Intracranial Hemorrhage in Patients with Coronavirus Disease 2019 (COVID-19): A Case Series

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■ BACKGROUND: **The coronavirus disease 2019 (COVID-19) pandemic is an ongoing public health emergency. While most cases end in asymptomatic or minor illness, there is growing evidence that some COVID-19 infections result in nonconventional dire consequences. We sought to describe the characteristics of patients with intracranial hemorrhage who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Also, with the existing literature, we raise the idea of a possible association between SARS-CoV-2 infection and intracranial hemorrhage and propose possible pathophysiological mechanisms connecting the two.**

■ METHODS: **We retrospectively collected and analyzed intracranial hemorrhage cases who were also positive for SARS-CoV-2 from 4 tertiary-care cerebrovascular centers.**

■ RESULTS: **We identified a total of 19 patients consisting of 11 males (58%) and 8 females (42%). Mean age was 52.2, with 95% younger than 75 years of age. With respect to COVID-19 illness, 50% had mild-to-moderate disease, 21% had severe disease, and 20% had critical disease requiring intubation. Of the 19 cases, 12 patients had intraparenchymal hemorrhage (63%), 6 had subarachnoid hemorrhage (32%), and 1 patient had a subdural hematoma (5%). A total of 43% had an intracerebral hemorrhage score of 0–2 and 57% a score of 3–6. Modified Rankin Scale cores at discharge were 0–2 in 23% and 3–6 in 77%. The mortality rate was 59%.**

■ CONCLUSIONS: **Our series sheds light on a distinct pattern of intracerebral hemorrhage in COVID-19–positive cases compared with typical non–COVID-19 cases, namely the severity of hemorrhage, high mortality rate, and the young age of patients. Further research is warranted to delineate a potential association between SARS-CoV-2 infection and intracranial hemorrhage.**

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed upwards of 2 million lives worldwide. While most infections are asymptomatic, symptomatic infection manifests mainly with respiratory symptoms including fever, shortness of breath, and cough, with death typically resulting from acute respiratory distress syndrome (ARDS).[1] Moreover, multiple studies have demonstrated the neurotropism of this virus and its ability to enter the central nervous system.[1] Neurologic consequences of COVID-19 range from mild

Key words
- COVID-19
- Intracranial hemorrhage
- Neurotropism
- Neurovascular disease
- SARS-CoV-2

Abbreviations and Acronyms
ACE-2: Angiotensin-converting enzyme-2
ARDS: Acute respiratory distress syndrome
COVID-19: Coronavirus disease 2019
CRP: C-reactive protein
HTN: Hypertension
ICH: Intracranial hemorrhage
IPH: Intraparenchymal hematoma
mRS: modified Rankin Scale
SAH: Subarachnoid hemorrhage
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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headache and loss of sense of smell to the more devastating acute large-vessel occlusions and intracranial hemorrhage (ICH).[2] While numerous studies have established the association of COVID-19 with hypercoagulable states and acute ischemic stroke,[3-7] that of COVID-19 and ICH is much less well-described, with few studies being published thus far.[5,8-10] Infected patients may present with ICH or develop ICH during the course of their hospitalization, often with debilitating consequences.[11] In this paper, we aim to highlight the clinical, radiologic, and laboratory characteristics, as well as functional outcomes of patients with COVID-19 who either presented with ICH or subsequently developed ICH in the course of their illness.

METHODS

In this retrospective case series, data were collected from 4 tertiary care, high-volume cerebrovascular centers for 19 patients from March through December of 2020. The diagnosis of SARS-CoV-2 infection was made based on reverse transcription quantitative polymerase chain reaction testing of a nasal swab sample from each patient. Patients with a positive test at admission or up to 28 days prior and who presented with ICH, or subsequently developed ICH during their hospital course, were included. Twenty-eight days is an arbitrary number agreed on by the authors to try to establish a potential timeline between COVID-19 and ICH. Patients who tested negative twice for COVID-19 and patients who tested positive more than 28 days before admission were excluded.

The study protocol was reviewed and approved by the Thomas Jefferson University institutional review board. Following our institutional guidelines, all protected health information was removed, and individual patient consent was not required for the analysis of this case series. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional review board or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The following data were collected from each patient's electronic medical record: age, sex, history of hypertension, history of hyperlipidemia, history of chronic heart, lung, kidney, or liver disease, history of diabetes, history of atrial fibrillation, history of anticoagulant/antiplatelet use, smoking status, COVID-19 symptoms, ICH data, laboratory data, management, length of stay, discharge location, and modified Rankin Scale (mRS) at discharge. Microsoft Excel (Microsoft, Redmond, Washington, USA) was used to run descriptive analyses of the data. To preserve patient anonymity and in compliance with institutional review board regulations, we do not present the full data for individual cases and instead report the aggregated data or individual deidentified data points.

