A COVID-19 FERTŐZÉS PATHOLOGIÁJA

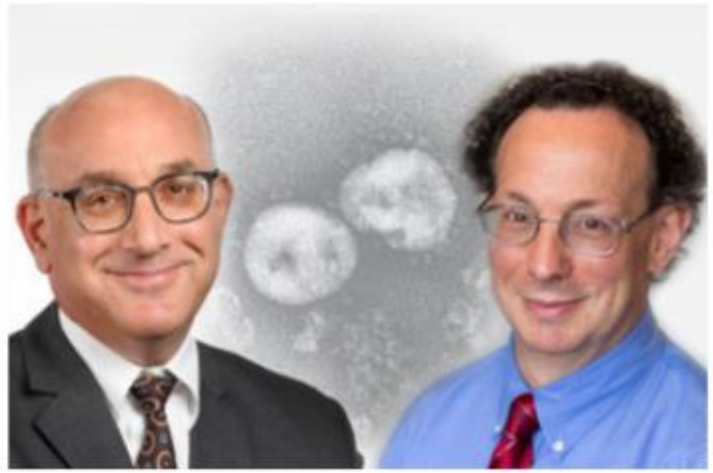
Dr. Molnár Péter
Egyetemi tanár
DE, ÁOK, Pathologiai Intézet

May 14, 2020 N Engl J Med 2020; 382:e8. DOI: 10.1056/NEJMe2017594

Interview with Dr. Eric Rubin and Dr. Lindsey Baden on finding reliable information about Covid-19

Supplement to the N Engl J Med 2020; 382:e81

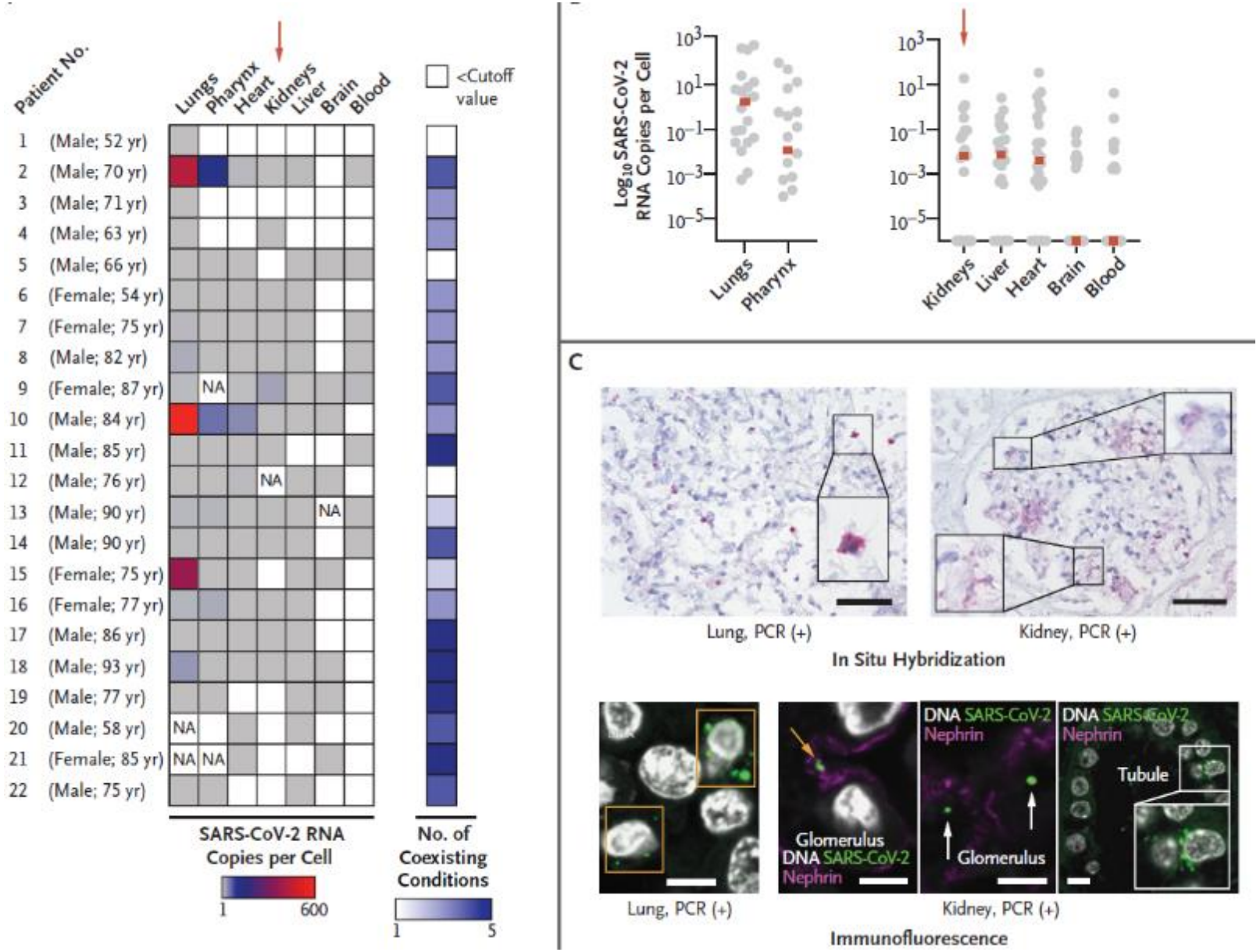
Eric Rubin is the Editor-in-Chief of the *Journal*. Lindsey Baden is a Deputy Editor of the *Journal*. Stephen Morrissey, the interviewer, is the Executive Managing Editor of the *Journal*.



AN AVALANCHE OF INFORMATION WITH A LOT OF NOISE….

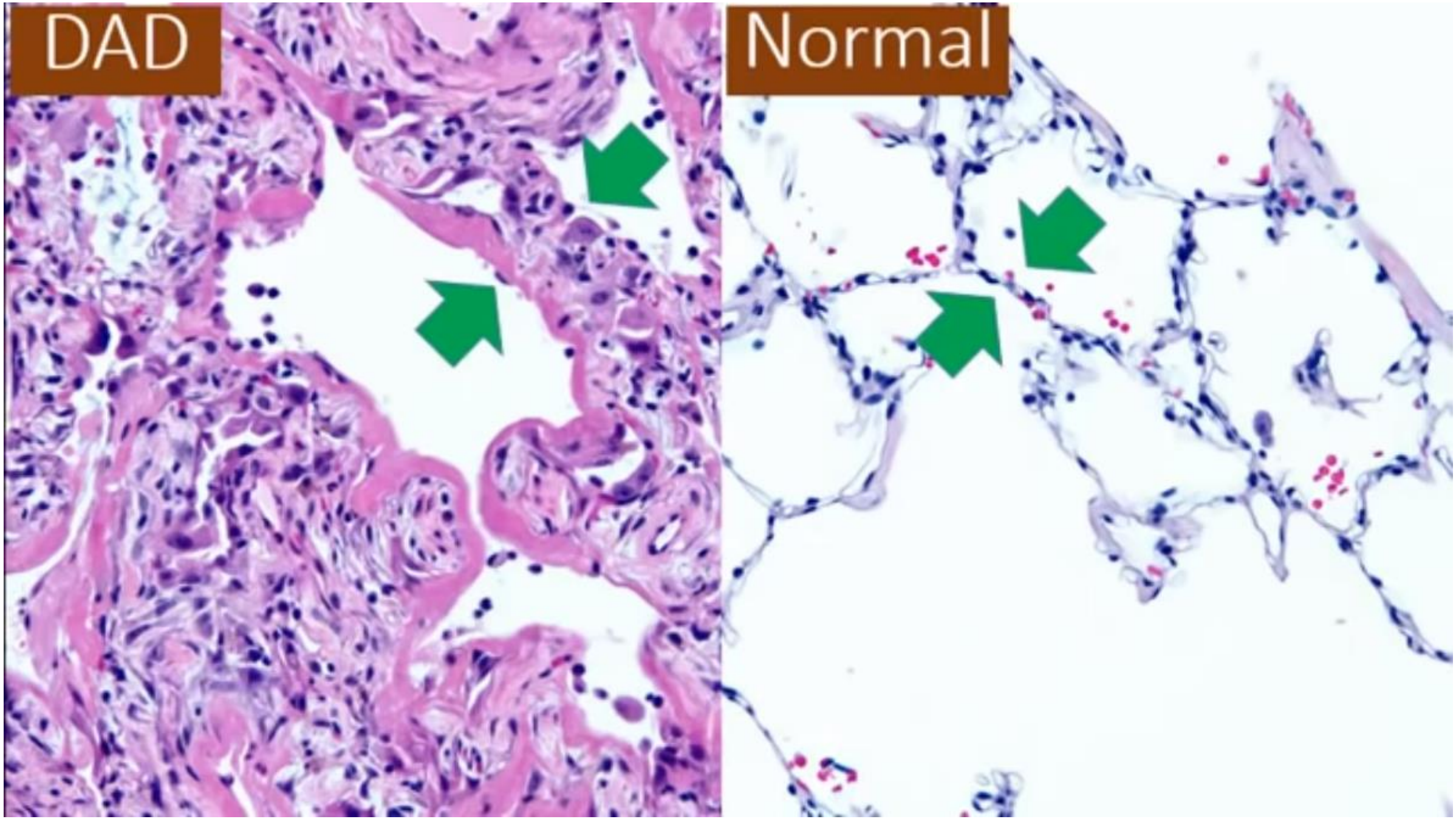
A „KLASSZIKUS” PATHOMORPHOLOGIAI ADATOKBAN KEVESEBB AZ „AVELANCHE”, DE MÉG TÖBB A „NOISE”!

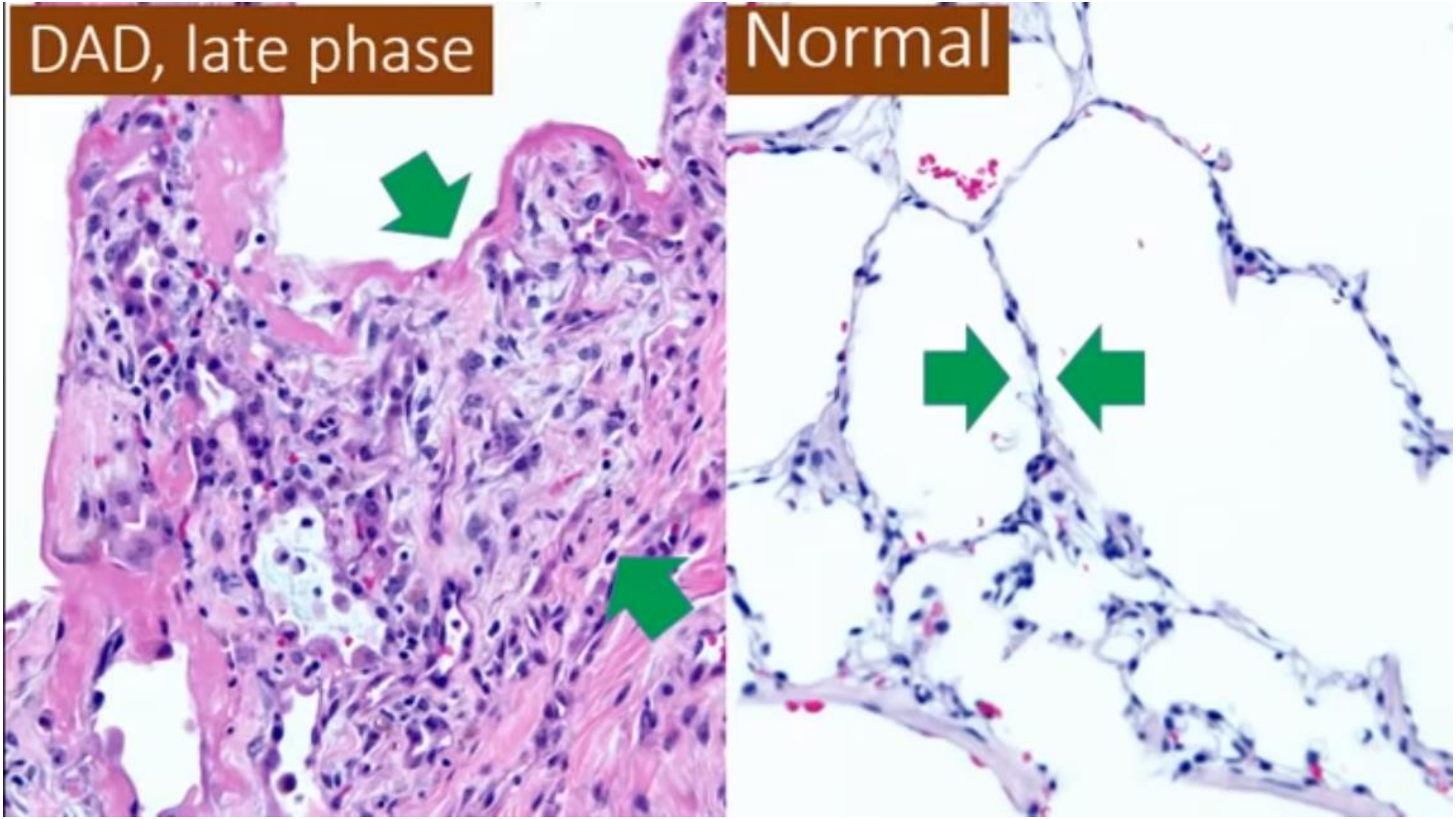
SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys

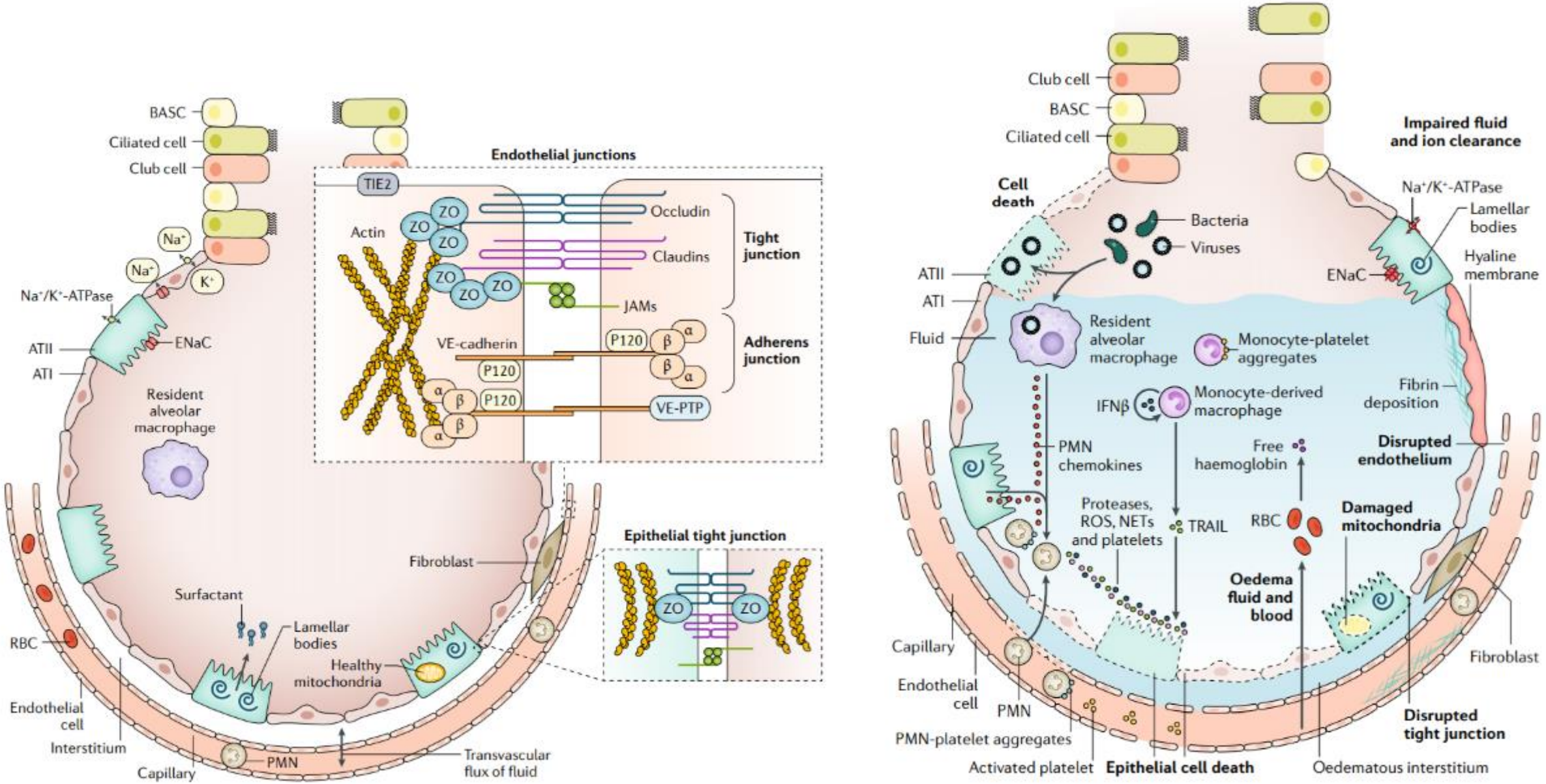


Puelles V et al. This letter was published on May 13, 2020, at NEJM.org

The coronavirus wreaked extensive damage (yellow) on the lungs of a 59-year-old man who died at George Washington University Hospital, as seen in a 3D model based on computerized tomography scans.

