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Intracranial Hemorrhage in COVID-19 Patients

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Objective: To describe the clinical, laboratory, temporal, radiographic, and outcome features of acute Intracranial Hemorrhage (ICH) in COVID-19 patients. *Methods:* Retrospective, observational, consecutive case series of patients admitted with ICH to Maimonides Medical Center from March 1 through July 31, 2020, who had confirmed or highly suspected COVID-19. Demographic, clinical, laboratory, imaging, and outcome data were analyzed. ICH rates among all strokes were compared to the same time period in 2019 in two-week time intervals. Correlation of systolic blood pressure variability (SBPV) and neutrophil-to-lymphocyte ratio (NLR) to clinical outcomes were performed. *Results:* Of 324 patients who presented with stroke, 65 (20%) were diagnosed with non-traumatic ICH: 8 had confirmed and 3 had highly suspected COVID-19. Nine (82%) had at least one associated risk factor for ICH. Three ICHs occurred during inpatient anticoagulation. More than half (6) suffered either deep or cerebellar hemorrhages; only 2 were lobar hemorrhages. Two of 8 patients with severe pneumonia survived. During the NYC COVID-19 peak period in April, ICH comprised the highest percentage of all strokes (40%), and then steadily decreased week-after-week ($p = 0.02$). SBPV and NLR were moderately and weakly positively correlated to discharge modified Rankin Scale, respectively. *Conclusions:* COVID-19 associated ICH is often associated with at least one known ICH risk factor and severe pneumonia. There was a suggestive relative surge in ICH among all stroke types during the first peak of the NYC pandemic. It is important to be vigilant of ICH as a possible and important manifestation of COVID-19.

Key Words: COVID-19—Intracranial Hemorrhage—Subarachnoid hemorrhage—Intracerebral Hemorrhage—Hemorrhagic Stroke

Introduction

Strokes can be associated with common bacterial or viral infections.[1] Coronaviruses such as SARS-CoV (the virus causing severe acute respiratory syndrome or SARS) have been reported to cause neurological manifestations.[2] It remains unknown if there is a direct causal effect between coronavirus disease 2019 (or COVID-19 caused by severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) and cerebrovascular

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events. A retrospective case series from Wuhan, China indicated that approximately 36% of COVID-19 patients had neurological manifestations; five of them were diagnosed with ischemic stroke and one with cerebral hemorrhage.[3] Multiple other cerebrovascular cases series have focused on ischemic stroke.[4,5,6]

Intracranial hemorrhage (ICH) has rarely been reported in patients with infections, including the family of coronaviruses. One case of Middle East Respiratory Syndrome coronavirus (MERS-CoV) and ICH has been published.[7] Rothstein et al. reported 8 cases of ICH amongst a group of 844 COVID-19 hospitalized patients, but these included traumatic cases, those on extracorporeal membrane oxygenation and those on anticoagulation.[8] Dogra et al. discussed 33 ICH cases but most of them received therapeutic anticoagution.[9]

We report 11 cases of concurrent non-traumatic intracerebral hemorrhage and non-traumatic, non-aneurysmal, subarachnoid hemorrhage (SAH): eight confirmed with COVID-19 and three where COVID-19 was clinically and radiologically highly suspected.

Methods

This is a single-center, retrospective, observational, consecutive case series. Maimonides Medical Center is a Comprehensive Stroke Center (CSC) in Brooklyn, NY with an approximate volume of 900 strokes (including ischemic stroke, intracranial hemorrhage, and TIA) annually.

Patients who suffered from intraparenchymal hemorrhage, intraventricular hemorrhage (IVH) or SAH and had a positive SARS-CoV-2 reverse-transcriptase−polymerase-chain-reaction (RT-PCR) from nasopharyngeal swab between March 1st and July 31st, 2020 were included. Traumatic cases, hemorrhagic conversion of ischemic infarcts and hemorrhagic tumors were excluded. Patients with a high suspicion for COVID-19 based on chest CT findings with or without clinical symptoms and negative SARS-CoV-2 RT-PCR or lack of PCR testing were also included. Sensitivity of RT-PCR has been reported as low as 71% and the use of chest CT for patients with clinical and epidemiological features has been suggested to make the diagnosis.[10−12] Additionally, one study showed that nasal swabs were positive in only about 63% and pharyngeal swabs in about 32% of the cases.[13] Clinical features included fever, fatigue, cough, sore throat, dyspnea and chest CT findings included bilateral peripheral and basal ground glass opacities (GGOs) or consolidation that have been reported in patients with COVID-19.[14]

Systematic chart reviews were performed to extract demographics including age, sex and race/ethnicity, clinical information such as symptoms, diagnosis, NIH Stroke Scale (NIHSS), laboratory data such as coagulation and inflammatory markers, neuroimaging findings, and outcomes. Amongst the various parameters, blood pressure variability (BPV)[15,16] and neutrophil to lymphocyte ratio (NLR)[17] were analyzed separately to determine if there was a correlation between them and ICH severity and outcome.

