3.42% for AIS and 1.20% for ICH.

Characteristics of COVID-19 positive and negative patients with cerebrovascular disease

Table 1 summarizes the differences between patients who had CVD possibly related to COVID-19 and unrelated to COVID-19. COVID-19 patients presenting with CVD were generally younger than those without COVID-19 (58.23 [12.03] vs 61.53 [15.11] years) and more predominantly male (22 [74%] vs 180 [59%]). The median admitting NIHSS was mild for both groups (4 vs 5) and the vascular risk factors of these groups were similar.

Among the stroke admissions during this time period, large artery atherothrombosis (LAA) was more predominant in COVID-19 positive patients (10 [33%] vs 55 [18%]).

Clinical characteristics of COVID-19 patients with cerebrovascular disease

Of the 27 patients, 10 (37%) were admitted due to focal neurologic symptoms without any generalized and pulmonary symptoms on the onset; 2 of them developed fever on the day of admission. The characteristics of COVID-19

Table 1: Demographic and clinical characteristics of stroke patients possibly related and unrelated to COVID-19

Variable	Stroke and COVID 19 Positive Patients (n : 27)	Stroke and COVID 19 Negative Patients (n : 303)
Demographic data		
Age (mean, SD)	59 (12.34)	61.53 (15.11)
Gender (male)	21 (77%)	180 (59%)
Admitting NIHSS (median)	4	5
Vascular risk factors (%)		
Hypertension	73	76
Diabetes mellitus	33	36
Hyperlipidemia	56	51
Atrial fibrillation	13	16
Smoker	10	11
Past stroke	30	28
Stroke subtypes (%)		
Acute ischemic stroke	20/27 (74%)	222/303 (73%)
Large artery atherothrombosis	10 (37%)	63 (21%)
Small vessel disease	6 (22%)	71 (24%)
Cardioembolic	2 (7%)	44 (14%)
Other embolic mechanism	1 (4%)	21 (7%)
Cryptogenic	1 (4%)	23 (7%)
Hemorrhagic stroke	7/27 (26%)	81/303 (27%)
Intraparenchymal hemorrhage	6/30 (22%)	71 (23%)
Subarachnoid hemorrhage	1/30 (4%)	8 (3%)
Treatment/management of acute ischemic stroke		
Arrival at the ER before 4.5 hours from neurologic deficit	4/20 (20%)	28 (14%)
IV- rtPa	3	12
Endovascular	0	5

positive patients with CVD are summarized in Table 2. Admitting chest radiograph showed that 11 (41%) did not have pneumonia, but 4 eventually developed pneumonia on subsequent study. For patients who had COVID-19 symptoms prior to onset of stroke, the median time of the focal neurologic deficit was 7 days (1-14 days), with most of them presenting with fever (13 [43%]), followed by cough (10 [33%]). Common co-morbidities included hypertension (73%), hyperlipidemia (56%), and diabetes mellitus (33%).

AIS was more common (20 [67%]) compared to ICH (7 [23%]).

Laboratory investigations showed that worse COVID-19 condition was related to higher laboratory markers. Among COVID-19 positive patients, procalcitonin, D-dimer, serum ferritin, C-reactive protein, and lactate dehydrogenase were elevated. Furthermore, serum ferritin, CRP and LDH were more elevated in patients who presented with LAA compared to those who suffered from ICH and small vessel disease. Table 3 details the comparison of laboratory findings between COVID positive patients with CVD.

