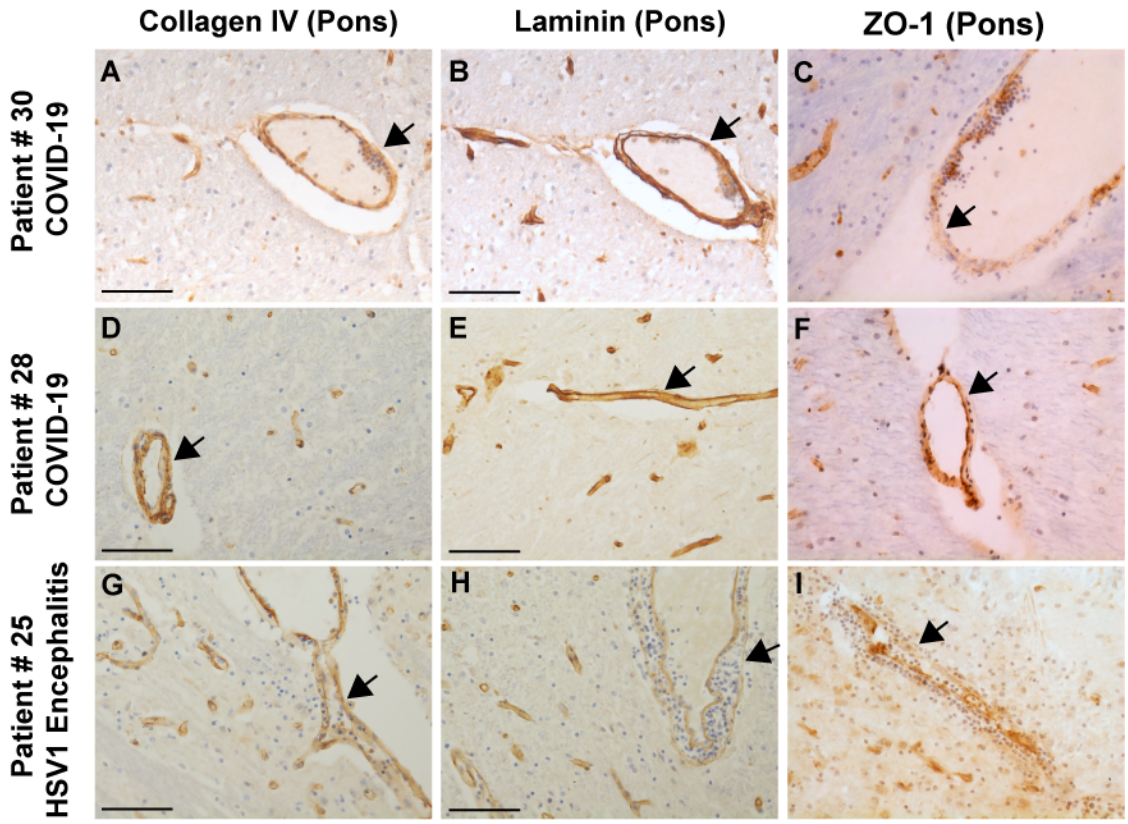
COVID-19 Neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital

Kiran T. Thakur[*1], Emily Happy Miller[*2], Michael D. Glendinning[*1], Osama Al-Dalahmah[3], Matei A.Banu[4], Amelia K. Boehme[1], Alexandra L. Boubour[1], Samuel L. Bruce[1], Alexander M. Chong[2], Jan Claassen[1], Phyllis L. Faust[3], Gunnar Hargus[3], Richard A. Hickman[3], Sachin Jambawalikar[5], Alexander G.Khandji[5], Carla Y. Kim[1], Robyn S. Klein[8], Angela Lignelli-Dipple[5], Chun-Chieh Lin[9], Yang Liu[3], Michael L. Miller[3], Gul Moonis[5], Anna S. Nordvig[1], Jonathan B. Overdevest[6], Morgan L. Prust[1], Serge Przedborski[1,3,7], William H. Roth[1], Allison Soung[8], Kurenai Tanji[3], Andrew F. Teich[3], Dritan Agalliu[**1,3], Anne-Catrin Uhlemann[**2], James E. Goldman[**3], Peter Canoll[**3]