As per our institutional protocol, BP was measured every 1 hour while a patient was in the Emergency Department (ED), and then either every 1 or 2 hours for the next 24 hours depending on their level of care (ICU versus stroke unit). BP measurements were recorded using an automated cuff placed in the upper arm. We used standard deviation (SD) and coefficient of variation (CV), which are the most commonly used measures of BPV. CV was calculated by Systolic Blood Pressure (SBP) SD divided by mean SBP X 100%. NLR was measured as a ratio of absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). ICH severity was assessed using the ICH score[18] and outcome was measured by modified Rankin Scale (mRS) at hospital discharge.

The number of patients with ICH during this time period were compared to previous months during 2020 and the same time period in 2019 and 2020.

Statistical analysis

All comparisons were made using a chi-square test, except for the change in ICH numbers by 2-week period, which was compared using a Cochran-Armitage test for trend. All p-values were considered significant at the $p = 0.05$ level, and were not adjusted for multiple comparisons. Spearman's rank correlation coefficient was used to compare SBPV parameters and NLR to ICH severity and outcome.

Standard protocol approvals, registrations, and patient consents

Local institutional review board approval was obtained. The requirement for informed consent was waived as per institutional policy.

Data availability statement

Any data not published within the article are available at the request of other investigators for purposes of replicating procedures and results.

Results

Prevalence of ICH

There were 324 patients with strokes who presented to our CSC during this time period with 65 (20%) diagnosed with non-traumatic ICH. We divided the study period into 2-week time periods from March 1st to July 31st, 2020. In NYC, COVID-19 cases were first noted in early March and appeared to first peak during the time period of April 1 − April 15th, 2020.[19] Additionally, by May, new cases

had dramatically reduced and by the beginning of June they remained at a stable weekly average of approximately 300 or more.

During the NYC COVID-19 peak period in April, ICH comprised the highest percentage of all strokes (40%) when compared to other two-week periods. Additionally, when comparing ICH incidence rates at our institution by roughly two-week time period, there was a descending trend as time increased ($p = 0.02$). During the study period during 2020, the ICH percentage rate was double the rate in the same time period in 2019 (20%), however we were underpowered to detect this difference ($p = 0.06$) (Fig. 1).

Case series

Eight patients were found to have concurrent confirmed COVID-19 and three had highly suspected COVID-19. The demographic, clinical, laboratory, and imaging characteristics of these patients are shown in Table 1.

Our index patient (Patient 1, Table 1) with confirmed concurrent COVID-19 and ICH was a 30-year-old male with no known medical history who presented with acute onset of slurred speech and right-sided weakness, preceded by nonproductive cough and fever for three days. He was mildly hypertensive on initial presentation with otherwise normal vital signs during hospitalization. CT head without contrast revealed a left basal ganglia hemorrhage with an ICH score of 0. CT angiography (CTA) of the head and neck with contrast showed normal vasculature but revealed patchy densities at the lung apices, which were confirmed on CT chest as bilateral peripheral GGOs. The patient tested positive for SARS-CoV-2 via RT-PCR testing. MRI brain without contrast revealed a 2 cm x 1 cm ovoid acute to early subacute hemorrhage in the left basal ganglia with possibility of adjacent small infarct. A transthoracic echocardiogram (TTE) with bubble study was unremarkable without evidence of interatrial shunt. Laboratory testing revealed low protein C antigen and functional assay, mild lymphopenia, mild elevations in Lactate Dehydrogenase (LDH) and C-reactive protein (CRP). Liver and renal functions were normal throughout admission. The patient was discharged home.

