

Letter: Thrombotic Neurovascular Disease in COVID-19 Patients

To the Editor:

Although the respiratory system is the primary target of the coronavirus, studies have demonstrated a strong tropism to the central nervous system (CNS).^{1,2} The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is also found in the CNS and plays a crucial role in autoregulating cerebral perfusion pressure.^{3,4} Additionally, epidemiological data demonstrated increased mortality due to cardiovascular and cerebrovascular diseases during flu pandemics due to a hypercoagulable state.^{5,6} The triad of neuroinvasion of SARS-CoV-2, induction of hypercoagulable state,⁵⁻⁹ and the inhibition of ACE2 blocking the formation of Angiotensin (1-7) serve as the pathophysiology for neurovascular insults.^{3,4} We present a case series of coronavirus disease 2019 (COVID-19) patients from 2 health systems developing cerebrovascular insult.

METHODS

Study Design

Institutional Review Board (IRB) approved the study protocol and waived the need for informed consent. A retrospective analysis was conducted across 2 institutions between March 20 and April 10, 2020. Fourteen patients were identified with the diagnosis of cerebrovascular insult and COVID-19 infection. COVID-19 was diagnosed using reverse-transcriptase/polymerase-chain-reaction assays of nasopharyngeal samples for SARS-CoV-2. Medical charts were queried for baseline patient characteristics, comorbidities, COVID-19 symptoms, duration between COVID-19 symptoms and the neurological manifestation, cerebrovascular insult, National Institutes of Health Stroke Scale (NIHSS) at presentation, procedure details, and mortality.

Data Sharing Statement

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

Ethical Approval

All procedures performed in the studies involving human participants were per the ethical standards of the IRB or National Research Committee, and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

The study protocol was reviewed and approved by the Thomas Jefferson University Institutional Review Board. Following our institutional guidelines, all protected health information were removed, and individual patient consent was not required for the analysis of this case series.

RESULTS

The total sample size was 14 patients. The mean age was 60.1 ± 11.1 yr, and 9 patients were males (64.3%). Six patients (42.8%) had no significant prior medical history. Seven patients (50.3%) had neurological insult as the initial manifestation of COVID-19. The average duration between the onset of COVID-19 symptoms and the cerebrovascular insult was 3.5 d (range: 0-17). The cerebrovascular pathologies were 12 cases of acute ischemic stroke (AIS) and 2 cases of sinus thrombosis. The mean NIHSS was 15.8 (range: 1-30), and all patients were treated within 6 h of symptoms onset. A total of 4 patients had carotid T occlusions, 2 had tandem occlusion (internal carotid artery [ICA] and middle cerebral artery [MCA] M1 occlusion), 1 patient had M1 and A2 occlusion, 2 patients had M1 occlusion, 2 patients had M2 occlusion, 2 patients had sinus thrombosis, and 1 patient had central retinal artery occlusion. Two patients developed hemorrhagic conversion requiring decompressive surgery. The mean duration of the mechanical thrombectomy (MT) procedures was 95.5 min (range: 17-428), and a favorable thrombolysis in cerebral infarction (TICI) score ($>2b$) was achieved in all patients. The total mortality incidence was 6 (42.8%; Table).

DISCUSSION

Despite the small sample size, the data demonstrate some unusual trends worth sharing, at least to draw awareness. First, the mean age of the population was 60 yr, 42% of the cohort was younger than 55, and 42% did not have any traditional cerebrovascular risk factors. Moreover, cerebrovascular insult was the primary manifestation of COVID-19 in patients who did not have the fulminant virus manifestations present. Occlusions occurred in multiple arterial territories and both on the arterial and on the venous sides; the latter are more challenging to treat, and the procedures require additional expertise. Selected procedures were more complex and challenging, requiring multiple attempts to retrieve the clot entirely due to the severe clot burden. Such an observation is evident in the relatively long procedure time compared to historical data. Also, mortality rates reached 42.8%, with TICI $\geq 2b$ achieved in all cases. Two patients developed hemorrhagic conversion requiring decompressive hemicraniectomy (Figure 1).

