HHP/HPH COVID-19 Community Webinar Series

Monday, September 28, 2020

5:30pm – 6:30pm

HAWAIʻI PACIFIC HEALTH | HAWAIʻI HEALTH PARTNERS

CREATING A HEALTHIER HAWAIʻI

Moderator – 09/28/20

Andy Lee, MD
Medical Director, *Hawai‘i Health Partners*
Chief of Staff, *Pali Momi Medical Center*
Hawai‘i Pacific Health

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- Specific areas may not pertain directly to your clinical practice area and/or may not be applicable to your practice based on your existing workflows, infrastructure, software (e.g. EHR), and communications processes.

Webinar Information

- You have been automatically muted.
  You cannot unmute yourself.
- You will be able to submit questions via the Q&A section.
  - Due to time constraints, any unanswered questions will be addressed this week and posted on the HHP website
- A recording of the meeting will be available tomorrow on the HHP website and intranet.

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1. Step 1: Confirm your attendance
   - You should have completed a brief questionnaire before joining today's live webinar.

2. Step 2: HPH CME team will email you instructions
   - Complete and submit evaluation survey that will be emailed to you within one week of the offering.
   - Your CE certificate will be immediately available to you upon completion of your evaluation.
   - Questions? Email hphcontinuingeduc@hawaiipacifichealth.org

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- Hawai‘i Pacific Health designates this webinar activity for a maximum of 1.0 AMA PRA Category 1 Credit (s) ™ for physicians. This activity is assigned 1.0 contact hour for attendance at the entire CE session.

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INTERPROFESSIONAL CONTINUING EDUCATION

Disclosures

- The planners and presenters of this activity report no relationships with companies whose products or services (may) pertain to the subject matter of this meeting

COVID-19 Updates

Melinda Ashton, MD
Executive Vice President
and Chief Quality Officer
Hawai‘i Pacific Health

Douglas Kwock, MD
Vice President of
Medical Staff Affairs

Gerard Livaudais, MD, MPH
Executive Vice President,
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Hawai‘i Pacific Health

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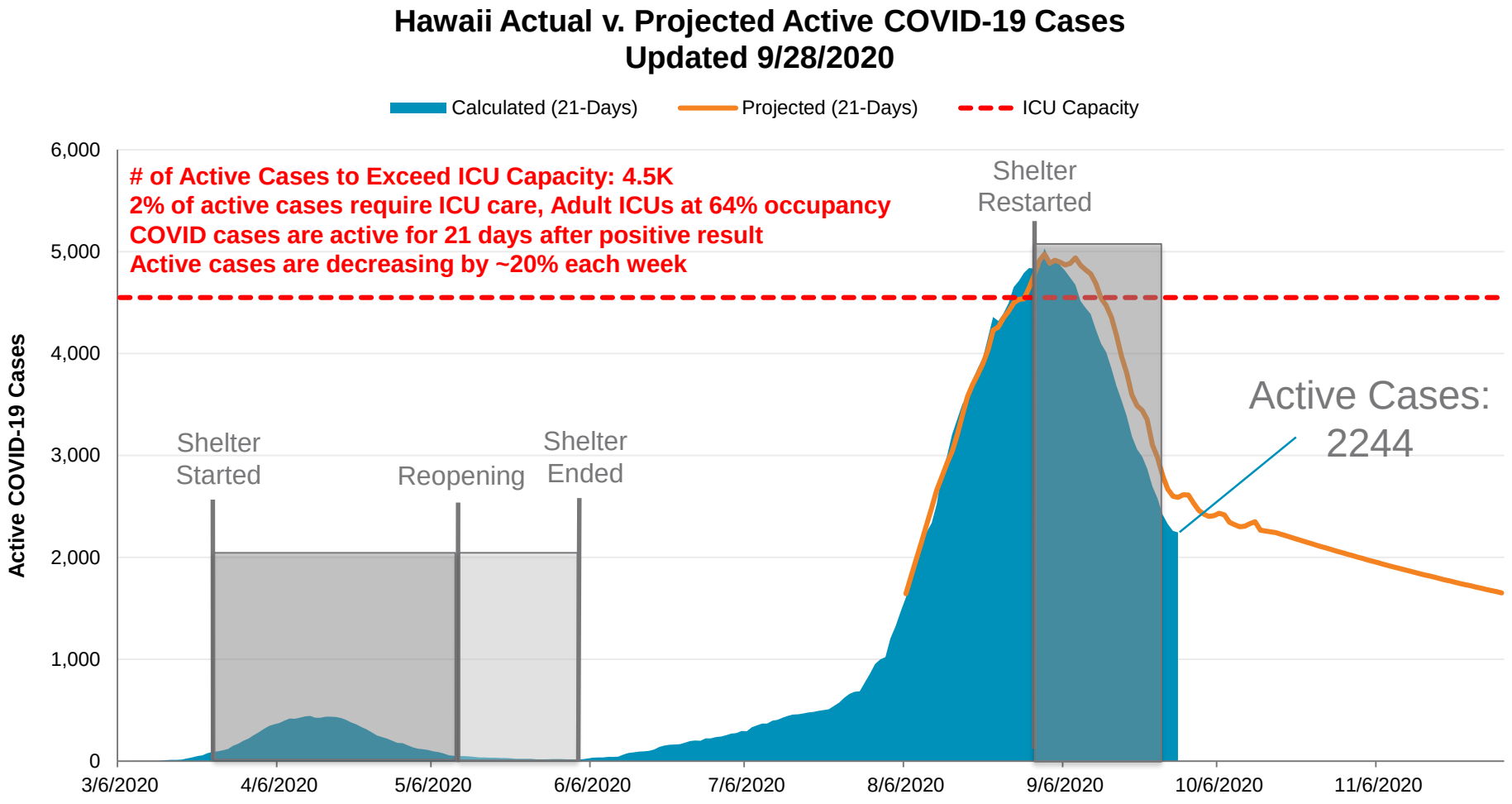
Projected Active COVID-19 Cases