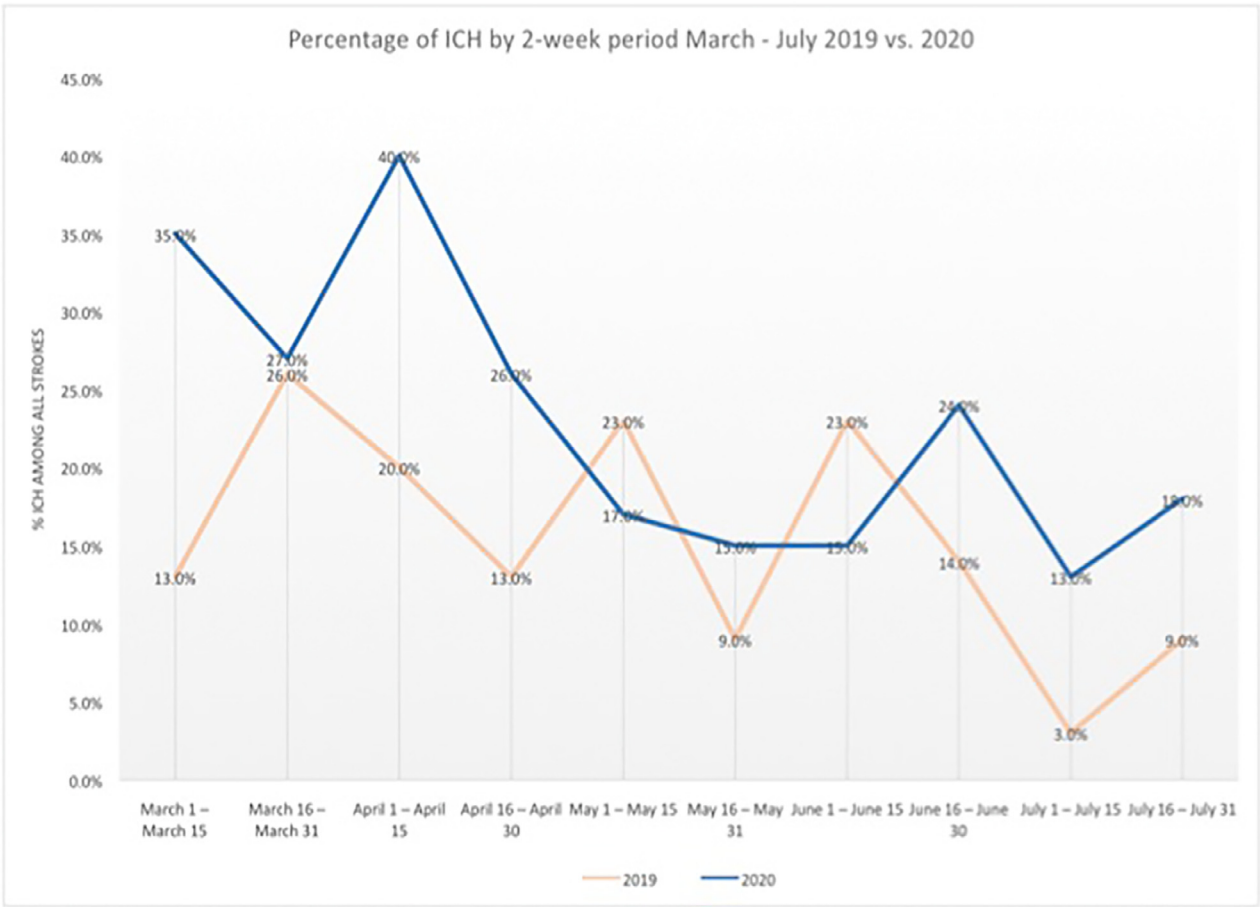

Fig. 1. *Cochran-Armitage Test For ICH from March - July 2019 versus March - July 2020.*
X axis = approximate 2-week time periods from 3/1/2020 to 7/31/2020
Y axis = percentage of ICH patients among all strokes during March - July in 2019 (orange) versus March - July in 2020 (blue).

