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Intracranial Hemorrhage in Hospitalized SARS-CoV-2 Patients: A Case Series

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The SARS-CoV-2 virus causing Coronavirus Disease 2019 (COVID-19) is a global pandemic with almost 30 million confirmed worldwide cases. Prothrombotic complications arising from those affected with severe symptoms have been reported in various medical journals. Currently, clinical trials are underway to address the questions regarding anticoagulation dosing strategies to prevent thrombosis for these critically ill patients. However, given the increasing use of therapeutic anticoagulation in patients admitted with COVID-19 to curtail this prothrombotic state, our institution has witnessed six cases of devastating intracranial hemorrhage as well as thrombosis leading to five fatalities and we examine their hospital course and anticoagulation used.

Key Words: COVID-19—Anticoagulation—SARS-CoV-2—Intracranial hemorrhage

Introduction

The SARS-CoV-2 virus has emerged as a global pandemic causing multiple complications for those who become infected. Upper respiratory tract symptoms are the most common presentations of COVID-19 when first reported from China in December, 2019. For the critically ill, deaths are most commonly caused by acute respiratory distress syndrome (ARDS).[1,2] Recently, multiple publications have revealed that SARS-CoV-2 affects the coagulation system, which can lead to increased rates of arterial or venous thrombosis as well as bleeding.[3,4] Retrospective studies have suggested that prophylactic anticoagulation may lead to reduced mortality in patients with severe COVID-19 pneumonia who have high sepsis-induced coagulopathy scores.[5] D-dimer elevation at admission predicts thrombosis, bleeding, and death in patients with COVID-19 and is now widely used to help triage anticoagulation guidelines upon initial presentation.[6] Due to the risk of arterial thrombosis, several studies have reported rates of acute ischemic stroke and even less so, cerebral hemorrhage. One study from Wuhan, China revealed that 10 (4.5%) of 221 inpatients with COVID-19 developed acute ischemic stroke and 1 (0.5%) suffered cerebral hemorrhage; furthermore, from the Netherlands, 3 of 184 critically ill COVID-19 patients had ischemic stroke.[4,7] Given the increasing use of therapeutic anticoagulation in patients admitted with COVID-19 ARDS, our institution has witnessed six cases of devastating intracranial hemorrhage as well as thrombosis leading to five fatalities.

Case presentations (Table 1)

Patient #1

A 54-year-old woman with controlled diabetes mellitus type II, hypertension, hyperlipidemia, asthma, sickle cell trait, recurrent supraventricular tachycardia, adrenal insufficiency, and hypothyroidism was admitted for acute hypoxic respiratory failure. On admission, she was SARS-CoV-2 positive. CXR revealed patchy interstitial infiltrates consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation. On Hospital Day (HD) 2, she was intubated and started on mechanical ventilation. She was also started on venous thromboembolism (VTE) prophylaxis with low-molecular weight

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Received August 28, 2020; revision received October 20, 2020; accepted October 22, 2020.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105428

