COVID-19 ASSOCIATED HIGH MORTALITY AMONG PATIENTS WITH ACUTE STROKE IN A UNIVERSITY HOSPITAL IN KUMASI, GHANA – A RETROSPECTIVE STUDY

Ayisi-Boateng NK [1,2]; Mohammed A[3]; Konadu E[2]; Sarfo FS[1,4]

[1]Department of Medicine, [2] University Hospital, [3]Department of Epidemiology and Biostatistics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [4]Department of Medicine, Komfo Anokye Teaching Hospital, Kumasi, Ghana

Abstract

Objectives: The World Stroke Organization (WSO) has raised concerns about the global impact of COVID-19 on occurrence of stroke and its implications for stroke care, especially in low-middle-income countries. We sought to describe the profile and outcomes of acute stroke admissions in relation to COVID-19 status.

Methodology: This is a retrospective study involving all stroke patients admitted to the University Hospital, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana from 1st March, 2020 to 30th November, 2020. Stroke was diagnosed clinically and confirmed with a head Computerized Tomography scan. After the diagnosis of stroke, all patients with presentations that fitted the case definition of COVID-19 were tested using real time polymerase chain reaction (RT-PCR). Bivariate analysis was performed to identify factors associated with in-patient mortality. Statistical significance level was set at $p < 0.05$.

Results: A total of 93 patients with confirmed acute stroke were hospitalized within a 9-month period with 3 (3.2%) having confirmed COVID-19 infection. All COVID-19 cases had ischemic stroke and all of them died. Bivariate analyses identified COVID-19 status (p=0.016), mean pulse rate (p=0.036) and patients who did not receive angiotensin receptor blocker (ARB) (p=0.029) or calcium channel blockers (CCB) (p=0.016) were associated with in-patient mortality.

Conclusion: COVID-19 occurring with acute stroke is a predictor of mortality in this sample of Ghanaians. In this era of COVID-19 pandemic, patients with acute stroke should also be screened for the infection and managed appropriately to minimize death.

Key Words: *COVID-19, Hospital, Mortality, Stroke, Ghana*

Introduction

The 2019 Coronavirus disease (COVID-19) is a pandemic associated with a multi-systemic involvement including causation of cerebrovascular diseases.[1,2] Stroke in patients with COVID-19 may arise from the exaggerated inflammatory response, vascular endothelial dysfunction, hypercoagulability and increased risk of thromboembolism associated with the disease.[1] The average duration for onset of cardiovascular events from severe acute respiratory syndrome 1 and 2 (SARS-CoV-1 and SARS-CoV-2) infections has been reported as 10 to 28 days.[2] The spike protein surface unit on SARS-CoV-2 adheres tightly to the angiotensin converting enzyme 2 (ACE2), impairs its end-organ protective properties, potentially causing endothelial damage and neurological injury.[1]The incidence of stroke and non-specific neurological manifestations among patients with COVID-19 admitted to hospitals in China has been reported as 5% and 36.4% respectively.[2,1] Several cases of COVID-19-related stroke have also been recorded in Italy,[3] United Kingdom[4] and the United States of America,[5] the epicentres of the pandemic. The World stroke Organisation (WSO) has raised concerns about the global impact of COVID-19 on occurrence of stroke, disease severity and their implications for stroke care, especially in low-middle-income countries (LMICs).[6] Since 12th March, 2020 when Ghana recorded her first two imported cases of COVID-19[7] a recent study has revealed a 7.5% increase in stroke admissions at a tertiary institution with an attendant rise in stroke case fatality.[8] In the present study, we sought to assess the impact of COVID-19 co-infection on stroke presentation and its outcomes in a Ghanaian medical center.

Corresponding Author**: Dr Nana Kwame Ayisi-Boateng**
Department of Medicine, Kwame Nkrumah University of Science & Technology, Kumasi, Ghana
Email Address: ayisi31@gmail.com
Conflict of Interest: None Declared

Methods and Materials

Study Design and Setting

The University Hospital, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi is one of the centres in Ghana designated for

testing of suspected cases and treatment of confirmed COVID-19 patients.[9] It is a 125-bed quasi-government facility equipped to provide specialist and general medical services. This was a retrospective study which included data of all 93 cases of acute stroke admitted between 1st March and 30th November, 2020. The data was obtained from medical records which were documented during their period of hospitalization.

