Risk factors for intracerebral hemorrhage in patients with COVID-19

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Abstract
Intracerebral hemorrhage (ICH) can be a devastating complication of coronavirus disease (COVID-19). We aimed to assess risk factors associated with ICH in this population. We performed a retrospective cohort study of adult patients admitted to NYU Langone Health system between March 1 and April 27 2020 with a positive nasopharyngeal swab polymerase chain reaction test result and presence of primary nontraumatic intracranial hemorrhage or hemorrhagic conversion of ischemic stroke on neuroimaging. Patients with intracranial procedures, malignancy, or vascular malformation were excluded. We used regression models to estimate odds ratios and 95% confidence intervals (OR, 95% CI) of the association between ICH and covariates. We also used regression models to determine association between ICH and mortality. Among 3824 patients admitted with COVID-19, 755 patients had neuroimaging and 416 patients were identified after exclusion criteria were applied. The mean (standard deviation) age was 69.3 (16.2), 35.8% were women, and 34.9% were on therapeutic anticoagulation. ICH occurred in 33 (7.9%) patients. Older age, non-Caucasian race, respiratory failure requiring mechanical ventilation, and therapeutic anticoagulation were associated with ICH on univariate analysis (p < 0.01 for each variable). In adjusted regression models, anticoagulation use was associated with a five-fold increased risk of ICH (OR 5.26, 95% CI 2.33–12.24, p < 0.001). ICH was associated with increased mortality (adjusted OR 2.6, 95 % CI 1.2–5.9). Anticoagulation use is associated with increased risk of ICH in patients with COVID-19. Further investigation is required to elucidate underlying mechanisms and prevention strategies in this population.

Keywords Anticoagulation · COVID-19 · Hemorrhagic stroke · Intracerebral hemorrhage · Mechanical ventilation

Highlights

- Intracerebral hemorrhage (ICH) occurs in patients with coronavirus disease (COVID-19).
- Older age and respiratory failure are associated with ICH.
- Anticoagulation use is associated with a five-fold increased risk of ICH.
- ICH is associated with mortality in patients with COVID-19.
- Further studies are warranted for improved prevention of ICH in this population.

Introduction

Intracerebral hemorrhage (ICH) is a devastating complication of coronavirus disease (COVID-19) and is associated with significant mortality [1–3]. In the general population,

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ICH portends a high mortality rate of 24–40%, [4, 5] and in anticoagulated patients, ICH is associated with an even higher mortality rate of 60% [6]. Older age, non-Caucasian ethnicity, prolonged activated partial thromboplastin time (aPTT) and therapeutic anticoagulation use are known risk factors for ICH [4–12].

We have previously examined the radiographic and clinical characteristics of 33 patients with COVID-19 who presented with ICH or developed ICH during hospitalization [1, 2, 13]. We have further studied a population of primary ICH and non-aneurysmal subarachnoid hemorrhage patients with COVID-19 in comparison with contemporary and historical controls [3]. Here, our aim is to examine all patients with COVID-19 with concomitant neuroimaging and compare patients with COVID-19 and ICH to those without ICH to assess risk factors associated with ICH and to further elucidate the association between anticoagulation use and ICH in this patient population.

Materials and methods

The study was approved by the NYU Grossman School of Medicine Institutional Review Board, IRB # i20-00567, who has granted the waiver for informed consent. Data from this study will be shared upon reasonable request by emailing the corresponding author.

Study population

We performed a retrospective cohort study of adult (age ≥ 18 years) patients admitted to the NYU Langone Health System (NYU Langone Medical Center, NYU Brooklyn, NYU Winthrop, or NYU Langone Orthopedic Hospital) who had both a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test result and neuroimaging performed between March 1 and April 27, 2020. Patients without neuroimaging were excluded due to the potential for unidentified ICH in this cohort.