Table 2: Characteristics of COVID-19 Positive Patients with Cerebrovascular Disease

	Demographic and Risk Factors	COVID 19 Severity and Symptoms	Days from COVID 19 Onset to Stroke	Diagnostic and Radiologic Findings				CVD Characteristics		Outcome
				Chest Xray Closest to Time of Stroke	P/F Ratio Closest to Time of Stroke	Laboratory Values Closest to Time of Stroke	Highest Laboratory Derangement Recorded	Stroke Subtype	Treatment	
Patient 1	51 male with HTN, HLPD and Smoker	moderate fever develops on admission	No symptoms prior	Bilateral Pneumonia	290 mmHg (Mild ARDS)	Ferritin 594.45 LDH 259.41 CRP 2.14	LDH 398.35 CRP 11.5	Small Vessel Disease	Clopidogrel	Discharged
Patient 2	77 male with HTN, AF, HLPD and post stroke	moderate fever and cough	1 day	Initial CXR was clear but subsequent showed bilateral Pneumonia	367 mmHg (Not ARDS)	Normal Blood Test	Ferritin 1223 CRP 28.26	Basal Ganglia Hypertensive Hemorrhage	Medical Decompression	Discharged
Patient 3	66 male with HTN, DM, HLPD	Critical Fever, Cough and Dyspnea	5 days	Progressive Bibasal Pneumonia	56 mmHg (Severe ARDS)	Procal 1.05 D-Dimer 1.19 Ferritin 2607.28 LDH 659.07 CRP 5.74	D-DImer 10.905 Ferritin 5298 LDH 769 CRP 7.9	Large Artery Atherosclerosis	Enoxaparin Clopidogrel	Discharged
Patient 4	50 female with HTN, CKD and post stroke	Severe Cough, fever and Dsypnea	7 days	Pneumonia, Bibasal. Cardiomegaly.	359 mmHg (Not ARDS)	D-Dimer 1.95 LDH 388.78 CRP 25.59	same as time of stroke labs	Large Artery Atherosclerosis	Aspirin	Discharged but readmitted after 6 days due to ICH and expired - readmission labs refused
Patient 5	60 male with HTN, DM, CKD, HLPD, Smoker and post stroke	Severe Fever	4 days	Bilateral Pneumonia	314 mmHg (Not ARDS)	Ferritin 4717 LDH 476 CRP 4.55	Ferritin 6396 CRP 63.61	Cryptogenic	Enoxaparin	Discharged
Patient 6	77 female with HTN, DM, HLPD	Severe Fever, Cough	7 days	Bilateral Pneumonia	286 mmHg (Mild ARDS)	Ferritin 3307 LDH 435.98 CRP 6.29	same as time of stroke labs	Large Artery Atherosclerosis	Enoxaparin Apixaban	Discharged
Patient 7	55 female with HTN, CA and post stroke	Critical Cough, Fever, Dyspnea, Headache	5 days	Bilateral Pneumonia	104 mmHg (Moderate ARDS)	D-Dimer 0.67 Ferritin 2390 LDH 244.42 CRP 13.31	LDH 597.22	Hypercoagulability from CA	Enoxaparin Aspirin	DAMA
Patient 8	62 female with HTN	Mild No pulmonary and generalized symptoms	No symptoms prior	Normal CXR	371 mmHg (Not ARDS)	Normal Blood Test	Normal Blood Test	Aneurysmal SAH	Coiling	Discharged