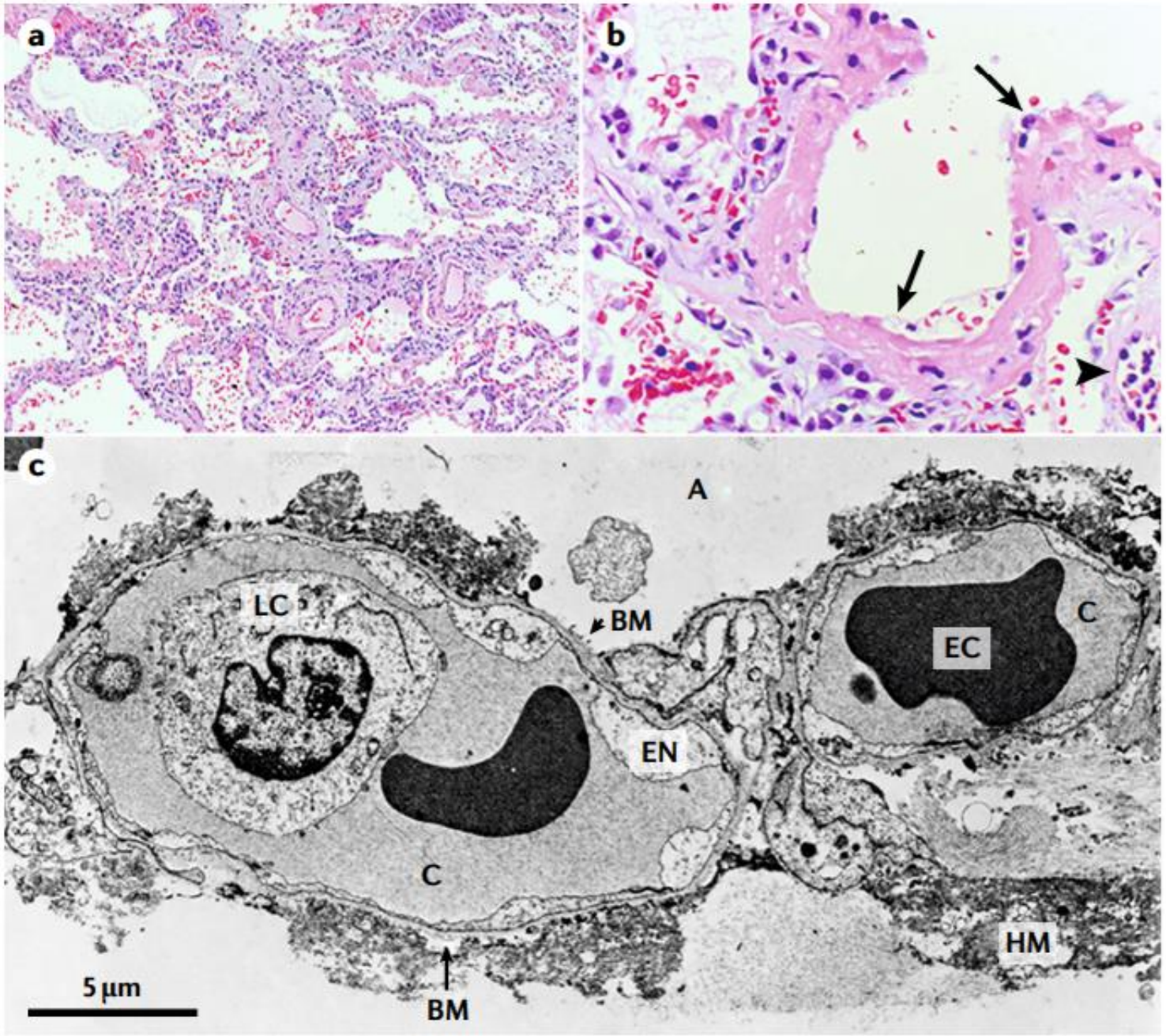

DAD
Normal


DAD, late phase
Normal



Matthay M: Acute respiratory distress syndrome. Nat Rev Dis Primers 5, 18 (2019). https://doi.org/10.1038/s41572-019-0069-0

Microscopic findings in lung tissue in patients with ARDS. In acute respiratory distress syndrome (ARDS), features of diffuse alveolar damage (DAD), such as in the acute 'exudative' phase (~7 days) (panel a), are typically followed by alveolar type II (ATII) cell hyperplasia and interstitial fibrosis in a 'proliferative' phase. Eosinophilic depositions termed hyaline membranes are defining features of DAD (pink structure lining the central alveolus, indicated by the arrowhead in panel b) are defining features of DAD. Leukocytes are embedded in the hyaline membranes (arrows in panel b). Electron microscopic analyses (panel c) demonstrate that alterations in endothelial and epithelial cells are critical features of acute alveolar injury in ARDS.



Matthay M: Acute respiratory distress syndrome. Nat Rev Dis Primers 5, 18 (2019). https://doi.org/10.1038/s41572-019-0069-0

A COVID-19 nem „klasszikus” ARDS

„However, the patients with Covid-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristics we are observing is the dissociation between their relatively well preserved lung mechanics and the severity of hypoxemia. Relatively high compliance indicates well preserved lung gas volume in this patient cohort, in sharp contrast to expectations for severe ARDS.” ,

Luciano Gattinoni AJRCCM Articles in Press. Published March 30, 2020 as 10.1164/rccm.202003-0817LE.

Increased amount of non-aerated tissue is associated with increased recruitability

Remarkable increases in lung weight seen on CT is comparable to severe ARDS

Due to fraction of Cardiac output perfusing non-aerated dependent lung regions

Increased edema = Decreases gas volumes & increases lung elastance

Variations of COVID-19	
L= Phenotype	**H Phenotype**
Low Elastance (High Compliance)	High Elastance (Low Compliance)
Low Ventilation Perfusion Ratio	High Right-to-Left Shunt
Low Lung Weight	High Lung Weight
Low Recruitability	High Recruitability

Nearly normal compliance = Nearly normal amount of gas in the lungs

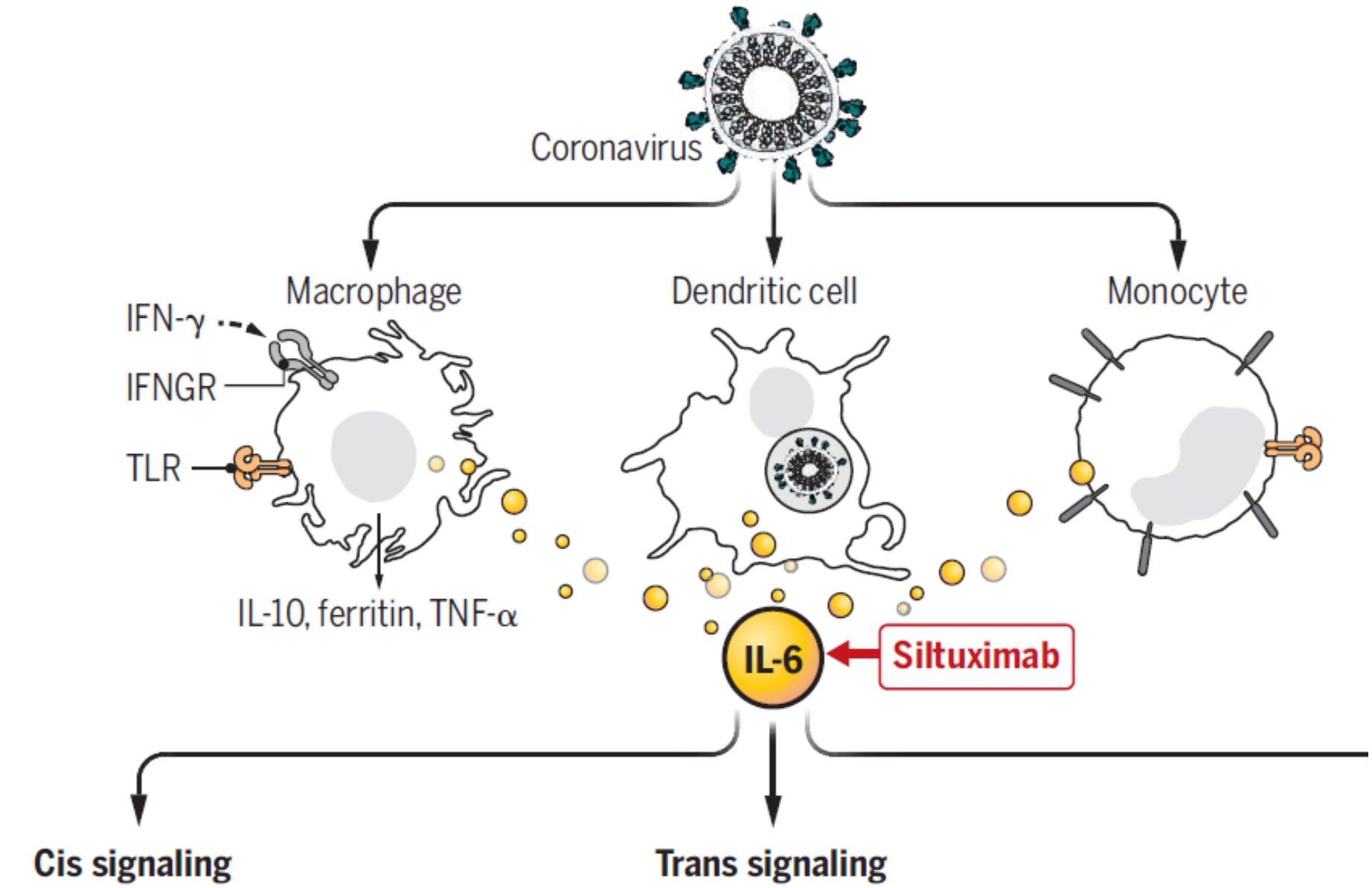
Low V/Q Ratio = Hypoxemia may be due to perfusion regulation loss & Hypoxic Vasoconstriction

Subpleural ground glass opacities on CT scan only moderately increases lung weight

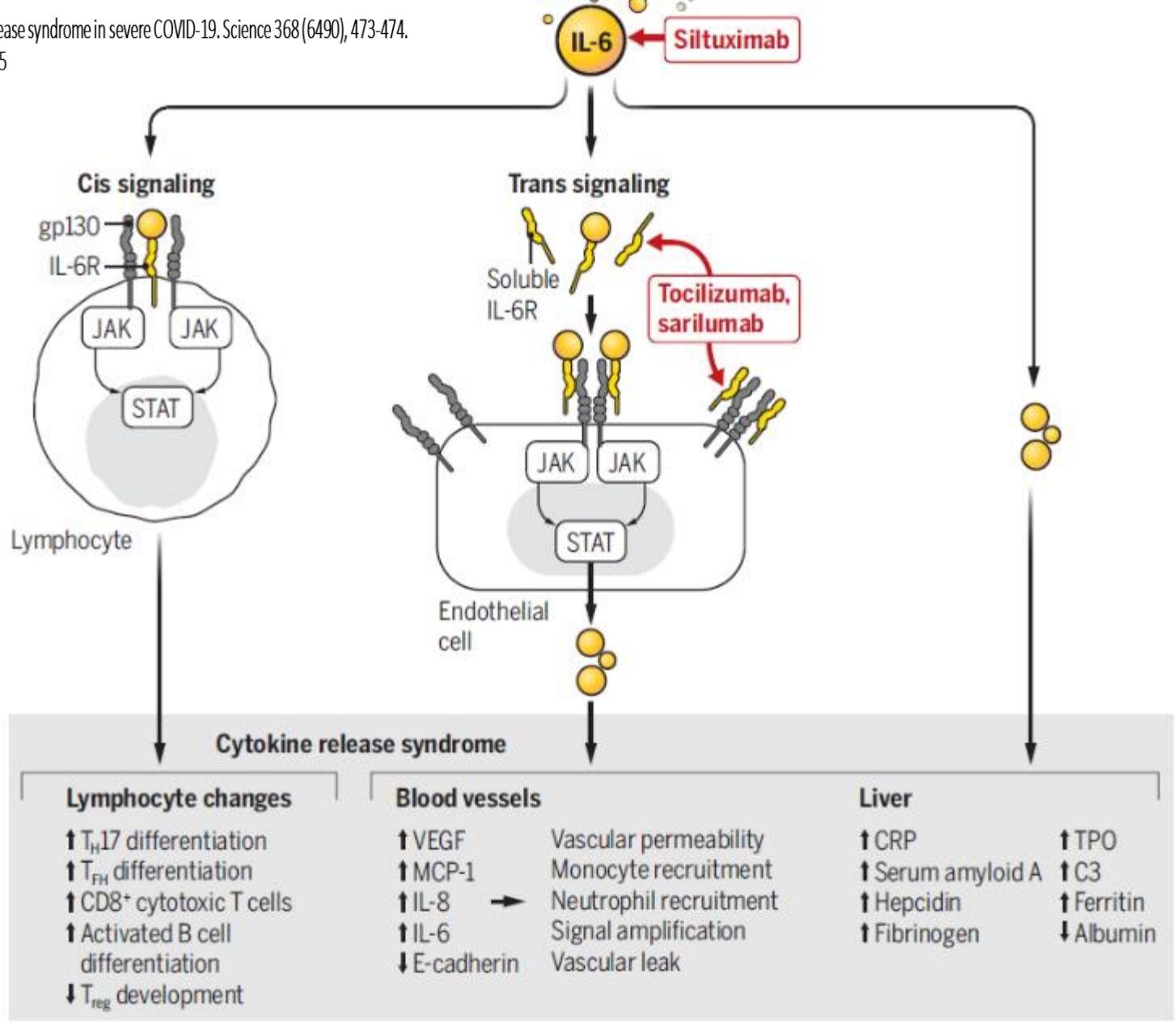
Amount of non-aerated tissue is very low = Recruitability is LOW