The level of causality between the SARS-CoV-2 and AIS is yet to be determined. However, maintaining a vigilant attitude is crucial, specifically if it leads to favorable outcomes. It is early to determine the exact impact of COVID-19 on the incidence of acute cerebrovascular diseases. The SARS-CoV-2 is neuroinvasive and neurovirulent (Figure 2),^{1,2} binds to ACE2 and reduces its downstream effect (Figure 3),^{3,4} and induces a hyperinflammatory response characterized by a cytokine storm

TABLE. Demographics, Procedure Details and Outcomes, and Laboratory Findings

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Age, yr	70	51	55	62	69	54	48	59	72	77	52	38	62	72
Gender	Female	Male	Male	Female	Female	Male	Male	Male	Female	Female	Male	Male	Male	Male
Medical history	A-Fib	Heart disease	None	Heart disease, A-Fib	HTN-DM-A-Fib	HTN	None	HTN	Lung disease, diabetes	Diabetes	None	None	Lung disease	None
Diagnosed before or after procedure	Before	Before	After	After	After	Before	After	Before	After	After	After	Before	Before	Before
Symptoms at disease onset	Fever, cough, pneumonia, ARDS	Fever	Fever, cough	Fever	None	Cough, Pneumonia	None	None	Pneumonia, ARDS	None	Pneumonia	Fever, pneumonia	Pneumonia	Cough, pneumonia
Symptom onset to presentation	11 d	4 d			0	17	0	0	0	0	14	2	5	5
Pathology	Stroke (M1-A2 occlusion)	Stroke (T occlusion)	Stroke (tandem ICA/ M1 occlusion)	Stroke (tandem ICA/ M1 occlusion)	Stroke (M2 occlusion)	Deep venous thrombosis (vein of Galen, straight sinus)	Stroke (M1 occlusion)	Stroke (CRAO due to a ICA occlusion)	Stroke (M1 occlusion)	Stroke (T occlusion)	Stroke (T occlusion)	Sinus thrombosis (sagittal and straight)	Stroke (T occlusion)	Stroke (M2 occlusion)
NIHSS/H&H	21	15	16	18	4	26	26	1	15	4	21	14	30	10
Management and treatment	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy, hemicraniectomy	Mechanical thrombectomy, hemicraniectomy	Mechanical thrombectomy	Heparin	Mechanical thrombectomy	LMWH	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy
Procedures required	Yes	Yes	Yes	Yes	No	NA	No	NA	Yes	Yes	Yes	Yes	Yes	Yes
Intubation														
Procedure duration (min)	66	150	45	20	17	NA	25	NA	27	428	59	254	37	67
TICI score	3	2b	2b	3	3	NA	3	NA	2c	2c	2b	NA	3	2c
Mortality	Yes	Yes	Still in hospital	Still in hospital	No	Yes	No	NA	Yes	No	No	Yes	Yes	No
White-cell count (x10 ³ /uL)	14.2	5.8	14.3	6.8	11	7.8	8.2	7.6	7.9	17.6	12.8	16.7	24.9	9.7
Differential cell C (B/L)														
Abs. neutrophils C	4.4	4.4	11.5	4.6	6.4	7.2	4.7	4.7	6.2	15.5	10.9	14.2	20	8.5
Abs. lymphocytes C	0.9	0.9	1.5	1.7	1.1	0.6	0.6	2	1.2	1.2	1.1	0.5	1.8	0.5
Abs. monocytes C	0.3	0.3	0.9	0.3	0.2	0.3	0.3	0.8	0.4	0.7	0.7	1.7	2.5	0.6
Platelet C (x10 ³ /uL)	415	273	472	130	339	339	237	327	331	379	104	141	476	226