Table 1. *Characteristics of Patients with Intracranial Hemorrhage and confirmed or suspected COVID-19*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age	30	89	66	89	69	83	70	72	95	32	79
Sex	Male	Male	Male	Female	Female	Male	Male	Female	Female	Male	Female
Race	Black	Asian	White	Black	White	White	White	White	White	White - Hispanic	White
Diagnosis	IPH	IPH, SAH	IPH	IPH, IVH	IPH, IVH, SAH	SAH, IVH (Non-aneurysmal)	IPH, IVH, SAH	IPH	IPH, IVH	IVH	SAH (Non-aneurysmal), embolic infarcts
Comorbidities*	Smoker	HTN	HTN, HLD, DM, CKD, obesity	HTN, HLD, DM	Obesity	HTN, DM, lung cancer, previous ischemic strokes, obesity	HTN, HLD, obesity	HTN, obesity	HTN, HLD, CAD	None	HTN, HLD
Antithrombotic use before ICH	None	None	None	clopidogrel	apixaban 5 mg twice daily, tPA 0.01 mg/kg	warfarin	argatroban 0.6 mcg/kg/min	heparin IV 18 units/kg/hr	aspirin, clopidogrel	None	None
Statin use before ICH	No	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes
Neuroimaging Modalities	CT, CTA, MRI	CT, CTA	CT, MRI, MRA	CT, CTA	CT, CTA	CT, CTA	CT	CT, MRI	CT	CT	CT, CTA, MRI
Brain Imaging Findings	L BG hemorrhage, small ischemic infarct on MRI	BL subcortical hemorrhages, R perimesencephalic cistern SAH, BL subdural hygromas and pontine hemorrhage on repeat CT	R thalamic hemorrhage	L occipital hemorrhage, IVH	Left F-P, BL occipital hemorrhage, IVH, left F-P SAH	BL F-T-P SAH, IVH, hydrocephalus	L BG hemorrhage, IVH, diffuse SAH	L cerebellar hemorrhage	L BG hemorrhage, IVH	Diffuse IVH, mild hydrocephalus	L F-P SAH, multiple, small embolic strokes on MRI
Vascular Imaging Findings	Unremarkable	Unremarkable	Unremarkable	Severe stenosis of L intracranial ICA, moderate stenosis of R intracranial ICA	Unremarkable	R intracranial ICA occlusion, high grade stenosis of L intracranial ICA	NP	NP	NP	NP	Unremarkable
NIHSS											
On admission	5	16	12	13	30	13	34	7	22	36	22
On discharge	3	24	11	24	N/A	N/A	N/A	4	N/A	N/A	N/A
ICH Score	0	1	0	3	4	N/A	5	1	4	N/A	N/A
Disposition	Home	SNF	SNF	SNF	Deceased	Deceased	Deceased	SNF	Deceased	Deceased	Deceased
SARS-CoV-2 nasopharyngeal RT-PCR	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	NP	Negative
Severity of SARS-CoV-2 pneumonia	Mild	Mild	Mild	Severe	Severe, intubated	Severe	Severe, intubated	Severe	Severe, intubated	Severe, intubated	Severe, intubated
BMI (kg/m^2)	N/A	21.4	40.8	17.8	31.4	32.6	35.2	35.4	26.9	N/A	22.8
Blood pressure (mmHg)											
Before or at the time of ICH	123/76	191/106	159/142	112/99	215/103	204/99	140/72	128/77	213/141	136/80	149/69
Max in first 24h after ICH	134/78	191/107	204/142	183/115	238/115	204/166	162/81	168/100	213/141	160/124	150/71
SBP mean**	123	140	151	150	143	151	126	130	N/A***	N/A***	126
SBP SD	6.7	23.5	18.7	21.2	33.9	17.7	18.8	22.2	N/A***	N/A***	22.6
SBP CV	5.4	16.7	12.4	14.1	23.7	11.7	15	17.1	N/A***	N/A***	17.9
Initial Symptoms – neurologic vs. respiratory vs. simultaneous	Respiratory	Neurologic	Neurologic	Simultaneous	Respiratory	Respiratory	Respiratory	Respiratory	Neurologic	Neurologic	Simultaneous
WBC (K/ul), [4.8-10.8]	4.6	4.9	27.1	5.1	20.9	10.5	24.8	16.2	5.7	15.8	24.3
Platelet (K/ul), [150-400]	147	147	380	148	192	275	274	344	89	230	214
Creatinine (mg/dl), [0.5-1.3]	1.0	1.1	4.9	1.2	1.0	1.4	0.9	0.6	1.8	1.3	1.2
Cholesterol (mg/dl), [101-200]	163	150	125	101	NP	NP	NP	171	NP	NP	NP
LDL (mg/dl), [40-100]	118	85	65	59	NP	NP	NP	118	NP	NP	NP
HDL (mg/dl), [>40]	27	40	39	25	NP	NP	NP	36	NP	NP	NP
HgbA1C% [4-6%]	5.5	5.9	8.1	6.6	5.7	NP	NP	4.9	5.8	NP	7.1

Table 1 (*Continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
INR, [0.9-1.2]	1.0	1.0	1.6	1.1	1.2	1.5	2.6	1	NP	1.0	1.2
PT (sec) [9.9-13.2]	11.6	11.7	18.4	12.2	14	17	31	11.1	NP	11.7	13.4
PTT (sec), [24.5-32.3])	26.6	30.1	24.7	26.1	22.3	29.3	65.9	71.0	NP	29.1	29
D-dimer (DDU ng/ml), [<318]	NP	351	NP	NP	58,804	437	2787	3263	NP	NP	14,622
LDH (IU/l), [108-199]	268	359	NP	295	1789	320	423	NP	NP	315	229
CRP (mg/dl), [0.0-0.9]	1.8	1.8	14.9	5.5	1.8	4.1	8.8	1.9	NP	0.1	31.8
Ferritin (ng/ml), [3.1-110.9]	NP	233.1	200.3	272.4	250.1	262.6	126	239.5	NP	157.6	294.6
IL-6 (pg/ml), [<5]	NP	NP	NP	NP	253.1	NP	NP	NP	NP	NP	419.8

Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, ICH = intracranial hemorrhage, IPH = intraparenchymal hemorrhage, IVH = intraventricular hemorrhage, SAH = subarachnoid hemorrhage, HTN = hypertension, HLD = hyperlipidemia, DM = diabetes mellitus, CKD = chronic kidney disease, HHS = Hunt & Hess Classification of SAH, CT = computed tomography, MRI = magnetic resonance imaging, CTA = CT angiography, MRA = MR angiography, ICA = internal carotid artery, BMI = body mass index, NP = not performed, SNF = skilled nursing facility, tPA = tissue plasminogen activator, CAA = cerebral amyloid angiopathy, L = left, R = right, BG = basal ganglia, F= frontal, P = parietal, T = temporal, SBP = systolic blood pressure, SD = standard deviation, CV = coefficient of variation, WBC = White Blood Cell, INR = International Normalized Ratio, PT = prothrombin time, PTT = Partial thromboplastin time, ESR = Erythrocyte sedimentation rate, CRP = C-reactive protein, LDH = Lactate dehydrogenase, IL-6 = Interleukin 6