Primary predictor—anticoagulation use

We classified anticoagulation use as therapeutic or prophylactic. Therapeutic anticoagulation was defined based on treatment with (1) therapeutic dose oral anticoagulation, (2) any dose of intravenous heparin or argatroban, (3) subcutaneous heparin at a total daily dose greater than 15,000 units (5000 units three times a day or 7500 units twice a day), or 4) enoxaparin at greater than 40 mg twice a day for BMI ≥ 40, and either 30 mg twice a day or 40 mg once a day for BMI < 40. All other anticoagulation use was considered prophylactic. At our institution, therapeutic anticoagulation was started for COVID-19 patients when there

was a known or highly suspected thrombotic event [14–17] or if the patient was considered to be extremely high risk for thrombosis based on elevated D-dimer using the following paradigm: possible therapeutic anticoagulation for D-dimer 2000–10,000 ng/mL and strong consideration of therapeutic anticoagulation for D-dimer >10,000 ng/mL.

Primary outcome

The primary outcome was ICH defined as acute hemorrhage (primary intraparenchymal bleed or hemorrhagic conversion of ischemic stroke) diagnosed on neuroimaing obtained during the index hospitalization. Patients with only subarachnoid hemorrhage or subdural hemorrhage were excluded.

Covariates

Through chart review, we obtained data on demographics, comorbid diseases, mechanical ventilation use, timing of intubation, intensive care unit (ICU) admission, laboratory values, imaging results, and discharge disposition as of May 30, 2020 for all patients. We obtained peak or nadir lab values for a period of 72 h prior to imaging. We calculated the Sequential Organ Failure Assessment (SOFA) [18] score was calculated at admission and the maximum during admission. Glasgow Coma Scale (GCS) was calculated at the time of imaging. A board certified neuroradiologist identified radiographic ICH characteristics including ICH location and etiological adjudication on the first neuroimaging study with evidence of ICH. ICH score [7] was calculated based on initial head CT by a board certified neurointensivist.

Statistical methods

Discrete variables are presented as frequency and percentage, and continuous variables are presented as means and standard deviation (SD) or median with the interquartile range (IQR). Unadjusted differences in variables comparing patients with ICH to those without ICH were evaluated using Pearson's χ^2 test, Students t test, and Wilcoxon rank sum test for categorical, parametric continuous, and non-parametric continuous variables respectively. We also compared unadjusted differences in patients on therapeutic anticoagulation to patients without. We further evaluated independent predictive values of coagulation function on ICH using a receiver operating characteristic (ROC) curve. The associations between lab parameters and the risk of ICH in COVID-19 patients were expressed as the area under the ROC curve (AUC) [19]. Discharge mortality rate was determined for the ICH and non-ICH cohort.

We used binary logistic regression models to estimate the odds ratios and 95% confidence intervals (OR, 95% CI) of therapeutic anticoagulation use and ICH in patients

hospitalized with COVID-19 adjusting for previously identified factors associated with ICH (age, gender, ethnicity, hypertension, systolic blood pressure) and might plausibly be associated with ICH in COVID-19 patients. Binary logistic regression models were used to assess for mortality in both ICH and non-ICH patients adjusting for previously reported risk factors, age [7] and maximum hospital SOFA score, [18] as a marker for disease severity.

As a sensitivity analysis, we performed binary logistic regression to determine the association between anticoagulation use and ICH adjusting for exposure variables associated with ICH on univariate analysis (excluding variables with co-linearity). We used p values that were two-tailed and we considered $p < 0.05$ significant. Analyses were performed using SPSS version 25.0 (Chicago, IL).

Results

Among 3824 patients admitted with positive SARS-CoV-2 PCR during the study period, 755 had brain imaging available for review, 416 (55%) of whom were identified after exclusion criteria were applied. Of those, 33 patients had ICH and 383 patients did not (Fig. 1). In our entire cohort, patient mean age (standard deviation) was 69.3 (16.2) and 35.8% of patients were women (Table 1). Median

(interquartile range) BMI was 27.4 (24.2–31.6). Comorbidities included atrial fibrillation in 31.5% of patients, coronary artery disease in 31.0% of patients, and hypertension in 78.8% of patients. Therapeutic anticoagulation was started in 145 (34.9%) patients. The most common indication for therapeutic anticoagulation was an elevated D-dimer in 18% of patients, and 8.7% of patients were diagnosed with an arterial or venous thrombosis. The most frequent indication for neuroimaging was encephalopathy (65% of non-ICH patients, and 51.5% of ICH patients).