TABLE 1. *Patient Characteristics*

	Patient 1	Patient 2	Patient 3
Age (y)	54	68	76
Sex	F	F	M
BMI (kg/m^2)	37.2	26.8	32.3
Past Medical History	Diabetes mellitus, sickle cell trait, adrenal insufficiency, hypothyroidism	Hypertension	Hypertension, hyperlipidemia, gout, GERD
Presenting Symptoms	Dyspnea	Left-sided weakness, ataxia, unsteady gait	Fever, cough, dyspnea and diarrhea
Admission CXR Findings	Patchy interstitial opacities	Normal	Bilateral lower lobe predominant airspace opacities and bilateral pleural effusions
COVID-19 PCR Positivity	3/27/20	5/10/20	5/28/20
COVID-19 Treatments	Hydroxychloroquine and doxycycline	None	Remdesivir and convalescent plasma
ARDS Treatment	Low tidal volume mechanical ventilation, prone positioning and diuresis	None	Low tidal volume mechanical ventilation, prone positioning and diuresis
Days intubated	24	N/A	11 days
ECMO	No	No	No
Deceased?	Yes	No	Yes
Admission Lab Findings			
WBC (K/uL)	10	5.7	8.8
ANC	8.7	2800	7.8
ALC	0.6	2400	0.6
Hb (g/dL)	15	14.2	15.1
PLT (K/UL) [150-400]	131	232	191
SCr (mg/dL)	1.34	0.5	1.0
LDH (U/L)	384	NA	620
D-Dimer (ng/mL) (<500)	1,469	NA	16,107
FBG	1000	NA	NA
FSP	40	NA	NA
PT/INR (9.7-13.1 s/0.8-1.20)	16.3/1.4	1.08	15.5/1.4
aPTT (25.1-36.5 s)	45.8	28.9	27.2
Ferritin (ng/mL)	800	NA	3901
CRP (mg/dL)	107.08	NA	23.4
Procalcitonin (ng/mL)	0.12	NA	0.37
Troponin I	0.03	NA	0.54
IL-6 (pg/mL)	N/A	NA	NA
Other infection?	Ventilator-associated pneumonia	None	Suspected bacterial pneumonia
Confirmed thrombosis?	No	Yes, superficial cortical vein (post-surgical intervention)	No
Type of VTE prophylaxis at Admission	LMWH (0.6 mg/kg BID) changed to unfractionated heparin infusion	Subcutaneous heparin every 12 hours (after the bleed)	LMWH 40 mg daily later changed to therapeutic heparin on HD2 due to rise in D-dimer and troponin
Type of intracranial bleeding and location	Posterior fossa	Subdural hematoma and post-surgical R frontal lobe intracerebral hemorrhage	Large right frontal lobe intraparenchymal hemorrhage with extension to the intraventricular and subarachnoid spaces (on HD12)
Intervention if intracranial bleed	No	Evacuation (craniotomy)	None
Location of acute CVA	No	None	None
Intervention if acute CVA	No	N/A	N/A
Seizures?	No	Yes	No
D-dimer level with CVA or ICH	29,396	Not done	3088
	17.1/1.5	Same as admission	16.0/1.4

TABLE 1. (*Continued*)

	Patient 1	Patient 2	Patient 3
PT/INR with CVA or ICH)9.7-13.1s/0.8-1.20)			
aPTT with CVA or ICH (25.1-36.5 s)	25	Same as admission	107.0
PLT count with CVA or ICH (150-400 K/UL)	324	Same as admission	169

	Patient 4	Patient 5	Patient 6
Age (y)	71	79	63
Sex	F	M	M
BMI (Kg/m^2)	33.9	29.8	23.5
Past Medical History	Hypertension, diabetes mellitus	Hypertension, hyperlipidemia, diabetes mellitus, CAD, atrial fibrillation	Diabetes mellitus
Presenting Symptoms	Cough, dyspnea, Headache	Dyspnea, fever	Dyspnea, cough, fever, loss of taste & smell, weight loss
CXR findings at admission	Bilateral airspace opacities	Bilateral patchy infiltrates	Reticular interstitial changes and patchy alveolar opacities
COVID-19 PCR Positivity	3/24/20	4/3/20	POCT 10 days prior
COVID Treatments	Hydroxychloroquine and azithromycin	Ceftriaxone, doxycycline, piperacillin-tazobactam	Tocilizumab
ARDS Treatment	Low tidal volume mechanical ventilation, prone positioning and diuresis	Low tidal volume mechanical ventilation	Low tidal volume mechanical ventilation, prone positioning and diuresis
Days intubated	26	24	40
ECMO	No	No	No
Deceased?	Yes	Yes	Yes
Admission Lab Findings			
WBC (K/ul)	8.7	7.5	5.8
ANC	7.1	5500	4700
ALC	0.7	1100	700
Hb (g/dL)	9.1	12.5	15.4
Plt (K/UL)	426	201	428
SCr (mg/dL)	0.6	0.93	1.17
LDH (U/L)	396	581	426
D-dimer (ng/mL)	5,684	1640	1585
FBG (mg/dL)	742	NA	NA
FSP	40	NA	NA
PT/INR (9.7-13.1 s/0.8-1.20)	13.1/1.2	10.3/1.0	NA
aPTT (25.1-36.5 s)	40.5	27.6	NA
Ferritin (ng/mL)	967	844	2289
CRP (mg/dL)	18.9	13.0	25.9
Procalcitonin (ng/mL)	0.33	0.04	0.15
Troponin I	.02	0.05	0.0
IL-6 (pg/mL)	n/a	NA	215.85
Other infection?	Hospital-acquired pneumonia, bacteremia	Presumed bacterial pneumonia	None
Confirmed thrombosis?	No	No	Yes (occlusive thrombi in the distal right common femoral artery extending into the superficial