Study Context

As of 1st January, 2021, the cumulative number of confirmed COVID-19 cases in Ghana was 75,836 with 533 deaths. Preventive and relief measures have been instituted by the Government, Health Ministry and their agencies. However, the population and health facilities continue to reel under the burden of COVID-19.

Clinical and laboratory assessments

Patients with suspected stroke on admission had a computerized tomography (CT) scan of the head to confirm the diagnosis. Cardiovascular co-morbidities such as hypertension and diabetes were assessed through self-reports. Basic laboratory investigations performed included a full blood count, blood urea and creatinine measurements, chest x-rays and chest CT scan when indicated. Stroke patients with symptoms suggestive of COVID-19 and who satisfied the Ghana Health Service/Ministry of Health case definition of COVID-19[10] had nasopharyngeal samples taken. The samples were taken to the Kumasi Centre for Collaborative Research into Tropical Medicine (KCCR) and tested for severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) using real time polymerase chain reaction (RT-PCR).[11] Patient disposition on discharge were classified into alive or dead.

Statistical analysis

Comparisons of demographic, vascular risk factors, laboratory results, treatment instituted and vital status were performed using Fishers' exact tests for categorical variables and Student's t-test for continuous variables. A multivariate logistic regression model was constructed to assess factors associated with in-patient mortality. Bivariable analyses were first conducted, and variables associated with stroke mortality at a p-value of <0.10 were included in the final adjusted model. In all analysis, p-value of <0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 7 and SPSS Stata version 16 (StataCorp LLC, College Station, TX, USA).

Results

Demographic and Clinical Characteristics of Patients

Over the period of observation, 93 stroke patients were admitted. The mean age of the patients was 62.2 (SD ±15.0) years with 50 (53.8%) of them being female. [Table 1] Of the 93 patients with acute stroke, 61 (65.6%) were ischaemic, 14 (15.1%) were haemorrhagic, seven were untyped, two were ischemic with hemorrhagic transformation, and nine had normal CT findings despite being symptomatic of stroke. Three (3.2%) stroke patients tested positive for COVID-19. Approximately 87% (n = 81) had hypertension with a mean systolic blood pressure of 181.1 (SD ± 33.5) and mean diastolic blood pressure of 118.0 (SD ± 107.2). Calcium channel blockers (CCBs) were the most prescribed antihypertensives (n = 71; 76.3%) followed by angiotensin-converting enzyme inhibitors (n = 51; 54.8%). Majority (n = 75; 80.7%) received antiplatelets and 61 (65.6%) were also on statins [Table 1].

Table 1. Demographic and Clinical Characteristics of patients

Characteristic	Frequency (n=93)	Percentage, %
Age, mean ± SD	62.2 (SD ±15.0)	
Gender		
Male	43	46.2
Female	50	53.8
Marital status		
Single	7	7.5
Married	67	72.0
Widowed	12	12.9
Divorced	3	3.2
Not Known	4	4.2
Stroke Type (CT Scan)		
Ischemic	61	65.6
Haemorrhagic	14	15.1
Ischemic with hemorrhagic transformation	2	2.2
Normal	9	9.7
Not known	7	7.5
Covid-19 status		
Positive	3	3.2
Negative	90	96.8
Co-morbidities		
Hypertension		
Yes	81	87.1
No	12	12.9
Diabetes Mellitus		
Yes	31	33.3
No	62	66.7
Old Stroke		
Yes	16	17.2
No	77	82.8
Chronic Kidney Disease		
Yes	4	4.3