TABLE. Continued

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Hemoglobin (g/dL)	10.3	11.5	9.1	9	12.4	14.4	13.3	13.1	11.6	8.2	12	14.3	12.9	13.5
Albumin (g/dL)	2.3	1.2	3.4	4.3	3.8	3.7	4.2	4	3	3.1	2.9	4.4	3	3.4
AST (IU/L)	65	31	213	30	37	44	21	38	71	10	18	31	55	48
ALT (IU/L)	91	8	227	17	29	67	44	88	34	17	19	27	78	46
LDH (IU/L)	586	689	478	265	382	272	269	272	430	179	267	448	520	474
Creatinine (mg/dL)	0.57	3.77	1.1	0.72	0.78	1.06	0.84	1	1.4	0.78	0.66	0.9	0.88	1.22
eGFR (units)	> 60	> 60	> 60	> 60	> 60	> 60	> 60	> 60	35	> 60	> 60	> 60	> 60	58.4
Creatine kinase (IU/L)	58	388				190	151	136	317	78	127	594	70	226
Troponin T high sensitivity (ng/L)	16			< 6	< 6	14	10	11	10	10	10	6	90	20
PT (s)	13.5	15.7	14.1	13.5	13	11.8	12.2	14.6	13.5	12.5	12.6	22.5	19.1	12.8
aPTT (s)	23	36	32	> 120	35	25	29	33	38.7	33.8	34	30.6	41.3	26.9
Fibrinogen (mg/dL)	719	970	331		429	429	243	545	634	654	235	121	84	
D-dimer (ng/mL)	9862	2476	995		5748	6383	6383	450	3,247	256	> 10,000	> 55,000	> 10,000	360
Serum ferritin (ng/mL)	3500	1085	749		508	508	270	1785	204	4.6	588.1	785	1028	2929
C-reactive protein (mg/dL)	41.7	21.6	5.3		0.6	0.6	0.3	2.1	72	10.1	11	188	154	94.4
Procalcitonin (ng/mL)	0.26	6.23	0.12				0.05		0.38		0.03		0.11	0.12
Interleukin-6 (pg/mL)		185.3	49.19				9.2		14	< 5			45	870

Abs: absolute; ALT: alanine aminotransferase; A-Fib: atrial fibrillation; aPTT: activated partial-thromboplastin time; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; A2: second segment of anterior cerebral artery; C: count; CRAO: central retina artery occlusion; eGFR: estimated glomerular filtration rate; ICA: internal carotid artery; LDH: lactate dehydrogenase; M1: first segment of middle cerebral artery; M2: second segment of middle cerebral artery; NIHSS: National Institutes of Health Stroke Scale; PT: prothrombin time; T: occlusion; terminus occlusion; TICI score: thrombolysis in cerebral infarction score; SAH: subarachnoid hemorrhage.

Bold values are above normal levels and red values are below normal levels.