(*Continued*)

TABLE 1. (*Continued*)

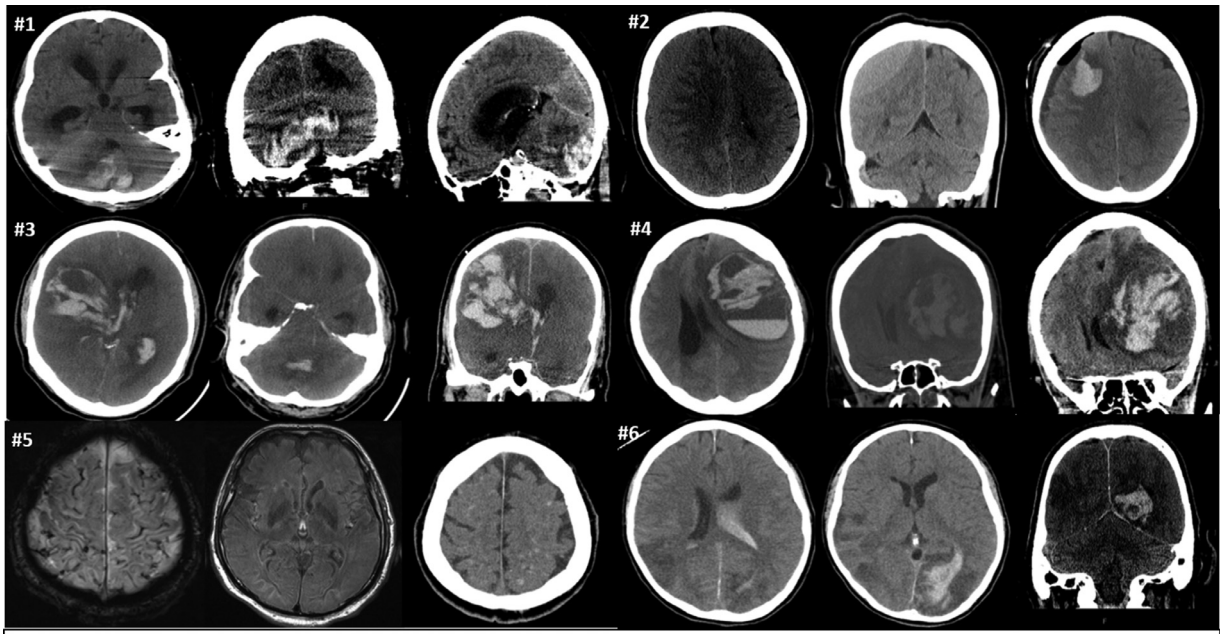
	Patient 4	Patient 5	Patient 6
			femoral and profunda femoris arteries, separate occlusive thrombus in the right popliteal artery extending into the calf arteries), treated with thrombolytic therapy and percutaneous mechanical thrombectomy
Type of VTE prophylaxis at Admission	LMWH (0.6 mg/kg BID)	Home apixaban 5 mg BID	LMWH (0.6 mg/kg BID), increased to 1 mg/kg BID due to concern for PE and worsening respiratory status
Type of intracranial bleeding and location	Large intraparenchymal hemorrhage centered in the left frontal lobe	Diffuse bilateral subarachnoid hemorrhage	Bilateral intraparenchymal hemorrhage (Bilateral right temporo-occipital and left occipital), with intraventricular extension/SAH
Intervention if intracranial bleed	Protamine	None	None
Location of acute CVA	No	N/A	Bilateral right temporo-occipital and left occipital (with hemorrhagic conversion)
Intervention if acute CVA	No	N/A	None
Seizures?	No	Yes	No
D-dimer with CVA or ICH	1073	15,763	13,874
PT/INR with CVA or ICH (9.7-13.1 s/0.8-1.20)	12.8/1.1	14.7/1.3	13.5/1.1
aPTT with CVA or ICH (25.1-36.5 s)	38.9	33.3	30.4
PLT count with CVA or ICH (150-400 K/UL)	376	380	309