RESULTS

Demographics

Patient characteristics are summarized in Table 1. A total of 19 patients were included in this series, 8 of whom were female (42.1%) and 11 (57.9%) were male. The mean age of patients was 52.6 ± 15.8 years (range 24–85 years) Fourteen patients (73.7%) were younger than 60 years of age. The most common comorbidities were hypertension (52.6%), chronic heart disease (31.6%), and diabetes (21.1%). Other notable comorbidities were hyperlipidemia (21.1%), chronic kidney disease (15.8%), and atrial fibrillation (15.8%). One patient (5.3%) had chronic lung disease, and 1 patient (5.3%) was a current smoker. Five patients (26.3%) did not have any comorbidities or medical history. In addition, 4 patients (21.1%) were on anticoagulation (3 patients were on heparin; 1 patient was on a drip, another 2 were taking 2500 and 5000 units subcutaneously every 12 hours and 8 hours respectively, and the fourth patient was on warfarin daily) and 2 patients (10.5%) were on antiplatelets. In addition, none of the patients were on steroids. 68.4% had a favorable preadmission mRS of 0–2.

Table 1. Baseline Characteristics

Variable	*n* (%)
Total number of patients	19 (100)
Age, years	52.6 ± 15.8
<60	14 (73.7)
60–75	4 (21.1)
>75	1 (5.2)
Female sex	8 (42.1)
Hypertension	10 (52.6)
Hyperlipidemia	4 (21.1)
Chronic heart disease	6 (31.6)
Chronic lung disease	1 (5.3)
Chronic kidney disease	3 (15.8)
Chronic liver disease	3 (15.8)
Diabetes	4 (21.1)
Atrial fibrillation	3 (15.8)
Anticoagulation use	4 (21.1)
Antiplatelet use	2 (10.5)
Smoking	1 (5.3)
Preadmission mRS 0–2	13 (68.4)

mRS, modified Rankin Scale.

COVID-19 Symptoms and Laboratory Findings

Seven patients (36.8%) had fever, 8 (42.1%) had cough, 6 (31.6%) had shortness of breath, and 2 patients (10.5) had chest pain. A total of 50% had moderate disease (evidence of lower respiratory disease and oxygen saturation >94%), 21.4% severe disease (evidence of lower respiratory disease and oxygen saturation <94%), and 28.6% critical disease (evidence of ARDS, septic shock, or multiorgan failure). Seven patients (36.8%) presented initially with ICH and subsequently tested positive for COVID-19 (Figure 1A–D), and 12 patients (63.2%) were initially diagnosed with COVID-19 then subsequently developed ICH. The mean time between COVID-19–related symptoms and ICH was 8.6 ± 12.4 days (Table 2).

Laboratory bloodwork were collected at the time of ICH. Complete blood count values included hemoglobin (12.1 ± 2.5), lymphocyte % (10 ± 6.2), and platelets (233.4 ± 96.4). More notable findings were C-reactive protein (CRP) (13.6 ± 19.4), D-dimer (1220.9 ± 976.4), and international normalized ratio (1.36 ± 0.7). Other laboratory findings are documented in **Table 3**.

ICH Characteristics

Of the 19 patients reviewed, 12 patients (63.1%) had an intraparenchymal hematoma (IPH), 6 (31.6%) had subarachnoid hemorrhage (SAH), and 1 patient (5.3%) had a subdural hematoma. Four patients (21.1%) had a ruptured aneurysm, and 15 patients (78.9%) had no intracranial pathology on imaging. Of the ruptured aneurysms, 1 patient (25%) and a Hunt and Hess grade III SAH and 3 patients (75%) had a Hunt and Hess grade IV SAH, one of whom ruptured the aneurysm during a protracted coughing episode. Out of available data from our institution, one aneurysm was a fusiform aneurysm of the distal posterior inferior cerebellar artery, and one was a blister aneurysm of the anterior choroidal artery. One patient had severe diffuse SAH on computed tomography angiography scan and the aneurysm was not visualized. The patient then died soon after presentation, and no further workup was done. From the patients who presented with IPH at our institution, 2 of the intraparenchymal hemorrhages were in the left and right frontal lobes with intraventricular extension, 2 were in the bilateral thalamic area, 1 was in the right parietal lobe, 1 in the

