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Letter: Thrombotic Neurovascular Disease in COVID-19 Patients.

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Thrombotic Neurovascular Disease in COVID-19 patients

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- Conception or design of the work: AS, ER, MS, ST, PJ
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Abbreviation List: Angiotensin-converting enzyme 2: ACE2; blood-brain barrier: BBB; Central nervous system: CNS; Cerebrospinal fluid: CSF; Coronavirus disease 2019: COVID-19; Human Corona Virus: HCoV; Intracerebral hemorrhage: ICH; Middle East Respiratory Syndrome coronavirus: MERS-CoV; Renin-angiotensin system: RAS; Severe Acute Respiratory Syndrome coronavirus: SARS-CoV; Severe Acute Respiratory Syndrome Coronavirus 2: SARS-CoV 2; World Health Organization (WHO).

Abstract

Background: COVID-19 pandemic is associated with neurological manifestations in critically ill patients.

Objective: A case series of COVID-19 patients from two institutions with acute ischemic stroke is presented. A comprehensive summary of the SARS-CoV-2 induced factors and pathophysiology associated with acute cerebrovascular disease is described.

Methods: A retrospective study across two institutions was conducted between March 20 and April 10, 2020, for patients developing acute cerebrovascular disease and are COVID-19 positive. Additional, vital stroke metrics such as admissions, teleconsults, and thrombectomy procedures were compared to previous years.

Results: The total sample size was 14 patients. The mean age was 60.1 years, and 9 patients were males. 6 (42.8%) patients had no significant prior medical history. Seven patients (50.3%) had the neurological insult as the initial manifestation of COVID-19. The cerebrovascular pathologies were: 12 cases of acute ischemic stroke, and two cases of sinus thrombosis. The mean NIHSS was 15.8 (range: 1-30). The mean duration of the thrombectomy procedure was 95 mins, and a favorable TICI score was achieved in all patients. The total mortality rate was 6 (42.8%).

Vital stroke metrics demonstrated a significant decline in AIS admissions by 23% and telestroke consults by 48% compared to similar period in previous years. Contrary, MT procedures increased by 50% (p=0.112) during the same period.

Conclusions: The mean age showed a left shift, procedure durations were prolonged, and mortality rate was high. There was a significant decline in AIS admission and telestroke consults during the pandemic.

Introduction

In 4 months, the number of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) cases approached 2 million, with more than 125,000 deaths. The World Health Organization (WHO) named the disease Coronavirus disease 2019 (COVID-19) and declared it a pandemic on March 11, 2020.[1] Despite a relatively low fatality rate (2.3%),[2] the virus has a high reproduction number (2.0-2.5). This indicates the potential to infect a large portion of the world population.[3] Historical epidemics are a valuable source of information and are a model to antedate challenges that may occur during the current pandemic.

Although respiratory system is the primary target of the coronavirus, studies have demonstrated a strong tropism to the central nervous system (CNS).[4-9] The SARS-CoV-2 infects cells by binding to the Angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is also found in the CNS and contributes a crucial role in autoregulating cerebral perfusion pressure.[10-12] Additionally, epidemiological data suggests an increased incidence of ischemic and hemorrhagic stroke during flu pandemics due to a hypercoagulable state.[13-15] The triad of neuroinvasion of SARS-CoV-2, induction of hypercoagulable state, and the inhibition of ACE2 blocking the formation of ANG (1-7) serve as the pathophysiology for neurovascular insults. In the current pandemic situation, a better understanding of the pathophysiological mechanisms associated with COVID-19 is critical not only to estimate the risk but also in the effective mamagement of cerebrovascular disease. Herein, we present a case series of COVID-14 patients from two different health systems developing thrombotic central nersvous system (CNS) events. Additionally, we reviewed the literature to present a comprehensive summary of the SARS-CoV-2 induced factors that are associated with neurovascular diseases.