Abbreviations: y: years; F: female' M: male; BMI: body mass index; CXR: chest X-ray; COVID-19: Coronavirus Disease 2019; PCR: polymerase chain reaction; POCT: point of care test; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membranous oxygenation; N/A: Not applicable; HD: hospital day; NA: Not available; WBC: white cell count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; Hb: hemoglobin; PLT: platelet; SCr: serum creatinine; LDH: lactate dehydrogenase; FBG: fasting blood glucose; FSP: fibrin split product; PT: prothrombin time; INR international normalized ratio; aPTT: activated partial thromboplastin time; s: second; CRP: C-reactive protein; IL-6: interleukin 6; VTE: venous thromboembolism; LMWH: low molecular weight heparin; BID: twice daily; CVA: cerebrovascular accident; ICH: intracranial hemorrhage

heparin (LMWH) since her admission D-dimer was <5 times the upper limit of normal (ULN) per institutional protocol. On HD8, her D-dimer rose to 6,677 ng/mL and she was transitioned to LMWH at 0.6 mg/kg twice daily. Her creatinine clearance declined to 46 mL/min; therefore, the LMWH was discontinued and therapeutic heparin was initiated on HD12. On HD15, her hemoglobin dropped, and computerized tomography (CT) of her chest/abdomen/pelvis showed a massive left thigh hematoma. Her anticoagulation was discontinued, and her hemoglobin improved. By HD21, she had shown improvement in respiratory status and was weaned off sedation but was not arousable after three days. CT head (CTH) demonstrated a large cerebellar hemorrhage (Fig. 1). D-dimer at the time was 19,679 ng/mL. She was transitioned to comfort care and expired after terminal extubation on HD27.

Patient #2

A 68-year-old woman with hypertension initially presented with left-sided weakness and unsteady gait of one-week duration following a mechanical fall at home. On admission, she was SARS-CoV-2 positive. Inflammatory markers along with D-dimer were not evaluated at initial presentation. CTH revealed a mixed density hematoma along the right convexity consistent with acute subdural hematoma that measured 2.4 cm in maximum dimension with a resultant 7 mm midline shift and mild effacement of the right frontal horn of the lateral ventricles. She underwent a right-sided craniotomy with evacuation of the hematoma on HD1. She was subsequently started on prophylactic anticoagulation with subcutaneous heparin. However, her post-operative course was complicated by a right frontal intraparenchymal hemorrhage,



Patient #1. CTH without contrast, axial/coronal/sagittal section: Large posterior fossa hematoma resulting in severe acute obstructive hydrocephalus, upward transtentorial herniation, and tonsillar herniation.
Patient #2. CTH without contrast, axial and coronal sections: Large acute right convexity subdural hematoma with 7 mm midline shift. Post op CTH without contrast axial section: Right frontal craniotomy and placement of a right frontal subdural drain trace residual blood products. Improved leftward midline shift to 4 mm. Interval development of a right frontal intraparenchymal hematoma with surrounding edema and scattered subarachnoid blood. Right frontal pneumocephalus.
Patient #3. CTH without contrast, axial section: Large right frontal lobe intraparenchymal hemorrhage with extension to the intraventricular and subarachnoid spaces. Downward transtentorial herniation, and 1.3cm midline shift. Left lateral ventricle enlargement and diffuse cerebral edema.
Patient #4. CTH without contrast, axial and coronal sections: Large left frontal lobe intraparenchymal hemorrhage with heterogeneous density. Mass effect, including uncal herniation resulting insignificant mass effect on the brainstem. Subfalcine herniation, with approximately 1.7 cm of rightward midline shift. Dilatation of the right lateral ventricle.
Patient #5. MRI Gradient Echo with diffuse bilateral subarachnoid hemorrhage: MRI T2/FLAIR with bilateral subarachnoid hemorrhage, more prominent in the right sylvian fissure. CTH without contrast, axial section: Diffuse Hyper-densities demonstrating subarachnoid hemorrhage.
Patient #7. CTH without contrast, axial and coronal sections: Large posterior fossa hematoma resulting in severe acute obstructive hydrocephalus, upward transtentorial herniation, and tonsillar herniation.

Fig. 1. *Patient images.*

pneumocephalus and localization-related seizures which occurred on HD6. Furthermore, her CTH showed worsening cerebral edema thought to be secondary to new superficial cortical vein thrombosis (Fig. 1). She was managed with supplemental oxygen, lacosamide, levetiracetam and hypertonic saline. She received physical therapy during the admission and discharged to acute inpatient rehab on HD21.