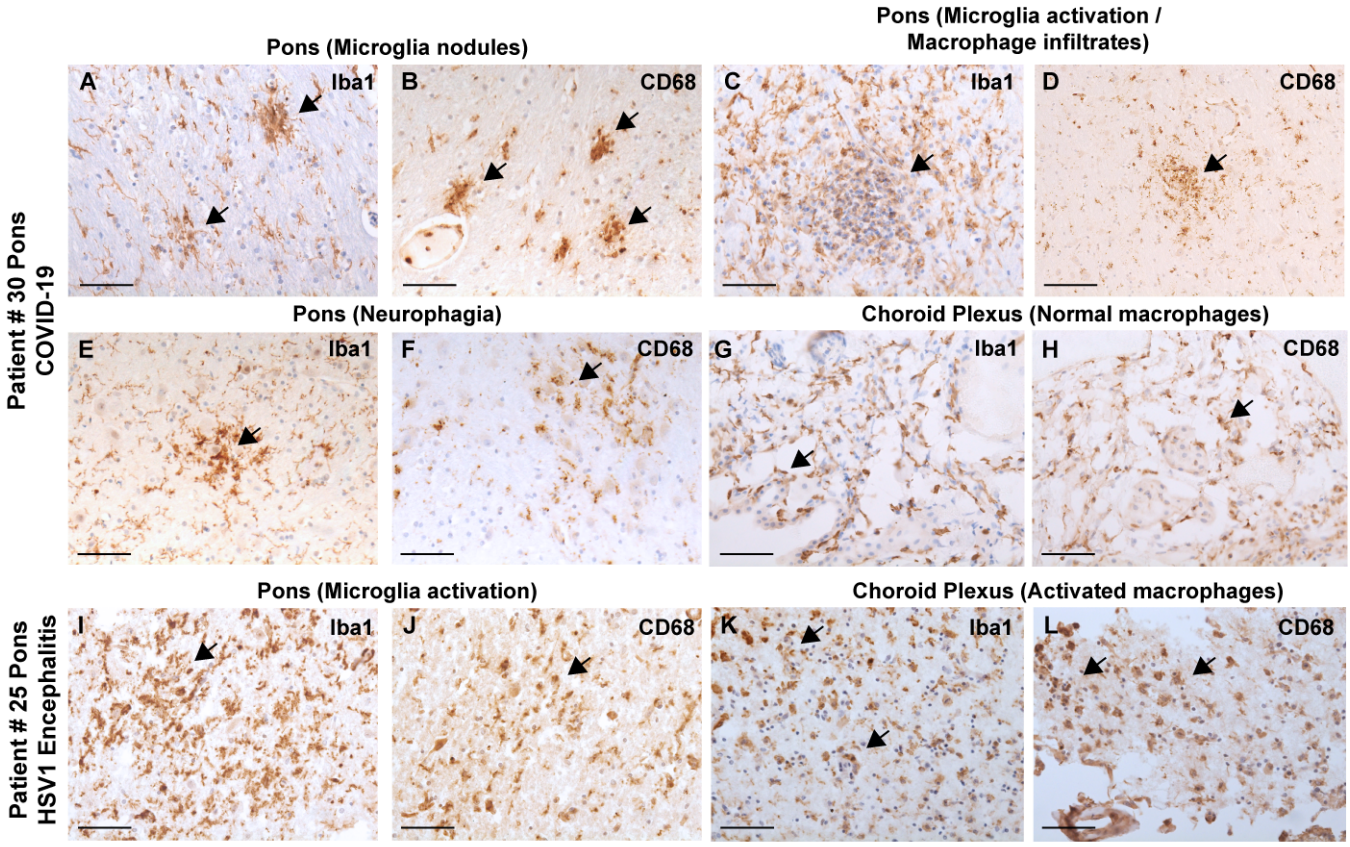
Supplementary Material

Supplementary Figure 1



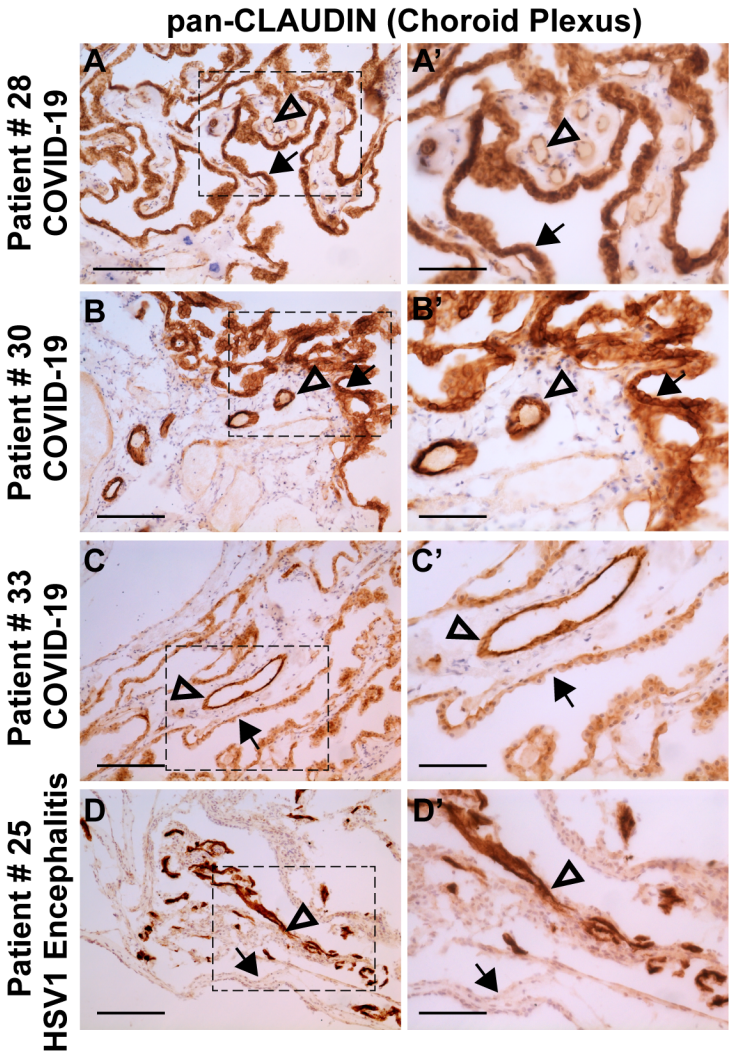
Supplementary Figure 1. Blood vessel pathology in COVID-19 brains. Blood vessel pathology visualized with antibodies for Collagen IV and Laminin (components of the vascular basal lamina) or for Zonula Occludens 1 (ZO-1), a tight junction protein. A-F) Representative sections from the pons of two COVID-19 patients show intact vascular basal lamina and tight junctions between endothelial cells. (G-I) Pontine vessels from the one patient with HSV-1 encephalitis show disrupted, separated, and poorly stained basal lamina with a large number of cellular infiltrates (G,H) or loss of tight junction staining near the cellular infiltrates (I). Arrows indicate positively stained vessels. Scale bars: A-I 200μm.

Supplementary Figure 2



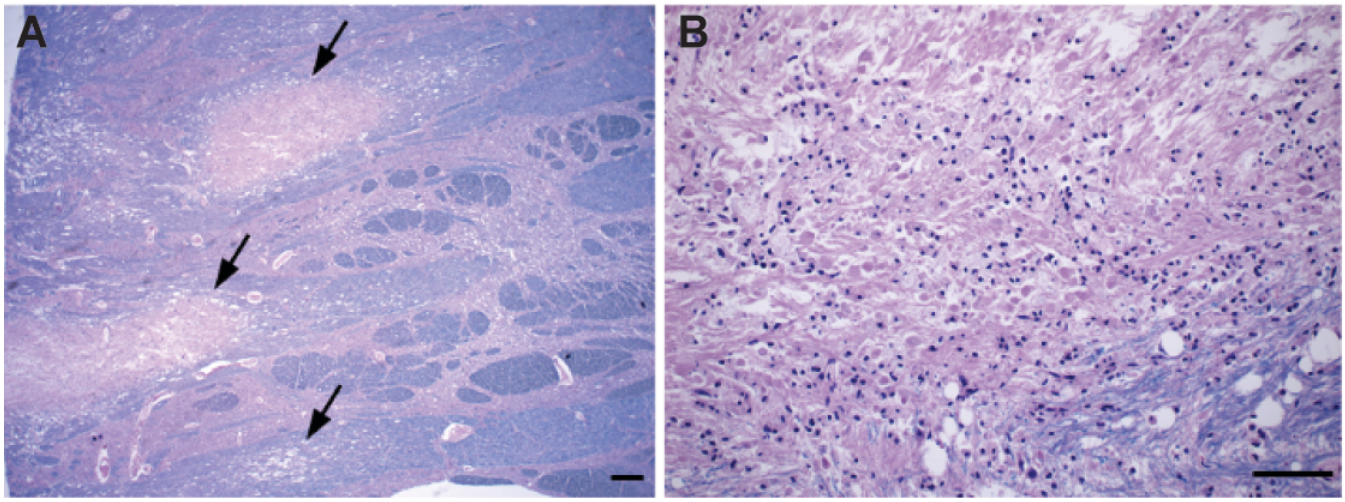
Supplementary Figure 2. Supplementary Figure 2. Microglial pathology in the brainstem (pons) of COVID-19 cases. Microglial pathology visualized with antibodies for Iba1 and CD68. (A-F) Representative sections from the pons of a COVID-19 patient shows examples of microglial nodules, macrophage infiltrates with some T cell involvement and neurophagia, the most prominent pathological features of the neuropathology in COVID-19 cases. G-H) Choroid plexus from the lateral ventricle stained with Iba1 and CD68 has very few macrophages. I-L) Pontine sections from the one patient with HSV-1 encephalitis shows microglia activation and macrophage infiltration into the CNS parenchyma and in the choroid plexus. Scale bars: A-L 200μm.

Supplementary Figure 3



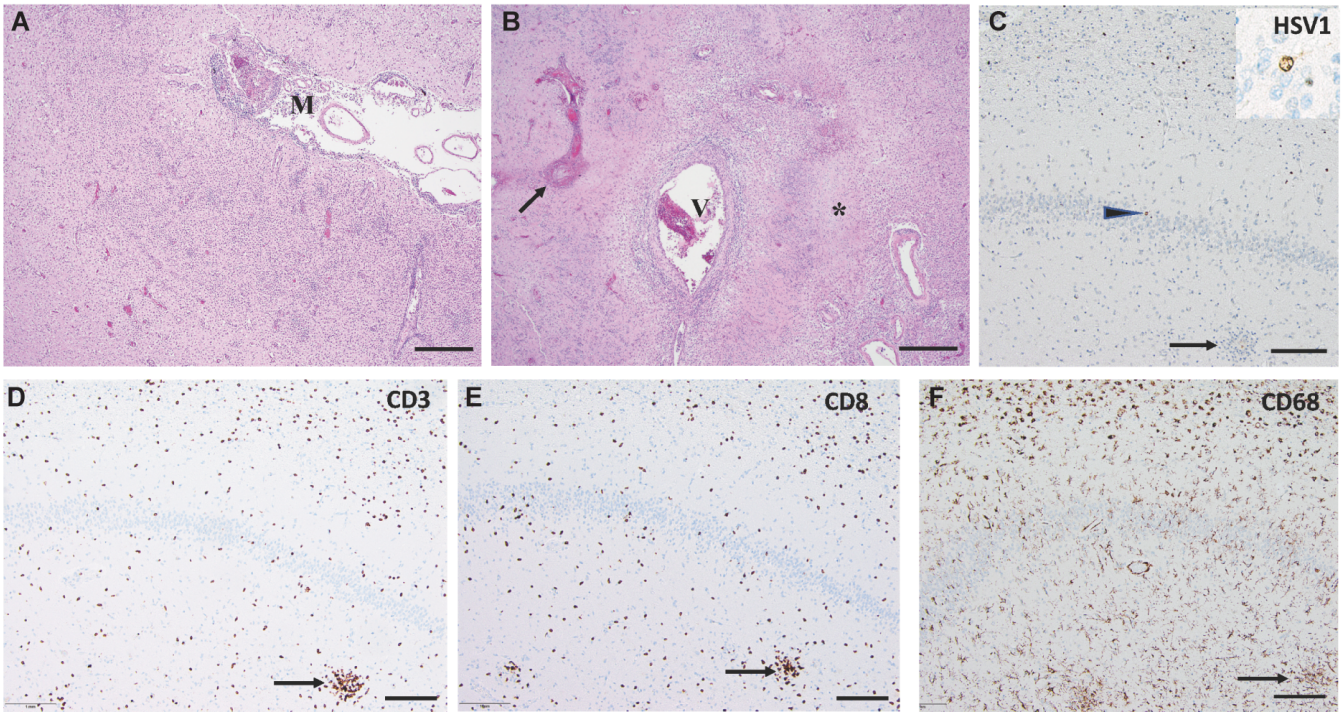
Supplemental Figure 3. Choroid plexus epithelial barrier is intact in COVID-19 brains. A-D') Immunohistochemistry of choroid plexus (ChP) from lateral ventricles using an antibody that recognizes both CLAUDIN-1 and CLAUDIN-5. Representative stains show expression in both the ChP epithelial cells and the ChP endothelial cells (A-C). ChP epithelium of one patient with HSV1 encephalitis shows complete loss of expression; ChP epithelia from COVID-19 patients show, to a varying extent, reduced expression. Arrows mark the ChP epithelium; open arrowheads mark the ChP endothelium. A'-D' are magnified images of boxed areas, arrows represent the same point in the corresponding images. Scale bars for A-D: 200µm. Scale bars for A'- D': 100µm.