Luciano Gattinonii

John B. Moore and Carl H. June: Cytokine release syndrome in severe COVID-19. Science 368 (6490), 473-474.
1 MAY 2020 • DOI: 10.1126/science.abb8925

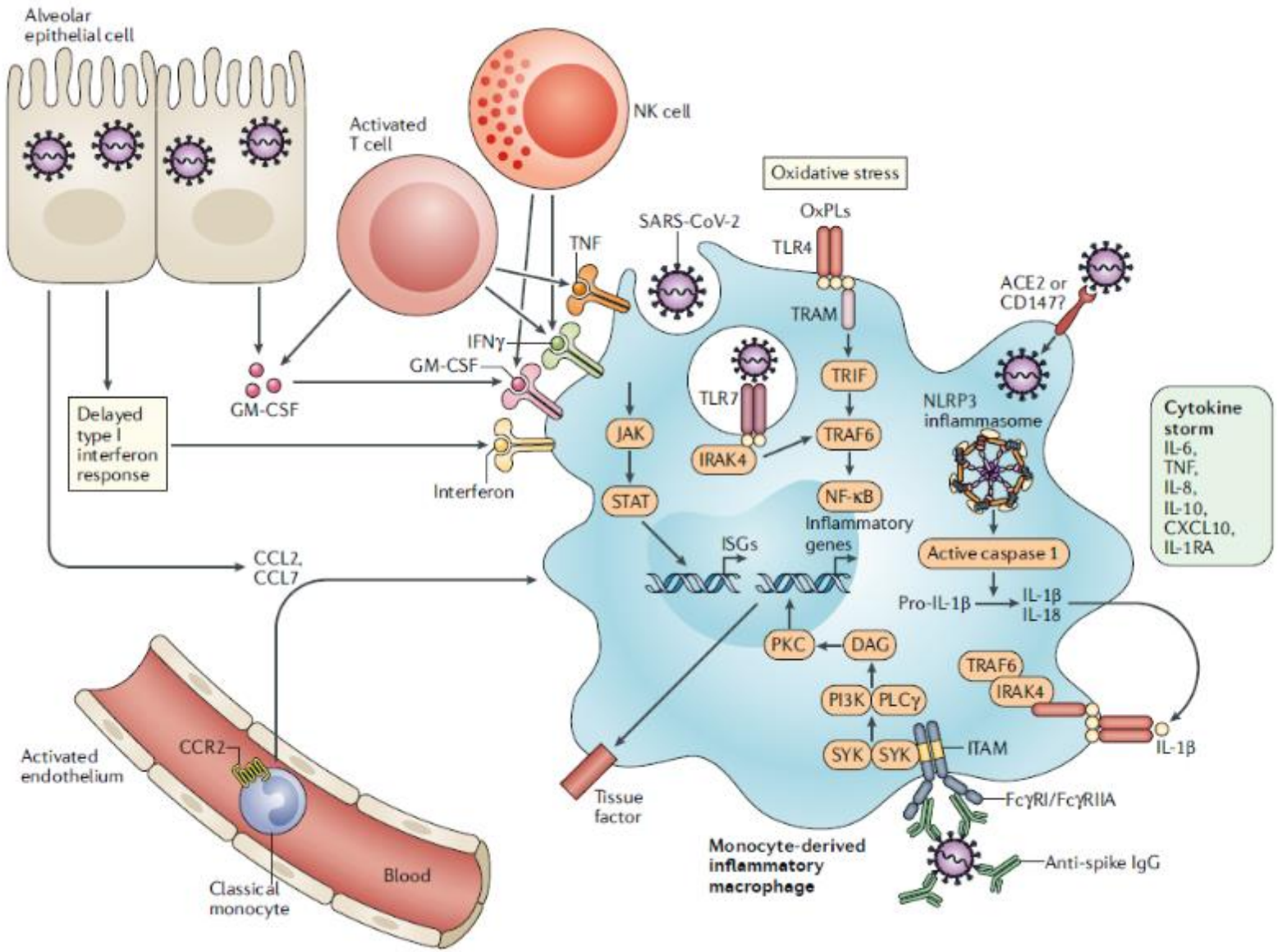


John B. Moore and Carl H. June:Cytokine release syndrome in severe COVID-19. Science 368 (6490), 473-474.
1 MAY 2020 • DOI: 10.1126/science.abb8925



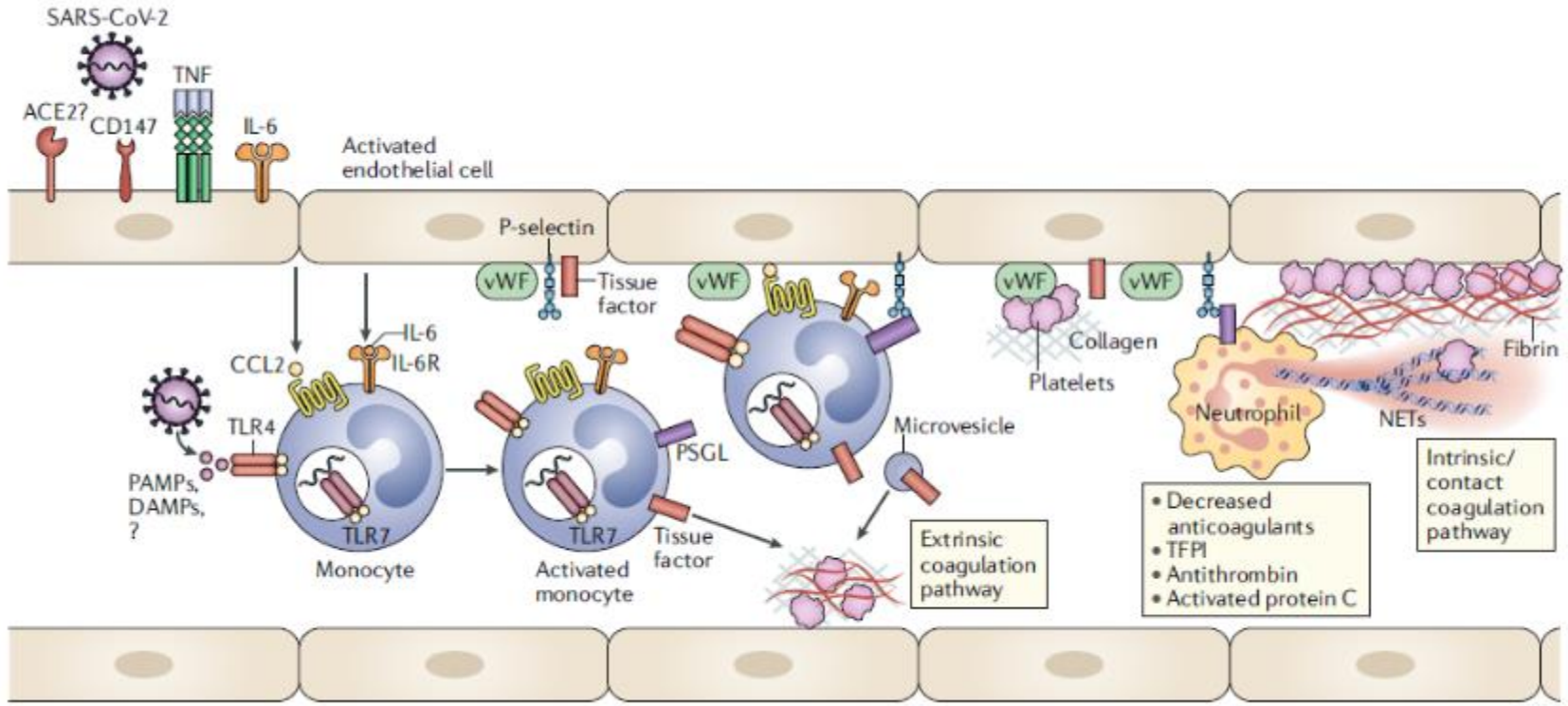
C3, complement 3; CRP, C reactive protein; IFN-g, interferon-g; IFNGR, IFN-g receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein–1; STAT3, signal transducer and activator of transcription 3; TFH, T follicular helper cell; TH17, T helper 17 cell; TNF-a, tumor necrosis factor–a; TLR, Toll-like receptor; TPO, thrombopoietin; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

Merad, M., Martin, J.C. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-0331-4



COVID-19 patients with acute respiratory failure present a severe hypercoagulability rather than consumptive coagulopathy. Fibrin formation and polymerization may predispose to thrombosis and correlate with a worse outcome.

Spiezia L et al.: COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost. 2020 Apr 21. doi: 10.1055/s-0040-1710018. [Epub ahead of print]



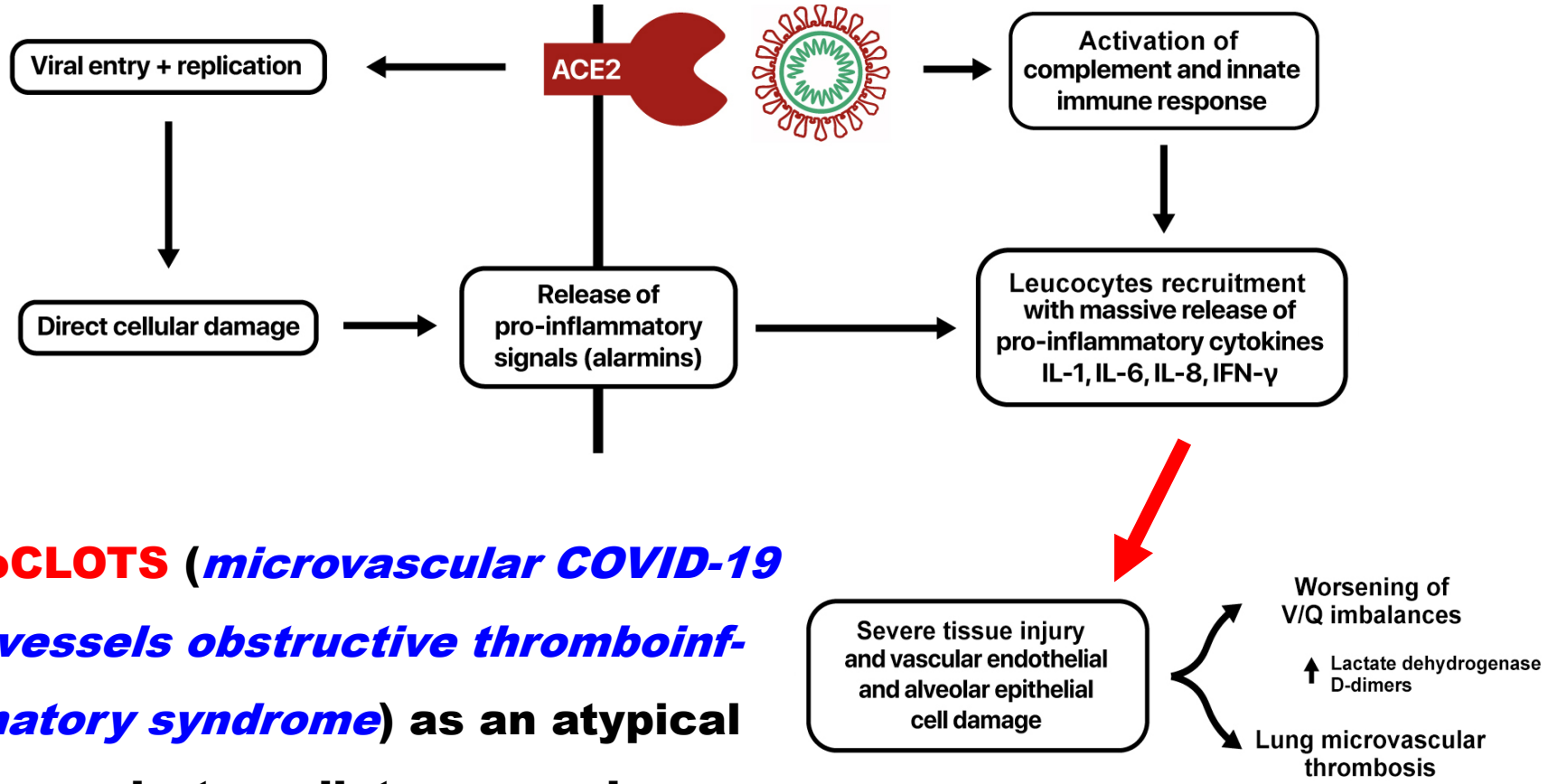
The SARS-CoV-2 entry receptor ACE2 is expressed on arterial and venous endothelial cells, where it plays an anti-inflammatory protective effect. **Whether the increased coagulopathy observed in patients with COVID-19 is also partly due to direct vascular damage induced by SARS-CoV-2 infection or ACE2 inhibition remains to be determined.**

Fabio Ciceri et. al: Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020. [Epub ahead of print]

We propose a mechanism of lung damage, primarily explained by a dramatic alveolar endothelial damage leading to a progressive endothelial pulmonary syndrome with microvascular thrombosis, and suggest MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as an atypical ARDS working hypothesis.

This progressive endothelial thromboinflammatory syndrome may also involve the microvascular bed of the brain and other vital organs, leading to multiple organ failure and death.

SARS-CoV-2 enters target cells through the cell surface receptor angiotensin-converting enzyme 2 (ACE2), which is expressed on the surface of lung epithelial cells and enterocytes of the small intestine. *ACE2 is also present in arterial and venous endothelial cells and in arterial smooth muscle cells of multiple organs.* Its replication causes direct cellular damage and release of pro-inflammatory alarmins from dying cells.



MicroCLOTS (*microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome*) as an atypical acute respiratory distress syndrome working hypothesis.