No	89	95.7
Sickle Cell Disease		
Yes	1	1.1
No	92	98.9
Methyldopa		
Yes	13	14.0
No	80	86.0
Hydralazine		
Yes	23	24.7
No	70	75.3
Diuretic		
Yes	43	46.2
No	50	53.8
ARB		
Yes	24	25.8
No	69	74.2
ACE		
Yes	51	54.8
No	42	45.2
BB		
Yes	37	39.8
No	56	60.2
CCB		
Yes	71	76.3
No	22	23.7
Statins		
Yes	61	65.6
No	32	34.4
Antiplatelet		
Yes	75	80.7
No	18	19.3
Anti-diabetic		
Yes	33	35.5
No	60	64.5
VTE prophylaxis		
Yes	36	38.7
No	57	61.3
WBC, mean ± SD	8.7 (SD ±4.3)	-
Neutrophils mean± SD	6.9 (SD ±8.7)	-
lymphocytes, mean ± SD	2.8 (SD ±7.3)	-
Platelets, mean ± SD	227.2 (SD ±84.3)	-
Haemoglobin, mean ± SD	13.0 (SD ±2.5)	-
eGFR, mean ± SD	65.7 (SD ±36.8)	-
Systolic BP, mean ± SD	181.1 (SD ±33.5)	-
Diastolic BP, mean ± SD	118.0 (SD ±107.2)	-
Pulse, mean ± SD	97.2 (SD ±21.3su)	-
Total cholesterol, mean ± SD	5.2 (SD ±1.5)	-
LDL-cholesterol, mean ± SD	3.2 (SD ±1.4)	-
HDL-cholesterol, mean ± SD	1.3 (SD ±0.5)	-
Triglyceride, mean ± SD	1.3 (SD ±0.5)	-
Duration of hospital stay, mean ± SD	5.8 (SD ±5.9)	-

Clinical and radiological characterization of COVID-19 cases with acute stroke

Three (3) of the hospitalized patients with acute stroke had confirmed COVID-19. One of them was an 81-year-old man who presented with altered level of consciousness but no obvious lateralizing sign. Computed tomography (CT) scan of the head showed subacute left temporal and occipital infarcts and left basal ganglia lacunar infarcts with microvascular disease (Figure 1). The second case was a 69-year-old woman who presented with sudden right sided weakness. Head CT scan showed a subacute left basal ganglia lacunar infarct with background microvascular disease and cerebral atrophy (Figure 2). The third patient was a 62-year-old man with right hemiparesis and right facial nerve palsy and expressive aphasia. A head CT scan taken on the day of presentation showed an effacement of sulci and gyri on the left in the middle cerebral artery territory (Figure 3).

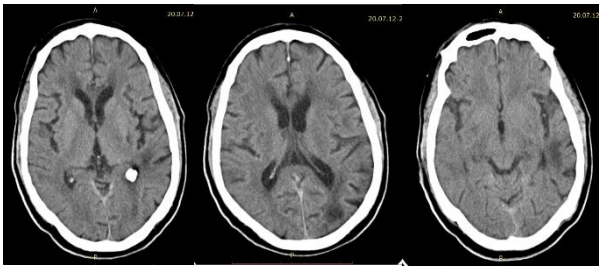

Figure 1. 81-year-old Ghanaian with COVID-19 with an ischemic stroke. Hypodense lesions in the left occipital and left temporal lobes are noted with periventricular and deep white matter hypodensities.

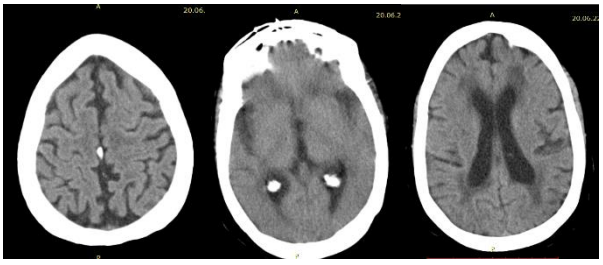

Figure 2. 69-year-old woman with COVID-19 who presented with sudden right-sided weakness *CT Scan image showed a sub-acute left basal ganglia infarct with periventricular and deep white matter hypodensities and prominence of the sulci and gyri with dilated ventricles.*