*Comorbidities include hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, lung disease, previous strokes, coronary artery disease, congestive heart failure, obesity (defined as body mass index equal to or greater than 30 kg/m^2), history or current use of alcohol, drug and tobacco, history of recent head or neck trauma

**SBP mean was rounded to the nearest whole number for the table and was used with one decimal point for Spearman's rank correlation coefficient

***Patient 9: BP was not measured regularly as palliative measures were initiated within 24 hours ***Patient 10: BP was not measured for 24 hours as patient died within that time period. All laboratory values listed are first recorded values on admission with ICH or closest (+/- 3 days) to the ICH if it occurred as an inpatient.

Demographics

Eight (72%) of the eleven patients were White, two were Black, and one was Asian. Six patients (~56%) were male and five patients (45%) were female. The median age of the group was 72 and the mean age was 70. Two patients were young (30 and 32 years old). Five of the patients were obese (BMI ≥30).

Medical history and antithrombotic status

Nine patients (81%) had at least one comorbidity that put them at higher risk for ICH.[20–22] Eight patients had hypertension (HTN), five had hyperlipidemia (HLD), three had diabetes mellitus (DM) and one was a cigarette smoker. None of the patients had a history of alcohol abuse. Less than half of the patients (45%) were on a statin at home. Two patients were on antiplatelet agents and one on warfarin at home and three were receiving anticoagulation during admission prior to their hemorrhages. Patient 5 received intravenous alteplase for popliteal arterial thrombus along with apixaban twelve hours prior to that shortly before the ICH was discovered; patient 7 had received argatroban for heparin induced thrombocytopenia (HIT), and patient 8 was on a heparin infusion for pulmonary embolism (PE). Anticoagulants were appropriately dosed according to body weight and creatinine clearance. Therapeutic levels for those patients on anticoagulants during admission were maintained within the normal range in the three days preceding identification of the hemorrhage.

Clinical features

Respiratory symptoms appeared first in five patients, neurological symptoms in four, while two patients had simultaneous symptoms. Three had mild pneumonia (no signs of severe pneumonia and no need for supplemental oxygen) and the rest had severe form of the disease (fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or blood oxygen saturation level ≤ 93% on room air) with five of them requiring mechanical ventilation.[23]

Laboratory features

Leukopenia was only seen in one patient. D-dimer was most elevated in patient 5 with confirmed peripheral artery thrombosis, patient 7 with HIT and patient 10 with SAH, ischemic infarcts, and multi-organ failure. Inflammatory markers when performed (CRP, ferritin, LDH, Interleukin 6) were elevated in all patients with confirmed COVID-19. NLR was weakly positively correlated with ICH score ($r_s = 0.29$) and mRS ($r_s = 0.35$) (Table 2).

Table 2. *Spearman's rank correlation coefficient for SBPV and NLR with ICH severity and outcome*

	ICH Score	Discharge mRS
SBP SD		
r_s	0.57	0.38
p-value	0.19	0.31
NOS	7	9
SBP Mean		
r_s	-0.05	0.14
p-value	0.91	0.72
NOS	7	9
SBP CV		
r_s	0.71	0.54
p-value	0.07	0.13
NOS	7	9
NLR		
r_s	0.29	0.35
p-value	0.48	0.29
NOS	8	11

r_s = Spearman's rank correlation coefficient, NOS = number of observations

r_s ranges from +1 to -1. r_s of +1 indicates a perfect association of ranks, a r_s of 0 indicates no association between ranks and a r_s of -1 indicates a perfect negative association of ranks. The closer r_s is to 0, the weaker the association between the ranks, and the closer r_s is to ± 1, the stronger the association between the two.

Abbreviations: SBP = systolic blood pressure, SD = standard deviation, CV = coefficient of variation, NLR = neutrophil-to-lymphocyte ratio, mRS = modified Rankin Scale.

Neuroradiological features

Head CT scan was performed in all patients and four underwent MRI of the brain without contrast. CTA was performed in six and one patient underwent magnetic resonance angiogram (MRA) of the head without contrast. Cerebral angiogram was not performed in any of the cases to minimize risk of COVID-19 exposure to the staff and without imaging features or clinical concerns for underlying lesions (such as arteriovenous malformations or tumors) on high-resolution and high sensitivity CTH/CTA/MRA studies.[24]

Most hemorrhages occurred either in deep areas such as basal ganglia or in the posterior circulation. Three patients suffered unilateral deep hemorrhages, while two others suffered lobar hemorrhages. One had extensive SAH and IVH on imaging without parenchymal involvement, and another one was noted with bilateral deep hemorrhages and SAH. IVH was a common feature and seen in six patients. CT scan images of the eleven patients are demonstrated in Fig. 2.