Methods

Study Design

Institutional review board approved the study protocol and waived the need for informed consent. A retrospective analysis was conducted across two institutions between March 20 and April 10, 2020. Fourteen patients were identified with the diagnosis of acute ischemic disease and COVID-19 infection. COVID-19 was diagnosed using reverse-transcriptase–polymerase-chain-reaction assays of nasopharyngeal samples for SARS-CoV-2. The total number of thrombectomy procedures were also collected for the same period (24 and 14 procedures per institution). Medical charts were queried for baseline patient characteristics (age, gender), comorbidities (heart disease, lung disease, liver disease, kidney disease, atrial fibrillation [Afib], and diabetes mellitus), COVID-19 symptoms (fever, cough, pneumonia) duration between COVID-19 symptoms and the neurological manifestation, cerebrovascular insult (aneurysm rupture, intracranial hemorrhage, and stroke), National Institute of Stroke Scale (NIHSS) at presentation, procedure detail (duration from the sheath into sheath out and Thrombolysis in cerebral infarction score (TICI), laboratory results, and mortality.

Additionaly, total ischemic stroke admissions, mechanical thrombectomy procedures, and telestroke consults during March-20 and April-10 of the current year were compared to the mean cases of the previous three years during the same period across one of the institutions which is a tertiary telestroke network.

Lastly, using the PubMed database, we performed a literature search without time limitations for all articles in English using different combinations of the terms *Coronavirus, COVID, SARS-CoV-2, ACE2.* Abstracts were screened to determine if the study matches our requirements. Then, full-texts were read in-depth to determine the correlation between viral infection and stroke.

Results

The total sample size was 14 patients. The mean age was 60.1 ± 11.1, and 9 patients were males (64.3%). 6 (42.8%) patients 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 days (range: 0-17). The cerebrovascular pathologies were: 12 cases of acute ischemic stroke, and two cases of sinus thrombosis. The mean NIHSS was 15.8 (range: 1-30), and all patients were treated within 6 hours of symptoms onset. Four patients had carotid T occlusions, two had tandem occlusion (internal carotid artery (ICA) and middle cerebral artery (MCA) M1 occlusion), one patient had M1 and A2 occlusion, two patients had M1 occlusion, two patients had M2 occlusion, two patients had sinus thrombosis, and one patient had central retinal artery occlusion. Two patients developed hemorrhagic conversion requiring decompressive surgery. The mean duration of the thrombectomy procedures was 95.5 mins (range: 17-428), and a favorable TICI score (> 2b) was achieved in all patients. The total mortality ratewas 6 (42.8%). (**Table 1**).

Vital stroke metrics across a tertiary telestroke network demonstrated a significant decline in AIS admissions by 23% (p=0.001) and telestroke consults by 48% (p=0.001) compared to similar period in previous years. Contrary, MT procedures increased by 50% (p=0.112) during the same period. Notably, of all thrombectomy cases (24), six were COVID-19 positive, constituting 25% of all thrombectomy patients at one institution **(Table 2)**. Across both institutions, 31.5% of stroke patients who underwent a MT during the study period were COVID-19 positive.

Discussion

Despite the small smaple size, the data demonstrates some unusual trends worth of sharing, at least to draw awareness. First, the mean age of the population was 60 years with 42% of the cohort younger than 55 years, and 42% did not have any traditional cerebrovascular risk factors. Moreover, AIS was the primary manifestation of COVID-19 in patients that did not have the virus fulminant manifestations present. Occlusions occurred in multiple arterial territories and both in the arterial and venous side; the latter is more challenging to treat, and the procedures require an additional level of expertise. Selected procedures were more complex and challenging, requiring multiple attempts to completely retrieve the clot due to the severe clot burden. Such observation is evident in the relative 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. We have sighted a substantial regression in total AIS admission by 23% and telestroke consults by 48% compared to previous years, signifying that either patients are not reporting neurological symptoms due to the fear of the contagion or the stroke incidence has decreased due to other variables; despite that, 31.5% of MT procedures were COVID-19 positive.

It is early to determine the exact impact of the coronavirus on the incidence of acute cerebrovascular diseases. The SARS-CoV-2 binds to ACE2 and reduces its downstream effect, is neuroinvasive and neurovirulent, and induces a hyper inflammatory phase characterized by a cytokine storm. This leads to vasculitis, increased sympathetic tone, arrhythmias, and a hypercoagulable state.