Crit Care Resusc 2020. [Epub ahead of print]

TÜDŐ

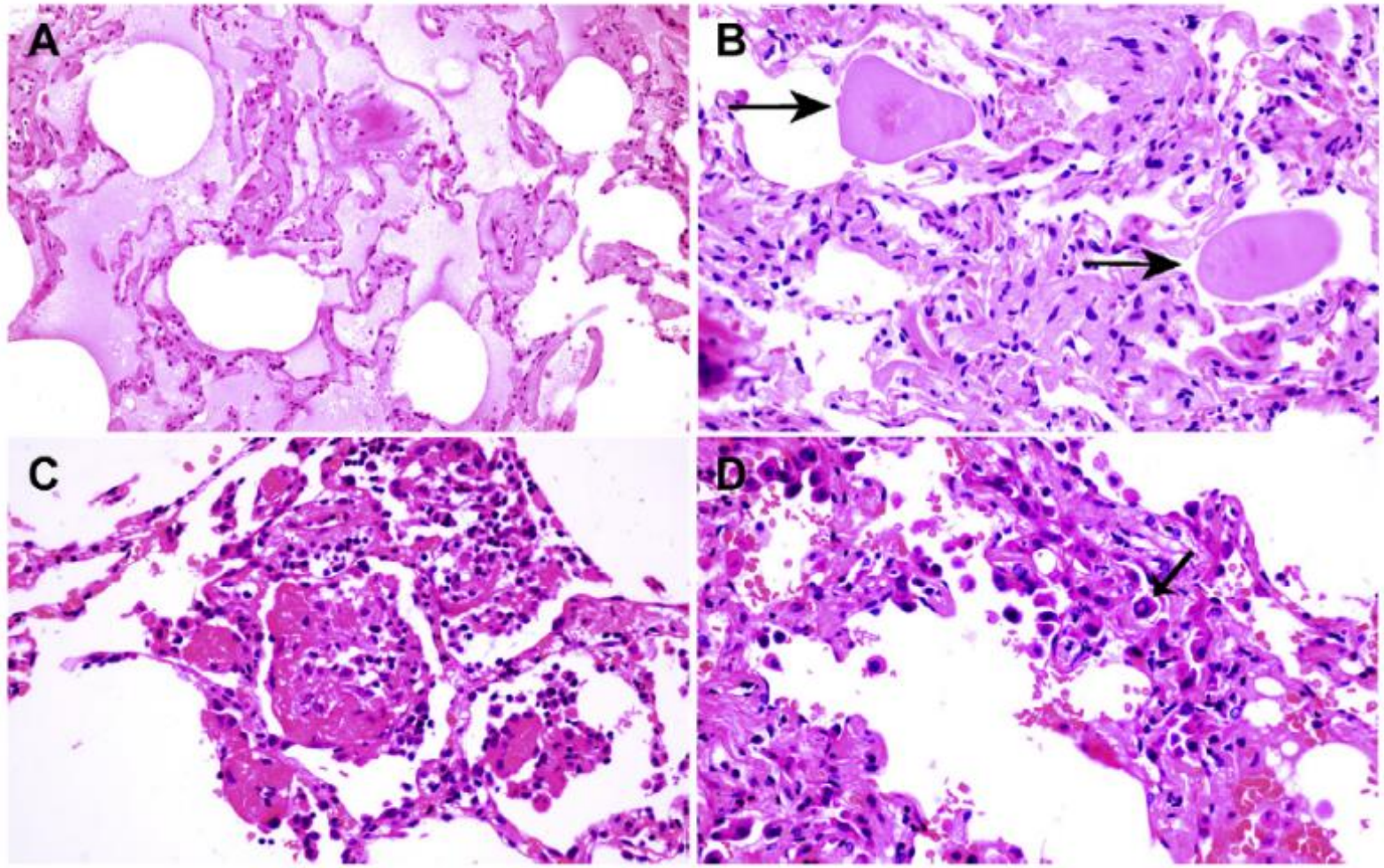


Figure 2. Histologic changes from case 1. (*A*) Proteinaceous exudates in alveolar spaces, with granules; (*B*) scattered large protein globules (arrows); (*C*) intra-alveolar fibrin with early organization, mononuclear inflammatory cells, and multinucleated giant cells; (*D*) hyperplastic pneumocytes, some with suspected viral inclusions (arrow).

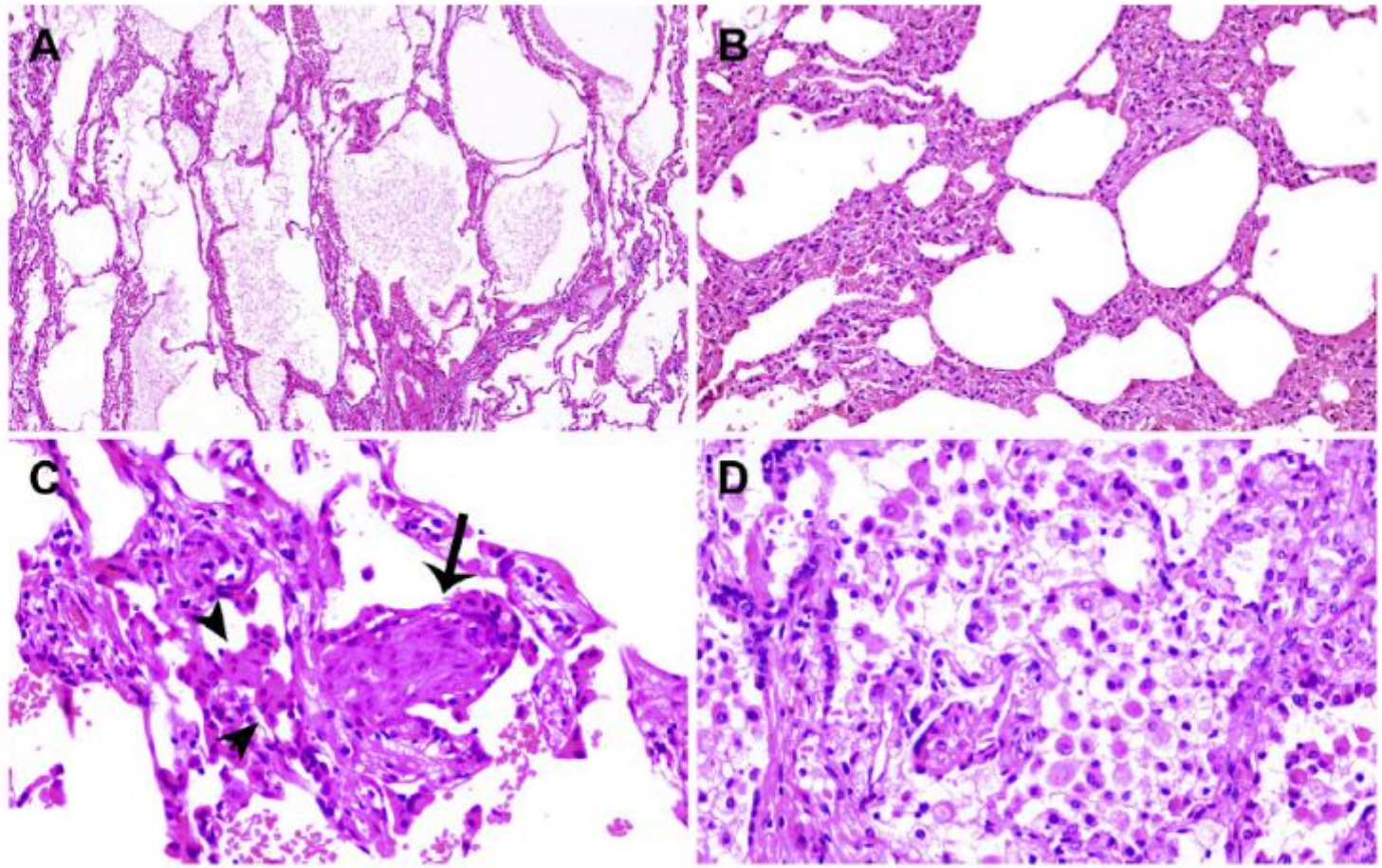
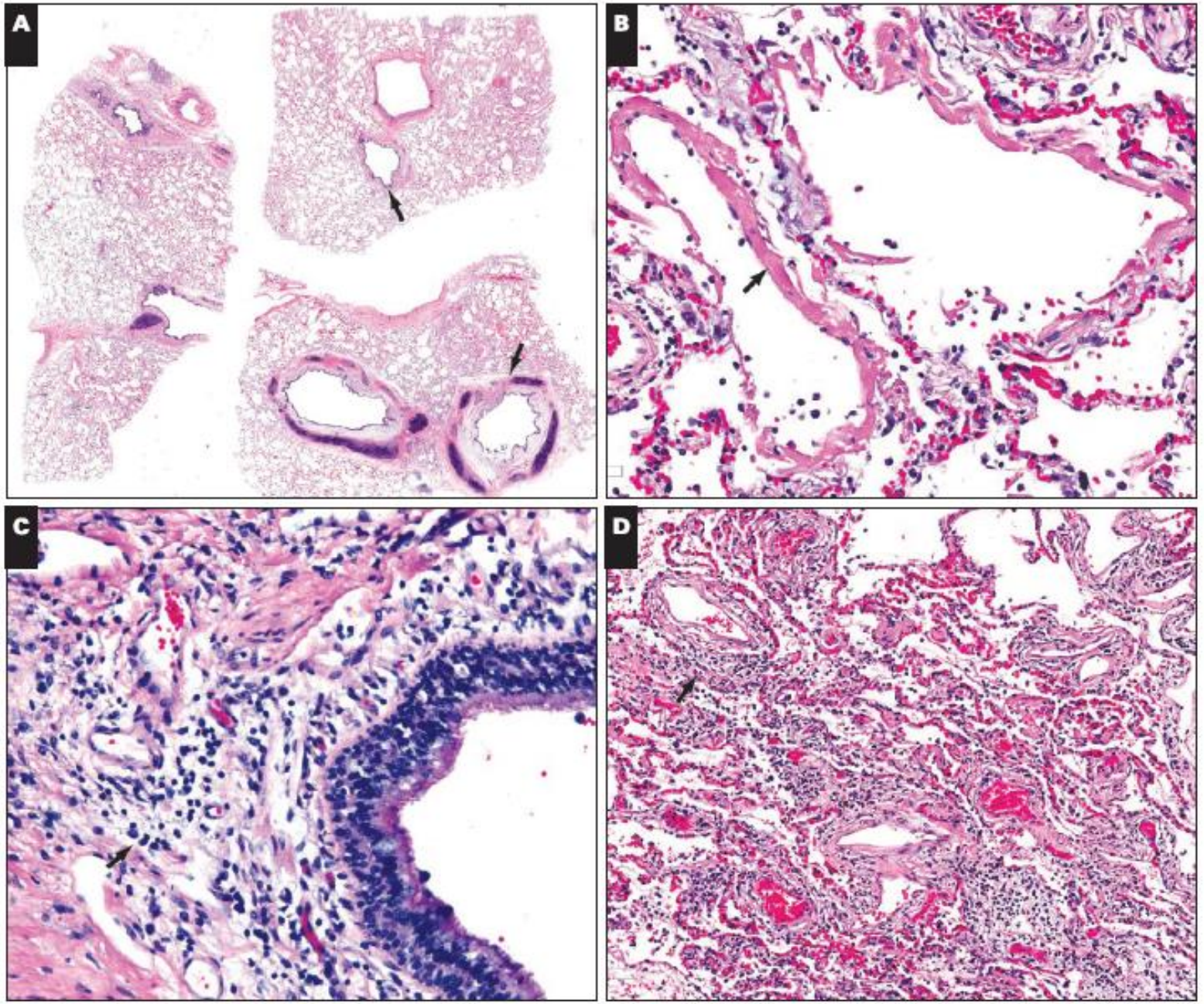


Figure 3. Histologic changes of coronavirus disease 2019 pneumonia in case 2. (*A*) Evident proteinaceous and fibrin exudate; (*B*) diffuse expansion of alveolar walls and septa owing to fibroblastic proliferations and type II pneumocyte hyperplasia, consistent with early diffuse alveolar damage pattern; (*C*) plugs of proliferating fibroblasts or "fibroblast balls" in the interstitium (arrow); (*D*) abundant macrophages infiltrating airspaces and type II pneumocyte hyperplasia.

Microscopic findings in the lungs of a 77-year-old man who died of coronavirus disease 2019 (COVID-19). A, The airways are pa-tent, with no evidence of mucus plugging. The upper arrow points to a patent bronchi-ole. The structure marked by the lower ar-row is a patent bronchus. Neither airway shows evidence of mucus plugging. The pale appearance of the thickened bronchial mucosa is caused by mucosal edema. B, Diffuse alveolar damage in the acute stage. Note hyaline membranes (arrow). C, Chronic inflammation in the mucosa of an airway (arrow). The inflammatory cells are mainly lymphocytes.

D, Patchy interstitial chronic inflammation. This image is taken from one of the few areas where interstitial inflammation was obvious even at low magnification. In most areas, the inflammatory infiltrate was very sparse or absent.



Barton LM: COVID-19 Autopsies, Oklahoma, USA*Am J Clin Pathol* 2020;XX:1-9. DOI: 10.1093/ajcp/aqaa062

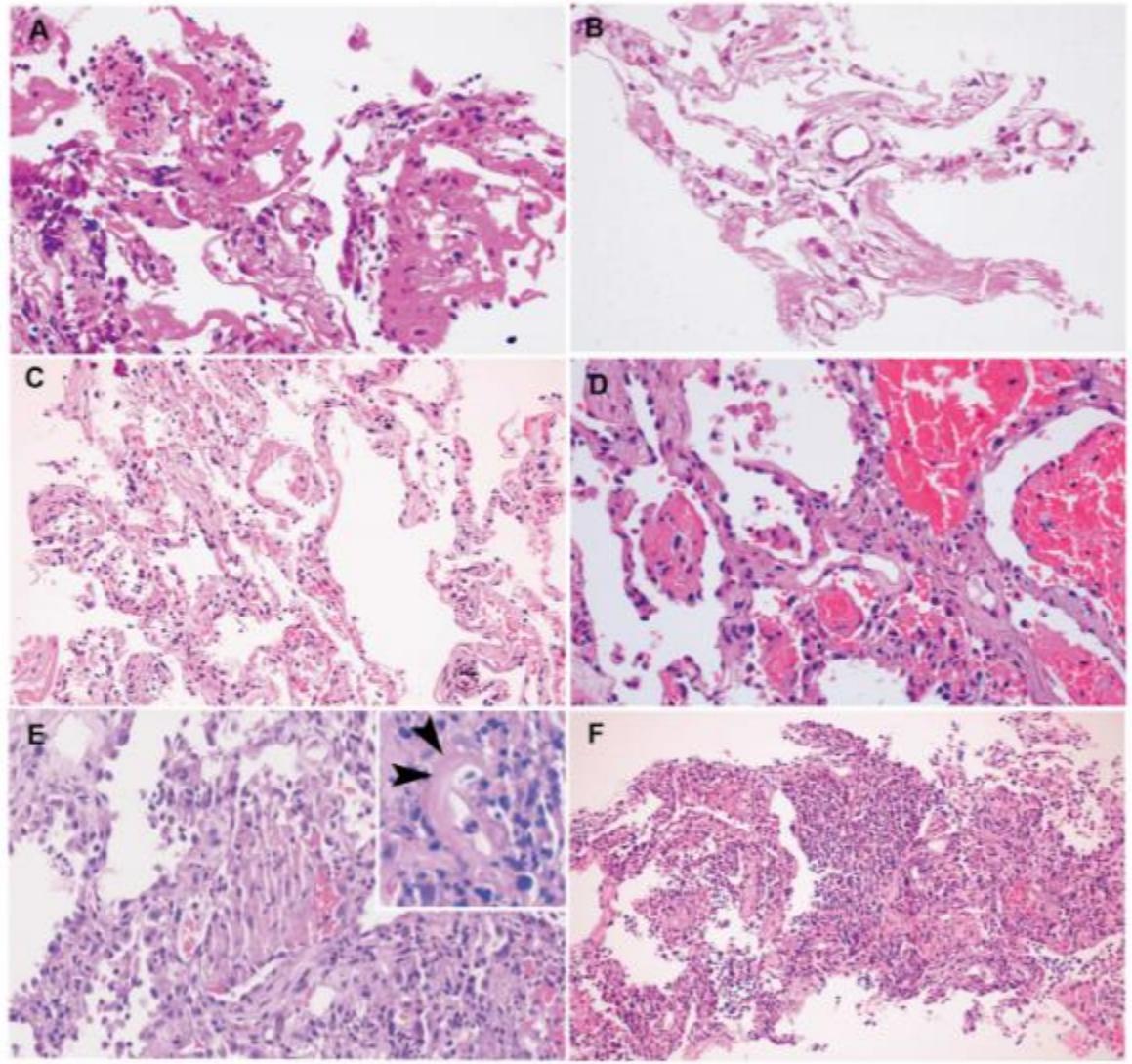


Fig. 3 Histologic changes in the lungs. **a** Case 1: thick hyaline membrane mixed with desquamative pneumocytes and mononuclear inflammatory cells. **b** Case 2: more delicate hyaline membranes without evident inflammatory infiltration. **c** Case 3: focal hyaline membrane, type II pneumocyte hyperplasia, and mild interstitial thickening. **d** Case 4: alveolar spaces were filled with red blood cell exudation, and small fibrin plugs seen in adjacent alveoli. **e** Organization with intra-alveolar fibroblasts mixed with fibrin and inflammatory cellular infiltration. Diffuse type II pneumocyte hyperplasia in the background (inset: fibrinoid vascular necrosis, arrow heads). **f** Changes of bronchopneumonia with prominent neutrophilic infiltration filling up alveolar spaces.