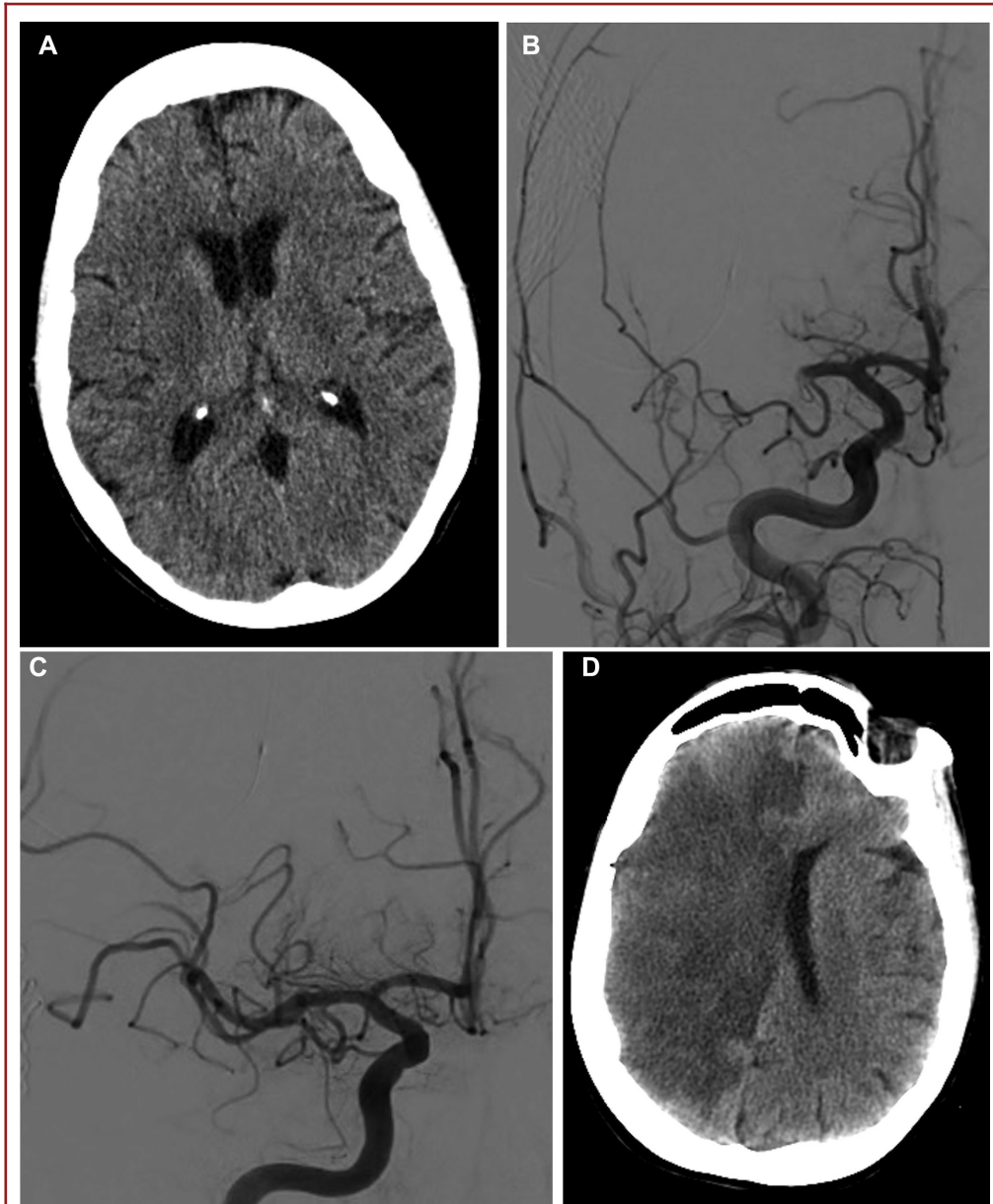
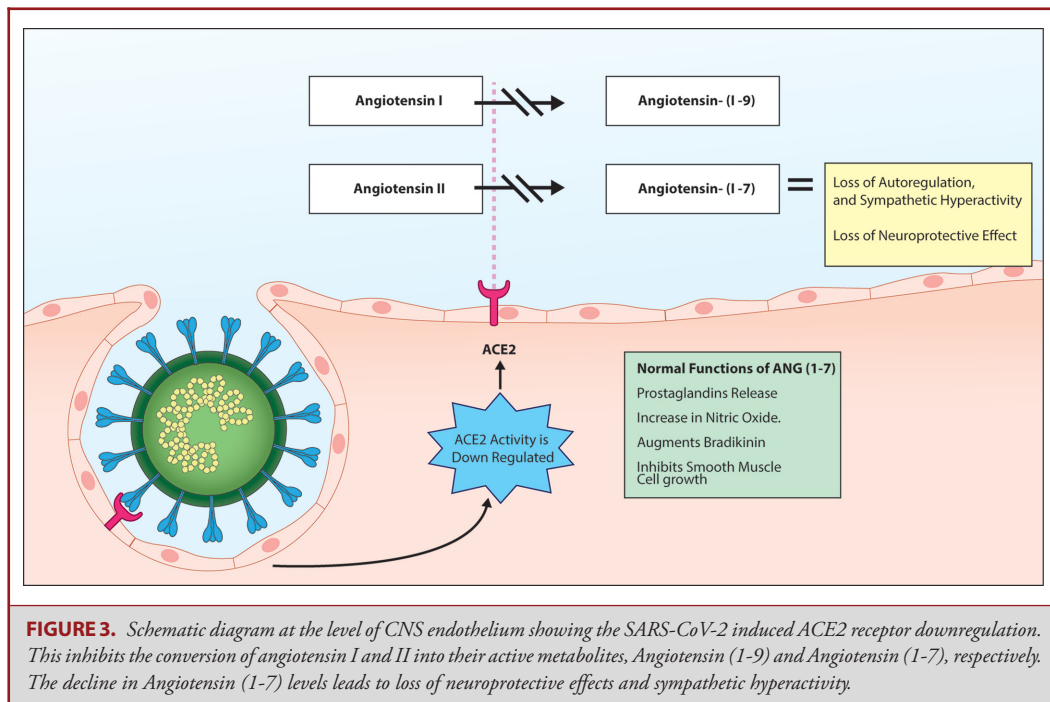