WORLD / COUNTRIES / USA / HAWAII

Last updated: September 29, 2020, 01:38 GMT

Hawaii

Coronavirus Cases:

12,203

Deaths:

132

Recovered:

10,215

$R_t = 0.96$

If Total Case is 10x # confirmed cases, then = 8% Herd Immunity (122,030 / 1,415,872)

https://www.worldometers.info/coronavirus/usa/hawaii/ accessed 09.28.20

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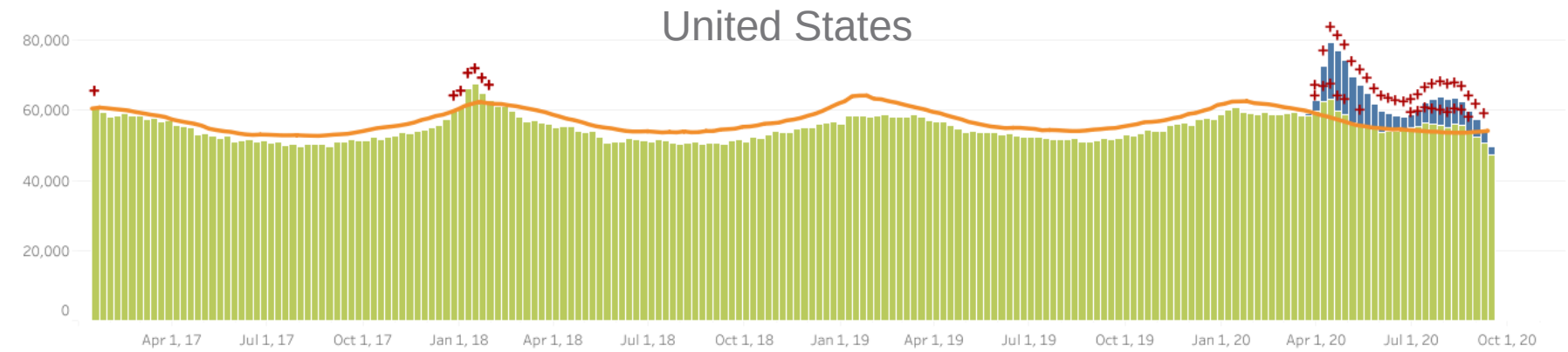
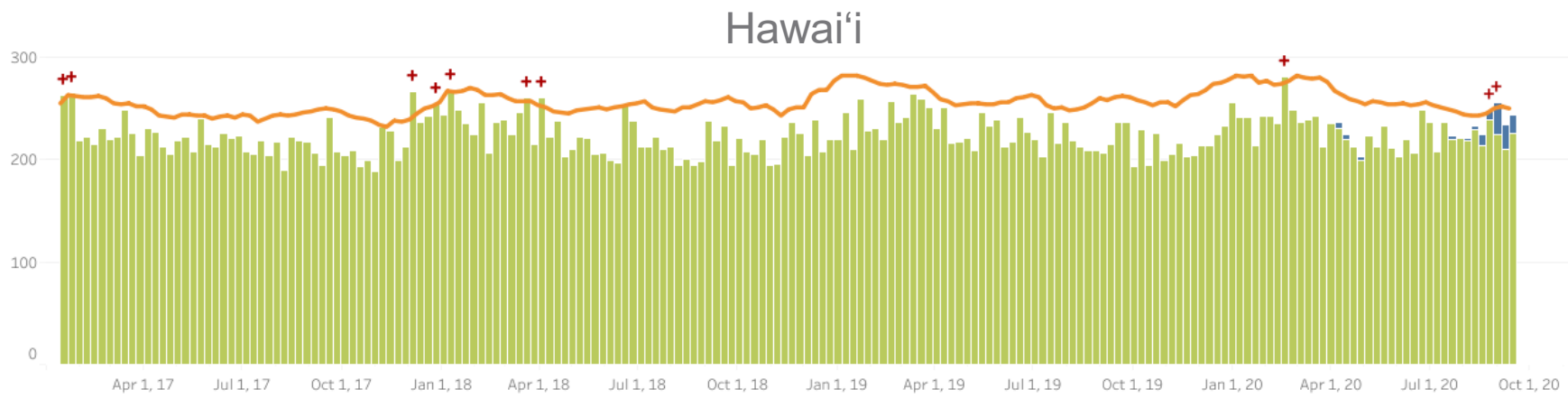
As of 09/28/20	Total Census	ICU beds occupied	# Ventilators in use	# New Admissions w/ COVID-19 screening	# New Admissions w/ positive COVID-19	# Patients currently hospitalized w/ suspect or confirmed COVID-19	# Patients currently on a ventilator w/ suspect or confirmed COVID-19	# Patients currently in ICU w/ suspect or confirmed COVID-19
KMCWC	155	AICU: 0 NICU: 68 PICU: 5	AICU: 0 NICU: 22 PICU: 3 Wilcox: 0	0	1	S: 1 (Peds) C: 1 (Adult)	S: 0 C: 0	S: 0 C: 0
PMMC	77	7	6	3	0	S: 0 C: 9	S: 0 C: 2	S: 0 C: 2
SMC	123	21	15	5	1	S: 3 C: 30	S: 0 C: 6	S: 0 C: 7
WMC	41	3	0	0	0	S: 1 C: 0	S: 0 C: 0	S: 0 C: 0