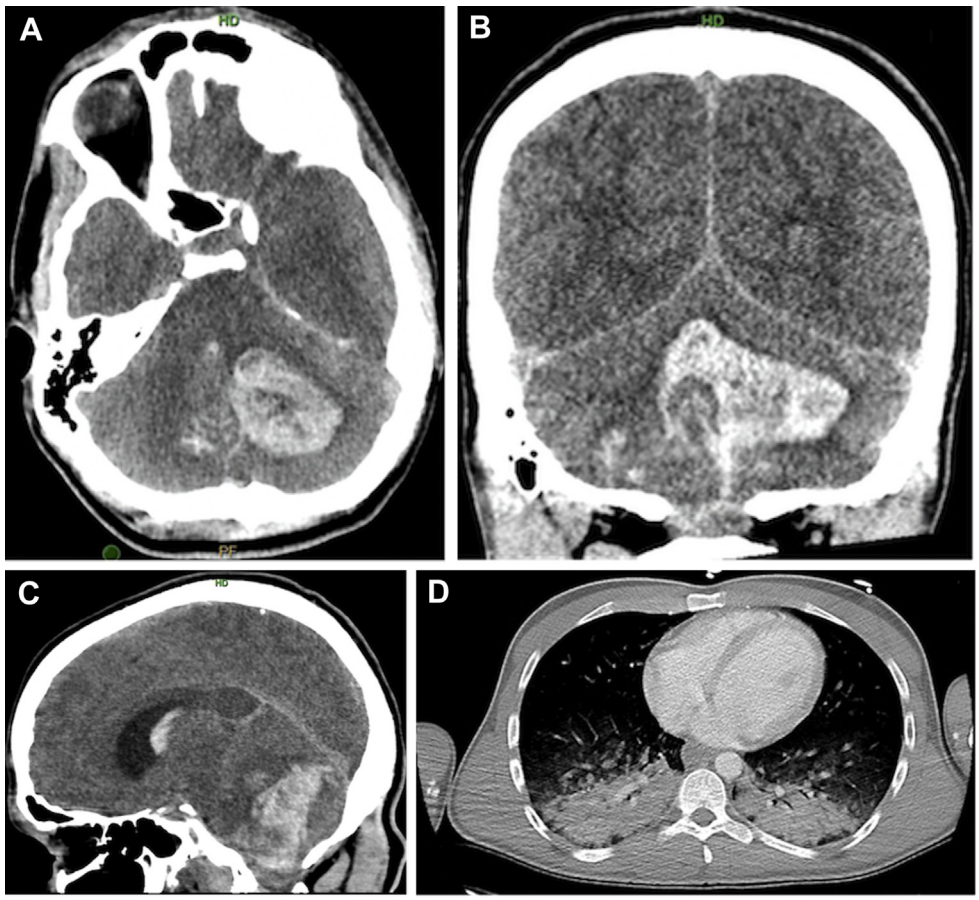

Figure 1. (**A**–**C**) Axial, coronal, and sagittal noncontrasted computed tomography (CT) images of the head of a previously healthy 24-year-old male patient who presented after a syncopal episode at home followed by unresponsiveness. On arrival, he had no extremity movements, pupils were fixed, dilated, and nonreactive, and he had no brainstem reflexes. CT of the head (pictured here) demonstrated a large posterior fossa hemorrhage centered in the left cerebellar hemisphere with intraventricular extension into the third and fourth ventricles, herniation, and significant brainstem compression. CT angiography did not show any vascular abnormality. The patient tested positive for coronavirus disease 2019 (COVID-19) and ultimately succumbed to severe neurologic damage and died. (**D**) The patient's CT image of the chest (axial) showing diffuse ground-glass opacities and consolidative airspace disease bilaterally.

Table 2. COVID-19 Characteristics

Variable	*n* (%)
COVID-19 severity ($N = 14$)	
Moderate disease	7 (50)
Sever disease	3 (21.4)
Critical disease	4 (28.6)
Case definition ($N = 15$)	
Confirmed	13 (86.7)
Probable	1 (6.7)
Suspected	1 (6.6)
Respiratory symptoms	
Fever	7 (36.8)
Cough	8 (42.1)
Dyspnea	6 (31.6)
Chest pain	2 (10.5)
Timing	
ICH at presentation	7 (36.8)
Duration between COVID-19–related symptoms and ICH, days	8.6 ± 12.4

COVID-19, coronavirus disease 2019; ICH, intracranial hemorrhage.