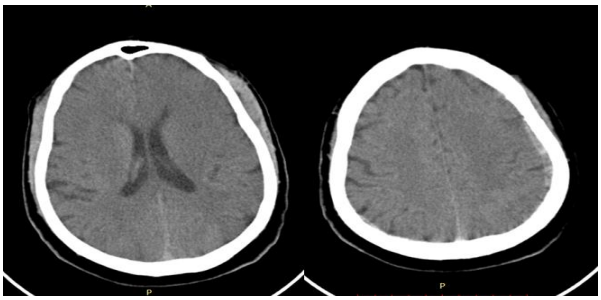

Figure 3. *62-year-old man with COVID-19 presented with right hemiparesis and right facial nerve palsy and expressive aphasia. Head CT shows effacement*

of sulci and gyri in the left middle cerebral artery territory indicative of an infarction.

Factors associated with mortality among stroke patients

Table 2 compares demographic and clinical characteristics of stroke cases that were discharged alive or dead. The mean age of patients with stroke that died was 64.5 years (SD ±13.7) and 61.4 years (SD ±15.5) in those discharged alive. There was statistically significant association between mortality and patient's COVID-19 status (p = 0.016), mean pulse rate whilst on admission (p = 0.036) and patient's medications such as angiotensin receptor blockers (ARB) (p = 0.029) and Calcium Channel Blockers (CCB) (p = 0.016) [Table 2].

Unadjusted analysis for factors associated with mortality were not being prescribed ARB nor CCB, higher white blood cell counts and pulse pressure. Upon adjustment for covariates, none of the factors were independently associated with mortality. [Table 3]

Table 2. Characteristics of stroke patients that Died and those Discharged alive (N=93)

Characteristic	Died (n=24)	Discharged Alive (n=69)	P-value
Age, mean ± SD	64.5 (SD ±13.7)	61.4 (SD ±15.5)	0.383
Gender, n (%)			0.646
Male	10 (41.7)	33 (47.8)	
Female	14 (58.3)	36 (52.2)	
Stroke Type (CT Scan) [a]			0.316
Ischaemic	13 (54.2)	48 (69.6)	
Haemorrhagic	4 (16.7)	10 (14.5)	
Both	1 (4.2)	1 (1.4)	
Normal	4 (16.7)	5 (7.2)	
Not known	2 (8.3)	5 (7.2)	
Covid-19 status[a]			0.016
Positive	3 (12.5)	0 (0.0)	
Negative	21 (87.5)	69 (100.0)	
Co-morbidities			
Hypertension			1.000
Yes	21 (87.5)	60 (87.0)	
No	3 (12.5)	9 (13.0)	
Diabetes Mellitus			0.615
Yes	7 (29.2)	24 (34.8)	
No	17 (70.8)	45 (65.2)	
Old Stroke			1.000
Yes	4 (16.7)	12 (17.4)	
No	20 (83.3)	57 (82.6)	
Chronic Kidney Disease			1.000
Yes	1 (4.2)	3 (4.4)	
No	23 (95.8)	66 (95.6)	
Sickle Cell Disease			1.000
Yes	0 (0.0)	1 (1.5)	
No	24 (100.0)	68 (98.5)	
None			1.000
Yes	1 (4.2)	4 (5.8)	
No	23 (95.8)	65 (94.2)	
Type of Medications			
Methylodpa[a]			0.503
Yes	2 (8.3)	11 (15.9)	
No	22 (91.7)	58 (84.1)	
Hydrallazine[a]			0.412
Yes	4 (16.7)	19 (27.5)	
No	20 (83.3)	50 (72.5)	
Diuretic			0.963
Yes	11 (45.8)	32 (46.4)	
No	13 (54.2)	37 (53.6)	
ARB[a]			0.029
Yes	2 (8.3)	22 (31.9)	
No	22 (91.7)	47 (68.1)	
ACE			0.580
Yes	12 (50.0)	39 (56.5)	
No	12 (50.0)	30 (43.5)	
BB			0.827
Yes	10 (41.7)	27 (39.1)	
No	14 (58.3)	42 (60.9)	
CCB			0.016
Yes	14 (58.3)	57 (82.6)	
No	10 (41.7)	12 (17.4)	
Statins			0.385
Yes	14 (58.3)	47 (68.1)	
No	10 (41.7)	22 (31.9)	
Antiplatelet			0.416
Yes	18 (75.0)	57 (82.6)	
No	6 (25.0)	12 (17.4)	
Anti-diabetic			0.082
Yes	5 (20.8)	28 (40.6)	
No	19 (79.2)	41 (59.4)	
VTE prophylaxis			0.187
Yes	12 (50.0)	24 (34.8)	
No	12 (50.0)	45 (65.2)	
WBC,mean ± SD[b]	10.2 (SD ±4.6)	8.2 (SD ±4.1)	0.050
Neutrophils mean± SD[b]	7.2 (SD ±4.8)	6.8 (SD ±9.7)	0.858
lymphocytes, mean ± SD[b]	2.0 (SD ±1.5)	3.1 (SD ±8.5)	0.511
Platelets, mean ± SD[b]	218.9 (SD ±78.0)	230.2 (SD ±86.7)	0.575
Haemoglobin, mean ± SD[b]	12.9 (SD ±2.8)	13.0 (SD ±2.4)	0.862
eGFR, mean ± SD[b]	60.1 (SD ±35.0)	67.4 (SD ±37.5)	0.455
Systolic BP, mean ± SD[b]	185.5 (SD ±33.3)	179.6 (SD ±33.7)	0.464
Diastolic BP, mean ± SD[b]	110.3 (SD ±20.9)	120.6 (SD ±123.4)	0.691
Pulse, mean ± SD[b]	105.2 (SD ±30.9)	94.5 (SD ±16.5)	0.036
Total cholesterol, mean ± SD[b]	5.5 (SD ±2.1)	5.1 (SD ±1.5)	0.652
LDL-cholesterol, mean ± SD[b]	3.2 (SD ±1.9)	3.2 (SD ±1.4)	0.970
HDL-cholesterol, mean ± SD[b]	1.6 (SD ±0.4)	1.2 (SD ±0.5)	0.130
Triglyceride, mean ± SD[b]	1.3 (SD ±0.4)	1.3 (SD ±0.5)	0.957
Duration of hospital stay, mean ± SD[b]	5.2 (SD ±6.9)	6.1 (SD ±5.5)	0.514