Patient #3

A 76-year-old man with hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), class I obesity and gout who presented with fever, non-productive cough, dyspnea and diarrhea of two days duration. SARS-CoV-2 polymerase chain reaction (PCR) test on admission was positive. CXR revealed bilateral lower lobe predominant airspace opacities and bilateral pleural effusions consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation. He was started on prophylactic anticoagulation with LMWH due to initial d-dimer of 16,107 ng/mL on HD1. Prophylactic anticoagulation was escalated to therapeutic heparin due to increasing D-dimer of 23,541 on HD2 and detectable troponin I; he was intubated and placed on mechanical ventilation for ARDS. He received remdesivir from HD3-7 and convalescent plasma on HD10. On HD12, he became unarousable to voice or noxious stimuli and his neurological exam revealed fixed and non-reactive pupils. CTH revealed a large right frontal lobe intraparenchymal hemorrhage with extension to the intraventricular and subarachnoid spaces, with associated transtentorial herniation, and a 1.3 cm midline shift (Fig. 1). Additional findings included left lateral ventricle enlargement concerning for entrapment, diffuse cerebral edema and small right cerebellar hemisphere intraparenchymal hemorrhage. Coagulation parameters at the time of the catastrophic hemorrhage showed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). He expired after terminal extubation on HD14.

Patient #4

A 71-year-old woman with diabetes mellitus type II, hypertension, hyperlipidemia, and class III obesity, was transferred from an outside hospital for management of COVID-19 ARDS on HD12. Inflammatory markers were elevated on presentation and HD12 D-dimer was 5,684 ng/mL. LMWH 0.6 mg/kg BID per protocol was initiated. She also had gram negative bacteremia and given a two-week course of antibiotics. On HD15, she developed a right pneumothorax and then left pneumothorax with subsequent chest tube placement. On HD26, a stroke code was called for impaired arousal and a

dilated left pupil. CTH revealed a large left frontal lobe intraparenchymal hemorrhage causing uncal and subfalcine herniation with approximately 1.7 cm of rightward midline shift and dilatation of the right lateral ventricle (Fig. 1). As prognosis was extremely poor for meaningful neurologic recovery, she was terminally extubated and expired shortly thereafter.

Patient #5

A 79-year-old man with hypertension, hyperlipidemia, diabetes mellitus type II, coronary artery disease and atrial fibrillation presented with fever and shortness of breath. He was positive for SARS-CoV-2 by PCR. CXR revealed bilateral patchy opacities consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation and D-dimer was <5x the ULN and was continued on previous full dose apixaban. On HD1, he was intubated and started on mechanical ventilation due to ARDS. On HD10, he was noted to have seizure-like activity and was treated with lorazepam, levetiracetam and fosphenytoin. CTH demonstrated numerous serpiginous areas of hyperdensity throughout the convexity consistent with acute subarachnoid and/or cortical hemorrhage. Apixaban was discontinued. D-dimer was 15,763 ng/mL. By HD14, he was weaned off all sedating medications but remained unresponsive. Serial electroencephalograms revealed low background activity consistent with diffuse encephalopathy. MRI brain showed diffuse bilateral cortical T2/FLAIR signal hyperintensity compatible with subarachnoid hemorrhage, diffuse cortical changes consistent with diffuse ischemic injury, and diffuse swelling of the cortex, most prominently over the bilateral temporal and parietal regions (Fig. 1). Prognosis for meaningful neurologic recovery was poor. He was terminally extubated and expired on HD24.