Table 3. Laboratory Characteristics

Variable	Mean ± SD
Hb, g/dL	12.1 ± 2.5
RBC, T/L	4.2 ± 0.7
WBC, B/L	14.8 ± 9.1
% lymphocytes, %	10 ± 6.2
Platelets, (B/L)	233.4 ± 96.4
CRP, mg/dL	13.6 ± 19.4
D-dimer, ng/mL	1220.9 ± 976.4
Fibrinogen, mg/dL	342.8 ± 344.6
INR,	1.36 ± 0.7
pTT, seconds	29.3 ± 16.2
Glucose, mmol/L	133.1 ± 83.9

SD, standard deviation; Hb, hemoglobin; RBC, red blood cells; WBC, white blood cells; CRP, C-reactive protein; INR, international normalized ratio; pTT, partial thromboplastin time.

left occipital lobe, and 1 in the left cerebellar hemisphere with extension into the fourth ventricle. All hemorrhages were of arterial origin. The mean IPH volume was 45.9 ± 66.7 cm^3, and the largest IPH diameter was 51.8 ± 37.5 mm. Moreover, unfavorable ICH scores (3–6) were documented in 57.2% of patients (Table 4).

Management and Outcome

Two patients (13.3%) received a decompressive hemicraniectomy, 3 (20%) underwent aneurysm embolization (1 patient died of irreversible neurologic damage and passed away), and 10 (66.7%) had supportive management. Six patients (31.6%) had complications during their hospital course; 1 patient with SAH (brain death), and 5 patients with IPH. Of these 5 patients, 1 developed brain death, 2 developed herniation, and 1 patient had refractory increased intracranial pressure and ventricular tachycardia. The mean length of hospital stay was 5.1 ± 6.5 days. Interestingly, unfavorable mRS scores at discharge (3–6) were in 76.5%, and the mortality rate was 58.8%. Of the patients who died, 60% and 90% were younger than 60 and 75 years of age, respectively (Table 5).

DISCUSSION

A little over a year into the pandemic and the medical community is still reporting novel and unexpected sequelae resulting from the SARS-CoV-2/COVID-19 infection.[12-14] Published studies on ICH in patients with COVID-19 are minimal and, in this series, we highlight potential disparities from established characteristics of patients with ICH.[5,8,10,11,15]

In this case series, the mean age at presentation was 52.6 years old, with 74% of patients younger than 60 years of age and 95% younger than 75 years of age. This is much younger than expected; many prospective cohort studies and meta-analyses on ICH report mean ages of patients at presentation ranging from 68 to ≥75 years.[16-18] In addition, over a period of 28 years, van Asch et al.[19] found the incidence of ICH in patients younger than 60 years of age to be 0.1 per 100,000 person-years. However, this does not hold true with COVID-19. Benger et al.[18] reported a mean age of 52.2 years in their COVID-19 and ICH series, similar to this cohort. Likewise, the mean age reported was 49.5 years in another series published by Nawabi et al.[20]

In our cohort, the majority of patients were male (58%), which is again reflected in recently published series whereby male patients comprised 60%–100% of the study population.[5,15,20] Moreover, male sex is a well-established risk factor for ICH; therefore, this is in accordance with current literature.[21,22]

The most prevalent vascular comorbidities were hypertension (HTN) and chronic heart disease, which have been reported in most studies on ICH in patients with COVID-19. Cheruiyot et al.[11] pooled all such studies in a comprehensive systematic review and found that HTN and diabetes were most evident in the majority of these study populations.[15] Historically, HTN is the most important vascular risk factor for ICH, regardless of COVID-19 status, which typically result in deep bleeding.[23-25] In our series, IPH type ICHs were mainly in lobar territories, which are generally associated with underlying vascular abnormalities.[26] However, none of our patients had any underlying pathology, with the exception of those who presented with aneurysmal SAH (21%), as was the case in other published

Table 4. ICH Characteristics

Variable	*N* (%)
Pathology (*N* = 19)	
Aneurysm	4 (21.1)
No pathology	15 (78.9)
Location (*N* = 15)	
Right	3 (20)
Left	6 (40)
Bilateral	6 (40)
ICH type (*N* = 19)	
SDH	1 (5.3)
SAH	6 (31.6)
IPH	12 (63.1)
Severity	
SAH HH grade III	1 (25)
SAH HH grade IV	3 (75)
IPH largest diameter, mm	51.8 ± 37.5
IPH volume, cm^3	45.9 ± 66.7
ICH score (*N* = 7)	
0	1 (14.3)
1	0 (0)
2	2 (28.6)
3	1 (14.3)
4	2 (28.6)
5	1 (14.3)

ICH, intracranial hemorrhage; SDH, subdural hematoma; SAH, subarachnoid hemorrhage; IPH, intraparenchymal hematoma.