Univariate analysis

Among patients with ICH, the mean (SD) age was 61.6 (11.2), 21.2% were women, 27.3% had atrial fibrillation, 12.1% had coronary artery disease, and 66.7 % had hypertension. In univariate analysis, we found 24 (72.7%) ICH patients had been on home anticoagulation or started on therapeutic anticoagulation during hospitalization, compared to 31.6% of non-ICH patients (OR 6.3, 95% CI 2.8–14.5, $p < 0.001$) (Table 1). There were six patients with ICH identified on admission scan and two of these patients were on anticoagulation prior to presentation. In ICH patients, the indication for therapeutic anticoagulation was elevated D-dimer in 18 (54.5%) patients, while this was the indication in only 14.9% of patients without ICH ($p < 0.001$). Patients
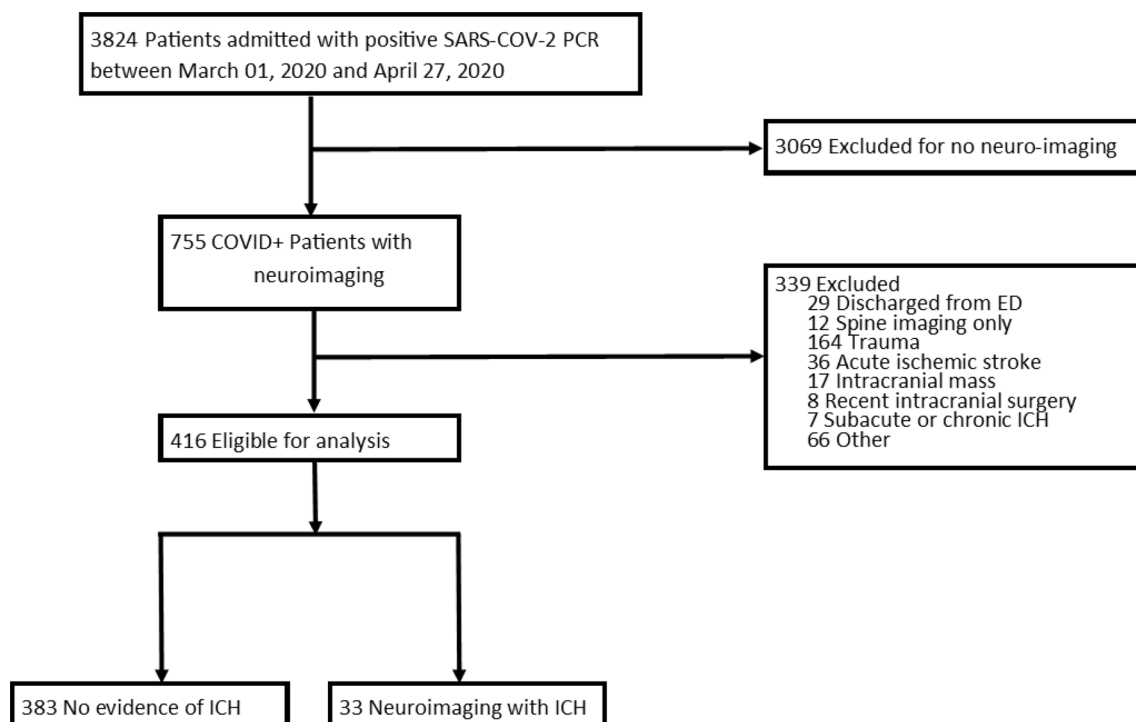

Fig. 1 3824 patients were admitted with COVID-19. Of these, 755 had brain imaging available for review, of which 416 met our inclusion criteria. We identified 37 patients with ICH, and further

excluded 4 patients for recent trauma (2), intracranial neoplasm (2) and thus 33 were included for analysis.

Table 1. Characteristics of both in ICH and non-ICH patients.

