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Hemorrhagic stroke and anticoagulation in COVID-19

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Background and Purpose: Patients with the Coronavirus Disease of 2019 (COVID-19) are at increased risk for thrombotic events and mortality. Various anticoagulation regimens are now being considered for these patients. Anticoagulation is known to increase the risk for adverse bleeding events, of which intracranial hemorrhage (ICH) is one of the most feared. We present a retrospective study of 33 patients positive for COVID-19 with neuroimaging-documented ICH and examine anticoagulation use in this population. *Methods:* Patients over the age of 18 with confirmed COVID-19 and radiographic evidence of ICH were included in this study. Evidence of hemorrhage was confirmed and categorized by a fellowship trained neuroradiologist. Electronic health records were analyzed for patient information including demographic data, medical history, hospital course, laboratory values, and medications. *Results:* We identified 33 COVID-19 positive patients with ICH, mean age 61.6 years (range 37−83 years), 21.2% of whom were female. Parenchymal hemorrhages with mass effect and herniation occurred in 5 (15.2%) patients, with a 100% mortality rate. Of the remaining 28 patients with ICH, 7 (25%) had punctate hemorrhages, 17 (60.7%) had small- moderate size hemorrhages, and 4 (14.3%) had a large single site of hemorrhage without evidence of herniation. Almost all patients received either therapeutic dose anticoagulation (in 22 [66.7%] patients) or prophylactic dose (in 3 [9.1] patients) prior to ICH discovery. *Conclusions:* Anticoagulation therapy may be considered in patients with COVID-19 though the risk of ICH should be taken into account when developing a treatment regimen.

Keywords: COVID-19—Intracranial hemorrhage—Anticoagulation—Hemorrhagic stroke

Introduction

Recent studies have shown that patients with Coronavirus Disease of 2019 (COVID-19) are predisposed to developing thrombotic events.[1–3] COVID-19 patients in intensive care units (ICU) have an increased rate of venous thromboembolism (VTE), ranging from 17% to

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25%.[1,2] Moreover, COVID-19 patients have elevated coagulation markers such as D-dimer, which in turn is correlated with increased mortality.[3] Recent expert opinion recommends that all admitted patients receive VTE prophylaxis, but some centers have escalated their anticoagulation regimen for patients with certain risk factors.[4] Some ICU centers have also begun to empirically use therapeutic anticoagulation for presumed pulmonary emboli.[4]

The greatest concern of increased anticoagulation use is an increased risk of bleeding in general and of intracranial hemorrhage (ICH) in particular. In studies of patients on oral anticoagulation, ICH was shown to be the most devastating adverse event overall; these patients also had more extensive bleeding and increased mortality compared to patients with spontaneous ICH.[5,6] While information on bleeding remains limited in COVID-19 patients, one study suggested that many COVID-19 patients with high risk of thrombosis were simultaneously at increased risk for bleeding.[7] Although there have been recent publications about ischemic stroke in COVID-19 patients,[1] literature regarding ICH in patients with COVID-19 is currently limited.[8,9] We evaluated the presence of ICH in hospitalized COVID-19 patients and correlated imaging findings with their anticoagulation status.

Materials and methods

This cohort study was approved by the Institutional Review Board with informed consent waived. Out of 3824 COVID-19 positive adult (age over 18) patients admitted to the NYU Langone Health system (Tisch Hospital, Kimmel Pavilion, NYU Brooklyn, NYU Winthrop, or NYU Langone Orthopedic Hospital) between March 1st and April 27th, 2020, neuroimaging was done in 755 patients. After reviewing the neuroimaging reports for these patients, 37 were found to have documented radiographic evidence of hemorrhage.

Neuroimaging for these patients was reviewed by a fellowship-trained neuroradiologist, blinded to clinical data and outcome, to verify the presence and type of hemorrhage. Four patients who had hemorrhage secondary to trauma (n = 2), bleeding in brain metastases (n = 1), or after tumor resection (n = 1) were excluded. Of the 33 remaining patients (4.4% of the 755 patients with COVID-19 diagnoses and neuroimaging), 24 had only a CT scan and 9 had both a CT and an MRI.