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				Chest Xray Closest to Time of Stroke	P/F Ratio Closest to Time of Stroke	Laboratory Values Closest to Time of Stroke	Highest Laboratory Derangement Recorded	Stroke Subtype	Treatment	
Patient 9	71 male with COPD	moderate Fever and generalized body weakness	7 days	Pneumonia, Right Lower Lung	314 mmHg (Not ARDS)	Refused Laboratory Test	Refused Laboratory Test	Large Arteery Atherosclerosis	Clopidogrel	DAMA
Patient 10	70 male with HTN, HLPD, DM, CKD, smoker and PTB	Critical Generalized body weakness and Dyspnea	1 day	Bibasal Pneumonia	300 mmHg (Mild ARDS)	D-Dimer 14.31 Ferritin 1024.54 LDH 599 CRP 4.16	Ferritin 11,852 LDH 2273	Large Artery Atherosclerosis (Probably with Cardioembolic due to New Onset AF)	Enoxaparin	Death due to Acute Respiratory Failure
Patient 11	55 male with HTN, DM	Critical Fever and Headache developed day of admission	No symptoms prior	Normal Chest on Initial CXR, Pneumonia on subsequent CXR	138 mmHg (Moderate ARDS)	D-Dimer 1.89 Ferritin 6614 LDH 500.67 CRP 26.75	LDH 587.68 CRP 33.0	Large Artery Atherosclerosis	IV-rtPa Enoxaparin	Death due to Acute Respiratory Failure
Patient 12	40 male with no known comorbidity	Moderate No pulmonary and generalized symptoms	No symptoms prior	Pneumonia, Bilateral	102 mmHg (Moderate ARDS)	Ferritin 356.74 LDH 275.00 CRP 0.17	Ferritin 365.51 CRP 33.76	Basal Ganglia Hypertensive Hemorrhage	Medical Decompression	Discharged
Patient 13	38 male with HTN, HLPD	Mild No pulmonary and generalized symptoms	No symptoms prior	Normal CXR	386 mmHg (Not ARDS)	CRP 3.86	same as time of stroke labs	Basal Ganglia Hypertensive Hemorrhage	Medical Decompression	DAMA
Patient 14	59 male with HTN, DM	Mild No pulmonary and generalized symptoms	No symptoms prior	Normal CXR	500 mmHg (Not ARDS)	Ferritin 514.69 LDH 234.55	Ferritin 759.53 LDH 275.98	Small Vessel Disease	Enoxaparin	Discharged
Patient 15	67 male with HTN, DM, HLPD	Critical Fever, Cough and Dyspnea	10 days	Bilateral Pneumonia	119 mmHg (Moderate ARDS)	Procal 0.26 D-Dimer 4.17 Ferritin 3297 LDH 365.54 CRP 14.15 Trop I 0.13	CRP 126.28	Large Artery Atherosclerosis	IV RTPA Enoxaparin	Death due to Acute Respiratory Failure

Table 2: Characteristics of COVID-19 Positive Patients with Cerebrovascular Disease

	Demographic and Risk Factors	COVID 19 Severity and Symptoms	Days from COVID 19 Onset to Stroke	Diagnostic and Radiologic Findings				CVD Characteristics		Outcome
				Chest Xray Closest to Time of Stroke	P/F Ratio Closest to Time of Stroke	Laboratory Values Closest to Time of Stroke	Highest Laboratory Derangement Recorded	Stroke Subtype	Treatment	
Patient 16	73 male smoker	Critical Cough, Fever, Dyspnea, Headache	4 days	Bilateral Pneumonia	107 mmHg (Moderate ARDS on AC Mode 70% FIO2)	Procal 0.43 D-Dimer 22.43 Ferritin 1331.45 LDH 713.25 CRP 24.38 Trop I 1.086	Ferritin 2909	Large Artery Atherosclerosis	Enoxaparin	Death due to Acute Respiratory Failure
Patient 17	50 female with HTN, HLPD and post stroke	Mild Fever	2 days	Normal CXR	Refused Laboratory Test	Refused Laboratory Test	Refused Laboratory Test	Small Vessel Disease	Clopidogrel	DAMA
Patient 18	65 male with COPD	Critical Fever, Cough and Myalgia	7 days	Bibasal Pneumonia	81 mmHg (Severe ARDS)	D-Dimer 3.81 Ferritin 5013 LDH 811.68 CRP 22.74	same as time of stroke labs	Large Artery Atherosclerosis Cryptogenic with Chronic Venous Insufficiency)	Aspirin Enoxaparin	Death due to Acute Respiratory Failure
Patient 19	63 male with no comorbidities	Critical Cough, Fever, Dyspnea, Myalgia	7 days	Bilateral Pneumonia	94 mmHg (Severe ARDS)	D-Dimer 0.98 Ferritin 4361 LDH 799.29 CRP 20.65	same as time of stroke labs	Large Artery Atherosclerosis	Enoxaparin	Death due to Acute Respiratory Failure
Patient 20	49 male HTN, DM, AF, HLPD	Mild No pulmonary and generalized symptoms	No symptoms prior	PTB, Left Upper Lung	645 mmHg (Not ARDS)	Ferritin 367.18 Trop I 0.742	same as time of stroke labs	Cardioembolic	Fondaparinux	Discharged
Patient 21	68 male with HTN, HLPD, NSTEMI and post stroke	Moderate No pulmonary and generalized symptoms	No symptoms prior	Normal CXR	252 mmHg (Mild ARDS)	Procal 0.59 D-Dimer 8.785 Ferritin 1542.59 LDH 367.14 Trop I 32.405 Crea 1.84	same as time of stroke labs	Pontine Hemorrhage	Medical Decompression	Death due to Acute Respiratory Failure
Patient 22	45 male with HTN, CAD, and HLPD	Moderate	7 days	Right Lower Lobe Pneumonia	629 mmHg (Not ARDS)	D-Dimer 0.641 Ferritin 764.87 LDH 272.17 CRP 0.83	same as time of stroke labs	Small Vessel Disease	IV RTPA Enoxaparin	Discharged