Human Corona Virus (HCoV)

Coronaviruses are a family of enveloped positive-stranded RNA viruses that are widespread.[16] The genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein. The spike protein (S) is a transmembrane protein responsible for the recognition of the cellular receptor used by the virus to infect susceptible cells. SARS-CoV-2 recognizes the ACE2 receptor,[17,18] which affords SARS-CoV-2 neurotropic and neuroinvasive properties.[19-21] In addition to severe respiratory syndromes, cases of severe acute disseminated encephalomyelitis, vasculopathy, brainstem encephalitis, and Guillain-Barré syndrome have also been described.[22,23]

SARS-CoV-2 Neurological Manifestations

Neurological manifestations caused by the SARS-CoV-2 range from mild symptoms, like anosmia, to severe symptoms, like acute ischemic attack or intracerebral hemorrhage.[24,25] Diagnosis and management of neurological complaints may be more challenging in such an uncharted time due to several reasons including staff allocations, lack of hospital beds, delay in patient presentation, delay in imaging acquisition, and the virtual consolations. Mao et al. reported the outcomes of 214 patients diagnosed with COVID-19 experiencing neurological manifestations.[25] 41.1% had a severe infection, and 36.4% experienced various neurologic manifestations. Patients with severe infection were older, had a higher incidence of hypertension, and higher incidence of neurologic manifestation (45.5% vs. 30.2%), specifically acute cerebrovascular disease (5.7% vs. 0.8%), consciousness disturbance, and skeletal muscle injury. Severe infection had a more robust inflammatory response compared to non-severe (higher leukocytes count, neutrophil count, CRP values, and D-Dimer while lower lymphocyte count and platelet count). Also, the severe infection was associated with a higher D-Dimer and a lower platelet count which is indicative of a consumptive coagulation system.[25]

Neuroinvasion and Neurovirulence

Viruses, including coronavirus, can penetrate the CNS (neuroinvasion), infect neurons and glial cells (neurotropism), and contribute to or cause neurological disease (neurovirulence).[26] Access may be achieved via two main routes: hematogenous or transneuronal through the olfactory bulb (**Figure 2**).[4,27] Mouse models for coronavirus encephalitis have shown that the virus can access the CNS via olfactory pathways.[26] On the other hand; the hematogenous route involves directly infecting the blood-brain barrier (BBB) or access via a trojan such as leukocytes.[4,28] HCoV strains may infect human monocytes/macrophages,[29,30] murine dendritic cells expressing the human aminopeptidase N,[31], and human endothelial cells of the BBB.[28] As for SARS-CoV-2, detection of the virus in the CSF of COVID-19 patients has been reported.[32-34] The potenial of the SARS-CoV-2 to infect endothelial cells leading to vasculitis may contribute to the pathophysiology of neurovascular insult. [28,35,36]

ACE2 Receptor and ANG (1-7)

The second component of the triad that plays a vital role in the neurological manifestations of SARV-CoV-2 is the ACE2 receptor. ACE2 is a carboxypeptidase that converts angiotensin II into angiotensin (1-7) [ANG (1-7)], which is an essential component of the renin-angiotensin system (RAS).[37] One of the main sites that ANG (1-7) is synthesized and has a downstream effect on are endothelial cells.[36] It stimulates the release of prostaglandin[38] and nitric oxide,[39] enhances the metabolic actions of bradykinin, and inhibits smooth muscle cell growth.[40] Additionally, ANG (1-7) enhances the vagal tone by stimulating the solitary tract nucleus and dorsal motor nucleus of the vagus nerve.[41,42] It also induces a decrease in tyrosine hydroxylase expression, the rate-limiting enzyme in catecholamine biosynthesis, decreasing brain catecholaminergic activity.[43] In a recent rat models, central administration of ANG-(1–7) reduced neurological deficits and infarct size in ischemic stroke demonstrating neuroportective properties (**Figure 3**).[12,44] Binding of SARS-CoV-2 to the ACE2 receptor may

inhibit its downstream effect via pathway downregulation or cell lysis, ultimately decreasing ANG (1-7) synthesis.