	TOTAL (N = 416)[α]	ICH (N = 33)	No ICH (N = 383)	p value
Admission Demographics				
Age; mean (SD) years	69.3 (16.2)	61.6 (11.2)	70.0 (16.4)	<0.01
Female	149 (35.8)	7 (21.1)	142 (37.1)	0.08
Caucasian	207 (50.1)	9 (22.3)	198 (52.1)	<0.01
BMI; median (IQR), kg/m^2	27.4 (24.2-31.6)	29.5 (25.7-31.6)	27.1 (23.8-31.6)	0.4
Medical Comorbidities				
Atrial Fibrillation	131 (31.5)	9 (27.3)	122 (31.9)	0.7
Coronary Artery Disease	129 (31.0)	4 (12.1)	125 (32.6)	0.01
Hypertension	328 (78.8)	22 (66.7)	306 (79.9)	0.08
Diabetes	200 (48.1)	12 (36.4)	188 (49.1)	0.2
Clinical variables at time of neuroimaging				
Admission to neuroimaging, mean (SD) days	7.0 (10.5)	13.9 (9.3)	6.4 (10.4)	0.7
Indication for neuroimaging				
Encephalopathy	266 (63.9)	17 (51.5)	249 (65.0)	0.1
Focal Neurologic Deficit	67 (16.1)	12 (36.4)	55 (14.3)	<0.01
Focal Weakness	49 (11.8)	7 (21.2)	42 (11.0)	0.09
Brainstem Abnormality	10 (2.4)	4 (12.1)	6 (1.6)	<0.01
Aphasia	6 (1.4)	1 (3.0)	5 (1.3)	0.4
Dysarthria	2 (0.5)	0 (0)	2 (0.5)	1
Syncope	18 (4.3)	0 (0)	18 (4.7)	0.4
Seizure	17 (4.1)	2 (6.1)	15 (3.9)	0.6
Headache	13 (3.1)	0 (0)	13 (3.4)	0.6
Vertigo	10 (2.4)	0 (0)	10 (2.6)	1
Fall	5 (1.2)	0 (0)	5 (1.3)	1
Cardiac Arrest	4 (1.0)	0 (0)	4 (1.0)	1
Other	16 (3.8)	2 (6.1)	14 (3.7)	0.4
Peak SBP; mean (SD) mm HG	130.3 (33.3)	121 (33.1)	130.8 (33.3)	0.8
D-dimer; mean (SD) ng/ul	3085.1 (6008.4)	3895.7 (4127.6)	2984.2 (6202.4)	0.4
INR; median (IQR)	1.2 (1.1-1.5)	1.3 (1.2-1.8)	1.2 (1.1-1.4)	0.03
aPTT; mean (SD) seconds	48.3 (48.0)	73.2 (58.1)	43.6 (44.4)	<0.01
Platelet nadir, mean (SD)103/uL	215.6 (113.0)	204.1 (119.1)	216 (119.5)	0.6
Peak, mean (SD) IU/mL	0.5 (0.3)	0.5 (0.2)	0.5 (0.3)	0.7
Therapeutic Anticoagulation	145 (34.9)	24 (72.7)	121 (31.6)	< 0.001
DOAC	3 (0.7)	1 (3.0)	2 (0.5)	0.2
Warfarin	3 (0.7)	1 (3.0)	2 (0.5)	0.2
Heparin Full Dose	104 (25.0)	21 (63.6)	83 (21.7)	< 0.001
Enoxaparin Full Dose	35 (8.4)	1 (3.0)	34 (8.9)	0.3
Indication for Therapeutic Anticoagulation Use				
Elevated D-dimer	75 (18.0)	18 (54.5)	57 (14.9)	< 0.001
Arterial or Venous Thrombus	36 (8.7)	4 (12.1)	23 (8.4)	0.5
Atrial Fibrillation	29 (7.0)	1 (3.0)	28 (7.3)	0.7
Other[β]	3 (0.7)	1 (3.0)	2 (0.5)	0.2
Clinical severity				
Admission SOFA score	0 (0-0)	0 (0-0)	0 (0-0)	0.8
Maximum SOFA Score	10 (4-15)	11 (7-16)	8.5 (4-14)	< 0.001
Mechanical Ventilation prior to neuroimaging	136 (32.7)	26 (78.8)	110 (28.7)	< 0.001
Mortality	126 (30.3)	17 (51.5)	109 (28.5)	0.01

aPTT activated partial thromboplastin time, *BMI* body mass index, *ICH* intracerebral hemorrhage, *INR* international normalized ratio, *SOFA* sequential organ failure assessment

[α]All numbers are n (%) unless otherwise specified.