Table 2: Characteristics of COVID-19 Positive Patients with Cerebrovascular Disease

	Demographic and Risk Factors	COVID 19 Severity and Symptoms	Days from COVID 19 Onset to Stroke	Diagnostic and Radiologic Findings				CVD Characteristics		Outcome
				Chest Xray Closest to Time of Stroke	P/F Ratio Closest to Time of Stroke	Laboratory Values Closest to Time of Stroke	Highest Laboratory Derangement Recorded	Stroke Subtype	Treatment	
Patient 23	41 female with no comorbidity	Mild No pulmonary and generalized symptoms	No symptoms prior	Normal CXR	476 mmHg (Not ARDS)	Normal Blood Test	Normal Blood Test	Small Vessel Disease	Apixaban	Discharged
Patient 24	45 male with DM, HLPD	Severe Cough, Fever, Myalgia, Dizziness	5 days	Pneumonia, Left Lower Lobe	371 mmHg (not ARDS)	Procal 0.12 Ferritin 3817 LDH 414.29 CRP 1.87	Ferritin 9060.91	Small Vessel Disease	Rivaroxaban	Discharged
Patient 25	45 male with HTN	Moderate Cough, Fever, Loss of Taste	13 days	Pneumonia , Right Lower Lobe	376 mmHg (not ARDS)	Procal 0.13 D-DImer 2.89 Ferritin 1102 LDH 366 CRP 1.34	Ferritin 1362	Basal Ganglia Hypertensive Hemorrhage	Medical Decompression	Discharged
Patient 26	74 female with HTN, DM, CKD, HLPD, and post stroke	Moderate No pulmonary and generalized symptoms	No symptoms prior	Normal Chest on Initial CXR, Pneumonia on subsequent CXR	390 mmHg (not ARDS)	D-Dimer 0.98 LDH 303	Ferritin 518 LDH 479	Cardioembolic	Enoxaparin	Death due to Acute Respiratory Failure
Patient 27	56 male with HTN, CKD, HLPD and smoker	Critical No pulmonary and generalized symptoms	No symptoms prior	Normal Chest on Initial CXR, Pneumonia on subsequent CXR	452 mmHg (not ARDS)	Procal 8.72 D-Dimer 2.28 Ferritin 686 LDH 253.36 CRP 1.9	D-Dimer 15.171 Ferritin 2854 LDH 465 CRP 12.9	Thalamocapsular Hemorrhage	Medical Decompression	Death due to Herniation

* Procalcitonin (Procal), Troponin I, Ferritin and Creatinine expressed in ng/ml. CRP in mg/dl, D-Dimer, in mcg/mL, LDH in U/L. DAMA is Discharged Against Medical Advice, HTN is Hypertension, DM is Diabetes Mellitus, HLPD is Hyperlipidemia, CKD is Chronic Kidney Disease, ARDS is Acute Respiratory Distress Syndrome, CXR is Chest Xray, NSTEMI is non ST elevation MI, AF is atrial Fibrillation

* Acute Ischemic Stroke Classification is defined using the TOAST Classification. Definition as follows : Large Artery atherosclerosis is 50% or more narrowing in an artery supplying the ischemic infarct, Small Vessel Disease is infarct less than or equal to 2 in MR-DWIS or 1.5 in CT Scan , or subcortical infarct for patients with risk factors for small vessel disease, Cardioembolic is based on the presence of major cardioembolic source, other mechanisms defined as presence of known hypercoagulability, Cryptogenic is defined as not meeting the any of the above criteria

PF ratio is calculated using Horowitz Index. Laboratory results included was taken on the time closest to onset of stroke disregarding the patients admission date (either by COVID or other conditions).