Hypercoagulable State

The third arm of the triad is the hypercoagulable state caused by the virus-induced cytokine storm. Surveillance studies following epidemics revealed that about 50% of the excess mortality was attributed to cerebrovascular and cardiovascular pathologies.[45,46] Animal experiments have also highlighted the interaction between vascular risk factors and viral infection on the risk of stroke.[47] Vascular risk factors lead to an augmented inflammatory response after endotoxin stimulation, which contributes to creating a hypercoagulable state.[47]

Viral disease progression can be divided into three phases based on the immune response.[48-50] The hyper inflammatory phase is characterized by the release of inflammatory markers and a cytokine storm.[51-56] Inflammatory markers are associated with high mortality as the exaggerated inflammatory response can have deleterious effects on distant organs.[3] In retrospective studies, critically-ill COVID-19 patients had increased proinflammatory cytokines including IL-2 and TNF-α4, which can upregulate the coagulation system (**Figure 4**).[25,57] Recently, three critically ill COVID-19 patients developed multiple cerebral infarcts with positive antiphospholipid antibodies.

Conclusion

Unusual trends have been seen in AIS patients who are COVID positive, while it is too early to establish the 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 in those patients. It is crucial in pandemic times to watch and follow closely unusual trends and investigate and report new findings.

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Legend:

Table 1: Demographics, Procedure Details and Outcomes, and Laboratory Findings.

Table 2: Frequency of Telestroke consults, AIS admission, and MT.

Figure 1 (A-G): A patient in the seventh decade with a history of A-Fib on eliqus was being treated for COVID-19, and on the 11th day of treatment, the patient developed an acute neurological insult. tPA was not given because of anticoagulation, and head CT did not show hemorrhage. The patient was transferred and underwent a mechanical thrombectomy procedure within 4 hours and 18 mins. The insult progressed into complete infarct, and the patient passed away three days later. (A) Non-contrast axial view of brain computed tomography (CT) scan showing no hemorrhage. (B) CT scan of the chest showing bilateral infiltrates. (C) showing the powered air-purifying respirator used by operators. (D) All the devices in the room are draped. (E) Antero-posterior (AP) digital subtraction angiography (DCA) of a right ICA injection showing an M1 and an A2 occlusion. (F) AP DCA showing complete revascularization of both vessels (TICI 3). (G) Non-contrast axial view of the brain day one post mechanical thrombectomy showing the progression of the insult into a complete infarct.

Figure 2 (A-B): (A) Schematic diagram showing CNS access by the SARS-CoV-2 virus through the olfactory nerve. (B) Schematic diagram showing CNS access by the SARS-CoV-2 hematogenous route via direct access or via a trojan. The SARS-CoV-2 can infect endothelial and glial cells.

Figure 3: Schematic diagram at the level of CNS endothelium showing the SARS-CoV-2 induced ACE2 receptor downregulation. This inhibits the conversion of Angiotensin I and II into their active metabolites, Angiotensin (1-9) and Angiotensin (1-7), respectively. The decline in Angiotensin (1-7) levels leads to loss of neuroprotective effects and sympathetic hyperactivity.

Figure 4: Schematic diagram at the level of alveoli showing the SARS-CoV-2 binding to ACE2 receptor and infection the pneumocyte. The immune system is activated, and a cascade of inflammatory reactions leads to a cytokine storm (triggered by an imbalanced response by type 1 and type 2 T helper cells)