[β]Other indications for anticoagulation use include mechanical valve (n = 2) and antiphospholipid syndrome (n = 1)

Lab values are peak (or nadir) within 72 h prior neuroimaging

with ICH underwent neuroimaging for an indication of focal neurologic deficit more commonly that patients without ICH ($p < 0.01$). There were no significant differences in hematoma size, location or ICH for patients who were or were not on therapeutic anticoagulation (Supplemental Table 1). Other variables associated with ICH were older age ($p < 0.01$), prolonged peak aPTT ($p < 0.01$) and higher INR ($p = 0.03$), while being Caucasian was associated with decreased likelihood of ICH ($p < 0.01$). Patients with ICH were more likely to have been admitted to the ICU, have respiratory failure requiring mechanical ventilation, and had higher SOFA scores during their hospitalization ($p < 0.001$ for all variables).

Patients on anticoagulation had a higher median BMI (IQR) of 29.5 (26.5–31.5) compared to those in whom anticoagulation was not started (25.9 (22.3–28.6), $p = 0.05$). They were more likely to have a history of atrial fibrillation (40% vs 26.9%, $p < 0.01$). Otherwise, there were no significant differences identified in admission demographics or ICH characteristics in patients who were and were not on therapeutic anticoagulation prior to neuroimaging (Supplemental Table 1). The indication for neuroimaging was most frequently encephalopathy in both groups; however, the indication was more frequently seizure or cardiac arrest in patients on anticoagulation, and was more commonly syncope or headache in patients not on anticoagulation ($p < 0.04$ for all). D-dimer and markers of coagulation were significantly higher in patients on anticoagulation ($p < 0.001$ for all), however there was no difference in peak D-dimer ($p = 0.5$), platelet nadir ($p = 0.6$), or peak anti-factor Xa levels ($p = 0.7$) at the time of neuroimaging in patients with ICH compared to those without.

Association between anticoagulation use and ICH

In unadjusted models, there was an association between anticoagulation use and ICH (OR 5.77 95% CI 2.61–12.80 $p < 0.001$). This association persists in fully adjusted models (OR 5.26 95% CI 2.33–11.85, $p < 0.001$) that includes age, ethnicity, sex, hypertension history, and peak systolic blood pressure prior to neuroimaging (see Table 2). Sensitivity analyses indicated the association between anticoagulation use and ICH persisted (adjusted OR 2.71, 95% CI 1.02–7.17, $p = 0.05$) after adjusting for factors associated with ICH in univariate analysis with $p < 0.01$ (Supplemental Table 2). In this model, we also found mechanical ventilation (OR 5.03, 95% CI 1.82–13.81, $p < 0.01$) and non-Caucasian ethnicity (OR 2.77, 95% CI 1.20–6.41, $p = 0.02$) were factors associated with an increased risk of ICH.