COVID 19 severity taken from 1. World Health Organization. (2020). Clinical management of COVID-19, interim guidance (WHO/2019-nCoV/clinical/2020.5). Retrieved from https://www.who.int/publications/i/item/clinical-management-of-covid-19

Table 3: Laboratory values nearest to the diagnosis of a cerebrovascular disease in COVID positive patients

	All types of Cerebrovascular Disease	Large Artery Atherothrombosis	Small Vessel Disease	Cardioembolic and Other Source of Embolism	Intracerebral Hemorrhage
Hemoglobin	13.71 (8.60 - 16.70)	13.46 (10.4 - 15.30)	13.70 (11.20 - 15.80)	14.50 (13.50 - 16.70)	13.62 (8.60 - 16.60)
WBC count	9.70 (4.10 - 18.0)	10.24 (5.40 - 18.8)	8.20 (5.50 - 18.00)	9.32 (4.18 - 13.10)	10.44 (6.20 - 13.70)
Platelet	264.88 (114 - 470)	226.10 (114 - 439)	258 (159 - 381)	280.75 (174 - 448)	317.14 (219 - 470)
Procalcitonin	0.33 (0.01 - 2.17)	0.70 (0.08 - 2.17)	0.04 (0.01 - 0.12)	0.14 (0.08 - 0.24)	0.28 (0.02 - 0.87)
D-dimer	1.60 (0.36 - 8.78)	1.61 (0.41 - 3.81)	0.46 (0.37 - 0.64)	0.68 (0.51 - 0.98)	3.61 (0.50 - 8.78)
Serum ferritin	1885.40 (63.62 - 6614)	3077.16 (137.25 - 6614)	1150.95 (63.62 - 3817.12)	1909.99 (165.80 - 4717)	693.39 (207.82 - 1542.59)
INR	1.05 (0.87 - 1.46)	1.10 (0.95 - 1.46)	0.96 (0.88 - 1.08)	0.98 (0.87 - 1.10)	1.06 (0.94 - 1.16)
C-reactive protein	8.29 (0.05 - 26.75)	16.71 (4.16 - 26.75)	1.52 (0.05 - 4.09)	4.67 (0.38 - 13.31)	5.34 0.10 - 19.29
Lactate dehydrogenase	395.14 (150.73 - 811.68)	585.91 (365.54 - 811.68)	267.89 (159.03 - 414.29)	309.25 (213.52 - 476)	272.28 (171.43 - 367.14)
Troponin I	2.18 (0.002 - 32.405)	0.46 (0.010 - 1.086)	0.006 (0.002 - 0.008)	0.29 (0.010 - 0.742)	6.72** (0.007 - 32.405)
AST	51.51 (18.89 - 133.95)	49.72 (31.41 - 76.20)	61.12 ((26.74 - 133.95)	65.81 (20.47 - 106.33)	38.00 (18.89 - 83.69)
ALT	45.51 (12.22 - 203.89)	27.52 (12.22 - 47.50)	66.23 (20.68 - 203.89)	50.49 (20.42 - 84.42)	40.33 (14.43 - 64.57)
Creatinine	1.84 (0.50 - 10.19)	2.31 (0.68 - 8.21)	0.78 (0.50 - 1.04)	1.62 (0.55 - 3.13)	2.42 (0.71 - 10.19)

*Hemoglobin expressed in g/L, WBC and Platelet in xx10^9/L, Procalcitonin (Procal), Troponin I, Ferritin and Creatinine expressed in ng/ml. D-Dimer in mcg/ml, CRP and Creatinine in mg/dl, AST, ALT and LDH in U/L.