Patient #6

A 63-year-old man with hypertension, diabetes mellitus type II, and tobacco use disorder presented with fever, non-productive cough, dyspnea, anosmia, ageusia and 10 pound weight loss over 5 days. He was known to be positive for SARS-CoV-2 ten days prior to symptom onset. CXR demonstrated reticular interstitial changes and patchy alveolar opacities consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation and D-dimer was <5x ULN. On HD1, he was started on LMWH 0.6 mg/kg twice daily per protocol which was increased to 1 mg/kg on HD2 due to worsening respiratory status and concern for acute PE. He received tocilizumab on HD2. He was noted to have a cold and numb right foot with decreased doppler tones concerning for arterial occlusion on HD7; therefore, his anticoagulation was switched to therapeutic heparin. A CT angiogram revealed occlusive thrombi in the right common femoral artery extending into the superficial femoral and profunda femoris arteries, a separate occlusive thrombus in the right popliteal artery extending into the calf (tibial) arteries and another occlusive thrombus in the distal right internal iliac artery. These were treated with both percutaneous mechanical thrombectomy and thrombolytic therapy using tissue plasminogen activator (tPA); postoperatively, the loss of left dorsalis pedis and posterior tibial pulsation necessitated the addition of alteplase infusion. He had recurrent surgical site bleeding due to these procedures. On HD8, he reported generalized headache. CTH revealed acute bilateral intraparenchymal hemorrhage, most evident in the left occipital lobe with intraventricular extension, subarachnoid hemorrhage and associated regional mass effect (Fig. 1). There was also a right parietal infarct with hemorrhagic conversion. Therapeutic heparin and tPA were discontinued and cryoprecipitate and tranexamic acid were administered. D-dimer at the time was 13,874 ng/mL. An extensive laboratory evaluation for thrombophilia was performed, including antiphospholipid antibodies was negative. On HD29, he was intubated due to declining respiratory status and subsequently went into septic shock. He was transitioned to comfort care and expired on HD47.

Discussion & conclusion

Here, we describe five critically ill patients with COVID-19 ARDS who developed intracranial hemorrhage while on intermediate or full-dose therapeutic anticoagulation and one patient who was SARS-CoV-2 positive but asymptomatic and suffered intracranial hemorrhage after prophylactic anticoagulation. Five out of six patients received therapy for COVID-19; two with hydroxychloroquine, one with remdesivir and convalescent plasma, one with antibiotics and the last one with tocilizumab. Two patients also had concurrent thrombosis (PE, lower extremity VTE, arterial). All five patients with COVID-19 ARDS had elevated inflammatory markers at presentation including LDH, ferritin, C-reactive protein, D-dimer but only two of five had D-dimer >5x the upper limit of normal (>2500 ng/mL). Additionally, three of five patients had D-dimer levels over 13,000 ng/mL at the time their hemorrhage occurred with all having normal platelet counts and four of five with normal coagulation parameters. Patient #6 also suffered from an acute ischemic stroke with eventual hemorrhagic conversion; due to the finding of arterial thrombosis, antiphospholipid antibodies were sent but not present. As reported in other case series describing intracranial hemorrhage, we are unable to determine if these neurological complications are due to ARDS from COVID-19; however, patient #2 was diagnosed at presentation with a subdural hematoma and then after evaluation had a right frontal lobe intracerebral hemorrhage after prophylactic anticoagulation was begun. None of the patients were treated with extracorporeal membrane oxygenation (ECMO).

COVID-19-associated coagulopathy has been well described. There is growing evidence that patients with COVID-19 have a predisposition to both intracranial hemorrhage and thrombosis.[9,10]. It has been proposed that the often-seen elevated hypertension (mediated by binding of SARS-CoV-2 to angiotensin converting enzyme), significant thrombocytopenia and deranged coagulation proteins (as indicated by prolongation of the PT and aPTT) contribute to the development of intracranial hemorrhage in these patients.[9,11] On the other hand, the establishment of a hypercoagulable state as indicated by markedly elevated markers of systemic inflammation caused by a robust inflamtory response resulting in a cytokine storm mediated by IL-1 and IL-6 biochemical cascades. Which in results in denoting ongoing fibrinolysis (e.g. D-dimer and fibrin split products) and other non-specific indicators such as ferritin, C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase which may represent the widespread endothelial damage thought to be associated with COVID-19.[9,10,12,13] However, therapeutic anticoagulation comes with an increased risk of bleeding. Evidence of the overall effect of therapeutic anticoagulation in critically ill COVID-19 patients without confirmed thrombosis is lacking.[14] Prospective clinical trials are needed and are underway to answer these important questions. In the interim, clinicians must carefully weigh the risks and benefits of anticoagulation in the COVID-19 patient; also, given the level of isolation, sedation and paralytics, neurological exams are challenging. When a change is recognized, the disease process has often advanced beyond intervention.[8]

Declaration of Competing Interest

None.

Grant support: None

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