Electronic health records of all patients with verified hemorrhage were then examined in order to review demographic data, medical history, hospital course, medications, and laboratory values including estimated glomerular filtration rate (eGFR) due to associations between impaired renal function and increased risk of venous thromboembolism as well as bleeding. Therapeutic anticoagulation for our cohort was classified as any intravenous heparin, any intravenous argatroban, or enoxaparin dose above prophylactic levels (40mg subcutaneously daily or 30mg subcutaneously twice daily for BMI <40; 40mg subcutaneously twice daily for BMI>40).[10,11] The closest D-dimer to the scan within 48 hours of imaging was recorded. Follow-up was performed through May 6th, 2020 to track mortality, continued hospitalization, or discharge for all patients.

A modified version of the classification system used for the European Cooperative Acute Stroke Study was used to classify hemorrhages as infarct with petechial hemorrhage, infarct with small hemorrhage (<5 cm), single site of large parenchymal hemorrhage with local mass effect but without herniation, and multiple sites of parenchymal hemorrhages with mass effect and herniation (Fig. 1).[12] ICH Score was calculated for all patients.[13]

Results

Patient demographics and pertinent laboratory data

We identified 33 COVID-19 positive patients with ICH, mean age 61.6 years (range 37−83 years), 21.2% were female, with a median ICH score of 2 (interquartile range [IQR] 1-2) (Table 1). As of May 6th, 2020, mortality occurred in 14 (42.4%) patients, 15 (45.5%) patients were still hospitalized, and 4 (12.1%) patients had been discharged. Initial radiographic evidence of hemorrhage was seen on median hospital day 17 (IQR 8-23) although 4 (12.1%) patients were found to have ICH on initial presentation. Immediately prior to discovery of the bleed, 10 (30.3%) patients had an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2. Within the 72 hours prior to hemorrhage discovery, 11 (33.3%) patients were thrombocytopenic with platelet counts below 150 × 10^3/μ. The median D-dimer value prior to hemorrhage discovery was 2204 ng/mL (IQR 1232−3074 ng/mL).

Anticoagulation and antiplatelet status

Therapeutic dose anticoagulation prior to ICH discovery was administered to 22 (66.7%) patients (Table 2). Prophylactic dose anticoagulation was administered to 3 (9.1%) patients. Two (6.1%) patients who presented with hemorrhage had been on long-term warfarin and dabigatran at home prior to admission. Six (18.2%) patients never received anticoagulation either before or during their hospitalization; three were on antiplatelet medication only, two had thrombocytopenia (platelet count <75 on admission), and a sixth presented with systemic hemorrhage of unknown etiology and thus anticoagulation was withheld. Six (27.3%) patients received concurrent inpatient therapeutic anticoagulation and antiplatelet therapy, and one (4.5%) patient received concurrent inpatient prophylactic anticoagulation and antiplatelet therapy.

Therapeutic anticoagulation cohort

Of the 22 patients that were on therapeutic anticoagulation as an inpatient, the indication in 18 (81.8%) patients