** the elevated troponin I is due to patient 21 who was also diagnosed with NSTEMI

Outcomes and treatment

Medical decompression was done to the 7 cases with intraparenchymal hemorrhage, of which 3 were discharged stable, 1 expired due to COVID-19 complications, 1 died due to uncal herniation (management refused due to advance directives), 1 was discharged against medical advice and 1 was still admitted.

Stroke admissions during March and April were managed with antiplatelet except for those who were diagnosed with atrial fibrillation and replacement heart valves. However, the increasing reports during the second quarter of 2020 about the hypercoagulable state in COVID-19[14-16,20] and anecdotal evidence of increasing thromboembolic risks in severe and critical cases prompted the shift to use anti-coagulation (LMWH) of patient with concomitant stroke (mostly LAA) and COVID-19.

Hyperacute stroke was managed with IV-rtPa. For the details of treatment, 4 (20%) arrived at the emergency room within 4 and 1/2 hours but only 3 (15%) were eligible for IV-rTPA. For those who received intravenous thrombolysis, 2 died due to complications of COVID-19 despite improving NIHSS after IV-rtPa, while 1 was discharged improved. We cannot fully evaluate the outcomes of using anti-platelet and anti-coagulation as 3 cases (2 on anti-platelet, 1 on anti-coagulant) were discharged against medical advice. Of the 20 patients, 4 (20%) received anti-platelet, while 80% received anticoagulation. Most patients admitted and managed with antiplatelet were discharged, but 1 patient was readmitted due to a hypertensive ICH. Among the 15 admitted patients who had

anticoagulation, 53% were discharged while 47% expired due to acute respiratory failure.

Among those with LAA, 8 out 10 (80%) were given low molecular weight heparin (Enoxaparin) while 2 out of 10 (20%) were managed with anti-platelets. Of those managed with anti-coagulation, 2 out of 8 (25%) were given IV rTPA at 0.9 mg/kg. They showed initial improvement of neurologic deficits and were started on Enoxaparin at 40 mg twice daily after 24 hours of IV rTPA. 2 out of 8 (25%) were already given Enoxaparin at 40 mg once daily prior to onset of neurologic symptoms for DVT and PE prophylaxis. Upon diagnosis of stroke, their dose was increased to 40mg twice daily. Lower dosage of Enoxaparin (20mg once daily) was given to 2 patients (25%) due to episode of melena, decreasing hemoglobin and increasing creatinine. The remaining 2 (25%) were maintained on Enoxaparin 40 mg twice daily. In the group which received anticoagulation, 6 out of the 8 patients (75%) eventually expired due to acute respiratory failure while 2 (25%) were discharged.

Patient outcome was only available for 23 cases. Ten (37%) of the COVID positive stroke patients died, 8 of which were from acute respiratory failure secondary to critical COVID. Of these 8 cases, 6 were cases of LAA. Two cases of intracerebral hemorrhage died due to uncal herniation.

DISCUSSION

In this study, we report the demographic and clinical characteristics of patients with CVD probably related to the multi-organ effects of COVID-19 infection.[17] There has been a significant 21% drop in stroke admission this year in comparison with last year's admission (464 vs 303). In this study, the incidence of stroke was slightly lower (4.62%) compared to the reported incidence of the previous studies, which was 5.0-5.9.[2,18,19] However, the rate of radiologically confirmed acute ischemic stroke (3.42%) was higher compared to the reported incidence in a recent meta-analysis, which was 0.9% to 2.7%.[5] The difference can possibly be related to the differences in the populations studied and protocols implemented for COVID-19 testing. Previous studies have used clinical suspicion for COVID-19 by history and chest radiography prior to COVID-19 test while the updated protocol for stroke in our institution performs routine COVID-19 test on all CVD patients. Another possible reason for overestimation of CVD incidence is the limited testing capabilities for COVID-19 in the general population resulting to under-reporting of COVID-19.[10]