Figure 1

Click here to access/download;Figure;ACA occlusion_2.tiff

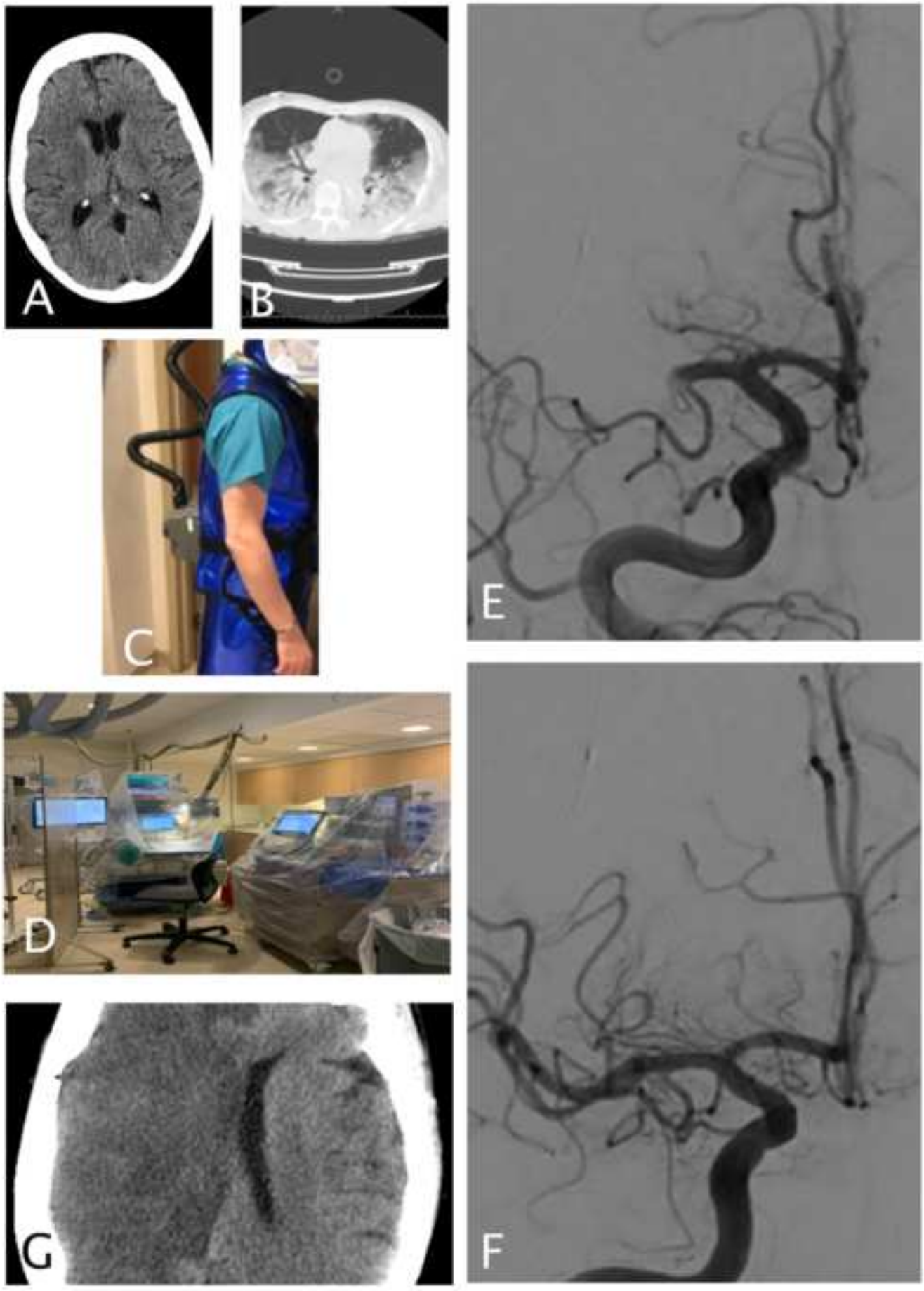

Figure 2

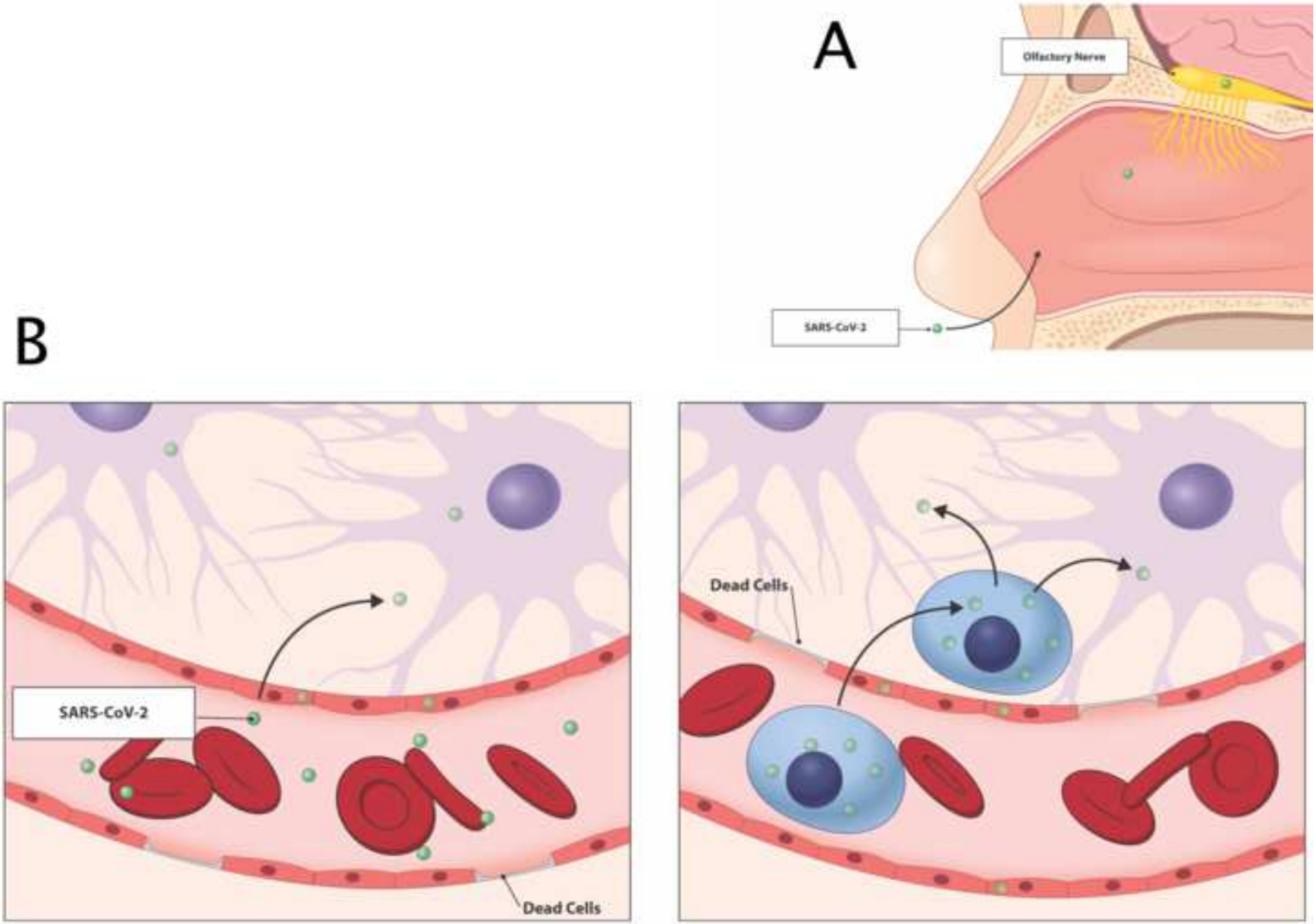

Figure 3

Click here to access/download;Figure;Figure 3 Downregulates.tif

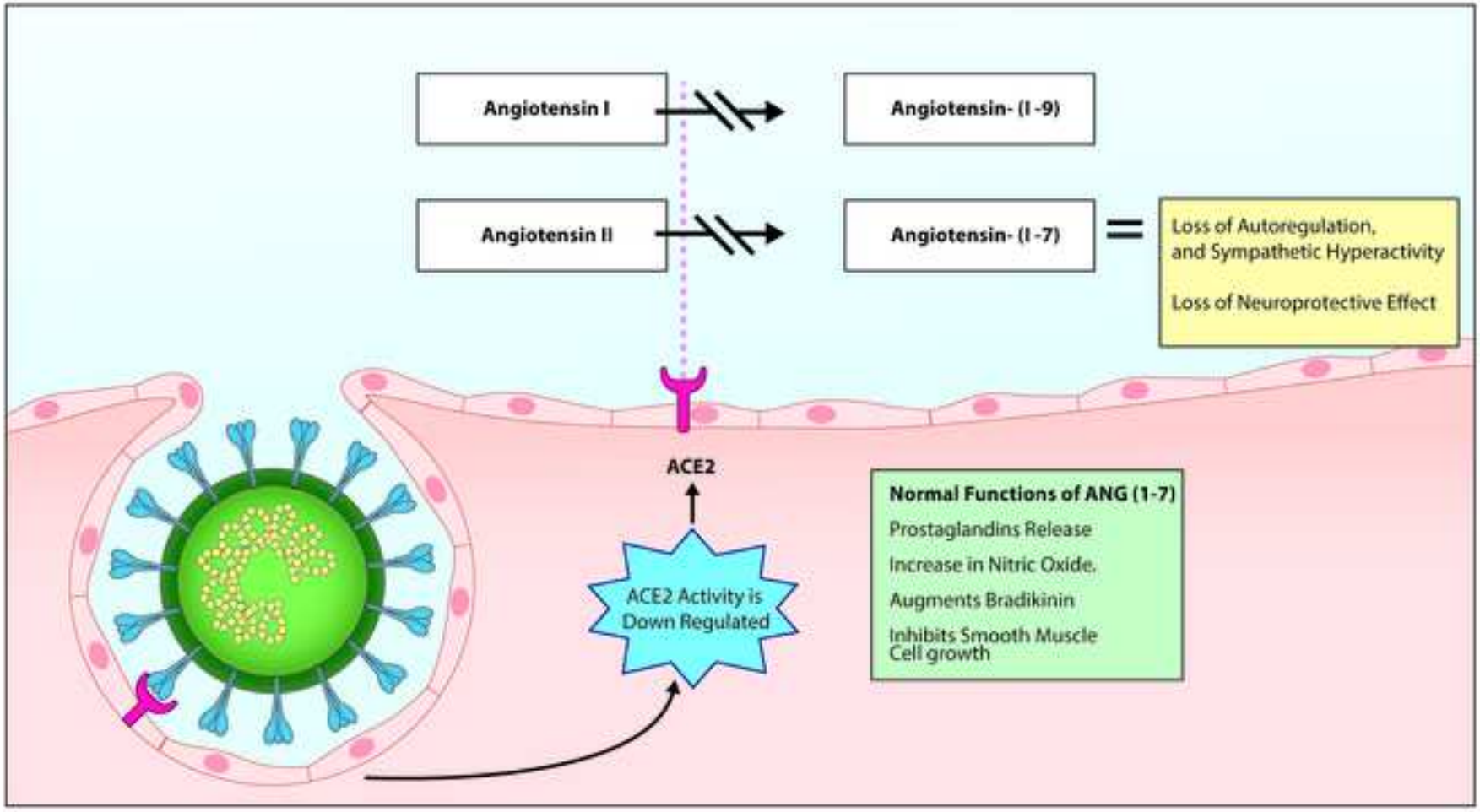

Figure 4

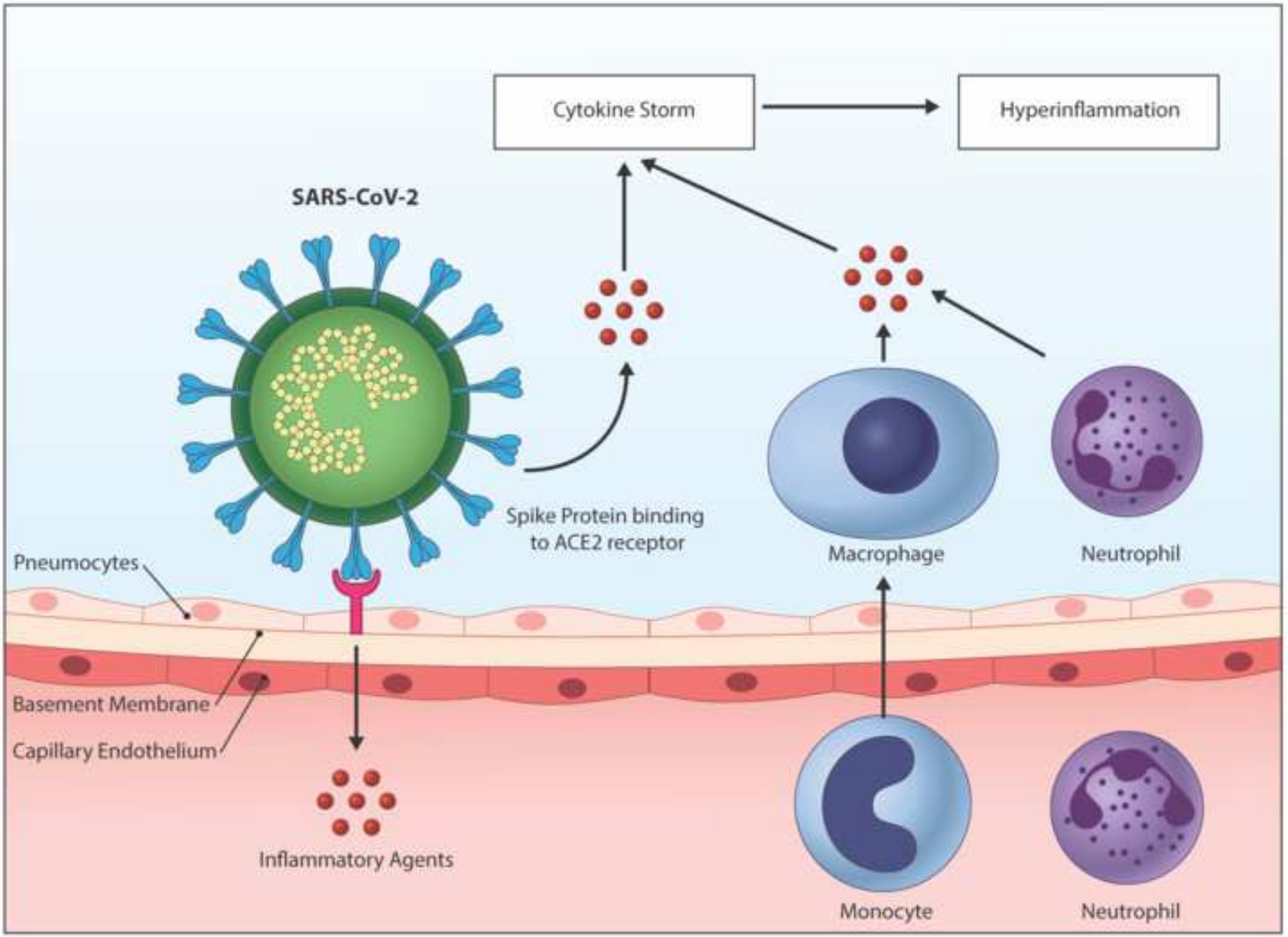

Table 1

Table 1: 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
	Demographics													
Age, years	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
	Initial findings and hospital course													
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		Pneumonia	Fever, Pneumonia	Pneumonia	Cough, Pneumonia
Symptom onset to presentation	11 days	4 days			0	17	0	0	0		14	2	5	5