Supplementary Figure 4



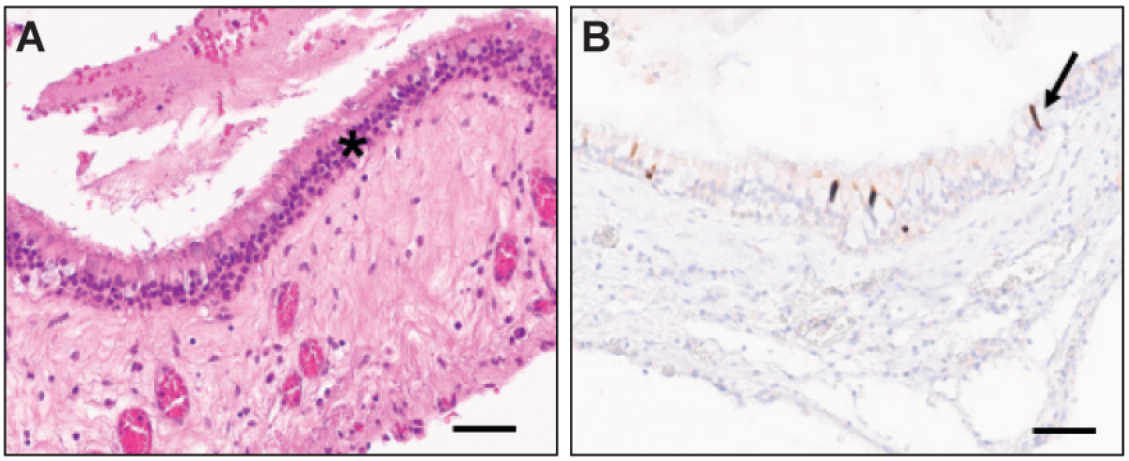
Supplementary Figure 4. Multifocal necrotizing leukoencephalopathy in one brain. A) Several foci of acute necrosis predominantly involving transverse fibers in the base of the pons (arrows). B) Higher magnification of a focus showing necrosis, loss of myelin, and axonal swellings. Sections are stained with Luxol fast blue stain for myelin, counterstained with H&E. Scale bars: A 1mm, B 250μm.

Supplementary Figure 5



Supplementary Figure 5. HSV-1 encephalitis in a COVID-19 patient. A) Frontal cortex, lymphocytic infiltrates in meninges (M) and brain tissue. B) Putamen with necrosis of blood vessel wall (arrow), perivascular lymphocytic infiltrate (V), and necrosis (*). C) Hippocampus, with cell nuclei stained with HSV-1 antibody, including dentate granule neuron (arrowhead and inset) and microglial nodule (arrow). D, E, F) Hippocampus stained with antibodies for CD3, CD8, and CD68 respectively. Microglial nodules are shown by arrows. Scale bars: 1mm.

Supplementary Figure 6



Supplementary Figure 6. Nasal epithelium immunostained for SARS-CoV-2 N protein. A) H&E stain or B) immunohistochemistry with the N protein antibody in the nasal epithelium (*) of a COVID-19 patient. Several epithelial cells are positive with the N protein antibody (one marked by arrow). Scale bars: A, B 100μm.

Supplementary Table 1. Existing primary COVID-19 neuropathology literature.

Authors	Study Population Location	Publication Date	Number of Patients with Brain Autopsy (%)	Histopathology	Viral and Other Tests	Gross Neuropathology	Other Findings
Meinhardt et al. [1]	Berlin, Germany	November 20	33	H&E;	qRT-PCR	Not specified	Thromboembolic events 6/33 (18%) and acute infarcts.
Matschke *et al.* [2]	Hamburg, Germany	October 5	43	H&E; GFAP, HLA-DR, TMEM119, IBA1, CD68, CD8 IHC	qRT-PCR	Six (14.0%) patients had recent ischemic infarctions.	Astrogliosis (to varying degrees) in all brains, microglia diffusely activated, with few microglial nodules in the brainstem and cerebellum. Parenchymal and perivascular $CD8^+$ cell infiltration. Cytotoxic T cells were in the frontal cortex, brainstem, and meninges. SARS-CoV-2 RNA detected in 13/27 (48.1%).
Hanley *et al*[3].	London, UK	October 1	10	H&E; CD3, CD20, CD4, CD8, CD68/PGM1 IHC	qRT-PCR	Varying ischemic changes in cortical neurons and white matter. One patient with large cerebral infarction with hemorrhagic transformation.	Microglial activation in 5/5 patients. Mild infiltration of T-cells observed around blood vessels and capillaries in five patients (no B cells). No necrosis or extensive inflammatory cell infiltration in parenchyma and meninges.
Al-Serraj *et al.* [4]	London, UK		8	Histology, Immunohistochemisty	RT-PCR, *in situ* hybridization	Hemorrhagic infarction (1, 17%)	Microglial activation, few T cells, no viral RNA or protein (4, 50%), brainstem encephalitis (1, 17%),
Bihlmaier *et al.* [5]	Erlangen, Germany	September 15	3	Immunohistochemistry (unspecified stains)	None	Two patients with white matter edema, small multifocal hemorrhages, and a bleeding patten with consecutive herniation.	No inflammatory processes in any brain. No SARS-CoV-2 RNA found in brain tissue.

Jensen *et al.*[6]	Cambridge, UK	September 8	2	CD3, CD68 IHC	RT-PCR; RNAscope® in situ hybridization using V-nCoV2019-S probe and RT-PCR SARS-CoV-2 RNA	Cerebral cortex thinning, darkening, and calcification (Case 1). Subacute cerebellar cortex infarct (Case 2).	Brainstem encephalitis with calcifying cerebral cortical infarction and megakaryocytes. Negative ISH and RT-PCR in tissue samples of interest; specifically, no viral RNA in post-mortem brain tissue.
Al-Dalahmah *et al.* [7]	New York, USA	August 26	1	H&E; CD3, CD8, CD68 IHC	qRT-PCR	Cerebral edema with cerebellar hemorrhage and acute infarcts in the dorsal pons and medulla.	SARS-CoV-2 RNA in the cerebellar clot, olfactory bulbs, and cerebellum. Brain sections showed severe global hypoxic changes, and several sections showed hyper-eosinophilic shrunken neurons. Microglial nodules and neuronophagia bilaterally in inferior olives and multifocally in the cerebellar dentate nuclei. Expansion of perivascular spaces in the ventral thalamus and sparce perivascular macrophages surrounding arterioles, which showed mild medial thickening.
Wichmann *et al.*[8]	Hamburg, Germany	August 18	12	H&E	qRT-PCR	Not Specified	SARS-CoV-2 RNA was detected in the brains of four patients (33.3%).
Deigendesch *et al*[9].	Basel, Switzerland	August 12	7	HLA-DR, GFAP IHC	None	Not Specified	No evidence for COVID-19-related meningitis or encephalitis with increased lymphocytic infiltration of the brain or leptomeninges. Although the observed microglia activation in COVID-19 patients is a histopathological correlate of a critical illness-related encephalopathy, it was not found to be a disease-specific finding.