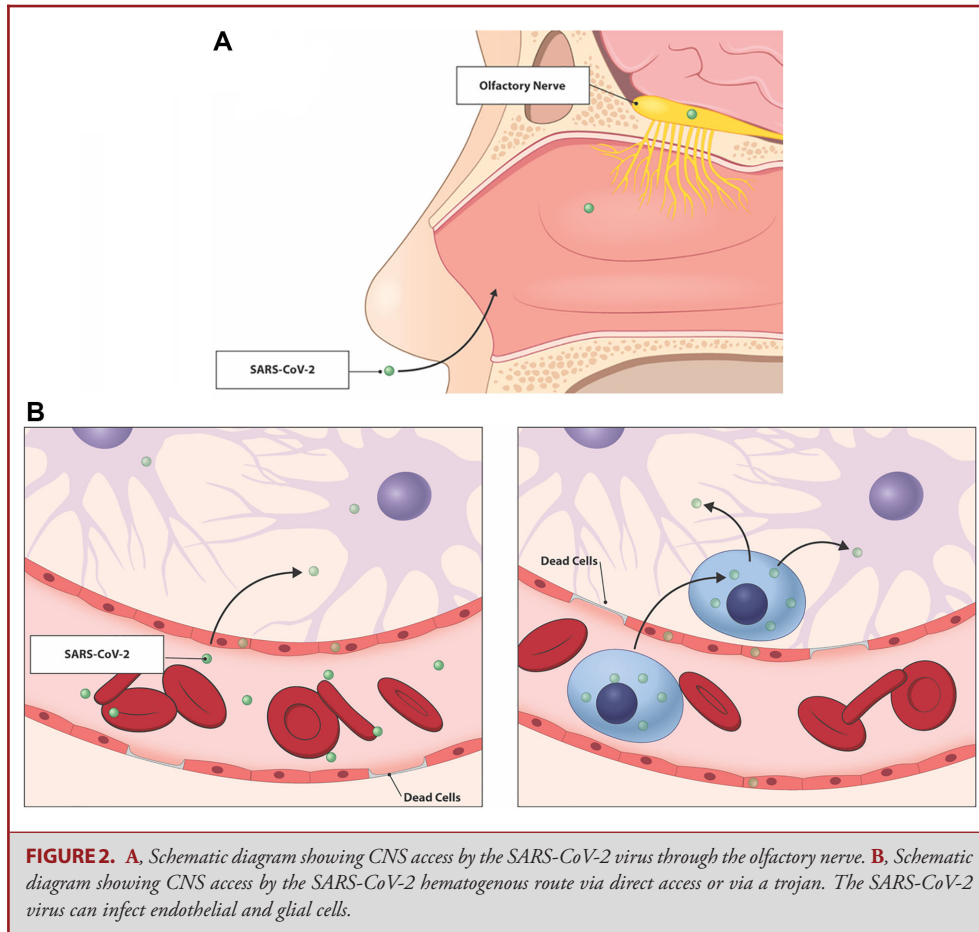
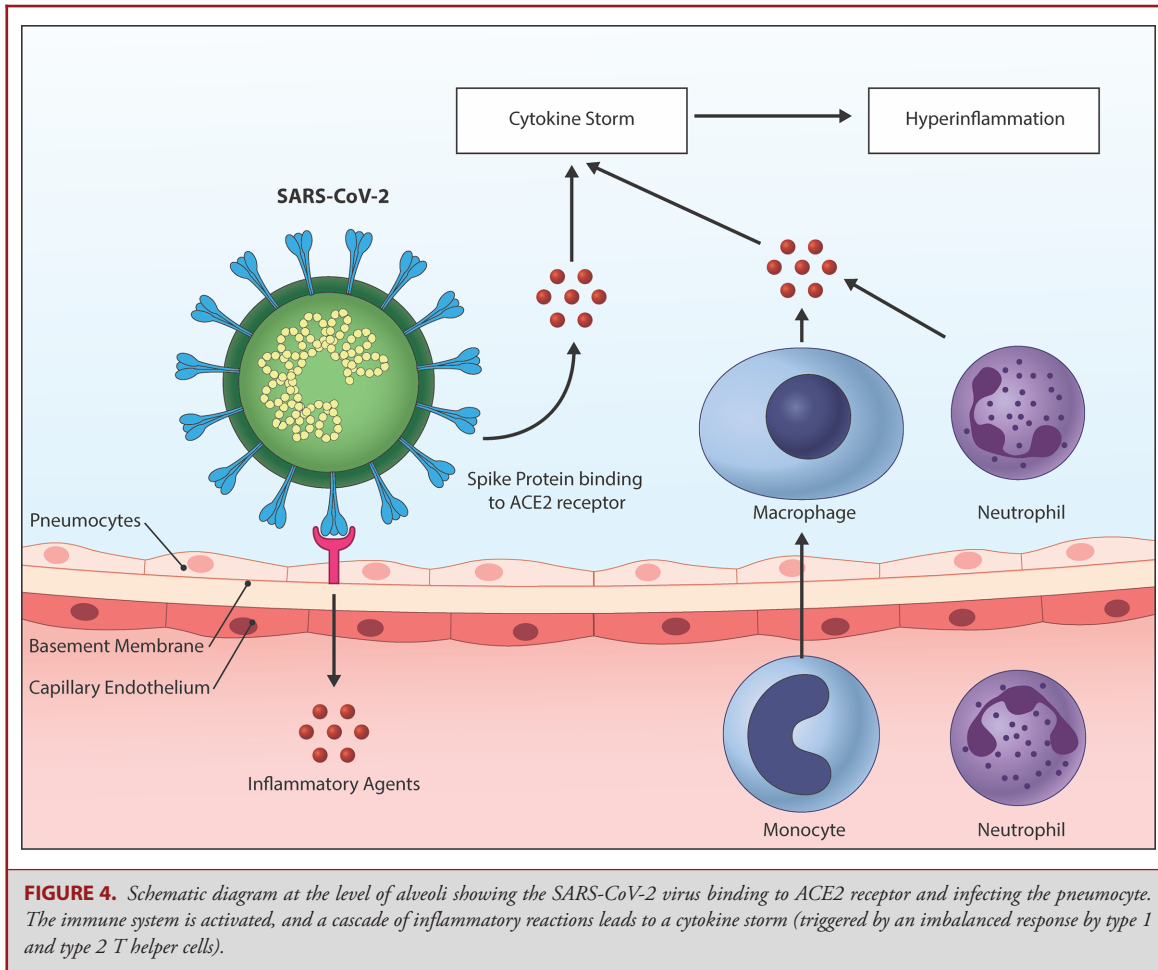