Table 3. Multivariate logistic regression model of associated factors of mortality among admitted stroke patients

Predictors	Unadjusted OR (95%CI)	P-value	Adjusted OR (95% CI)	P-value
Type of medications				
ARB				
Yes	1.00		1.00	
No	5.15 (1.11 – 23.86)	0.036	3.56 (0.73 – 17.46)	0.118
CCB				
Yes	1.00		1.00	
No	3.39 (1.22 – 9.44)	0.019	2.91 (0.93 – 9.18)	0.068
WBC				
Increasing WBC	1.11 (1.00 – 1.23)	0.056	1.07 (0.95 – 1.20)	0.277
Pulse				
Increasing Pulse	1.02 (1.00 – 1.05)	0.064	1.03 (1.00 – 1.05)	0.053

Discussion

In our study, majority of patients (64.9%) presented with acute ischaemic stroke with 87% having a history of hypertension. In West Africa, as in the rest of the world, hypertension is the most dominant risk factor for stroke.[12] In a large epidemiological study in Ghana and Nigeria, we found that the dominant ischemic stroke subtype is small vessel occlusive disease followed by large vessel atherosclerotic disease and cardio-embolic strokes. [12,13,14] In our study, three (3.2%) of the stroke patients tested positive for COVID-19 and all three had ischemic strokes based on non-contrast enhanced CT scans. In Spain, 19% of stroke patients admitted to a hospital were COVID-19 positive.[15] Our relatively low incidence of COVID-19 in stroke patients may be due to the fact that we performed SARS-COV-2 PCR testing for only stroke patients with suggestive symptoms. However, our findings support two studies from the United States of America and China which reported ischaemic stroke as the dominant stroke type in COVID-19 patients.[16,17]

In this study, two of the ischemic strokes among COVID-19 positive patients were attributed non-lacunar strokes in the middle cerebral artery territory and one was a lacunar or small vessel occlusive disease. Pathophysiologically, the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), though a respiratory virus, is able to evoke thrombosis in the arterial vasculature via inflammation, endothelial dysfunction, thrombin generation and platelet activation.[4,16] There have been reports linking COVID-19 with large-vessel acute ischemic strokes.[18,19] A rare case of small vessel cryptogenic stroke has been reported elsewhere.[20] Due to limited resources, severity of illness of patients and restrictions with movement of COVID-19 patients, we could not carry out detailed investigations such as cerebral angiography, carotid doppler ultrasonography or echocardiography.