Remmelink *et al.* [10]	Brussels, Belgium	August 12	17	IHC not performed on brain tissue	RT-PCR	Eight patients (47.1%) with hemorrhage, three (17.6%) with focal necrosis, five (29.4%) with edema and/or congestion, and ten (58.8%) with spongiosis. No patients demonstrated encephalitis nor vasculitis.	No patients showed isolated neuronal necrosis nor perivascular lymphocytes. Nine of eleven (81.8%) brain tissue samples had a positive RT-PCR.
Kantonen *et al.*[11]	Helsinki, Finland	August 6	4	H&E, Luxol Fast Blue,Iron	RT-PCR	One patient (25.0%) demonstrated mild brain swelling and acute microhemorrhages with enlarged perivascular spaces most pronounced in the white and deep gray matter. No meningitis nor encephalitis observed.	Three patients (75.0%) demonstrated mild-moderate hypoxic-associated changes. Few inflammatory cells found. One patient (25.0%) had few small perivascular white matter lesions and macrophages engulfing myelin. Immunostaining and RT-PCR were all negative.
Bradley *et al.*[12]	Washington, USA	August 1	5	H&E	None	One of five (20.0%) patients demonstrated punctate subarachnoid hemorrhages and rare microhemorrhages in the brainstem.	N/A
Jaunmuktane *et al.*[13]	London, UK	July 8	2	CD34, CD68, SMI31, and SMI94 IHC	None	One (50.0%) case with multifocal infarcts in the	One case showed dense inner rim of degenerating neutrophils and an outer rim of macrophages. The

						middle and posterior cerebral arteries. One case (50.0%) with bilateral pallidal infarcts.	second case showed cortical and white matter microlesions (including hemorrhages and small infarcts), chronic infarcts, and microinfarcts in the cerebral cortex and thalamus.
Schaller *et al.*[14]	Augsburg, Germany	June 23	10	H&E	RT-PCR	No detectable pathology.	No evidence of COVID-related encephalitis nor vasculitis. No RNA in the brain or CSF.
Solomon *et al.*[15]	Massachusetts, USA	June 12	18	H&E; CD45, tau, amyloid-beta, and alpha-synuclein IHC	RT-PCR	Upon gross inspection, atherosclerosis was observed in 14 (77.8%) brain specimens. No acute stroke, herniation, nor olfactory bulb damage were observed.	SARS-CoV-2 was found at low levels in six brain sections of five patients. Acute hypoxic injury in the cerebrum and cerebellum. Neuronal loss in the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer (no thrombi or vasculitis). In two (11.1%) brain specimens, rare foci of perivascular lymphocytes. In one (5.6%) brain specimen, focal leptomeningeal inflammation was observed. In the olfactory bulbs and tracts, no microscopic abnormalities were detected. On immunohistochemical analysis, there was no cytoplasmic viral staining. No encephalitis nor other SARS-CoV-2-specific brain changes were observed.
Von Weyhern *et al*[16].	Munich, Germany	June 4	6	H&E, Luxol Fast Blue; CD3 IHC	None	Neuronal cell loss and axonal degeneration were observed in the dorsal motor nuclei of the vagus nerve, trigeminal nerves, nucleus tractus solitarii, dorsal raphe nuclei, and fasciculus	Localized perivascular and interstitial encephalitis was observed. Hypoxic alterations of the brain were observed in all patients. Images showed very mild inflammatory infiltrates. Hypoxic pathology demonstrated shrunken or dying neurons and edema in many areas.

						longitudinalis medialis. No territorial infarctions nor endotheliitis were observed.	
Efe *et al*[17] .	Samsun, Turkey	May 29	1	Unspecified histopathologic examination	None	Left temporal lobe lesion.	Biopsy demonstrated perivascular lymphocytic accumulations and "hypoxic" changes. Patient was diagnosed with "encephalitis."
Reichard *et al.*[18]	Minnesota, USA	May 24	1	H&E; CD68, APP, LFB/PAS, PLP, GFAP, CD3, and CD20 IHC	None	Lesions of likely vascular and demyelinating etiology. Hemorrhagic white matter lesions with surrounding macrophages and axonal injury. Perivascular acute disseminated encephalomyelitis (ADEM)-like lesions.	Focal necrosis with central loss of white matter and marked axonal injury. Rare neocortical organizing microscopic infarcts.
Duarte-Neto *et al.*[19]	São Paulo, Brazil	May 22	9	H&E; TTF-1, p63, Ki67, CD4, CD8, CD20, CD57, and CD68 IHC	Ultrasound-Guided Minimally Invasive Autopsy; transsphenoidal needle puncture	Not Specified	Reactive gliosis in 8 patients (88.9%), neuronal satellitosis in 5 patients (55.6%), small vessels disease in three patients (33.3%), and perivascular hemorrhages in one patient (11.1%).
Paniz-Mondolfi *et al.*[20]	New York, USA	April 21	1	None	Transmission Electron Microscope	Not Specified	Particles (80-110nm) spherical and pleomorphic with stalk-like projections suggestive of SARS-CoV-2 in cytoplasmic vacuoles of cells in the frontal lobe and in small vesicles of endothelium cells. Particles

H&E = Hematoxylin and Eosin; IHC = immunohistochemistry,

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Supplementary Table 2. Patient Demographics, Inpatient Characteristics, Complications and Mortality related data

Demographics	
Age	74.0 years (range 38 - 97)
Gender	27 Male (65.9%)
Race/Ethnicity	34 Hispanic/Latinx (82.9%)
Body Mass Index (BMI) (average); >30	28.0 (range 19.3 - 41.4); 9 (22.0%)
Symptoms at Presentation	
Average Time of Symptom(s) to Presentation (days)	6.0 (range 0 – 12)
Presenting Symptoms	
Confusion	13 (34.1%)
Impaired consciousness	11 (26.8%)
Generalized weakness	9 (22.0%)
Fatigue	9 (22.0%)
Anorexia	6 (14.6%)
Headache	2 (4.8%)
Anosmia	1 (2.4%)
Ageusia	1 (2.4%)
Sensory Symptoms	1 (2.4%)
Dyspnea	27 (65.9%)
Cough	18 (43.9%)
Subjective Fever	17 (41.5%)
Myalgias/arthralgias	8 (19.5%)
Abdominal pain	6 (14.6%)
Diarrhea	5 (12.2%)
Chills	5 (12.2%)
Sore throat	4 (9.8%)
Rhinorrhea	3 (7.3%)
Nausea/Vomiting	3 (7.3%)
Chest pain	3 (7.3%)