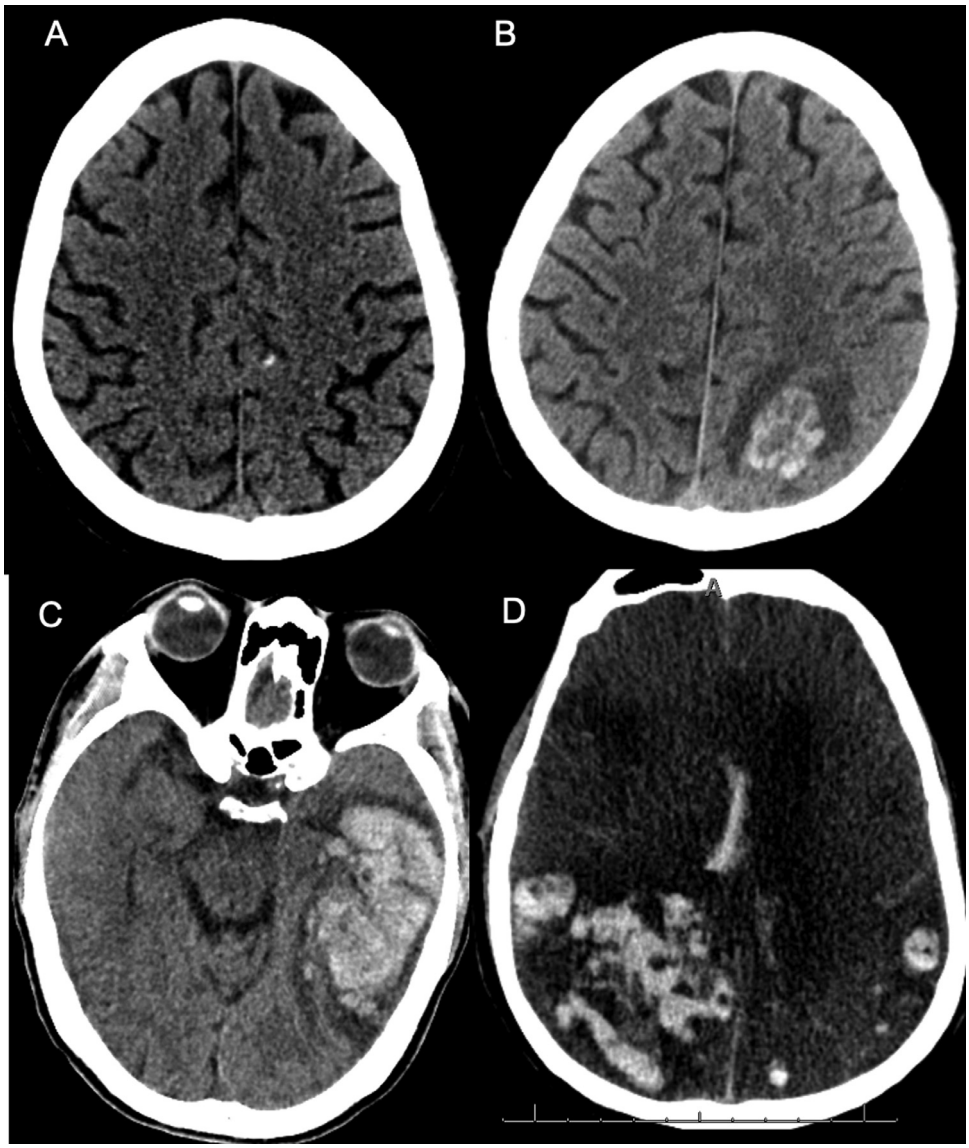

Fig. 1. *CT images of four different patients demonstrating petechial hemorrhage in a small cortical infarct (A), infarct with small hemorrhage (<5 cm) (B), single site of large parenchymal hemorrhage with local mass effect (C), and multiple sites of parenchymal hemorrhages with mass effect and herniation (D).*

was elevated D-dimer levels (median 3493 ng/mL, IQR 2468−9296 ng/ml), and 4 (18.2%) had a known or suspected thrombus (Table 2). For these 22 patients, the therapeutic anticoagulation regimen was as follows: 15 (68.2%) received only intravenous unfractionated heparin (UFH), 3 (13.6%) received UFH and enoxaparin at different times, 3 (13.6%) received UFH and argatroban at different times, and 1 (4.5%) received only enoxaparin. Changes between UFH and enoxaparin and vice versa were made based on eGFR. Argatroban was used when there was concern for heparin-induced thrombocytopenia (HIT); however, four patients were tested for HIT antibodies, and all were eventually noted to be negative. Of the 22 patients on therapeutic anticoagulation, 12 (54.5%) had a supratherapeutic anti-factor Xa or partial thromboplastin time (PTT) within 72 h prior to the ICH.

Types of parenchymal hemorrhage and clinical correlation

Of the 33 patients with ICH, 5 (15.2%) had parenchymal hemorrhages with mass effect and herniation. These images were particularly notable as all 5 patients also had radiographic evidence of diffuse hypoxic ischemic injury and brain swelling and a 100% mortality rate (Table 1). All 5 patients had received therapeutic anticoagulation, 3 (60%) for a high D-dimer and 2 (40%) for a known thrombus. Imaging evidence of hemorrhage was seen on median day 22 (IQR 19−28) of hospitalization. Among these 5 patients, 4 (80%) patients had an anti-factor Xa or PTT above the upper limit of normal within 72 hours prior to the bleed (Table 2). Based on review by the study neuroradiologist, all of these hemorrhages were thought to be primary ICH rather than hemorrhagic conversion of ischemic stroke.