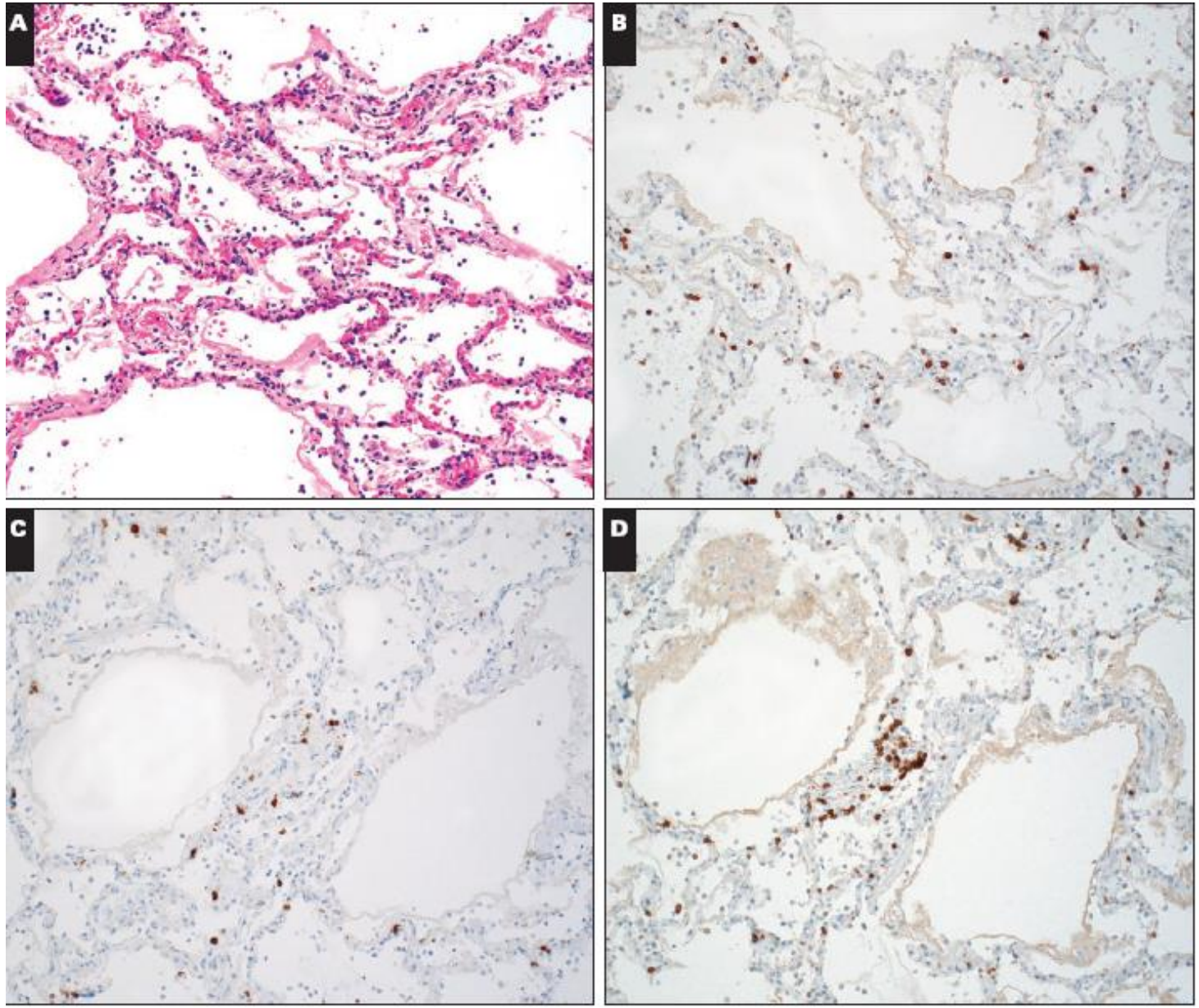
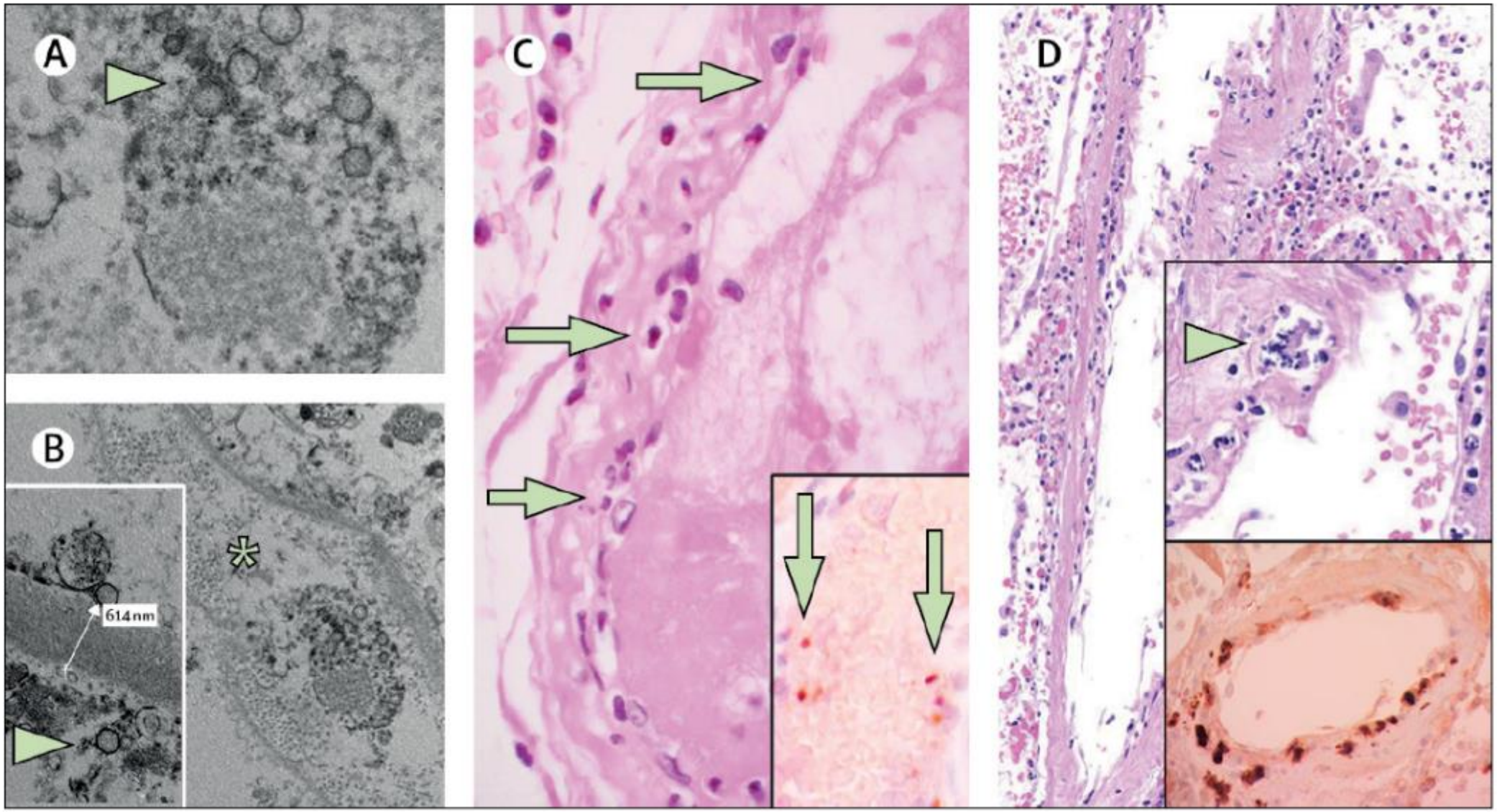
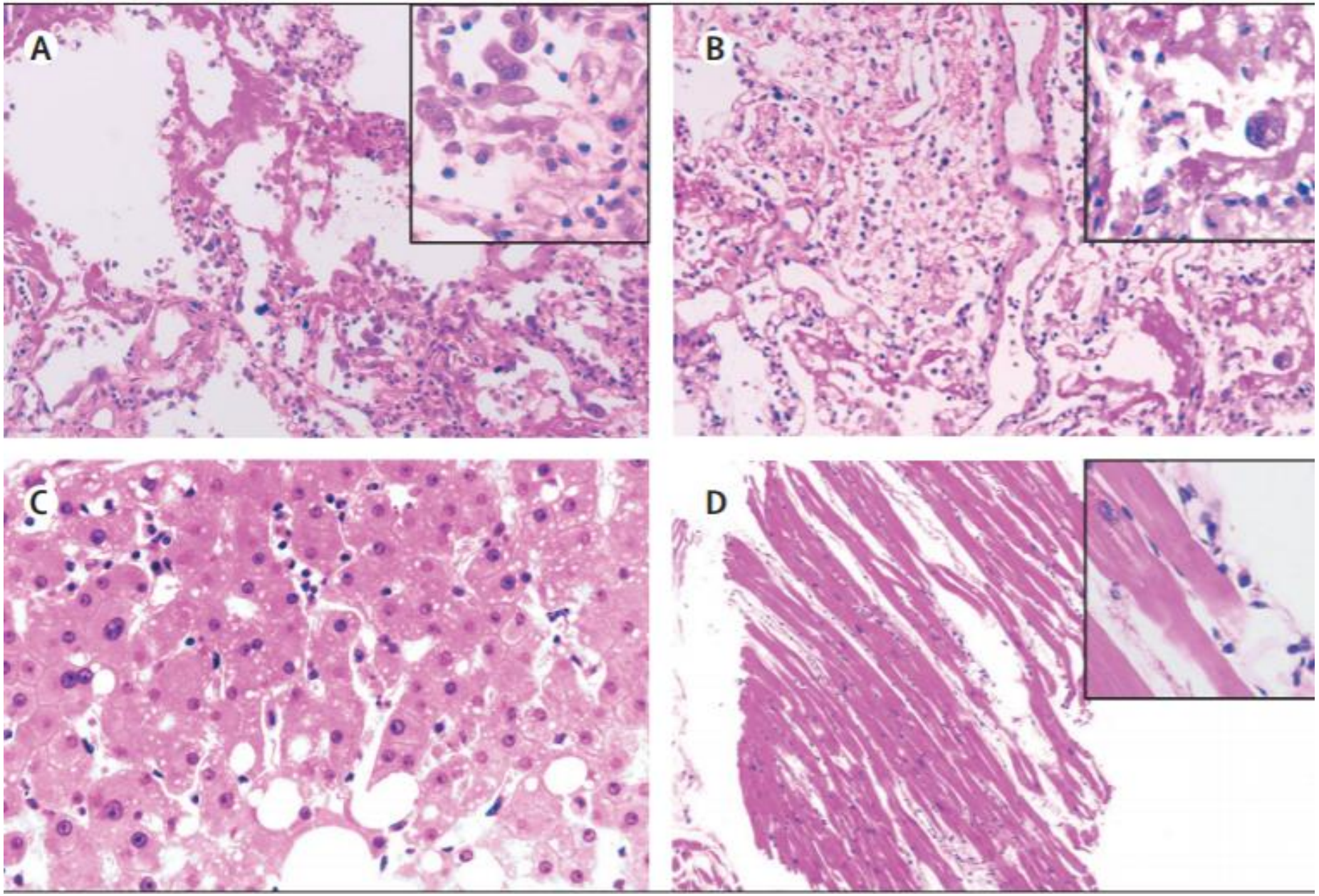


Image 4 Immunohistochemistry in case 1. **A**, Diffuse alveolar damage with minimal, patchy chronic inflammation (H&E, ×200). T-lymphocytes are highlighted by immunohistochemical stains for CD3 (**B**), CD4 (**C**), and CD8 (**D**).

Varga Zs et al: Endothelial cell infection and endotheliitis in COVID-19



www.thelancet.com Published online April 17, 2020 https://doi.org/10.1016/S0140-6736(20)30937-5



Xu Z, Shi L, Wang Y. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;DOI: 10.1016/S2213-2600(20)30076.

MÁJ

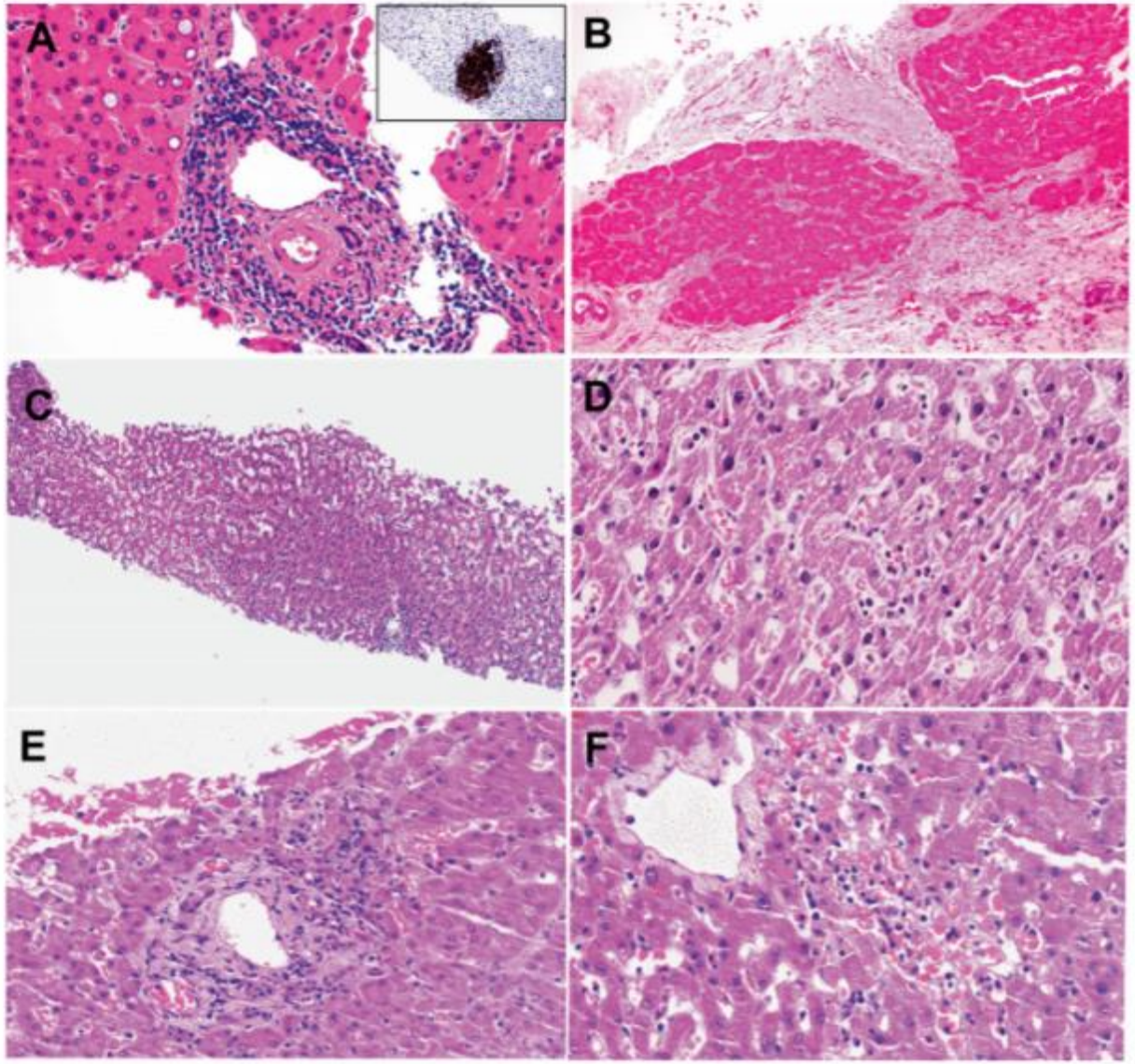


Fig. 4 Pathological findings in liver from all four cases. a Dense portal infiltration by atypical small lymphocytes (insert: CD20 immunostaining), and focal glycogenated nuclei in hepatocyte in Case 1. **b** Cirrhotic nodules with thick fibrosis in Case 2. **c** Mild sinusoidal dilatation with increased lymphocytic infiltration. **d** Higher power view showing sinusoidal lymphocytes. **e** Focal hepatic necrosis in periportal zone. **f** Focal centrilobular hepatic necrosis in Case 4.