S = Suspected; C= Confirmed

Weekly number of deaths

Comparing excess deaths including/excluding COVID-19

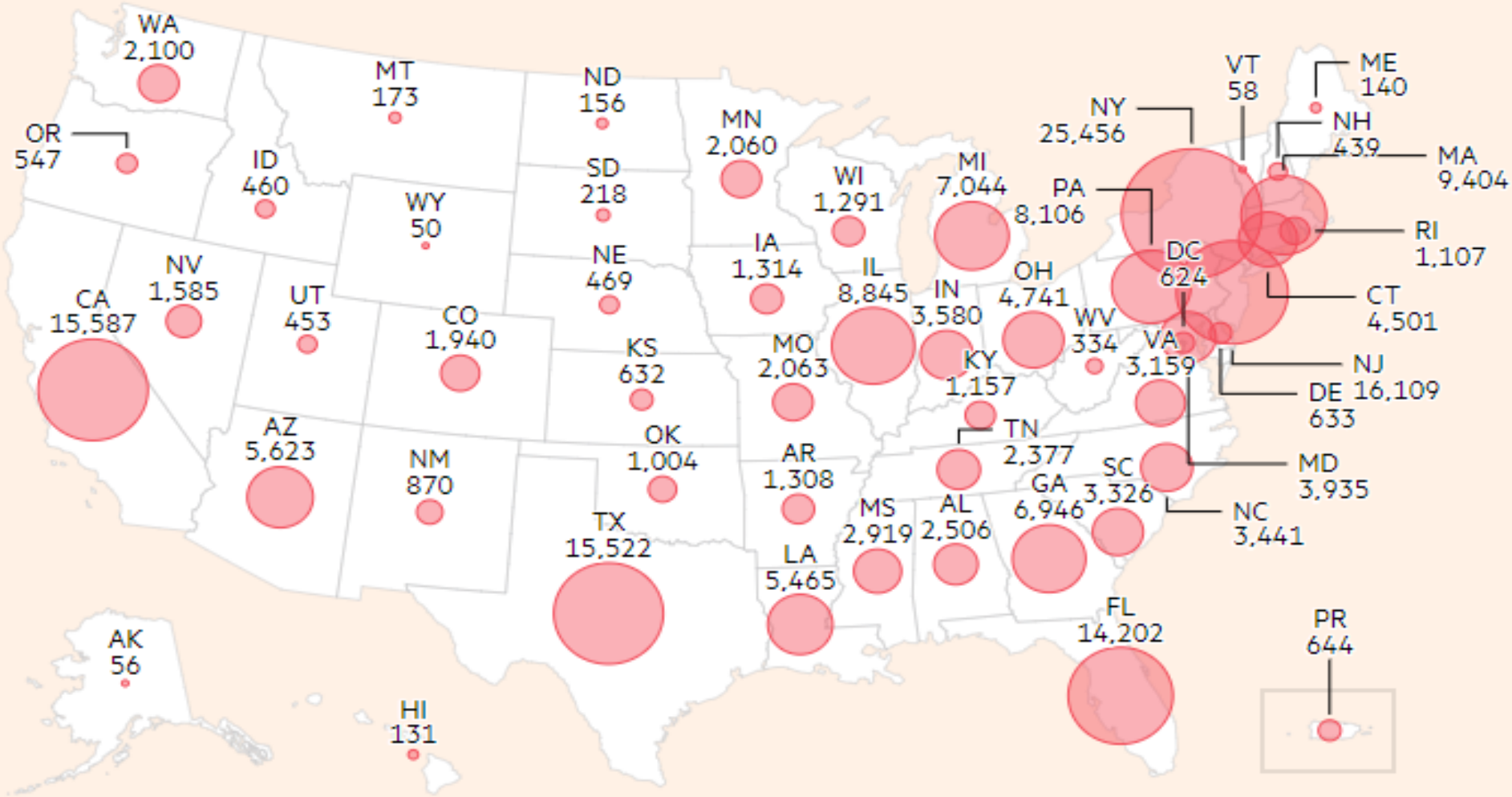




https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm#dashboard accessed 09.26.20