In this cohort of patients with acute stroke, all three patients with COVID-19 died and therefore COVID-19 status could not be included in our multivariable analysis. COVID-19 associated strokes have been suggested to be more severe with high mortality rate due to a direct viral endotheliopathy or creation of a prothrombotic state engendered by infection-induced cardiac arrhythmias, immune-mediated platelet activation and perhaps dehydration.[16,21] Multivariate logistic regression showed that non-usage of calcium channel blockers (CCBs) and angiotensin receptor antagonists (ARBs) were marginally but not significantly associated with increased risk of mortality. CCBs are effective in mitigating the so-called ischaemic cascade, have an excellent anti-atherosclerotic properties and hence have the potential to prevent, as well as ameliorate, the severity of the atherothrombotic type of stroke at the large pre-cerebral artery level.[22] Some CCBs, especially the dihydropyridines, are also effective in the management of small vessel disease of the brain.[23]

The pathophysiology of COVID-19 and hypertension share a common pathway of the renin–angiotensin system (RAS).[24] A study during the early phase of the COVID-19 pandemic suggested a worsening outcome for infected patients with hypertension who were prescribed ARBs,[25] however, another study reported beneficial effects.[26] Angiotensin receptor blockers (ARBs) confer reno-protective advantage to patients and hence as renal function improves there is enhanced stroke survival.[27] ARBs have been recommended for BP control in people with stroke ahead of angiotensin converting enzyme inhibitors (ACE)[28]. This may explain why among our patients with stroke, those who were not on CCBs or ARBs were at increased risk of mortality.

In previous studies, high pulse rate was found as a predictor of mortality in acute stroke.[29,30] Bivariate analysis in our study showed mean pulse rate to be associated with stroke outcomes but this was lost in multivariate analysis. Tachycardia may be as a result of severe stroke (NIHSS > 15), large vessel stroke or atrial fibrillation.[31] The pulse rate of patients with stroke should be monitored and measures taken to control it to prevent mortality.

A limitation of our study is the small sample size. However, this was the total number of acute stroke cases admitted to the hospital over a period of 9 months. This is a reflection of the impact of COVID-19 on overall patient attendance at the University Hospital.[9] Additionally, COVID-19 testing was conducted only on patients with stroke who had additional symptoms suggestive of respiratory tract infections. Magnetic resonance imaging would have been ideal as a neuroimaging modality to characterize ischemic lesions but this was not available at the study site. We also did not assess stroke severity with validated stroke severity assessment instruments. In spite of these, our study, which to our knowledge is the first in sub-Saharan Africa, characterizes stroke presentations in this era of COVID-19 pandemic and provides useful data on predictors of mortality. A bigger multi-centre study which involves testing all stroke patients for COVID-19 will increase the statistical power of causality and generalizability.

Conclusion

Approximately 3% of patients with acute stroke had COVID-19 and all of them died. Due to atypical presentations of COVID-19 and its high risk of stroke, we recommend that patients with acute stroke admitted to hospitals should be actively screened for possible SARS-CoV-2 infection.