Outcomes

All three patients with mild COVID-19 disease were safely discharged from the hospital. Out of the four patients with severe COVID-19 pneumonia, three died during their admission and one was discharged to a skilled nursing facility (SNF). Out of the three deaths, one received fibrinolytic and anticoagulation therapy while another received anticoagulation therapy before the ICH.

Patients with highly suspected COVID-19

Amongst the three cases of highly suspected COVID-19 cases, two patients had HTN, one was on antiplatelet therapy and two were on a statin before the event. Two patients had a negative SARS-CoV RT-PCR, and one did not undergo testing due to fatal ICH and impending death. One had cerebral infarction and SAH, one had IVH, and the last patient suffered a deep hemorrhage. All three patients died.

One of the abovementioned patients with suspected COVID-19 was a healthy, 32-year-old man with a history of asthma who presented with cardiac arrest (pulseless electrical activity). On presentation, he was quadriplegic and did not have any brainstem reflexes. Urine toxicology was positive for cannabinoids. Inflammatory markers (ferritin, LDH) were elevated. CT head showed diffuse IVH with mild hydrocephalus. Further vascular imaging was not performed given the catastrophic nature of the ICH.

BP variability

For BPV, SBP SD ($r_s = 0.56$) and CV ($r_s = 0.71$), were both moderately positively correlated with ICH score. SBP CV was also moderately positively correlated with mRS at discharge ($r_s = 0.54$). Higher SD and CV correlated with higher ICH score/more severe ICH and higher mRS/worse outcomes at discharge.

Discussion

In our consecutive case series of ICH in patients with definite or highly likely COVID-19, more than 80% had vascular risk factors that could predispose them to ICH, such as HTN, HLD, DM. Obesity has been linked to severe or critical illness among COVID19 patients; a little less than half of our patients were obese with most of them having the severe form of the disease.[25] Five of our patients were not on antiplatelet or anticoagulation therapy. Four patients were on therapeutic anticoagulation, with two of them suffering fatal ICH, raising the safety concern of anticoagulation in COVID-19 patients. Only two of our patients had thrombotic complications, which have been reported in many COVID-19 patients.[26] More than 70% of our patients suffered from severe COVID-19 pneumonia, with five of them requiring mechanical ventilation. Inflammatory markers and D-dimer when performed were elevated in all patients, especially those with confirmed COVID-19.

Another common, if not universal, feature of these hemorrhages is their location being either in deep areas such as basal ganglia or in the posterior circulation.