Coronavirus situation in the US

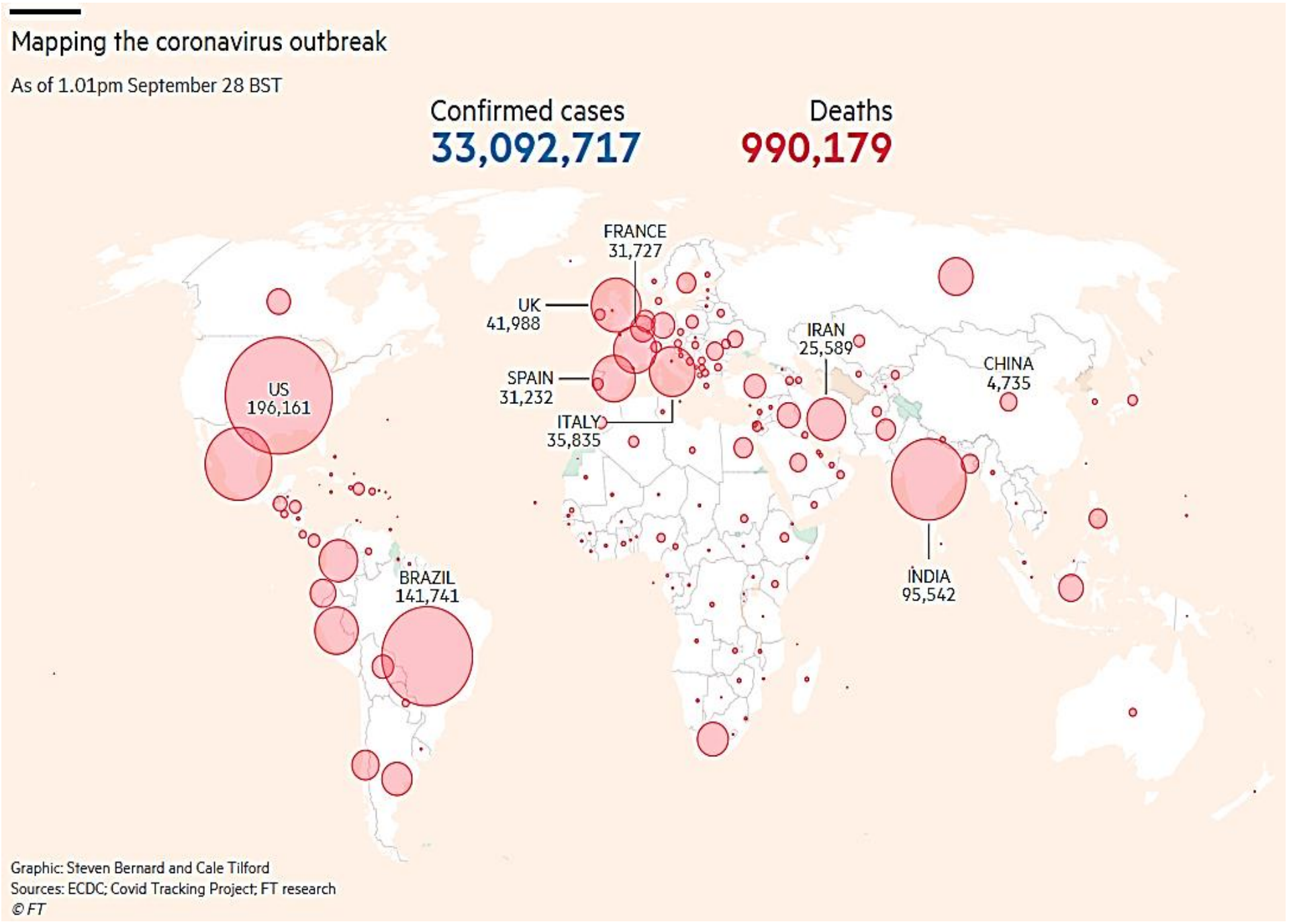
Total deaths as of 1.01pm September 28 BST