Syncope	2 (4.9%)
Neurological Comorbidities	
Dementia/Mild cognitive impairment (MCI)	8 (19.5%)
Stroke	6 (14.6%)
Parkinson's Disease	3 (7.3%)
Epilepsy	1 (2.4%)
Other Comorbidities	
Obesity	9 (22.0%)
Hypertension (HTN)	27 (65.9%)
Hyperlipidemia (HLD)	13 (31.7%)
Diabetes Mellitus (DM) / pre-DM	13 (31.7%)
Chronic Kidney Disease (CKD)	9 (22.0%)
Coronary Artery Disease (CAD)	8 (19.5%)
Atrial Fibrillation (AF)	3 (7.3%)
Congestive Heart Failure (CHF)	2 (4.9%)
Peripheral Artery Disease (PAD)	1 (2.4%)
Asthma	2 (4.9%)
Immunosuppressant medication	5 (12.2%)
Post-organ Transplant	4 (9.8%)
Chronic Obstructive Pulmonary Disease (COPD)	3 (7.3%)
Obstructive Sleep Apnea (OSA)	3 (7.3%)
Anticoagulation medication (at home)	5 (12.2%)
Deep Vein Thrombosis/Pulmonary Embolism (DVT/PE)	3 (7.3%)
Former smoker	3 (7.3%)
Current smoker	2 (4.9%)
Hypothyroidism	2 (4.9%)
Past Cancer	5 (12.2%)
Current Cancer	1 (2.4%)
Liver disease	1 (2.4%)
Depression	5 (12.2%)

Schizophrenia	1 (2.4%)
Hospital Related Data	
Average length of hospital stay (days)	19.3 (0 – 69)
Number of patients on ventilators at least once	24 (58.5%)
Average time on ventilators (days)	21.9 (1 – 68)
Number of patients in ICU	24 (58.5%)
Average length of ICU stay (days)	22.5 (1 – 68)
Clinical Course and Management	
Use of sedative medications	28 (68.3%)
Use of paralytic medications	15 (36.6%)
Number of patients proned	14 (34.1%)
Acute Respiratory Distress Syndrome (ARDS)	15 (36.6%)
Extracorporeal Membrane Oxygenation (ECMO)	1 (2.4%)
Number of patients administered Tocilizumab	7 (17.1%)
Number of patients administered Remdesivir	2 (4.9%)
Number of patients administered steroids	23 (56.1%)
Number of patients administered antibiotics	34 (82.9%)
Number of patients with positive blood culture(s)	10 (24.4%)
DVT during hospital stay	5 (12.2%)
PE during hospital stay	3 (7.3%)
Acute Kidney Injury (AKI)	28 (68.3%)
Initiation of Dialysis	7 (17.1%)
Imaging Data	
Chest x-ray with multifocal pneumonia	33 (80.5%)
Number of patients with premortem non-contrast Head CT	11 (26.8%)
Number of patients with premortem Brain MRI	2 (4.9%)
Number of patients with post-mortem Brain MRI	9 (22%)
Mortality Related Data	
Average time of last COVID+ (NP PCR) to death (days)	11.9 (0 – 59)
Number of patients with COVID+ (NP PCR) at autopsy	11 (26.8%)

Average time of death to autopsy (hours)	26.4 (2-177)
Cardiac Arrest	5 (12.2%)
Withdrawal of Care	21 (51.2%)

Pt #	Sex	Age	Race/ Ethnicity	Medical Comorbidities	Neurological Comorbidities	Presenting Neuro Symptoms	Other Presenting Symptoms	Summary of Hospital Course	Cause of Death	Neurology consult obtained (Y/N); reason for consult; time of neuro consult/neurology admission to death	Neuroimaging Findings	Length of Mechanical Ventilation (days)	Length of hospital stay (LOHS) (days)	Length of ICU stay (days)
1	M	70	Hispanic	HTN, CAD	None	Impaired consciousness, weakness	Cough, SOB, myalgias, syncope collapse/agonal breathing	Found down by EMS, in ventricular fibrillation, resuscitation was attempted for 50 minutes, unsuccessful	Cardiac arrest as consequence of respiratory failure with contributing possible infection	N		1	0	NA
2	M	90	Hispanic	Ischemic cardiomyopathy, complete heart block with PPM, interstitial lung disease with pulmonary hypertension, urothelial cancer, former smoker, DM2	None	Weakness/fatigue, confusion, gait instability and falls	Cough, SOB, myalgias, rhinorrhea, fatigue, anorexia	He had increased work of breathing and was placed on NRB, AKI, shortly after admission cardiac arrest. 6 minutes of cardiopulmonary resuscitation and 1 round of epinephrine before death was declared.	Cardiorespiratory failure triggered by SARS-CoV-2 infection acting on preexisting chronic conditions that include advanced ILD, pulmonary hypertrophy, lung cancer and congestive heart failure	N	Past imaging MRI brain 1/262008 small L inferior parietal hemorrhagic infarct L>R inferior frontal encephalomalacia	0	1	NA
3	M	83	Hispanic	Afib on AC, HTN. HLD, CKD, CVA, osteoporosis, depression	MCI, dementia	Confusion	None	AMS, AF w RVR, transitioned to hospice care.	Cardiopulmonary failure secondary to SARS-CoV-2 infection as consequence of CVA, a-fib with RVR with contributing CKD	N	Head CT 3/12 Mild MVID Bilateral BG lacunar infarcts tiny Head CT 3/30 no change Prior 1/9/2001 small right parietal infarct	0	3	NA
4	M	74	Hispanic	HTN, BPH, depression prediabetes	None	Impaired consciousness, weakness	Melena, syncope, anorexia, nausea, vomiting, fever, cough,	Found on floor in a pool of bright red blood, hypoxic on arrival requiring NRB, hypotensive, tachycardic, worsening respiratory function-intubated. AKI,	ARDS secondary to SARS-CoV-2 with diffuse alveolar damage, congestion and pulmonary edema, and pulmonary thromboemboli.	N		4	7	5

							myalgias, fatigue	metabolic acidosis and shock, acute liver failure, coagulaopathy, GI bleed. Comfort care, extubated						
5	M	57	White	HTN	Unknown	None	Cough, exertional intolerance	Had arrest in the field, intubated and CPR was performed by EMS en route to ER. Ongoing efforts at resuscitation were unsuccessful in ED.	Cardiorespiratory arrest in the setting of SARS-C0V-2 infection	N		1 (intubated by EMS en route)	0	NA
6	M	66	Hispanic	Unknown	Unknown	None	None	Cardiac arrest during ED transport, resuscitation unsuccessful	Respiratory failure in the setting of SARS-COV2 infection, with DAD with organizing PNA, aspiration, edema and scattered microthrombi	N		1 (intubated by EMS en route)	0	NA
7	F	65	Hispanic	Asthma, OSA, DVT on coumadin, depression	None	Weakness/fatigue, confusion in ED (AOx2)	SOB, fever, sore throat, myalgias, anorexia	AMS, DVT, right ventricular clot, PE, AKI, hepatic dysfunction, thrombolysis and heparin drip, developed asymmetric pupils and no response to painful stimuli. Cardiac arrest en route to CT scanner	Cerebral hemorrhage involving the basal ganglia, including the putamen and portions of the internal capsule	N		0	9	2
8	F	85	Hispanic	COPD, CKD, HLD, osteoporosis, pelvic fractures	Dementia	Impaired consciousness	Dry cough	Hypoxic and hypernatremic on presentation, oxygen requirement worsened, AKI, transitioned to inpatient hospice.	Cardiac arrest as consequence of SARS-CoV-2 with contributing COPD	N		0	3	NA
9	M	73	White	Obesity, CAD s/p 5 stents, DM2	None	None	SOB, cough, fever, nausea, diarrhea, vomiting, fatigue	NRB in ED-worsening respiratory status during admission, myocarditis, made DNR/DNI, cardiac arrest	Acute myocardial infarction and severe pulmonary disease in the setting of SARS-CoV-2	N		0	8	NA
10*	M	73	Hispanic	HTN, DM2	None	Headache	SOB, abdominal pain, vomiting	Severely hypoxic and intubated by EMS, PEA arrest with ROSC 17 minutes, No brainstem reflexes-L cerebellar hemorrhage. Made comfort care.	Cerebellar hemorrhage with uncal herniation in the setting of SARS-CoV-2 infection	Y: initiation of hypothermia protocol (1 day)	Head CT 4/21/20 Large R cerebellar hemorrhage with intraventricular extension, surrounding edema in cerebellum, pons and medulla	1 (intubated at nursing home before admission)	1	NA