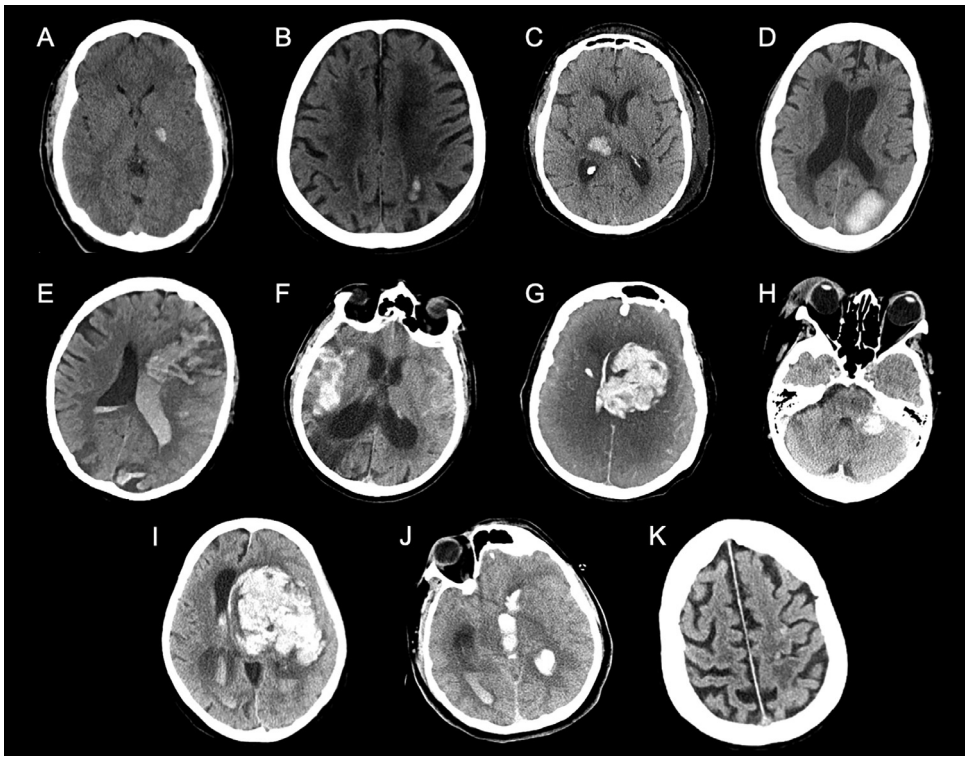

Fig. 2. *Axial CT head without contrast for all patients.*

(A) Patient 1 – Left basal ganglia hemorrhage. (B) Patient 2 – Bilateral subcortical hemorrhages and right perimesencephalic cistern subarachnoid hemorrhage (not visualized on this cut). (C) Patient 3 – Right thalamic hemorrhage. (D) Patient 4 – Left occipital and intraventricular hemorrhage. (E) Patient 5 – Left frontoparietal, bilateral occipital and intraventricular hemorrhage, left frontoparietal subarachnoid hemorrhage. (F) Patient 6 – Bilateral frontotemporoparietal subarachnoid hemorrhage, intraventricular hemorrhage and hydrocephalus. (G) Patient 7 – Left basal ganglia and intraventricular hemorrhage, diffuse subarachnoid hemorrhage. (H) Patient 8 – Left cerebellar hemorrhage, quadrigeminal cistern subarachnoid hemorrhage (not visualized on this cut), chronic right frontal subdural hematoma (not visualized on this cut). (I) Patient 9 – Left basal ganglia and intraventricular hemorrhage, 2 cm left to right midline shift, left uncal herniation (not visualized on this cut). (J) Patient 10 – Diffuse intraventricular hemorrhage and mild hydrocephalus. (K) Patient 11 – Left frontal SAH.

Additionally, IVH is also seen frequently amongst our case series. These locations may represent the "vulnerable areas" for SARS-CoV-2's selectivity for vascular invasion or compromise. As seen with COVID-19 patients without ICH, those with non-severe disease did better and were discharged from the hospital.[27] All three patients with highly suspected COVID-19 died.

Ischemic strokes have been reported with COVID-19.[3–6] Hemorrhagic strokes have also been seen, though not as commonly. A recently reported olfactory gyrus hemorrhage, a rare location for spontaneous ICH, also suggests a connection with COVID-19.[28] Benger et al. reported five cases of intracerebral hemorrhage in COVID-19 patients from London, UK.[29] Patients were younger than our cohort with a mean range of 52.2 years. Four out of the hemorrhages were in lobar areas as compared to two in our patients. There was a delay from COVID-19 symptom to ICH diagnosis with a median of 32 days, while more than half of our patients had either simultaneous or neurological symptoms first. Three of their patients were on therapeutic anticoagulation. In the retrospective study by Dogra et al, 33 patients were identified with ICH.[9] The mean age was 61.6 years and most of the patients were male. 22 patients were on therapeutic anticoagulation and 11 patients were on antiplatelets. Most patients had punctate cortical hemorrhages or small hemorrhages. Rothstein et al. reported 8 cases of ICH amongst a group of 844 COVID-19 hospitalized patients.[8] Four patients were on extracorporeal membrane oxygenation and on intravenous anticoagulation. Five were lobar, parenchymal ICH while three were SAH. Traumatic cases were excluded from our case series.

Concerning the BPV data, higher SD and CV correlated with higher ICH score/more severe ICH and higher mRS/worse outcomes at discharge. There were weak correlations between NLR ratio and ICH severity and outcomes. However, our sample size is small and further studies with a larger population will need to be performed.

Emerging evidence suggests that BPV, especially SBPV might affect outcomes of patients with ICH.[30] In a post-hoc analysis of INTERACT-2, SBPV that was measured using the standard deviation of SBP appeared to predict a poor outcome in patients with acute intracerebral hemorrhage. Additionally, a systematic review showed that greater SBPV is associated with poor long-term functional

outcome in patients with ischemic stroke or intracerebral hemorrhage.[31] Divani et al showed that higher SBPV in the first 24 hours of admission was associated with unfavorable in-hospital outcome (mRS 4-6) among 762 ICH patients.[15] BPV can be measured using various parameters such SD, CV, residual SD, successive variation (SV), mean absolute change (MAC), and average real variability (ARV).[16,32]

Inflammatory markers such as NLR have also been proposed to affect outcomes of patients with ischemic stroke and ICH.[33] Wang et al showed an association of high NLR with 30-day mortality in ICH patients[34] and a system review by Lattanzi et al described various other studies which indicate that NLR might be an independent predictor of ICH outcomes.[17] SARS-CoV-2 produces an inflammatory cascade and a higher NLR at hospital admission has been associated with a more severe outcome.[35] Therefore, it is reasonable to question if there is also a correlation between NLR and ICH severity and outcomes in patients with COVID-19.