GASTROINTESTINALIS TRACTUS

Images of histologic and immunofluorescent staining of gastrointestinal tissues. Shown are images of histologic and immunofluorescent staining of esophagus, stomach, duodenum, and rectum. The scale bar in the histologic image represents 100 mm. The scale bar in the immuno-fluo-rescent image represents 20 mm.

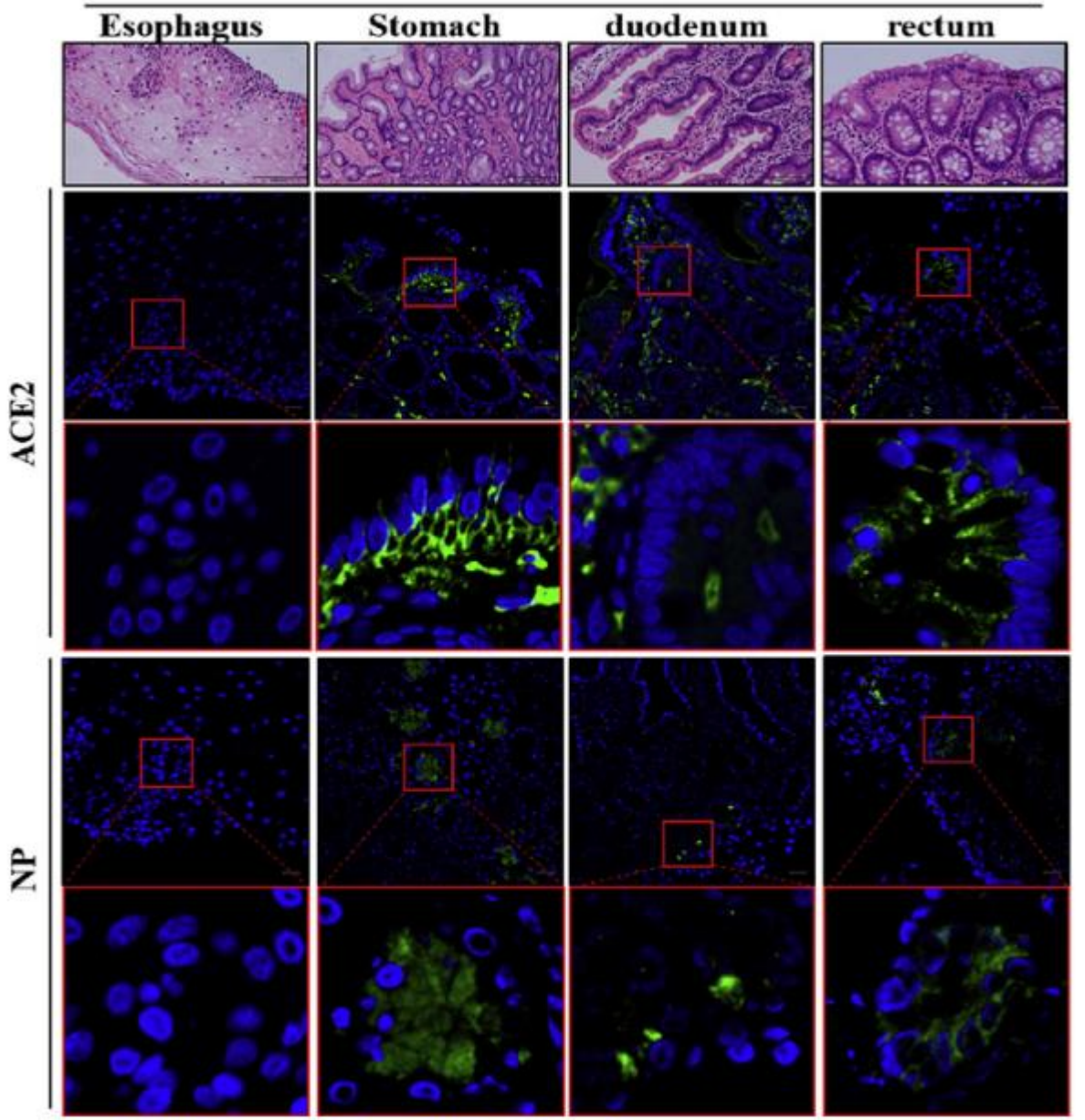


Figure 1. Images of histologic and immunofluorescent staining of gastrointestinal tissues. Shown are images of

Xiao Fei et al: Evidence for Gastrointestinal Infection of SARS-CoV-2 Gastroenterology https://doi.org/10.1053/j.gastro.2020.02.055.

VESE

Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China

Study Cohort

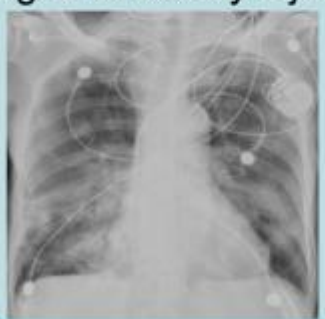
Light microscopy: ATI, RBC aggregates

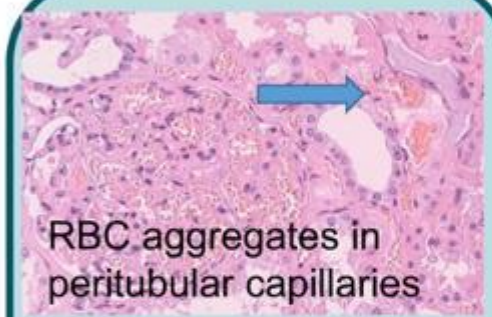
Electron microscopy: virus in tubules and podocytes

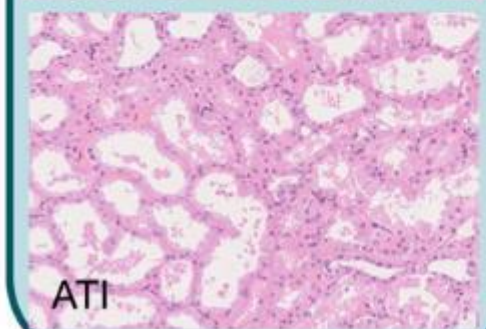
SARS-CoV nuclear protein detection

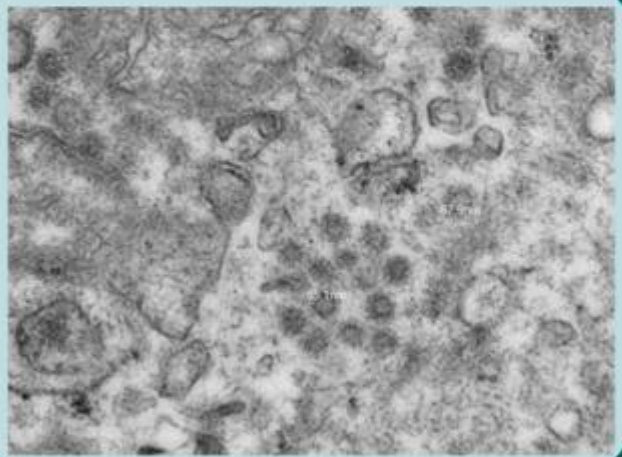
26 autopsies in COVID-19 patients

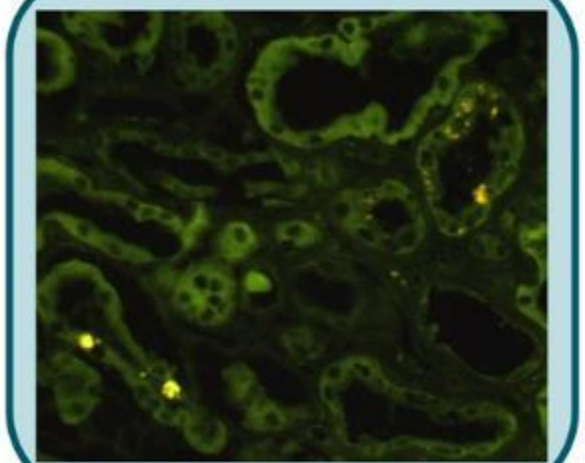
-death due to respiratory failure
-average age 69 years
-19 males; 7 females
-9/26 showed clinical signs of kidney injury











CONCLUSION:

Direct parenchymal infection of tubular epithelial cells and podocytes with marked acute tubular injury (ATI) and erythrocyte aggregation occurs in severe lethal COVID-19.

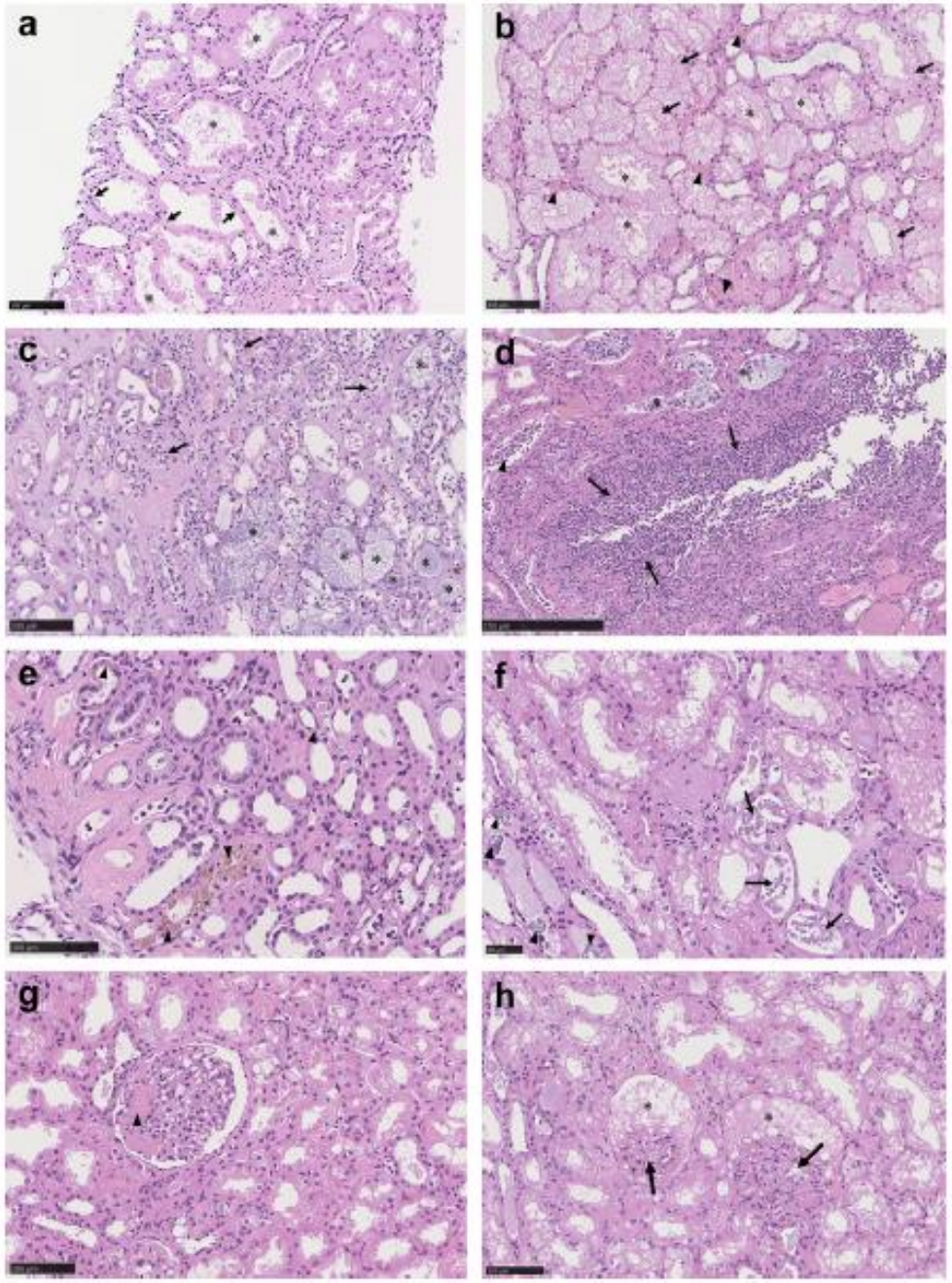
ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Su et al, 2020

Kidney International DOI: (10.1016/j.kint.2020.04.003)

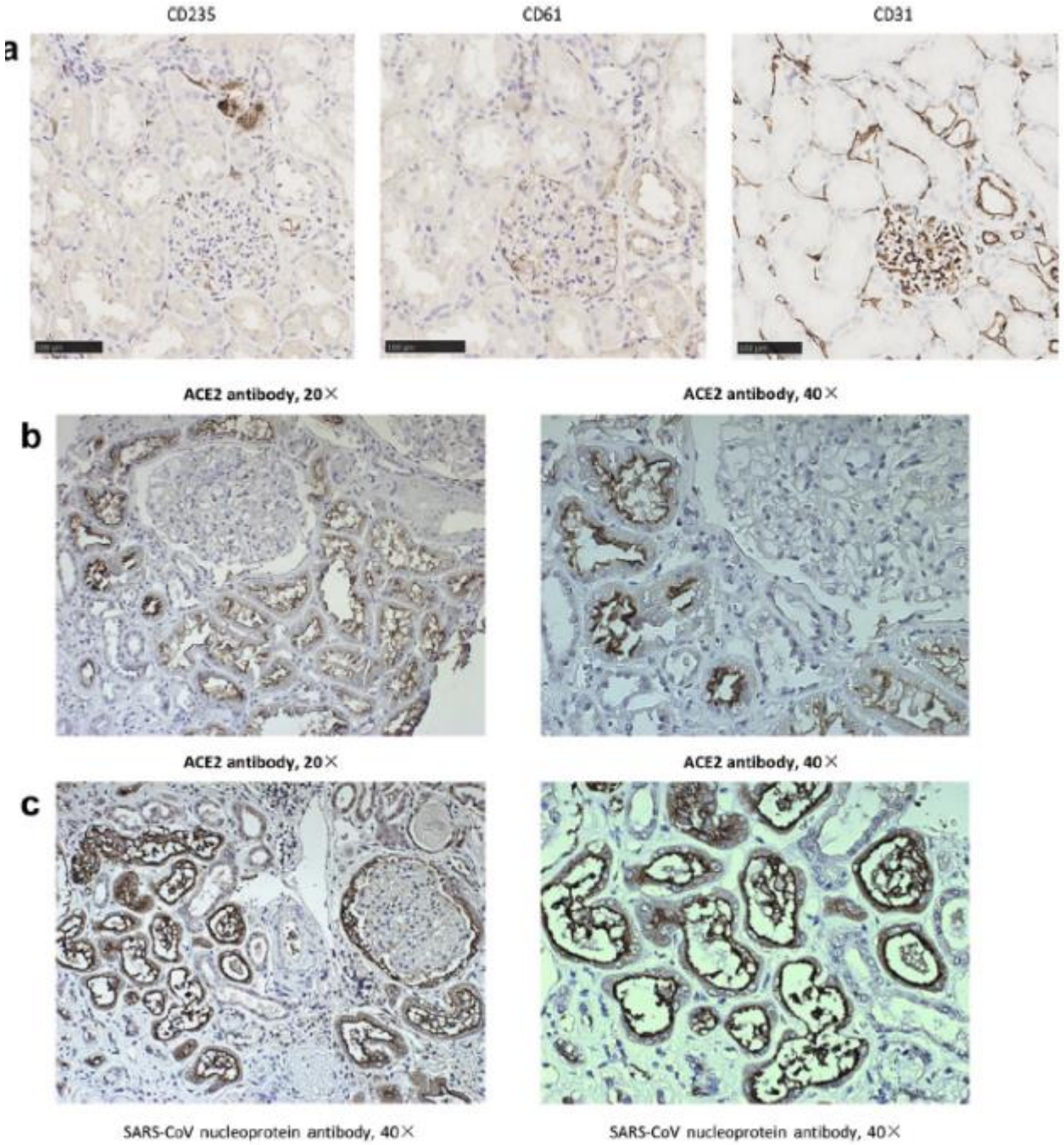
VESE

By light microscopy, diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, and even frank necrosis was observed. Occasional hemosiderin granules and pigmented casts were identified. There were prominent erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material. Evidence of vasculitis, interstitial inflammation or hemorrhage was absent.