Association between ICH and mortality

As of May 30th, 126 (30.3%) patients expired in the hospital or were discharged to hospice, including 17 (51.5%) patients with ICH and 109 (28.5%) patients without ICH. Patients with ICH who were on therapeutic anticoagulation had a non-statistically significant higher mortality than ICH patients who were not on anticoagulation (14 vs 3 patients with ICH, OR 2.8, 95% CI 0.56–13.59). ICH was associated with mortality in univariate analysis (OR 2.67, 95 % CI 1.30–5.47), $p < 0.01$. The remaining patients were discharged to home (140; 33.7%), a nursing facility (106; 25.5%), acute rehab (19; 4.6%), or another acute care facility 7 (1.7%). A small portion (4.3%) remained hospitalized as of May 30, 2020. After adjusting for age and maximum SOFA score during hospitalization, the odds of mortality following ICH was 2.65 (95 % CI 1.18–5.92), $p = 0.02$.
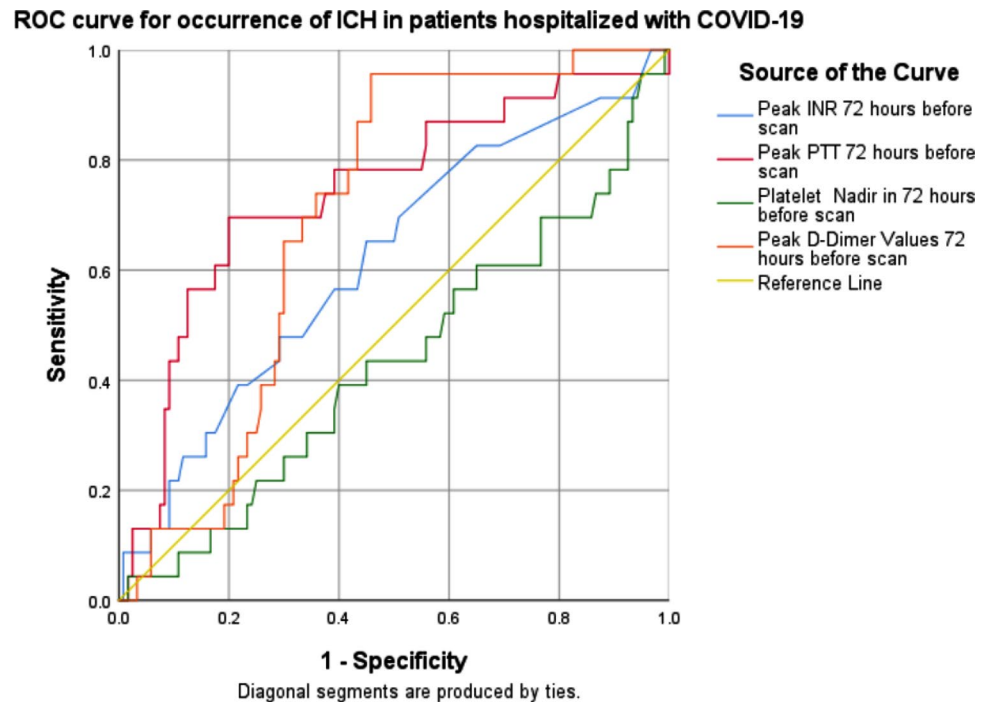
Additional analyses

To further determine the predictive value of markers of coagulation for ICH, the ROC curve for coagulation abnormalities was plotted (Fig. 2). The AUC of peak aPTT for ICH in patients with COVID-19 was 0.73 (95% CI 0.62-0.86); the AUC of D-dimer peak was 0.67 (95% CI 0.57–0.76); the AUC for peak INR was 0.64 (95% CI 0.52–0.76); and the AUC of the platelet nadir was 0.45 (95% CI 0.32–0.57).

Table 2 Regression models for risk factors associated with ICH in COVID-19 patients

Covariates	Model 1	Model 2	Model 3
Therapeutic anticoagulation	5.77 (2.61–12.80), p < 0.001	5.45 (2.42–12.24), p < 0.001	5.26 (2.33–11.85), p < 0.001
Age		0.98 (0.96–1.00), p = 0.1	0.99 (0.96–1.01), p = 0.2
Caucasian		0.38 (0.17–0.87), p = 0.02	0.38 (0.16–0.87), p = 0.02
Male		1.90 (0.78–4.67), p = 0.2	1.86 (0.76–4.58), p = 0.2
Hypertension			0.74 (0.31–1.75), p = 0.5
Peak systolic blood pressure			1.00 (0.99–1.01), p = 0.5

Values are represented as OR (95% CI), p value

Fig. 2 ROC curve for occurrence of ICH predicted by coagulation parameters. ROC curve analysis indicated that the area under the curve of INR, aPTT, platelet nadir and peak D-dimer in patients with ICH was 0.64, 0.73, 0.45 and 0.67, respectively (p = 0.01, p < 0.01, p = 0.4 and p < 0.01; respectively). aPTT: activated partial thromboplastin time; ICH: intracerebral hemorrhage cerebral microbleeds; ROC: receiver operating characteristic

ROC curve for occurrence of ICH in patients hospitalized with COVID-19

Source of the Curve
— Peak INR 72 hours before scan
— Peak PTT 72 hours before scan
— Platelet Nadir in 72 hours before scan
— Peak D-Dimer Values 72 hours before scan
— Reference Line

Diagonal segments are produced by ties.

Discussion

Bleeding diathesis seen in COVID-19 can have devastating outcomes, particularly when occurring in the brain [1, 3, 20]. We have previously explored the clinical and radiographic features seen with ICH in COVID-19 patients [1, 2, 13] and here we evaluate the risk associated with ICH in all COVID-19 patients with neuroimaging. We found anticoagulation use was strongly associated with ICH in patients with COVID-19. We found ICH is significantly associated with mortality in our cohort after adjusting for age and SOFA as a marker of illness severity.