											SAH in posterior fossa, basal cisterns and r MCA cistern Hydrocephalus and loss of grey white differentiation concerning for hypoxic injury CTA 4/21/20 negative Prior MRI IAC 12/3/19 mild MVID			
11	F	38	Hispanic	Post-liver transplant 2017, TB	Hepatic encephalopathy	None	Diarrhea, abdominal pain, jaundice, dark urine	Admitted for allograft rejection, developed leukocytosis in hospital-COVID 19 positive. Hypoxemic respiratory failure, fungemia , AKI, coagulopathy , pancytopenia and AMS. Hospital day 27 non-reactive pupils, Multifocal ICH, global edema, herniation. Brain death.	Hypoxemic respiratory failure and Intracerebral hemorrhage in the setting of SARS-CoV-2	Y: ICH found on Head CT in setting of persistent AMS (2 days)	4/20/20 head CT Large Right temporal hemorrhage, extensive SAH, focal small parenchymal hemorrhages bilateral frontal, parietal , temporal lobes and cerebellar hemispheres – possible embolic infarcts Effacement of cisterns and loss of gray white c/w severe hypoxemic injury and cerebral edema 3/26/20 head CT WNL Prior head CT 4/25/17 WNL	13	28	13
12	F	78	Hispanic	DM2, HTN, congenital solitary kidney	None	None	Cough, fever, SOB, chills	NRB in ED, intubated, AKI, CVVH, pneumothorax, chest tube and Gill procedure, ischemic left upper extremity started on AC,	Severe bilateral lung injury with organizing pneumonia and DAD due to SARS-CoV-2 infection	N		12	19	11

								bacteremia, persistent elevated oxygen requirements, transitioned to comfort care and compassionately extubated.						
13	F	80	Hispanic	Asthma, CAD, CVA, PAD, CKD	Stroke	None	Cough, SOB, fatigue	NC and NRB in ED, AKI, DNR/DNI, transitioned to comfort care.	Respiratory failure with DAD in setting of SARS-CoV-2 infection	N		0	15	NA
14	M	80	Hispanic	HTN, CAD, COPD	Dementia	Confusion, impaired consciousness, combativeness	Lethargy, poor PO intake	AMS, AKI, hyponatremia on presentation, agitated delirium, intestinal ileus, witnessed aspiration event, made comfort care.	Respiratory failure due to extensive necrotizing bronchopneumonia with severe pulmonary edema. In the setting of SARS-CoV-2 and possible bacterial or fungal superinfection	N		0	17	NA
15	M	63	Hispanic	HTN	None	Headache	Fever, SOB, fatigue, diarrhea	In ED on NRB, respiratory status worsened, intubated , developed ARDS, ARF requiring CRRT, worsening lactatemia, anion gap metabolic acidosis and shock liver. Hospital day 13, cardiac arrest.	SARS-CoV-2 with multiorgan failure and sepsis with contributing ARDS/respiratory failure	N		3	13	3
16	M	83	Hispanic	HTN	PD	Confusion	SOB, chest tightness	NRB in ED, UTI, Day 8, oxygen requirement increased and made comfort care.	Cardiac arrest due to hypoxemic respiratory failure in the setting of SARS-CoV-2	N		0	9	NA
17	M	79	Black	HTN, HLD, DM2, CAD, HFrEF, CKD	Dementia	Confusion	Fever, cough, SOB, poor PO intake	AMS, Acute on chronic renal failure. Worsening respiratory status, made DNR/DNI. Oliguric renal function, decision not to pursue dialysis. Transferred to inpatient hospice.	Acute hypoxic respiratory failure and renal failure in the setting of SARS-CoV-2 infection	N		0	11	NA
18	M	84	Hispanic	Bedbound with joint contractures, schizophrenia, prostate cancer	Seizure disorder	Confusion, impaired consciousness	SOB, hypoxia	AKI and hypernatremia on arrival to ED, made DNR. Intubated, started on vasopressors, urosepsis, atrial fibrillation with RVR, extubated, though mental status remained poor, transitioned to hospice care.	Aspiration bronchopneumonia with secondary hyaline membrane formation and organizing pneumonia, and acute myocardial infarction in the setting of SARS CoV-2 infection	N		10	14	10
19	F	97	Hispanic	HTN, HL, CAD, CVA,	Dementia, stroke	Confusion	None	In ED became more lethargic, severe	Cardiac arrest as consequence of hypoxia	N	No images in PACS	0	0	NA

				SVT, Depression				hypoxemia and bradycardia. DNR/DNI, transitioned to comfort care, and died in the ED.	due to SARS-CoV-2 with contributing myelodysplastic syndrome		No CXR Prior head CT 8/8/2012 no images			
20	F	80	Hispanic	DM2, HTN, former cigar smoker	None	Weakness	SOB, fever	Intubated in ED, AKI, CVVH, bacterial pneumonia. Progressive multiorgan failure, made DNR, no escalation of therapy.	Hypoxic respiratory failure secondary to SARS-CoV-2 as consequence of respiratory arrest with contributing hypertension, diabetes ii, obesity, renal failure	N		25	25	21
21	M	68	Hispanic	HLD, HTN, past prostate cancer	None	Back pain	SOB, fever, fatigue	AMS, DVT, DKA, intubated for hypoxic respiratory failure, new seizures and embolic infarcts. Transferred to hospice.	SARS-CoV-2 pneumonia and associated ARDS	Y: Multifocal acute infarcts found on Head CT, new onset seizure (1 day)	5/7/2020 Head CT and CTA Acute infarcts R basal ganglia, Right inferior frontal lobe and left superior frontal/ parietal acute infarcts possibly embolic CTA no large vessel occlusion AUTOPSY BRAIN Right inferior frontal, right basal ganglia and left frontal parietal subacute infarcts all with associated hemorrhage	21	26	21
22	F	74	Hispanic	HLD, hypothyroidism	None	None	SOB, fever, chills, cough, myalgias	Intubated during hospitalization, ARDS, AKI, CRRT, bacterial pneumonia, UTI. Tracheostomy, not awakening despite sedation wean, worsening mental status.	Hypoxemic respiratory failure due to SARS COV-2 infection and pneumonia	N	Head CT 5/7/20 Mild MVID, small l> R basal ganglia old lacunar infarcts AUTOPSY right parietal signal abnormality possible recent WM infarct, suggestion of cortical	39	39	38

											hemorrhage (side of largest brain cuts)			
23	M	75	Hispanic	ESRD on HD, CAD s/p CABG, HFpEF, pHTN, HTN, HLD, DM2, OSA, CKD	None	Impaired consciousness	None	Cardiac arrest at home, ROSC 15 minutes, refractory shock, global cerebral edema	Severe ischemic heart disease and superimposed SARS-CoV-2 infection with contributing ESRD	N	Head CT 5/10/20 Extensive loss of grey white matter c/w severe hypoxemic injury	0	0	0
24	M	66	Hispanic	HTN, HLD, DM	None	Weakness	Fever, cough, sore throat, SOB, fatigue, anorexia, rhinorrhea, diarrhea	Respiratory failure, intubated in hospital, course c/b ICH, seizures, AKI, CVVH, made comfort care	Cardiopulmonary failure in the setting of complications related to SARS-CoV-2 infection, with multilobar acute and organizing bronchopneumonia, positive for Klebsiella pneumoniae	Y: SDH found on Head CT, frontal mass and SAH found on Brain MRI, new onset seizure (17 days)	Head CT 4/25/20 Left frontal parenchymal hemorrhagic lesion likely subacute infarct with moderate surrounding edema right frontal small acute subdural hemorrhage and diffuse SAH 4/25 head Ct later same day no change brain MRI 4/29/20 Diffuse hypoxemic, hypoperfusion injury Punctate hemorrhages throughout the bilateral basal ganglia And bilateral pons with few scattered inferior frontal lobes and left parietal lobe	41	46	41
25	F	70	Hispanic	HTN	None	Weakness	Fever, SOB	NRB in ED, intubated. ARDS. AKI, bacteremia, VAP, CMV viremia, UTI. Palliatively extubated in	ARDS from SARS-CoV-2 complicated vasodilatory shock and disseminated HSV infection	N		42	42	41