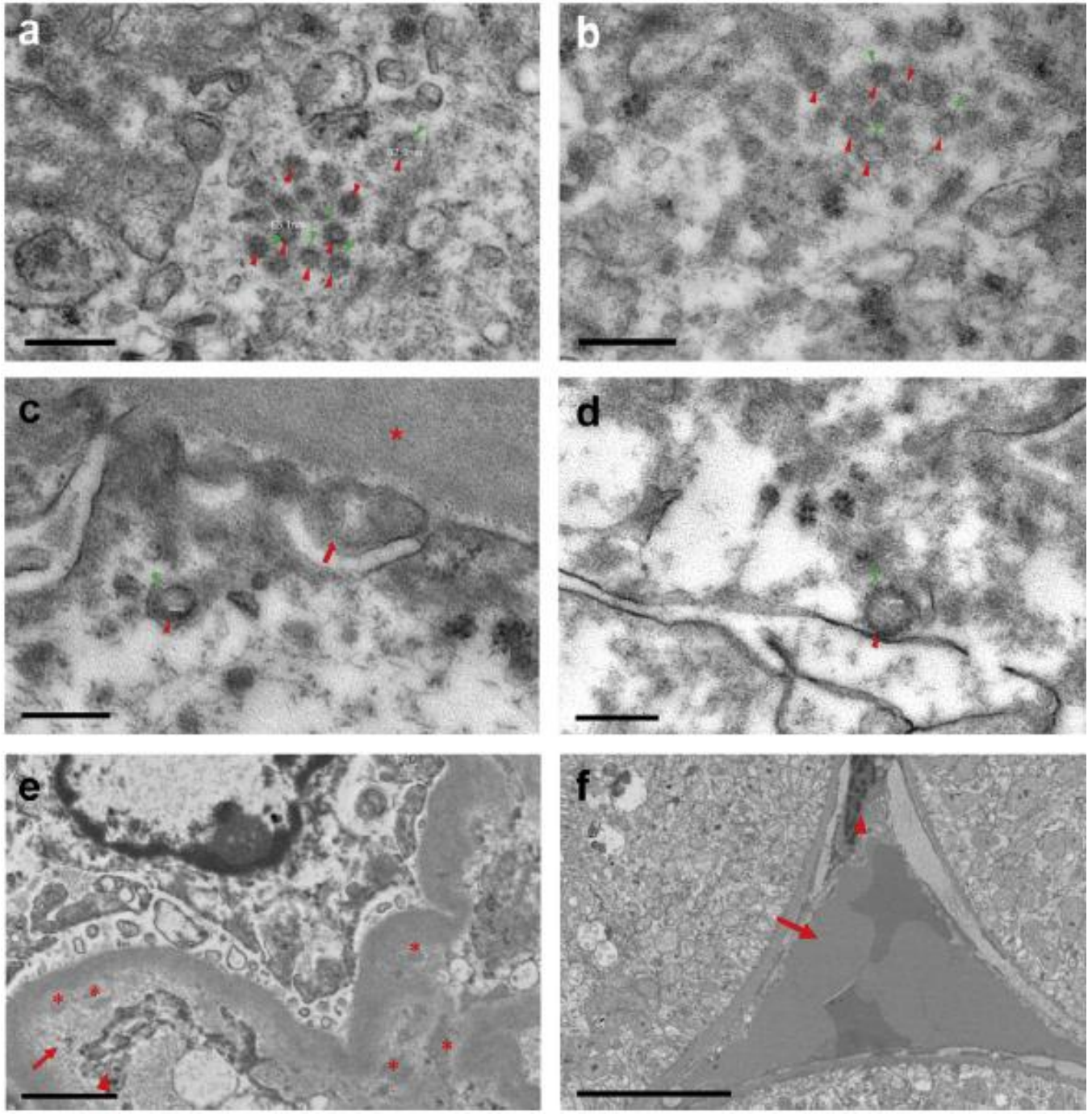
VESE

Immunostaining of paraffin-embedded kidney tissue from patients with coronavirus disease 2019 (COVID-19). (a) Serial sections stained for CD235, CD61, and CD31 showing stasis of red blood cells without platelets in peritubular capillaries. Bars Ľ 100 mm. (b,c) Angiotensin-converting enzyme II (ACE2) stained mainly proximal tubules in (b) non–coronavirus disease 2019 case, with (c) strong proximal tubular staining and parietal epithelial cell staining with occasional weak podocyte staining in some COVID-19 cases.



VESE

Electron microscopic examination showed clusters of coronavirus-like particles with distinctive spikes in the tubular epithelium and podocytes. Furthermore, the receptor of SARS-CoV-2, ACE2 was found to be upregulated in patients with COVID-19, and immunostaining with SARS-CoV nucleoprotein antibody was positive in tubules.



Központi idegrendszer

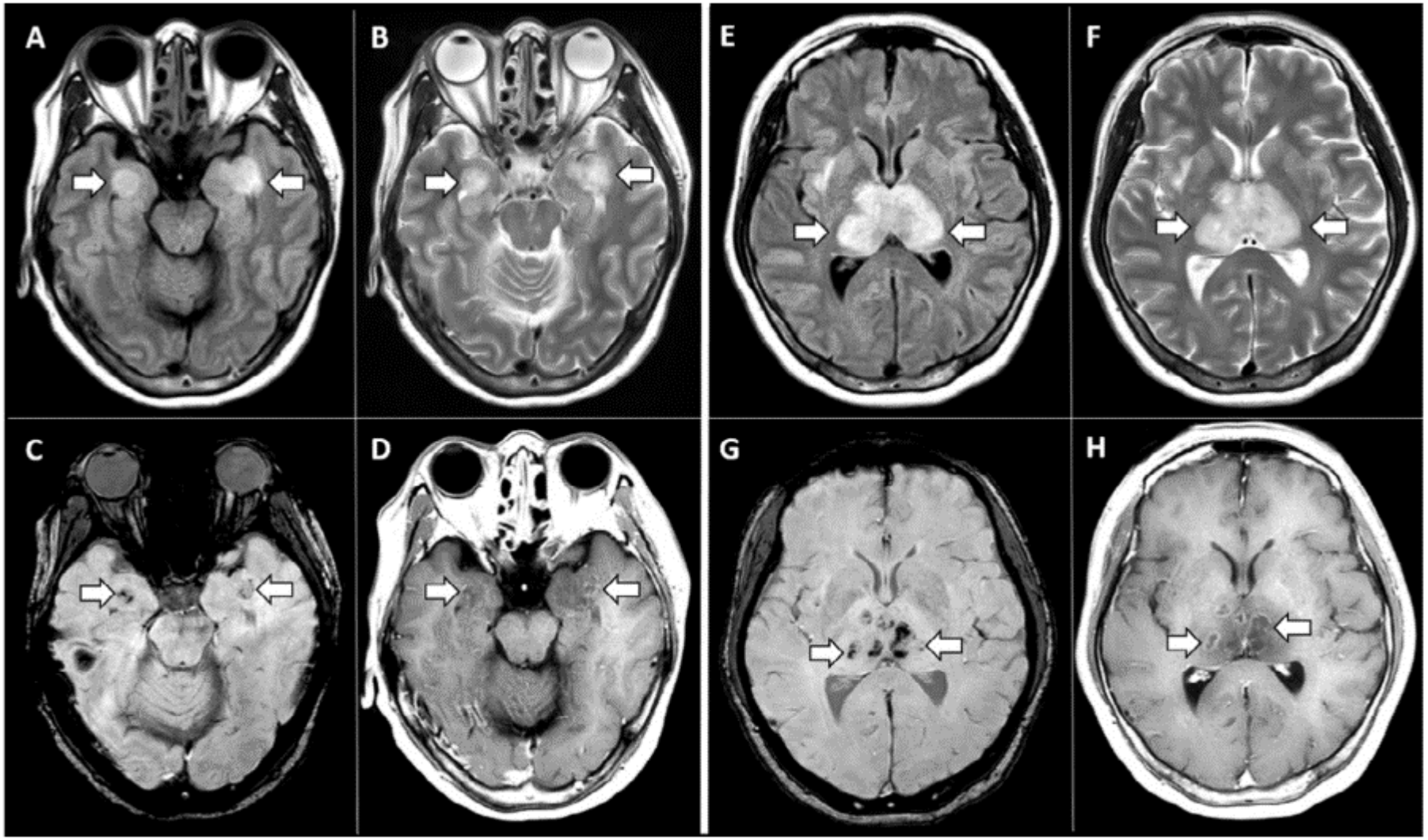
SZÁMOS KÖZLEMÉNY: PATHOLOGIA NINCS!

Oxley TJ et al: Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. This case was published on April 28, 2020, at NEJM.org.

Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study.

March 13, 2020 (https://papers.ssrn.com/sol3/papers.cfm

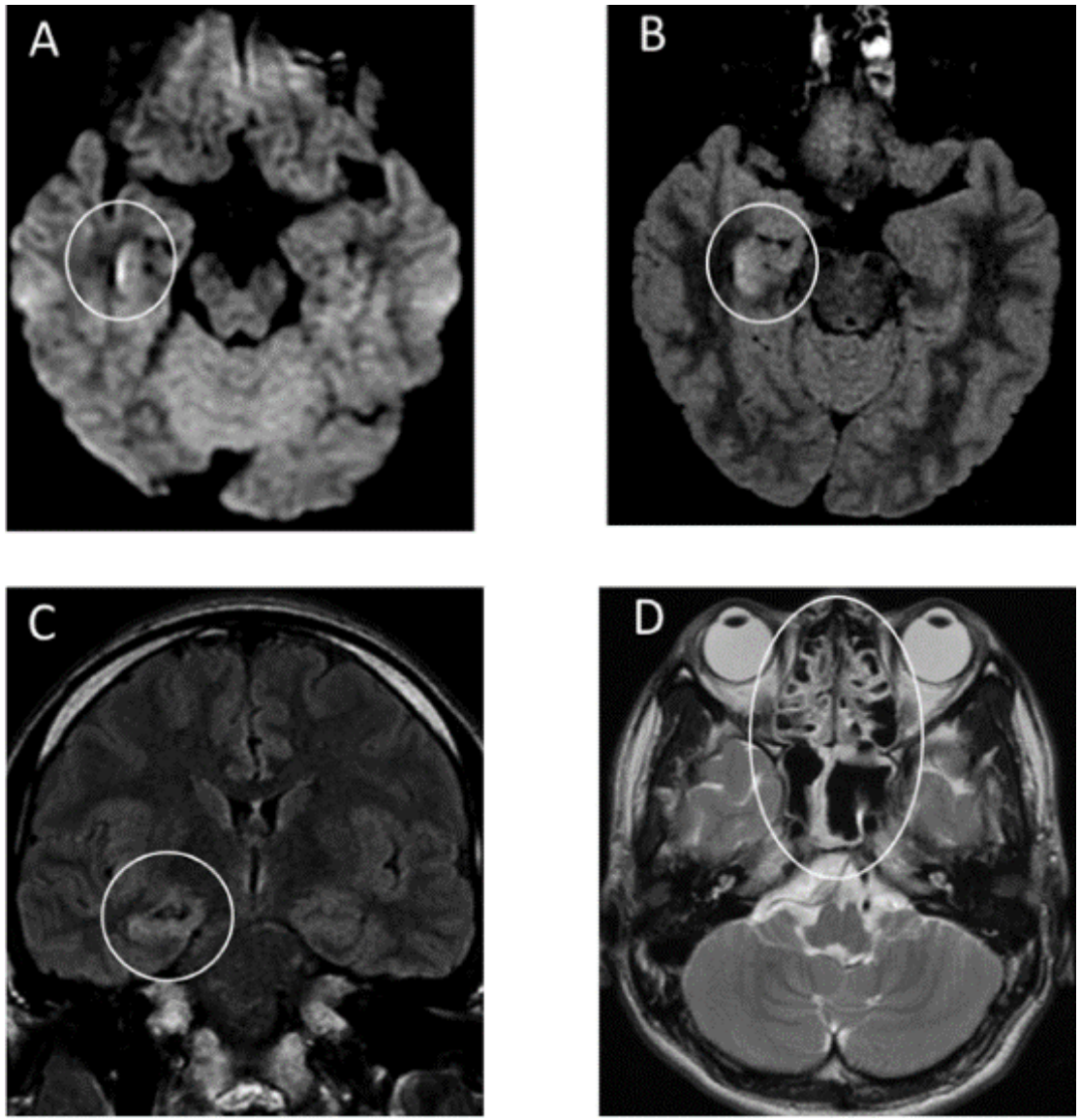
?abstract_id=3550025) (preprint).



MRI images demonstrate T2 FLAIR hyperintensity within the bilateral medial temporal lobes and thalami (A, B, E, F) with evidence of hemorrhage indicated by hypointense signal intensity on susceptibility-weighted images (C, G) and rim enhancement on postcontrast images (D, H).