Pathophysiology underlying ICH in COVID-19 patients is uncertain and may be variable. Literature from related coronavirus types has demonstrated evidence of the neuroinvasive potential of coronavirus, [21–23] autopsy proven vasculitis in SARS-CoV-1, [24] and reports of ICH as a result of thrombocytopenia, disseminated intravascular coagulation (DIC), and platelet dysfunction in patients with Middle East Respiratory Syndrome Coronavirus [25].

Proposed theories regarding etiology of ICH in SARS-CoV-2 similarly include a DIC like response [20] in which a consumptive coagulopathy makes the cerebral tissue more prone to bleeding. However, elevated D-dimer is also an acute phase reactant and a marker of increased thrombogenesis and propensity for clot formation. Despite the proposed association between ICH and DIC, D-dimer peak levels and platelet nadir at the time of neuroimaging are not statistically different in our cohort.

The significant association between respiratory failure requiring mechanical ventilation and ICH in patients with COVID-19 deserves further attention. These hypoxic patients might have hypoxia induced blood brain barrier disruption (similar what occurs in high altitude cerebral edema) leaving them more susceptible to ICH [26]. Alternatively, the downstream effects of the hypoxic, inflammatory milieu might contribute to endothelial dysfunction and cerebral injury [27]. Endothelial damage has been shown to occur in SARS-CoV-2 [28, 29] and microscopic disruption of the endothelium of cerebral veins could lead to microbleeds and eventual ICH [27]. Another proposed hypothesis is the microvascular thrombosis suggested to result in hypoxemic respiratory failure in some patients with COVID-19 might also result in direct neural injury and/or the microbleeds observed in patients with COVID-19 [30–32] Microbleeds could portend further risks for cerebral hemorrhage, particularly in the setting of anticoagulation use [11, 32, 33].

The common use of anticoagulation in patients with COVID-19 [16, 34] is not surprising given these patients have been shown to be predisposed to thrombotic events [15–17, 35–38]. In non-COVID-19 patients with atrial fibrillation, anticoagulation use increases the risk of ICH by a 2–10 fold increase [6, 10, 11, 39–42]. The indication for therapeutic anticoagulation in our cohort was elevated D-dimers in over half of the patients with ICH. In contrast, less than a quarter of patients without ICH were on anticoagulation for this indication. It is possible that patients with higher D-dimers requiring anticoagulation might represent a sicker patient more likely to have ICH. There was no

difference in admission D-dimer levels nor in the 72 hours prior to neuroimaging. There was a significant difference in anticoagulation type in patients who did and did not experience ICH. Again, the fact that a greater percentage of ICH patients were on full dose heparin might be a marker of disease severity rather than represent a difference in ICH risk when on full dose heparin vs full dose enoxaparin [43]. Only patients with a clear indication and no contraindication should receive anticoagulation and the benefit versus risk of different doses of anticoagulation in hospitalized COVID-19 patients is currently being investigated. (URL: https://www.clinicaltrials.gov. Unique identifier: NCT04359277).

There are several limitations to our study, particularly the retrospective nature of the study of a somewhat heterogeneous population. We found it necessary to include patients with hemorrhagic conversion of ischemic stroke primarily because of the difficulty in distinguishing this entity from primary ICH on CT scan alone, and it was not always feasible to obtain an MRI given constraints of the pandemic. Furthermore, it is possible the CT findings considered to represent ischemic stroke might be consistent with viral associated subcortical microvascular inflammation and/or thrombosis. Excluding patients without neuroimaging may limit the generalization of these conclusions to all COVID-19 patients, but we felt it was important to limit the comparison of ICH patients to patients we could be certain did not have ICH. It is plausible we missed the diagnosis of ICH in a small number of patients who did not have head imaging. Finally, other factors that we did not evaluate may also be associated with ICH and outcome.

Conclusion

Anticoagulation use is independently associated with subsequent risk of ICH among patients with COVID-19. Further investigation is required to elucidate mechanisms of ICH and to explore means to prevent ICH in this patient population.

Compliance with ethical standards

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