								context of refractory hypoxemia.						
26	M	72	Hispanic	HTN, history of colon cancer	None	None	Fever, cough, SOB, myalgias, fatigue, abdominal pain	ARDS, intubated, bacterial pneumonia, candidemia, acidemia, suspected PE, AKI, GI bleeding. terminally extubated.	Severe pulmonary disease with DAD in the setting of SARS-CoV-2 infection	N		21	29	21
27	M	80	Hispanic	HTN, former smoker, CKD s/p nephrectomy, AF on home AC	None	None	SOB, chills	Prior two week admission for COVID, on NRB during admission but not intubated. Possible bacterial pneumonia, AKI, DVT, worsening respiratory status, AMS, cardiac arrest	SARS CoV-2 Pneumonia and ARDS	N	Head CT 5/11/20 Mild MVID small superior bifrontal lobe infarcts unhanged Medial L.R temporal lobe hypodensities , possible subacute infarcts Prior head CT 7/25/19	0	5	NA
28	F	76	Hispanic	HTN, DM2, renal transplant, CAD, depression	None	Confusion, impaired consciousness	SOB, fatigue, chest pain, abdominal pain	Hypotensive requiring pressors, DVT, AKI. DNR/DNI.	SARS-CoV-2 pneumonia and hypoxic respiratory failure	N		0	2	1
29	M	65	Hispanic	HTN, CKD, ILD s/p lung transplant, chronic strongyloides infection	PD	None	SOB	Suspected PE, worsening grant involvement, bacterial pneumonia, AKI, CVVH, ARDS, pneumothorax. Terminally extubated.	Respiratory failure in setting of SARS-CoV-2 infection	N	Prior brain MRI 11/4/16 Mild MVID, old Right frontal, Left insula, Left superior temporal infarcts	7	22	10
30	M	65	Hispanic	None	None	None	Fever, cough, SOB, chills, sore throat, chest pain	NRB in ED intubation, ARDs, tension pneumothorax with chest tubes, diffuse subcutaneous emphysema, VAP, tracheostomy, AKI, DVT, Persistent pressor requirement.	Sepsis and SARS-CoV-2 pneumonia, superimposed Serratia ventilator-associated pneumonia, and acute and organizing pulmonary thrombi	N		33	35	33
31	F	68	Declined	HTN, DM2, hypothyroidism	None	Anosmia, Ageusia	Fever, cough, SOB, myalgias	NRB, intubated, ARDS, bacterial pneumonia, AKI, right facial droop. Initial clinical improvement,	SARS-CoV-2 pneumonia and acute respiratory distress syndrome, complicated by Klebsiella ventilator-associated	N	AUTOPSY Possible punctate BG hemorrhage	18	38	35

								then persistent tongue swelling and airway edema, treated by allergy. R facial droop noted two days before death, cardiac arrest.	pneumonia and Pseudomonas pneumonia					
32	M	72	Hispanic	HTN, HLD, DM2, BPH	None	None	Fever, cough, SOB, sore throat, chills, myalgias	NRB in ED, intubated. ARDS, pneumothorax with chest tube placement, subcutaneous emphysema. Bacterial pneumonia, AKI, CVVH, diabetic ketoacidosis requiring insulin drip, anemia requiring multiple blood transfusions, hypernatremia and vasodilatory shock, tracheostomy with persistent oxygen requirements, transitioned to comfort care.	Severe respiratory disease due to SARS-CoV-2 with superimposed bacterial infection and septicemia	N	AUTOPSY Possibly right occipital horn hemorrhage	45	48	45
33	M	70	Hispanic	CKD	Dementia, PD	Impaired consciousness, confusion	Fever, SOB	Intubated on admission, septic shock, bacterial pneumonia, AKI, CVVH, tracheostomy placed, initial improvement in respiratory status. Persistent agitated delirium. Transitioned to comfort care.	Bacterial pneumonia superimposed on SARS-CoV-2 viral infection	Y: Parkinson's medication initiation in setting of AMS (17 days)		31	39	38
34	M	92	Hispanic	HTN, BPH	None	Impaired consciousness, confusion, weakness	Anorexia	Rhabdomyolysis, SARS-Cov2 PCR positive during admission, UTI, bacteremia, necrotic sacral decubitus ulcer, atrial fibrillation with RVR, non-ST elevation MI, worsening heart failure, PHTN. Found unresponsive, pulseless. No resuscitation per family wishes.	Cardiac arrest due to SARS-CoV-2 related respiratory failure	Y: dysarthria (46 days)	Head CT 4/12/20 brain MRI stroke protocol moderate MVID no acute infarct, no hemorrhage L parietal tiny WM infarct AUTOPSY Left cerebellar infarcts on T2 (T2 not obtained in vivo)	0	48	NA

35	F	87	Hispanic	HTN, HLD, PPM, AF, iron deficiency anemia	Dementia, stroke	Decreased consciousness, confusion	None	On arrival patient was unresponsive, stroke code activated. Head CTA possible hyperdense basilar artery, VAP, comfort care.	Sepsis and multi-organ shock in the setting of SARS-CoV-2 infection	Y: concern for stroke (5 days)		0	5	NA
36	M	76	White	Waldenstrom macroglobulinemia, Asthma, OSA, COPD	None	None	Fever, cough, SOB	ARDS, AKI, CRRT, pneumothorax. Transitioned to comfort care 10 weeks after initial presentation.	Multisystem organ failure in the setting of multiple viral, bacterial, and fungal infections and SARS-CoV-2 infection	N	AUTOPSY No significant abnormality	68	60	60
37	M	56	Unknown	stroke	None	None	SOB	Cardiac arrest during ED transport, unsuccessful attempts of intubation by EMS, supraglottic airway was placed. Pulseless on arrival to the ED, died in ED.	Respiratory failure due to severe bronchopneumonia in setting of infection by SARS-CoV-2	N		0	0	NA
38	M	71	Hispanic	HTN, CAD, CKD, s/p renal transplant	None	None	Cough, SOB, diarrhea, abdominal pain	AKI, Shigella colitis, progressive hypoxemic respiratory failure. Empiric therapeutic anticoagulation. CMV viremia, received ganciclovir, transferred to ICU for worsening respiratory status and made comfort care 33 days after admission.	Severe chronic and active DAD in bilateral lungs following SARS-CoV-2 infection	N	AUTOPSY Bilateral occipital small intraventricular hemorrhage Parietal parenchymal possible small hemorrhage Superior white matter infarct /MVID	0	33	15
39	F	72	Hispanic	HTN	None	None	Cough, rhinorrhea	Intubated in ED, AKI, VAP, unable to wean from ventilatory support, transitioned to comfort care 68 days after admission.	SARS-CoV-2 pneumonia with respiratory failure. With Klebsiella ventilator associated pneumonia as a contributing factor to respiratory compromise.	N	AUTOPSY possible intraventricular temporal horn hemorrhage Suggestion of Tiny parietal hemorrhage	68	69	68
40	F	89	Hispanic	HLD, HTN, DM, PVD, depression	Dementia, L MCA stroke	Decreased consciousness, confusion	Nausea/vomiting, anorexia, abdominal pain	Hypotensive in ED, transitioned to comfort care.	intestinal infarction of the colon with severe occlusive atherosclerosis of the inferior mesenteric artery following SARS-CoV-2 infection	N		0	1	1
41	M	71	Declined	HTN, obesity, former smoker	None	Back pain, right leg weakness, sensory symptoms	None	Developed sudden onset tearing back pain and right leg weakness with CT angiogram showing aortic dissection extending from the aortic	Massive bilateral pulmonary emboli, multilobar organizing pneumonia in the setting of SARS-CoV2 infection, with contributing thoracic	Y: initiation of hypothermia protocol (9 days)	Head CT 6/2/20 Moderate MVID Left thalamic, Left anterior limb IC	10	22	10

								root to the infrarenal aorta with hemopericardium. Tested positive for COVID 19, not a surgical candidate. AKI, PE, AMS. Started on anticoagulation, cardiac arrest with no ROSC achieved until he was cannulated to VA_ECMO after 26 minutes of ischemic time. Intubated, targeted temperature management with mental status remained poor prompting head CTA global anoxic brain injury. Transitioned to comfort care 22 days after initial presentation.	aortic dissection, anoxic brain injury		Left pons small infarcts indeterminate age Acute left occipital lobe infarct Head CT 6/7/20 No change Basilar artery appears slightly dense, possible thrombus 6/11/20 As above plus loss of grey white slight, early hypoxemic injury			