FIGURE 1. A patient in the seventh decade with a history of A-Fib on eliquis was being treated for COVID-19, and on the 11th day of treatment, the patient developed an acute neurological insult. Tissue plasminogen activator was not given because of anticoagulation, and head computed tomography (CT) did not show hemorrhage. The patient was transferred and underwent a mechanical thrombectomy procedure within 4 h and 18 min. The insult progressed into complete infarct, and the patient passed away 3 d later. **A**, Noncontrast axial view of brain CT scan showing no hemorrhage. **B**, Anteroposterior (AP) digital subtraction angiography (DCA) of a right ICA injection showing an M1 and an A2 occlusion. **C**, AP DCA showing complete revascularization of both vessels (TICI 3). **D**, Noncontrast axial view of the brain day 1 post mechanical thrombectomy showing the progression of the insult into a complete infarct.





(Figure 4).⁷⁻⁹ This leads to vasculitis,¹⁰ increased sympathetic tone, arrhythmias, and a hypercoagulable state.

CONCLUSION

Unusual trends have been seen in AIS patients who are COVID-19 positive; while it is too early to establish direct causality, our preliminary data can be used to raise awareness in the population. We are seeing younger patients with no risk factors presenting with AIS and MT procedures are more challenging to deal with. It is crucial in pandemic times to watch and follow closely noteworthy trends and investigate and report new findings.

Disclosures

Dr Jabbour is a consultant for Medtronic and MicroVention. Dr Tjoumakaris and Dr Gooch are consultants for Stryker. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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