Graphic: Steven Bernard and Cale Tilford

Sources: Covid Tracking Project

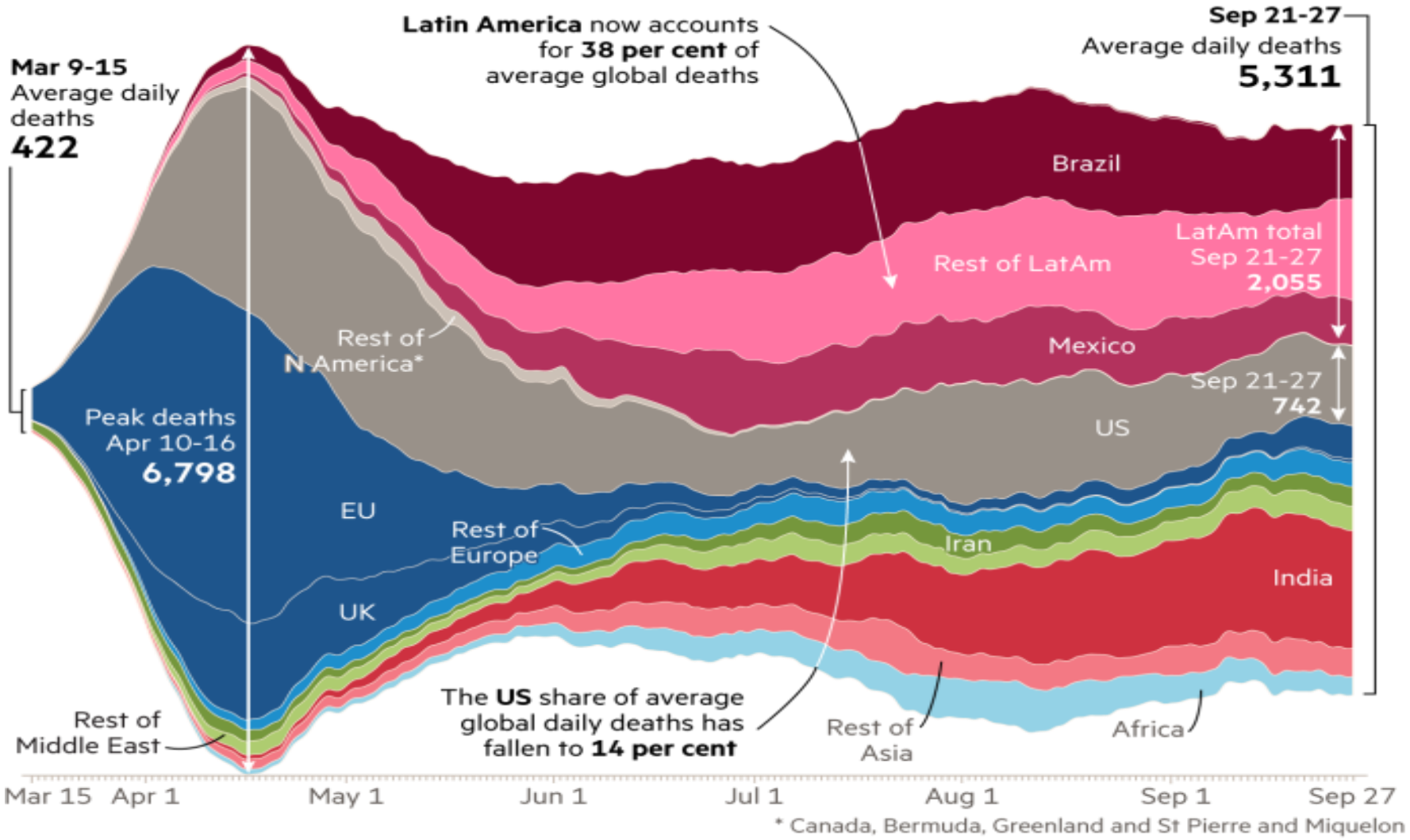
https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938 accessed 09.28.20