References

1. Vonck K, Garrez I, De Herdt V, Hemelsoet D, Laureys G, Raedt R, Boon P. Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2. *Eur J Neurol*. 2020;27:1578-1587. doi:10.1111/ene.14329
2. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: A single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020:1-6. doi:10.1136/svn-2020-000431
3. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan AM, Tiberio I, Munari M, Causin F. Acute stroke management pathway during Coronavirus-19 pandemic. *Neurol Sci*. 2020;41(5):1003-1005. doi:10.1007/s10072-020-04375-9
4. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humphries F, Jäger HR, Losseff NA, Perry RJ, Shah S, Simister RJ, Turner D, Chandratheva A, Werring DJ. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. 2020;0:8-11. doi:10.1136/jnnp-2020-323586
5. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, Glaser A, Elsayegh D. COVID-19 presenting as stroke. *Brain Behav Immun*. 2020;87:115-119. doi:10.1016/j.bbi.2020.04.077
6. Markus HS, Brainin M. COVID-19 and stroke—a global World Stroke Organization perspective. *Int J Stroke*. 2020;15:361-364. doi:10.1177/1747493020923472
7. GHS. covid_19_first_confirmed_GH.pdf. 2020:1.
8. Sarfo FS, Mensah NO, Opoku FA, Adusei-Mensah N, Ampofo M, Ovbiagele B. COVID-19 and stroke: Experience in a Ghanaian healthcare system. *J Neurol Sci*. 2020;416:78-81. doi:10.1016/j.jns.2020.117044
9. Ayisi-boateng NK, Singh A, Abu-sakyi J, Tawiah P, Darkwa I, Wusu-ansah OK. Commentary Fighting the COVID-19 pandemic in Ghana : a report from the Kwame Nkrumah University of Science and. 2020;37:1-5.
10. World Health Organization., Ministry of Health, Ghana Health Service. Case Management Manual for COVID-19. 2020:126.
11. Owusu M, Sylverken AA, Ankrah ST, El-Duah P, Ayisi-Boateng NK, Yeboah R, Gorman R, Asamoah J, Binger T, Acheampong G, Bekoe FA, Ohene S-A, Larsen-Reindorf R, Afum-Adjei Awuah A, Amuasi J, Owusu-Dabo E, Adu-Sarkodie Y, Phillips RO. Epidemiological profile of SARS-CoV-2 among selected regions in Ghana : A cross-sectional retrospective study. 2020:1-15. doi:10.1371/journal.pone.0243711
12. Akpalu A, Gebregziabher M, Ovbiagele B, Sarfo F, Iheonye H, Akinyemi R, Akpa O, Tiwari H.K, Arnett D, Wahab K, Lackland D, Abiodun A, Ogbole G, Jenkins C, Arulogun O, Akpalu J, Obiako R, Olowoyo P, Fawale M, Komolafe M, Osaigbovo G, Obiabo Y, Chukwuonye I, Owolabi L, Adebayo P, Sunmonu T, Owolabi M. Differential Impact of Risk Factors on Stroke Occurrence Among Men Versus Women in West Africa: The SIREN Study. *Stroke*. 2019;50:820-827. doi:10.1161/STROKEAHA.118.022786
13. Owolabi MO, Sarfo F, Akinyemi R, Gebregziabher M, Akpa O, Akpalu A, Wahab K, Obiako RL, Owolabi Ovbiagele B, SIREN Team; as part of H3Africa Consortium. Dominant modifiable risk factors for stroke in Ghana and Nigeria (SIREN): a case-control study. *Lancet Glob Heal*. 2018;6:e436-e446. doi:10.1016/S2214-109X(18)30002-0
14. Sarfo FS, Ovbiagele B, Gebregziabher M, Wahab K, Akinyemi R, Akpalu A, Akpa O, Obiako R, Owolabi L, Jenkins C, Owolabi M, SIREN. Stroke among young West Africans: Evidence from the SIREN (stroke investigative research and educational network) large multisite