A significant number of COVID-19 positive CVD patients were admitted without generalized and respiratory symptoms typical of COVID-19 and with unremarkable chest radiograph. This raises the question of whether CVD should be considered criterion for COVID-19 testing and whether COVID-19 testing should be done routinely for CVD patients. Furthermore, these data show that the onset of CVD in relation to COVID-19 varied, ranging from onset prior to presenting with generalized symptoms to delayed-onset of 7 days. This raises the suspicion that cerebrovascular events can rise both early and late in the course of COVID-19. A substantial amount of literature posits that onset of CVD in the late phase of infection may be secondary to a prothrombotic state; nevertheless, the risk factors of early onset CVD should be further evaluated.[5,21]

It is important to note that 74% of the COVID-19 positive CVD patients in this study suffered from AIS. Of these, large vessel atherosclerosis was the most frequent type (37%). These observations are in line with findings from several studies.[5] COVID-19 has been linked with a hypercoagulable state due to increase inflammatory markers and cytokines following the infection.[5] Derangement of inflammatory markers, a possible effect of COVID-19, can lead to a prothombotic state, putting patients at risk for developing large artery occlusions. As shown in Table 3, inflammatory markers tended to be highest in large vessel atherosclerosis relative to other ischemic stroke subtypes and intracerebral hemorrhage.

The relationship between COVID-19 and intraparenchymal hemorrhage cannot be ascertained through this study, but it is important to note that patients who suffered from COVID-19 possibly related to Intracerebral Hemorrhage tended to be younger and mostly had hypertension. On the other hand, there were no significant differences between pre-pandemic and post-pandemic ICH admissions. Patients admitted with COVID-19 and ICH tended to have the usual cause identified. None of the patients who suffered from severe and critical COVID-19 were referred due to ICH. Only 1 patient who was initially admitted with AIS was readmitted with ICH, but the area of ICH was unrelated to the previously noted infarct. Furthermore, 6 out of 7 (86 %) ICH cases were admitted without prior COVID-19 symptoms.

Therapeutic implications and outcomes

In our study, the number of cases with COVID-19 infection and concomitant CVD mortality was noted to be high at 10 (37%). Of the patients who died, 2 received IV thrombolysis but eventually succumbed to death due to acute respiratory failure despite initial improvement neurologically from their baseline NIHSS.

It is difficult to establish the effect of anti-platelets on the outcome of COVID-19 with AIS due to the small number of cases admitted. Among the 15 admitted patients who had anticoagulation, there was high mortality due to acute respiratory failure. This is inconsistent with previous reports[19], but is probably due to a smaller population used for this study.

This study shows a possible link between COVID-19 and AIS. Despite the difficulty of assessment, a routine neurological evaluation should be done to patients suffering from COVID-19 and routine testing should be encouraged.

This study has several limitations; thus, the findings should be interpreted with caution. First, this is a single center study with a limited population; therefore, this study is not representative of all stroke cases admitted. Second, the retrospective observational nature of the study has potential for selection bias. Third, we did not have data on the complete diagnostic work-up of some patients and the outcomes of some patients were not included, especially those discharged against medical advice. Fourth, there is a possibility that cases of minor stroke were not detected due to difficulty performing a complete neurological evaluation of critically ill patients and fear of seeking medical consult for minor neurological complaints. Fifth, we did not provide information on transient ischemic attacks occurring in patients with COVID-19.

In conclusion, less than 5 % of the COVID-19 patients admitted present with CVD. These patients are usually younger but share similar vascular risk factors with COVID-19 negative stroke patients. There is a possible association between COVID-19 and acute ischemic stroke, especially LAA types. In this study, LAA was more frequent among patients with COVID-19 and laboratory investigation showed more derangement in this type of stroke; however, specific mechanisms should be further investigated. The relationship between ICH and COVID-19 is more difficult to establish and further study regarding this is merited.

DISCLOSURE

Financial support: None

Conflict of interest: None

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