Poyiadji N et al. Radiology. **COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features.**

From the Department of Radiology, Henry Ford Health System, 2799 West Grand Blvd Detroit MI 48202



Moriguchi et al: A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int. J. Infect. Dis. 2020; 94: 55–58. https://doi.org/10.1016/j.ijid.2020.03.062

IMAGING FEATURES

CASE1

Multiple cerebral infarctions in bilateral frontal parietal occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres

CASE2

Multiple cerebral infarctions in right frontal and bilateral parietal lobe

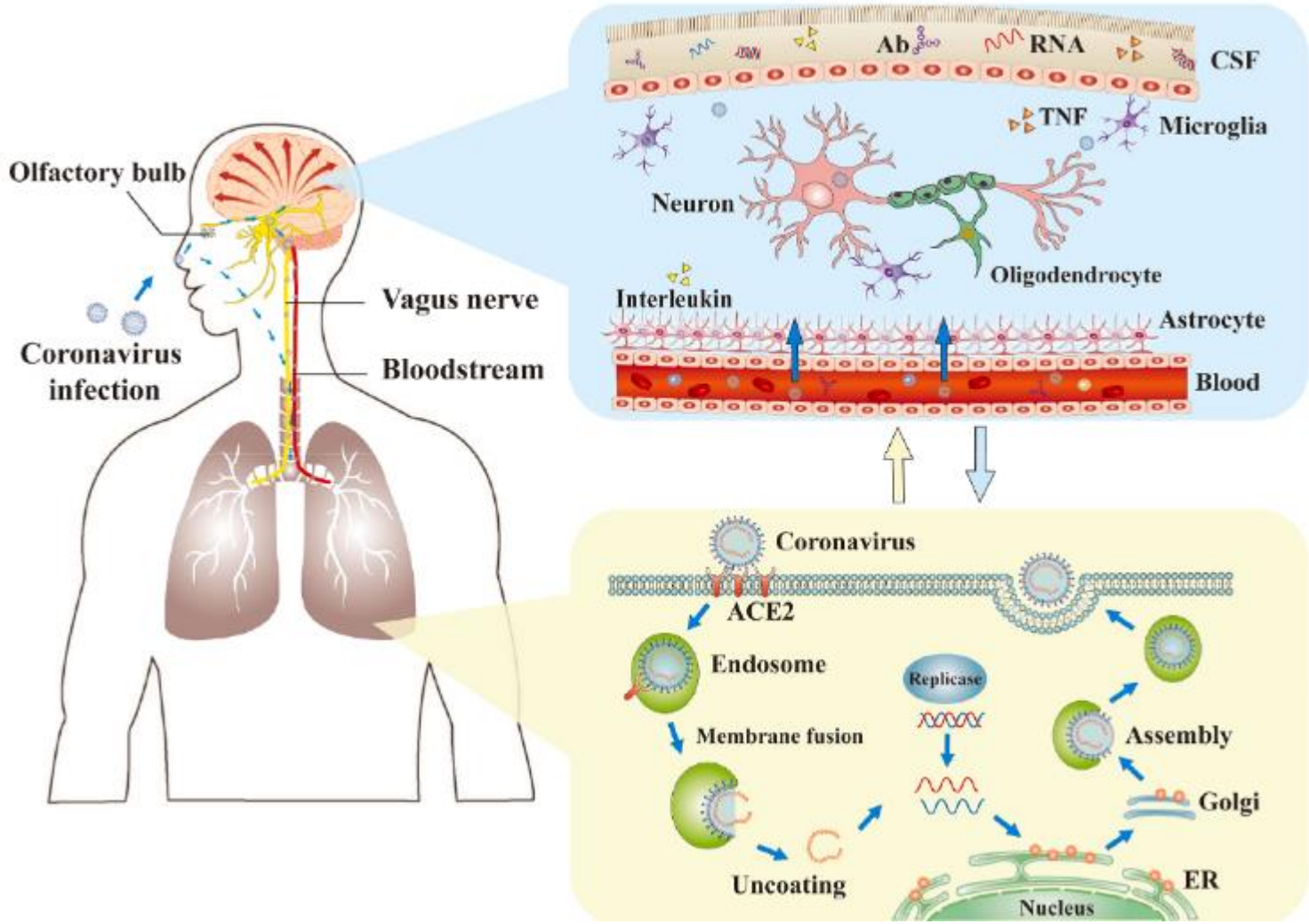
CASE3

Multiple cerebral infarctions in frontal lobe, right frontal parietal temporal occipital lobe, and bilateral cerebellar hemispheres

Yan Zang et al: Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

n engl j med 382;17 nejm.org April 23, 2020

Yeshun WU et al. Nervous system involvement after infection with COVID-19 and other coronaviruses



Brain, Behavior, and Immunity. In press. https://doi.org/10.1016/j.bbi.2020.03.031

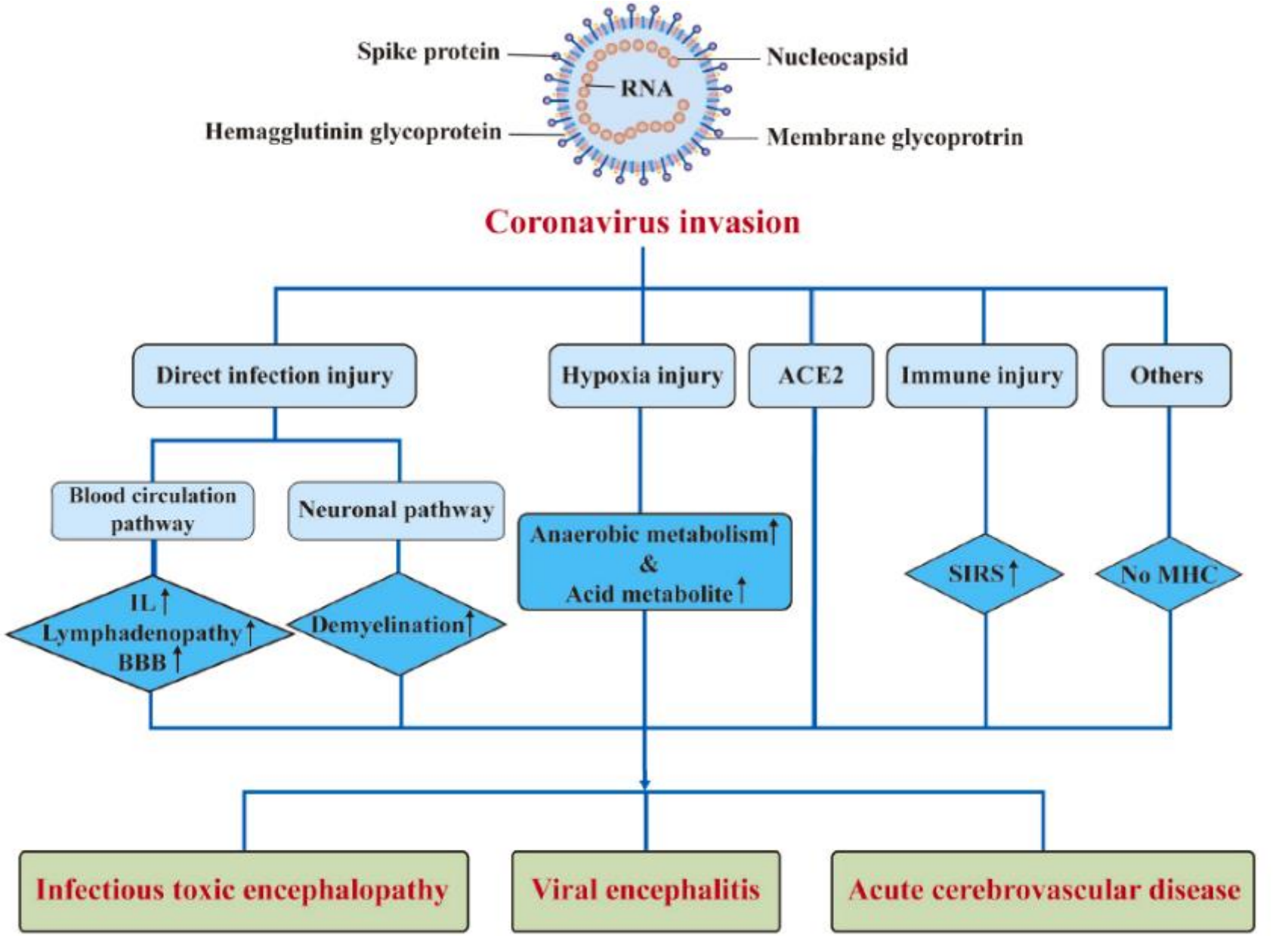
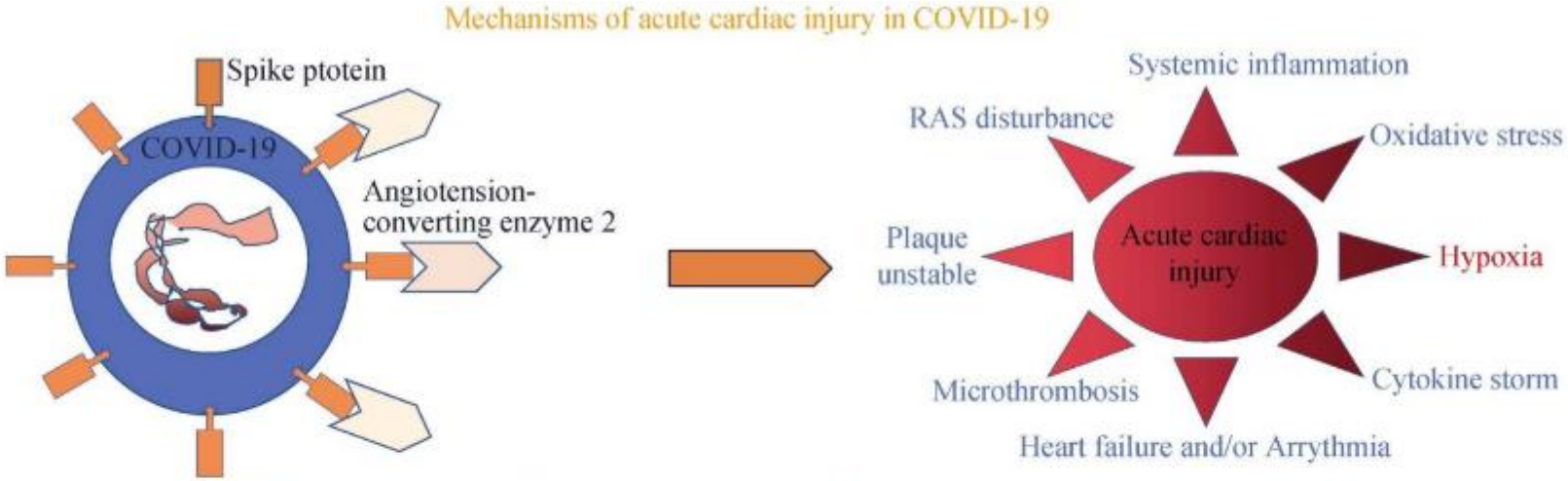


Fig. 2. Pathogenesis of nervous system injury caused by coronaviruses. ACE2: angiotensin-converting enzyme 2; BBB: blood brain barrier; IL: interleukin; MHC: major histocompatibility complexes; SIRS: systemic inflammatory response syndrome.

MYOCARDIUM

Acut myocardialis károsodás: Nincs egyértelmű bizonyíték arra, hogy a vírus direkt szívizom károsodást okozna.



	Mild type	Common type	Severe type	Critical type
Treatment strategy	Anti viral	Anti viral Supportive therapy Oxygen	Supportive therapy Oxygen Mechanical ventilation if needed	Immunosuppressive +/– Supportive: mechanical ventilation, circulation support, CRRT, ECMO as needed
Clinical manifestations	Asymptomatic or mild symptom	Fever Respiratory symptoms	Hypoxia	Respiratory failure Shock MODS
Laboratory test results	No signs of pneumonia	Signs of pneumonia	Transaminitis Low-normal procalcitonin	Decreased lymphocytes count Elevated inflammatory markers
Acute cardiac injury	Elevated Troponin levels, elevated NT-proBNP, abnormal findings in ECG and/or UCG			

Jing Nan, Yu-Bo Jin, Yunjung Myo, and Ge Zhang: Hypoxia in acute cardiac injury of coronavirus disease 2019: lesson learned from pathological studies. J Geriatr Cardiol. 2020; 17: 221–223.

Részletes irodalmi áttekintés: minimális morphologiai adat létezik. A hipotetikus okok között első helyen a hypoxia, második helyen a „cytokin vihar” áll (2020. április).

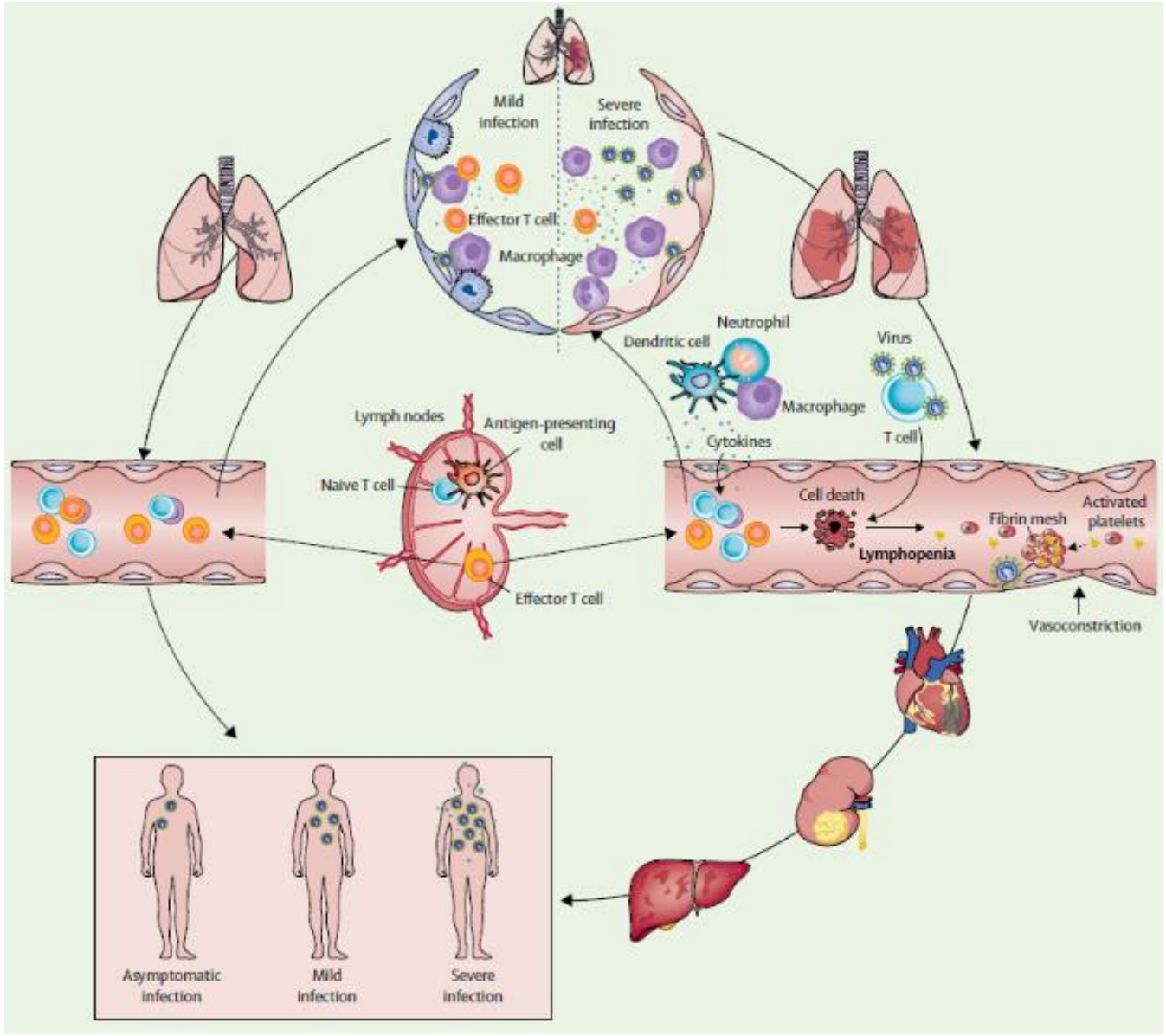
The Science Underlying COVID-19: Implications for the Cardiovascular System. Running Title: Liu et al.; Science & COVID-19.

10.1161/CIRCULATIONAHA.120.047549

Whether the virus can directly proliferate in the heart is unknown. It is not known whether the observed cardiac damage is due to viral injury, or due to an immunological response impacting the myocardium and related structures, such as the pericardium and conduction system.

This virus does proliferate, likely at low levels, in the host's heart, possibly involving inflammatory responses, as troponin can be released very early during disease presentation and portends poor prognosis

A LEGÚJABB HIPOTÉZIS



Hui Li et al: SARS-CoV-2 and viral sepsis: observations and hypotheses.

www.thelancet.com Vol 395 May 9, 2020

KÖSZÖNÖM SZÉPEN!