Table 1. *Demographic, admission, imaging, and laboratory data for all patients with intracranial hemorrhage. Data is presented as* n *(%) unless otherwise specified. Lab values are within 72 h prior to hemorrhage discovery, besides D-dimer, which is the closest value within 48 h of imaging.*

Parameter	Total (n = 33)	Large hemorrhage with herniation (n = 5)	Other hemorrhages (n = 28)
Age, median (range) in years	62 (37−83)	62 (37−74)	62 (40−83)
Female	7 (21.2)	0 (0)	7 (25.0)
Comorbidities			
BMI, mean (SD)	28.9 (5.6)	32.9 (9.0)	28.1 (4.6)
Congestive heart failure	3 (9.1)	0 (0)	3 (10.7)
Coronary artery disease	4 (12.1)	1 (20.0)	3 (10.7)
Diabetes	10 (30.3)	2 (40.0)	8 (28.6)
Hyperlipidemia	12 (36.4)	2 (40.0)	10 (35.7)
Hypertension	16 (48.5)	3 (60.0)	13 (46.4)
Hypothyroidism	2 (6.1)	0 (0)	2 (7.1)
Liver disease	1 (3.0)	0 (0)	1 (3.6)
Prior malignancy	3 (9.1)	2 (40.0)	1 (3.6)
Prior stroke	1 (3.0)	0 (0)	1 (3.6)
Renal disease	1 (3.0)	0 (0)	1 (3.6)
Time to Hemorrhage Identification, median days (IQR)	17 (8−23)	22 (19−28)	16 (8−33)
GCS at time of Scan, median (IQR)	3 (3−9)	3 (3-3)	3 (3−10)
ICH Score, median (IQR)	2 (1-2)	5 (5-5)	2 (1-2)
Indication for Brain Imaging			
Encephalopathy	17 (51.5)	1 (20)	16 (57.1)
Focal weakness	7 (21.2)	0 (0)	7 (25.0)
Absent brainstem reflexes	4 (12.1)	4 (80)	0 (0)
Incidental finding	2 (6.1)	0 (0)	2 (7.1)
Seizure like symptoms	2 (6.1)	0 (0)	2 (7.1)
Aphasia	1 (3.0)	0 (0)	1 (3.6)
Hemorrhage on initial presentation	4 (12.1)	0 (0)	4 (14.3)
eGFR <30 prior to ICH	10 (30.3)	2 (40)	8 (28.6)
Platelet nadir prior to ICH, median [IQR]	200 (123−270)	147 (123−187)	227 (118−274)
Nadir 100 to 149, n (range)	4 (101−147)	2 (123−147)	2 (101−124)
Nadir 50 to 99, n (range)	6 (50−97)	1 (50)	5 (51−97)
Nadir 0 to 49, n (range)	1 (15)	0	1 (15)
D-dimer prior to ICH, median (IQR)	2204 (1232−3074)	2069 (1791−4488)	2338 (1209−3030)
Peak INR prior to ICH, median (IQR)	1.3 (1.2−2.0)	1.6 (1.3−2.9)	1.3 (1.2−1.7)
Peak PTT prior to ICH, median (IQR)	77.0 (42.2−96.2)	86.1 (66.8−121.4)	75.1 (41.7−85.8)
Peak Xa prior to ICH, median (IQR)	0.7 (0.4−1.0)	1.1 (1.0−1.1)	0.6 (0.3−0.8)
Mortality	14 (42.4)	5 (100)	9 (32.1)

Abbreviations: SD = standard deviation; IQR =interquartile range; BMI = body mass index; ICH = intracranial hemorrhage; eGFR = estimated glomerular filtration fraction; INR: international normalized ratio; PTT = partial thromboplastin time

Of the other 28 patients with ICH, 7 (25%) had punctate hemorrhages, mostly involving the cortex, 17 (60.7%) had small hemorrhages, and 4 (14.3%) had a large single site of hemorrhage without evidence of herniation (Table 1). Based on review by the study neuroradiologist, 26/28 (92.9%) bleeds were considered to have suffered hemorrhagic conversion of an ischemic infarct. Mortality was 8/24 (33.3%) of the patients with punctate and small hemorrhages and 1/4 (25%) of the patients with large single hemorrhages without herniation.