Table 5. Management and Functional Outcome

Variable	*N* (%)
Management (*N* = 15)	
DCH	2 (13.3)
Aneurysm embolization	3 (20)
Supportive	10 (66.7)
Outcome	
Complications	6 (31.6)
IPH	5 (41.7)
SAH	1 (16.7)
Length of stay	5.1 ± 6.5
Discharge home	4 (66.7)
Discharge to rehab	2 (33.3)
mRS at discharge (*N* = 17)	
0	2 (11.8)
1	1 (5.9)
2	1 (5.9)
3	2 (11.8)
4	0 (0)
5	1 (5.9)
6	10 (58.8)
Mortality, years	10 (58.8)
Age <60	6 (60)
Age 60–75	3 (30)
Age >75	1 (10)

DCH, decompressive hemicraniectomy; IPH, intraparenchymal hematoma; SAH, subarachnoid hemorrhage; mRS, modified Rankin Scale.

series.[15,20] Furthermore, the mean duration between the onset of COVID-19 symptoms and ICH was 8.6 ± 12.4 days (range 0–37 days). During this latency period, patients had ongoing acute inflammation, as reflected by their markedly elevated D-dimer and CRP values. This particular trend also was observed in various other studies and reports.[11,15,20,27] Hence, it appears that the pathophysiology behind these hemorrhages differs from what has already been established for non-COVID-19–related spontaneous ICH.

Anticoagulation in the setting of COVID-19 is not a straightforward process and should balance the hypercoagulable state brought upon by COVID-19. In our series, 4 patients were receiving therapeutic as well as prophylactic anticoagulation. Specifically, 1 patient was placed on a heparin drip for a deep venous thrombosis and subsequently developed a large right frontal IPH with intraventricular extension and died. This may introduce a trend that heparinization in the setting of COVID-19 may lead to ICH. One case report reported that a 42-year-old patient hospitalized for COVID-19–related ARDS developed large bilateral ICH after initiating a heparin drip.[28] Moreover, a recent retrospective study found that most intracerebral hemorrhages in COVID-19 occurred in the setting of therapeutic anticoagulation and was associated with increased mortality (86.4% vs. 4.6%, $P < 0.001$).[29]

SARS-CoV-2 gains entry into the cell via interaction of the viral "S" protein (homotrimeric spike glycoprotein) with the angiotensin converting enzyme-2 (ACE-2) receptor,[30] which is known to be expressed in the cerebrovascular endothelium.[31] A multitude of early studies have demonstrated endothelial cell injury and toxicity as a focal point in SARS-CoV-2 pathogenesis and histological analysis identified viral elements and inflammatory cell accumulation in endothelial cells, leading to apoptosis.[20,32-34] Direct endothelial toxicity may lead to rupture of intracerebral capillaries and ultimately result in fatal ICH.[35] Moreover, endothelial injury

can trigger a chain of events involving proinflammatory cytokines, the coagulation cascade, and the complement system that would breakdown cellular tight junctions, thereby increasing the permeability and leading to the disruption of the blood–brain barrier and subsequently, ICH.[36]

In addition to endothelial dysfunction, SARS-CoV-2 down-regulates the expression of the ACE-2 receptor, disrupting the renin–angiotensin–aldosterone system.[15,20,37] Consequently, cerebral blood flow autoregulation is impaired and dangerously high levels of angiotensin II accumulate in the local endothelium.[38-40] This would then lead to uncontrolled elevation in blood pressure, which is exacerbated by preexisting HTN, thereby substantially increasing the risk of ICH.

Organ injury and poor outcome with SARS-Cov-2 infection is meticulously associated with the extent of ongoing inflammation and multiple studies have established the role of D-dimer levels as a biomarker for SARS-CoV-2 severity.[41-43] Further, a recent systematic review and meta-analysis by Zhou et al.[43] looked into the association between levels of plasma D-dimer and ICH and found that elevated levels of D-dimer were associated with ICH. Therefore, it is reasonable to conclude that the increase in D-dimer levels stemming from SARS-CoV-2 add to the risk of ICH.