Pathology	Stroke (M1-A2 occlusion)	Stroke (T Occlusion)	Stroke (Tandem ICA/ M1 occlusion)	Stoke (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 intubation	Yes	Yes	Yes	Yes	No	NA	No	NA	Yes	Yes	Yes	Yes	Yes	Yes
Procedure Duration (mins)	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
	Laboratory Findings													
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	**11.5**	4.6		6.4	7.2	4.7	6.2	**15.5**	**10.9**	**14.2**	**20**	**8.5**
Abs. lymphocytes C		0.9	1.5	1.7		1.1	0.6	2	1.2	1.2	1.1	0.5	1.8	0.5
Abs. monocytes C		0.3	0.9	0.3		0.2	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	234	339	237	327	331	379	104	141	**476**	226

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**	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	30	>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 hs (ng/L)	16			<6	<6	14	10	11	10	10	10	6	**90**	20
PT (sec)	**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 (sec)	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	243	**545**	**634**	**654**	235	121	84	
D-dimer (ng/mL)	**9,862**	**2,476**	**995**			**5748**	**6383**	**450**	**3.247**	**256**	**>10,000**	**>55,000**	**>10,000**	**360**
Serum ferritin (ng/mL)	**3,500**	**1,085**	**749**			**508**	270	**1785**	204	4.6	**588.1**	**785**	**1,028**	**2,929**
C-reactive protein (mg/dL)	**41.7**	**21.6**	**5.3**			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**

Abbreviations: 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; PCOM: PICA: Posterior Inferior Cerebellar Artery Aneurysm; Posterior Communicating Artery Aneurysm; PT: Prothrombin time; T: Terminus Occlusion; TICI score: The thrombolysis in cerebral infarction; SAH: Subarachnoid Hemorrhage.
Bold Values are above normal level, and Red values are below normal levels.

Table 2

Table 2: Frequency of Telestroke consults, AIS admission, and MT.

Variable	Prior Years		2020		P-value	Change	% Change
	March-April	Total	March-April	Total			
Telestroke Consults	202	616	106	496	**0.001**	-96	48
AIS Admission	91	219	70	257	**0.001**	-21	23
MT Procedures	16	31	24	69	0.112	8	50

Abbreviations: AIS: Acute Ischemic Stroke; MT: Mechanical Thrombectomy; OTG: Onset to Groin duration.

* Mean value

Bold values indicate significant value ($p \leq 0.05$).