Our study period from March to July 2020 had a higher (statistical trend) proportion of ICH cases when compared to the same time period in 2019. A retrospective, observational study from India also noted similar findings, in which 56% of their stroke cases were ICH which had increased from previous year, despite a small sample size of 25 stroke patients.[36] These observations raise the question of an association between COVID-19 and ICH.

Despite our observations, it should be noted that ICH patients tend to have severe or disabling deficits, which could motivate them to seek medical care and early despite the pandemic. TIAs or ischemic strokes can occur with transient or mild deficits, for which patients might not necessarily want to seek urgent care due to the fear of contracting COVID-19 in the hospital.[37] This could explain the higher proportion of ICH patients seeking hospital care amongst all strokes when comparing 2019 to 2020.

Infections, though rare, have been associated with ICH and SAH.[1,38,39] In one case-control study, infection within four weeks was associated with SAH independently of hypertension and smoking.[38] Central nervous system (CNS) viral infections such as by herpes simplex virus (HSV) have been known to cause hemorrhagic strokes.[39] The pathogenesis most likely involves damage to the neurovascular unit due to cytokine, chemokine, and protease actions increasing blood brain barrier (BBB) permeability.

Increasing evidence suggests that COVID-19 also produces a hyperinflammatory syndrome characterized by the cytokine cascade and multi-organ failure, which in turn can cause ICH.[40] SARS-CoV-2 could invade the CNS similarly to SARS-CoV and MERS-CoV through the hematogenous or retrograde neuronal route.[3] The angiotensin-converting enzyme 2 (ACE2) receptor has been proposed as a possible major cellular mediator of COVID-19 invasion and is found in the cerebral cortex, hypothalamus and brainstem.[41] SARS-CoV-2 has been documented to enter vascular endothelium leading to endothelitis that could trigger microthrombosis of small penetrating arteries and lead to increased risk for ICH.[42–44] Additionally, the coronavirus−ACE 2 binding is responsible for direct damage to the BBB, which might cause loss of homeostatic regulation of blood flow to the brain, increased susceptibility to blood pressure (BP) changes or elevations in BP and predispose to the occurrence of cerebral hemorrhage.[40,45] Neuronal ACE2 expression could also be a significant factor in COVID-19 cases associated with ICH.[46] Chen et al. reported decreased ACE2 expression in the lungs of COVID-19 patients.[47] Downregulation of ACE2 expression may increase risk of hemorrhagic stroke as ACE2 deficiency in the brain may impair endothelial function in cerebral arteries leading to cerebrovascular events, and may increase local angiotensin-II levels, which acting on angiotensin II receptor type 1 (AT1) receptors may rise BP and facilitate hypertrophy and fibrosis.[46]

Emerging data also suggest that hyperfibrinolysis potentially leading to increased bleeding risk can also be seen with COVID-19 infection.[48] Possible fibrinolysis mechanisms from COVID-19 include elevated plasminogen levels that are described in comorbid conditions such as HTN, DM and cardiovascular disease, elevated urokinase (uPA), tissue plasminogen activator (tPA) and plasminogen, and alternative pathways of fibrinogen cleavage and D-dimer formation (viral proteases) as well as the immune response itself (elastase, cathepsin G, matrix metalloproteinase-3).[48-50] Systemic microthrombi in the circulatory system and hemorrhage in the affected organs might result from uncoordinated responses between the coagulation and fibrinolysis systems.[49] Additionally, disseminated intravascular coagulation (DIC), which has been reported with COVID-19, can increase bleeding risk.[51] There appears to be a relationship between inflammation and coagulation, and slightly prolonged prothrombin time (PT) and partial thromboplastin time (PTT) have been noted along with mild thrombocytopenia. In one retrospective study, thrombocytopenia with platelet count $<150 \times 10^9$/L and elevations in D-dimer >2500 ng/mL at initial presentation were also predictive of bleeding complications during hospitalization.[51]

The limitations of our study include its relatively small sample size and single center population. Additionally, it is a retrospective, observational case series, and lacks a control group. Our CSC experienced an increase (statistical trend) in ICH at the height of the COVID-19 pandemic. Typically more severe clinical features of ICH likely prompted hospital visits and admissions as opposed to those COVID-19 patients with mild ischemic stroke symptoms fearful of hospital acquired infection. Although it may not be the most frequent COVID-19 neurological manifestation, ICH remains an important consideration,

often with severe morbidity or mortality, in the setting of this global pandemic.

Conclusions

COVID-19 associated ICH is often associated with at least one known ICH risk factor and severe pneumonia. There was a suggestive relative surge in ICH among all stroke types during the first peak of the NYC pandemic. While we cannot be certain of an independent causal connection between the two, it is important to be vigilant of ICH as a possible and important manifestation of COVID-19.

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