OSA=obstructive sleep apnea. DVT=deep venous thrombosis. PE=pulmonary embolism. AMS=altered mental status. HTN=hypertension. HLD=hyperlipidemia. DM2=Diabetes Mellitus type 2. SOB=Shortness of breath. EMS=Emergency Medical Services. PEA=Pulseless electrical activity. ROSC=Return of spontaneous circulation. PPM=Permanent pacemaker. NRB=nonrebreather mask. CAD=Coronary artery disease. DAD=Diffuse Alveolar Damage. DNR=Do not resuscitate. DNI=Do not intubate. CRRT=Continuous renal replacement therapy. CVVT=Continuous veno-venous dialysis. UTI=Urinary tract infection. CRF=Chronic renal failure. ARF=Acute renal failure. AF=Atrial fibrillation. RVR=Rapid ventricular rate. MCA=Middle cerebral artery. PD=Parkinson's Disease. PVD=Peripheral vascular disease. PHTN=Pulmonary hypertension. DKA=Diabetic ketoacidosis. ECMO=Extracorporeal membrane oxygenation. NA=Not applicable. *Patient published (Al Dalahmah *et al.,* 2020)

Supplementary Table 3. Summary of cases: Patient Characteristics including neuroimaging findings

Supplementary Table 4. Laboratory Values

Pt #	WBC on admission [x(10^3)/uL]	Peak WBC [(10^3)/uL]	Peak CRP [mg/L]	Peak ESR [mm/hr]	Peak LDH [U/L]	Peak Ferritin [ng/mL]	Peak IL-6 [pg/mL]	Peak D-dimer [ug/mL]	Peak Fibrinogen [mg/dL]	Peak Glucose [mg/dL]	Peak Creatine Kinase[U/L]	Peak Creatinine [mg/dL]	Peak Lactate [mmol/L]	Peak Procalcitonin [ng/mL]
Patient numbers	3.48 - 9.42	3.48 - 9.42	0.00 - 10.0	0 - 20	135-214	13.0 - 150.0	< = 5.0	0.00 - 0.80	191 – 430	75 - 100	40.0 - 308.0	0.50 - 0.95	0.5 - 2.2	< = 0.08
1														
2	5.7	6.8							14.1	335		1.6	3.4	0.16
3	3.4	10.5		46						131			3.5	
4	5.1	14.0	297.1	63	1119	9897	>315.0	>20.00	107	415	3074	4.5	9.1	45.95
5										115				
6												13.49		
7	29.9	40.9	300	130	4305	3623	66.1	>20.00	>700	265	823	2.5	2.1	7.38
8	12.7	12.7	30.3	53	417	762.8				114	287	2.2	3.6	0.24
9	24.1	24.1	211.8	56	1406	4460	>315.0	>20.00		285		1.2	5.4	0.46
10	5.8	13.3	8.7	27		38				462		2.7	8.4	
11	6.9	17.5	155	66	1336	5868	>315.0	19.14	662	392	162	3.48	3.2	9.61
12	5.1	22.0	300	130	591	1056	>315.0	>20.00		528	199	6	3.8	6.63
13	6.8	25.1	205.59	117	512	391.8	248	9.44	205.6	172	71	1.4	3.8	0.25
14	22.4	25.3	98.4	28		730.8				159	974	3.53	5.1	0.37
15	25.3	49.9	300	105	5000	100000	>315.0	>20.00	415	>571	783	3.22	16	3.19
16	7.3	23.5	123.9	35	642	1181	206.8	1.01	461	208	675	1.14	1.7	16.3
17	9.7	15.1	205.9	102	1058	2171	135.4	11.99	697	182	434		1.5	1.47
18	13.6	40.9	285.2	126	810	505.8	>315.0	9.56		321	2486	2.87	4.6	36.09
19	1.4	4.8			352	3194							3.1	0.11
20	10.8	50.9	300	80	549	1992	>315.0	>20.00		371	566	6.83	3.7	6.98
21	5.4	19.7	277.83	63	955	1003	>315.0	>20.00		286	796	1.91	2.9	1.69
22	17.35	20.9	300	130	887	1341	>315.0	6.04	564	241	704	6.12	4.2	15.39
23	6.3	15.2	156.5	115	4538	39616	8.3	13.49		130	119		11.8	15.1
24	9.7	19.4	300	112	1647	3896	>315.0	>20.00					2.2	20.6
25	15.67	24.73	300	115	601	1160	>315.0	>20.00		180	154	1.95	2.4	60.45
26	15.95	35.3	300	65	626	2371	>315.0	16.05	349	163	5293	0.84	3.2	0.55
27	19.5	19.5	373.06	130	638	1639		>20.00	>700	219	31	2.21	2.1	1.38
28	13.9	13.9			291	1213				419	136	1.26	3.5	18.1
29	31.6	40.6	233.93	39	1730	2853	>315.0	>20.00	667	320	612	3.21	4.5	0.92
30	9.6	30.4	300	118	1083	1282	>315.0	>20.00	877	267	2522	3.97	2.5	31.3
31	11.6	14.7	202.64	80	865	2465	76.6	>20.00	296	422	3950	1.22	4.3	1.07
32	11.2	30.8	300	100	397	2995	>315.0	>20.00	1053	398	838	2.69	6.2	5.19
33	11.03	21.5	300	130	517	2395	>315.0	>20.00	411	160	645	6.56	2.1	25.6
34	7.3	23.5	223.65	130	574	2458	120.6	11.39		160	13074	2.29	1.4	0.28
35	8.9	8.9	0.44	10				1.23		136	61	1.06	1.2	0.81

36	11.18	40.8	12.87	130	380	2823	>315.0	>20	613	226	49	8.66	2.1	7.19
37														
38	6.4	31.2	300	94	681	1877	>315.0	3.95	548	583	786	1.95	4.9	2.15
39	26.6	33.1	237.2	130	773	1988	>315.0	14.39	529	5782	684	4.52	3.1	6.1
40	15.6	15.6								220		0.95	10	
41	13.6	14.8	213.98	73	1599	516.7	74.4	>20.00	507	181	1743	6.43	4.1	65.6

Supplemental Table: Laboratory values

Supplementary Table 5: SARS-CoV-2 is Detected in Different Areas of the Brain by qRT-PCR

Brain Autopsy Section (n=)	Number of samples positive for SARS-CoV-2 (%)	Median viral copy/sample (IQR)
Nasal Epithelium (21)	19 (91%)	43,840 (99,360)
Olfactory Bulb (25)	10 (40%)	680 (256)
Temporal Lobe (25)	9 (36%)	928 (416)
Cerebellum (23)	10 (44%)	264 (216)
Medulla (24)	8 (33%)	1440 (272)
Superior Frontal Gyrus (7)	1 (14%)	368 (0)

Supplementary Table 6: RNAscope data from fresh frozen brains of COVID-19 cases

Case #	Region	RT-PCR	RNAscope	Case #	Region	RT-PCR	RNAscope
1	OB ME	High (+) Low (+)	Negative Negative	16	ME	Positive	Negative
3	ME	Low (+)	Negative	18	ME	Low (+)	Negative
5	ME	Low (+)	Negative	21	ME	Positive	Negative
6	OB ME	Positive Positive	Negative Negative	22	ME	Negative	Negative
7	ME	Indeterminate	Negative	24	ME	Negative	Negative
9	ME	Low (+)	Negative	36	ME	ND	Negative
11	OB CE	Positive Positive	Negative Negative	37	ME	ND	Negative
12	ME	Negative	Negative	40	ME	ND	Negative

OB: Olfactory bulb
ME: Medulla
CE: Cerebellum
ND: Not Determined
Low (+): Low positive