Two patients in our series developed spontaneous non-aneurysmal SAH. The exact mechanism of this occurrence has yet to be fully understood. One recent case series reported one incidental aneurysm of 4 patients with SAH and therefore introduced spontaneous SAH as a severe neurologic manifestation of COVID-19 and postulated the hyperinflammatory state in the setting of COVID-19 as a potential mechanism.[44] Similarly, a recent review hypothesized that hypercytokinemia and inflammation may contribute to vascular degeneration leading to aneurysm formation and size/morphology change, therefore resulting in rupture and SAH.[45]

It is noteworthy to mention that in this series unfavorable ICH scores (3–6) were recorded in 57% of IPHs when reported, and poor outcome (mRS 3–6) in 77% with a mortality rate (mRS 6) of 59%. Also, 6 of 10 patients who passed away were younger than the age of 60 years. These findings deviate from existing literature on spontaneous ICH. A recent, comprehensive systematic review and meta-analysis of 30 population-based studies reported mortality rates of 36.3% at 1 month, 35.3% at 3 months, and 50.7% at 1 year, all of which are all less than in our series.[19,46] In addition, multiple studies have robustly established older age as an independent predictor of short and long-term mortality, and that case fatality declines in patients younger than 75 years old.[18,47-49] For a small series, it is intriguing that 90% of deaths occurred in patients younger than 75 years of age. In fact, in the overwhelming majority of studies reporting on COVID-19 and ICH, the mortality rate ranged from 42% to 100%.[15] One postulation is that consistently elevated CRP levels, given the active inflammation from SARS-CoV-2, impair proper healing, and thus portend higher mortality and poor functional outcome.[50] Another postulation is that impaired autoregulation and disruption of the signaling cascade initiated by ACE-2 would lead to greater hemorrhage volume, which is independently associated with increased mortality.[51] However, the precise pathophysiology is likely multifactorial and still poorly understood. Further investigation is warranted.

This series is intended to highlight certain characteristics of ICH in patients with COVID-19. It is beyond the scope of this study to establish a causal relationship between SARS-CoV-2 infection and ICH. Nevertheless, the trends identified in this study should raise concern about the unusual features of ICH in this subset of patients and should be the focus of future investigation.

Limitations

Our study aims to shed light over a potential association between COVID-19 and ICH. However, our study has some limitations that are worth mentioning. First, it is a retrospective case series, with a small sample size. Thus, data interpretation cannot establish a causal relationship between specific type of bleeds and COVID-19. A larger sample size in a prospective study design would better contribute to further understanding of the cause of hemorrhage and improve generalizability of our results. In addition, the heterogeneous collection of intraparenchymal, SAH, and subdural hematomas together make the interpretation harder, especially when both the infratentorial and supratentorial hemorrhages are included as well. Furthermore, many patients were in critical condition on presentation and passed away soon thereafter and computed tomography angiography scans were not performed for every patient potentially masking an underlying vascular pathology. Finally, central nervous system biopsies were not available at the point of data acquisition.

CONCLUSIONS

In this case series, we report 19 ICH cases in patients positive for SARS-CoV-2. These cases add to and support the existing pool of evidence on the distinctly different characteristics of ICH in patients with COVID-19. In addition, they shed light on unique features, predominantly young age, severe hemorrhage, and markedly high mortality, especially in the younger age group, and should therefore raise questions about a likely association between SARS-CoV-2 infection and ICH.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Rawad Abbas: Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Kareem El Naamani:** Funding acquisition, Formal analysis, Data curation, Writing - original draft. **Ahmad Sweid:** Writing - original draft, Writing - review & editing. **Joseph W. Schaefer:** Data curation. **Kimon Bekelis:** Writing - review & editing. **Nader Sourour:** Writing - review & editing. **Mahmoud Elhorany:** Writing - review & editing. **Aditya S. Pandey:** Writing - review & editing. **Stavropoula Tjoumakaris:** Writing - review & editing. **Michael R. Gooch:** Writing - review & editing. **Nabeel A. Herial:** Writing - review & editing. **Robert H. Rosenwasser:** Writing - review & editing. **Pascal Jabbour:** Conceptualization, Methodology, Data curation, Writing - review & editing, Final approval of the version.

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Data-sharing statement: The relevant anonymized patient-level data are available on reasonable request from the authors.

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