case-control study. *Stroke*. 2018;49:1116-1120. doi:10.1161/STROKEAHA.118.020783
15. Naval-Baudin P, Caamaño IR., Rubio-Maicas C, Pons-Escoda A, Viñas MMF, Nuñez A, Cardona P, Majos C, Cos M, Calvo N. COVID-19 and Ischemic Stroke: Clinical and Neuroimaging Findings. *J Neuroimaging*. 2021;31:62-66. doi:10.1111/jon.12790
16. Yaghi S, Ishida K, Torres J, Grory BM, Raz E, Humbert K, Henninger N, Trivedi T, Lillemoe K, Alam S, Sanger M, Kim S, Scher E, Dehkharghani S, Wachs M, Tanweer O, Volpicelli F, Bosworth B, Lord A, Frontera J. SARS-CoV-2 and Stroke in a New York Healthcare System. 2020;Jul:2002-2011. doi:10.1161/STROKEAHA.120.030335
17. Zhang L, Sun W, Wang Y, Wang X, Liu Y, Zhao S, Long D, Chen L, Yu L. Clinical Course and Mortality of Stroke Patients with Coronavirus Disease 2019 in Wuhan, China. *Stroke*. 2020;Sept:2674-2682. doi:10.1161/STROKEAHA.120.030642
18. Arnaoutakis K. c or r e sp ondence Crizotinib in. 2015;60:683-684.
19. Square Q. Characteristics of ischaemic stroke associated with COVID-19 | *J. Neurol. Neurosurg. Psychiatry*. 2019:889-891. https://jnnp.bmj.com/content/91/8/889.long.
20. Frisullo G, Bellavia S, Scala I, Piano C, Morosetti R, Brunetti V, Calabresi P, Marca GD. Stroke and COVID19: Not only a large-vessel disease. *J Stroke Cerebrovasc Dis*. 2020;29:1-2. doi:10.1016/j.jstrokecerebrovasdis.2020.105074
21. Miller EC, Elkind MSV. Infection and Stroke: an Update on Recent Progress. *Curr Neurol Neurosci Rep*. 2016;16:1-10. doi:10.1007/s11910-015-0602-9
22. Merkel MJ, Brambrink AM. Ischämische komplikationen in der neurochirurgie: Einsatz von kalziumantagonisten. *Anaesthesist*. 2008;57:794-802. doi:10.1007/s00101-008-1394-y
23. Li YV, Zhang JH. *Metal Ion in Stroke*.; 2012. doi:10.1007/978-1-4419-9663-3
24. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol*. 2020;215:108427. doi:10.1016/j.clim.2020.108427
25. Selçuk M, Çınar T, Keskin M, Çiçek V, Kılıç Ş, Kenan B, Doğan S, Asal S, Günay N, Yıldırım E, Keskin Ü, Orhan AL. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? *Clin Exp Hypertens*. 2020;42:738-742. doi:10.1080/10641963.2020.1783549
26. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, Cai J, Yang R, Han J, Huang Y, He S. Effects of angiotensin II receptor blockers and ACE (Angiotensin-Converting Enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. *Hypertension*. 2020;76:51-58. doi:10.1161/HYPERTENSIONAHA.120.15143
27. Sarfo FS, Mobula LM, Sarfo-Kantanka O, Adamu S, Plange-Rhule J, Ansong D, Gyamfi RA, Duah J, Abraham B, Ofori-Adjei D. Estimated glomerular filtration rate predicts incident stroke among Ghanaians with diabetes and hypertension. *J Neurol Sci*. 2019;396:140-147. doi:10.1016/j.jns.2018.11.017
28. Pai PY, Muo CH., Sung FC, Ho HC., Lee YT. Angiotensin receptor blockers (ARB) outperform angiotensin-converting enzyme (ACE) inhibitors on ischemic stroke prevention in patients with hypertension and diabetes - A real-world population study in Taiwan. *Int J Cardiol*. 2016;215:114-119. doi:10.1016/j.ijcard.2016.04.096
29. Shah B, Bartaula B, Adhikari J, Neupane H, Shah B, Poudel G. Predictors of in-hospital mortality of acute ischemic stroke in adult population. *J Neurosci Rural Pract*. 2017;8:591-594. doi:10.4103/jnrp.jnrp_265_17
30. Böhm M, Cotton D, Foster L, Custodis F, Laufs U, Sacco R, Bath PMW, Yusuf S., Diener H.-C. Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J*. 2012;33:2804-2812. doi:10.1093/eurheartj/ehs250
31. Ritter MA, Rohde A, Heuschmann PU, Dziewas R, Stypmann J, Nabavi DG, Ringelstein BE. Heart rate monitoring on the stroke unit. What does heart beat tell about prognosis? An observational study. *BMC Neurol*. 2011;11. doi:10.1186/1471-2377-11-47