Discussion

Discussions regarding anticoagulation for COVID-19 patients have been intensifying as evidence of hypercoagulability in this population continues to accumulate. Decisions about anticoagulation must, in part, take the risk of ICH following anticoagulation into consideration. Our data will certainly be helpful in this regard. We found that 4.4% of 755 patients diagnosed with positive COVID-19 and with concurrent neuroimaging had ICH. The majority of these patients received therapeutic anticoagulation, most commonly UFH. The most frequent indication for starting anticoagulation was elevated D-dimer levels, reflecting a trend among centers to intensify anticoagulation regimens in COVID-19 positive patients based on evidence of hypercoagulability including increased D-dimer.[4] Although the large hemorrhages causing herniation were thought to be the result of primary intracranial

Table 2. *Anticoagulation and antiplatelet therapy for all patients with intracranial hemorrhage. Data is presented as* n *(%) unless otherwise specified.*

Parameter	Total (n = 33)	Large hemorrhage with herniation (n = 5)	Other hemorrhages (n = 28)
Supratherapeutic anti-factor Xa or PTT within 72 h prior to bleed	15 (45.5)	4 (80)	11 (39.3)
Anticoagulation prior to bleed*			
Therapeutic dose	22 (66.7)	5 (100.0)	17 (60.7)
Unfractionated heparin, n	21	5	16
Enoxaparin, n	4	0	4
Argatroban, n	3	0	3
Prophylactic dose	3 (9.1)	0 (0)	3 (10.7)
Anticoagulation prior to admission	2 (6.1)	0 (0)	2 (7.1)
None	6 (18.2)	0 (0)	6 (21.4)
Indication for Inpatient Anticoagulation			
Elevated D-dimer	18 (72.0)	3 (60.0)	15 (75.0)
Thrombus	4 (16.0)	2 (40.0)	2 (10.0)
Standard prophylaxis	3 (12.0)	0 (0)	3 (15.0)
Antiplatelet therapy prior to bleed			
None	22 (66.7)	3 (60)	19 (67.9)
Aspirin alone	7 (21.2)	1 (20)	6 (21.4)
Aspirin and clopidogrel	2 (6.1)	0 (0)	2 (7.1)
Cilostazol alone	1 (3.0)	0 (0)	1 (3.6)
Clopidogrel alone	1 (3.0)	1 (20)	0 (0.0)

*Therapeutic dose numbers sum to more than the number of patients receiving therapeutic anticoagulation as patients received multiple types of therapeutic anticoagulation at different periods of their hospitalization.

hemorrhage, the majority of the other hemorrhages were hemorrhagic transformation of ischemic stroke.

Of particular interest is our subgroup of 5 patients with large parenchymal hemorrhages causing mass effect and herniation. Mortality was 100% in these patients, all of whom were on continuous UFH and were found to have hemorrhages many days into their hospitalization. Although two of these patients were placed on therapeutic anticoagulation due to known or suspected thrombosis, the other three were started on therapeutic anticoagulation because of increasing D-dimer levels. Although empiric anticoagulation has been shown to lower 28-day mortality in COVID-19 patients with severely elevated D-dimer,[14] this sobering outcome underscores the need for randomized clinical trials to properly assess benefit versus risk regarding anticoagulation strategies in COVID-19. It also raises the question of whether a screening head CT should be done prior to starting anticoagulation in patients with mental status too impaired to obtain a good neurological assessment, so as to avoid the risk of catastrophic hemorrhage in an unsuspected large acute infarct.

In our study, many patients had punctate hemorrhages that were characterized as cortical in nature on MRI, but that were either mischaracterized as subarachnoid hemorrhage or not seen on CT. MRI is known to have better sensitivity than CT for detecting small ICH,[15] but as neuroimaging use, and particularly MRI use, has decreased significantly during the COVID-19 pandemic, some patients with ICH may have an ICH that is diagnosed late or missed entirely.

Our study has multiple limitations, most importantly its descriptive nature as well as a small sample size. It is possible that additional patients with ICH in this cohort were not identified either because the patients were heavily sedated and there was no opportunity for a detailed neurological examination and there was a desire to limit transport out of the room for neuroimaging. As such, MRI use was limited in this cohort and adjudication of ICH etiology were made to the best of our ability. We were not able to review all COVID-19 patients getting anticoagulation to see how many of them had ICH, and we did not include patients with neuroimaging but no hemorrhage in this descriptive paper. We did not compare our patients to COVID-19 patients who had neuroimaging without evidence of hemorrhage.

Nevertheless, we believe our study provides important initial data regarding ICH and anticoagulation in patients hospitalized with COVID-19. Future work must look more deeply into the benefits and consequences of anticoagulation for COVID-19 patients, through outcomes analysis and well-powered, prospective, randomized clinical trials.

Declaration of Competing Interest

R. Jain is a consultant for Cancer Panels Inc., receive royalties from Thieme Inc., and is on the advisory board

for Nuevozen Inc. S. Galetta has served as a consultant to Biogen. The other authors report no conflicts.

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