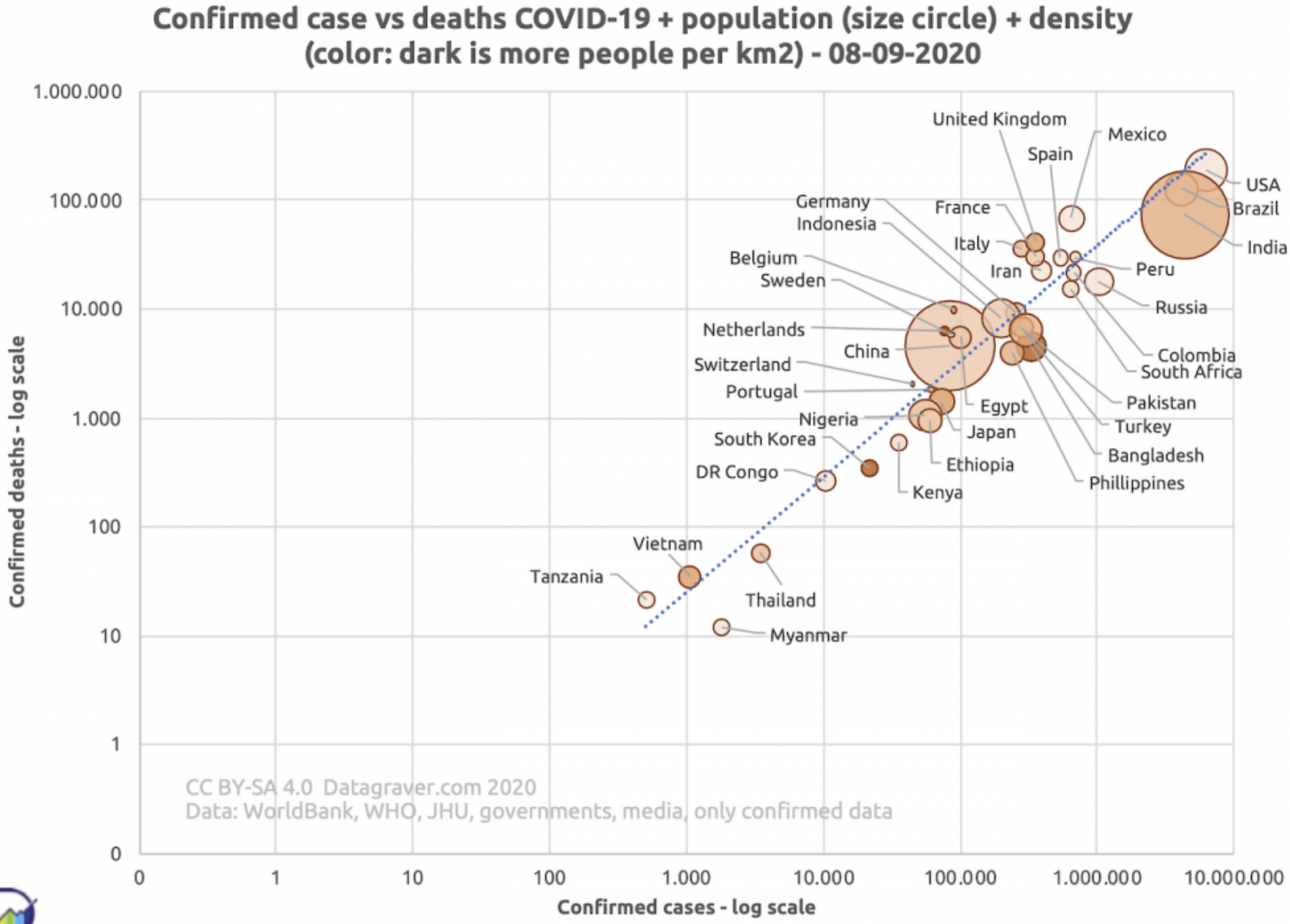
https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938 accessed 09.26.20

India's death toll surges as the Americas continue to struggle with Covid-19

Daily deaths of patients diagnosed with coronavirus (7-day rolling average)



https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938 accessed 09.28.20



https://datagraver.com/case/tracking-the-worldwide-covid-19-pandemic accessed 09.28.20

83% Sensitivity, 96% Specificity, pennies per test and extremely scalable?

https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05281-3 accessed 09.26.20

Care of the COVID-19 Survivor – in it for the Long Haul

John Mickey, MD
Internal Medicine,
Hawai‘i Pacific Health Medical Group

Gerard Livaudais, MD, MPH
Executive Vice President, Population Health and Provider Networks
Hawai‘i Pacific Health

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Question

Does COVID-19 result in unique long term medical problems that merit development of new, multi-disciplinary “best practice” approaches?

or

Should symptoms in the COVID-19 survivor be managed in standard Internal Medicine fashion on an individualized basis?

Since COVID-19 is so new, there is no long term imaging or functional data on survivors. **So, what can we learn from previous Corona virus infections?**

Following SARS-1 outbreak in 2003:

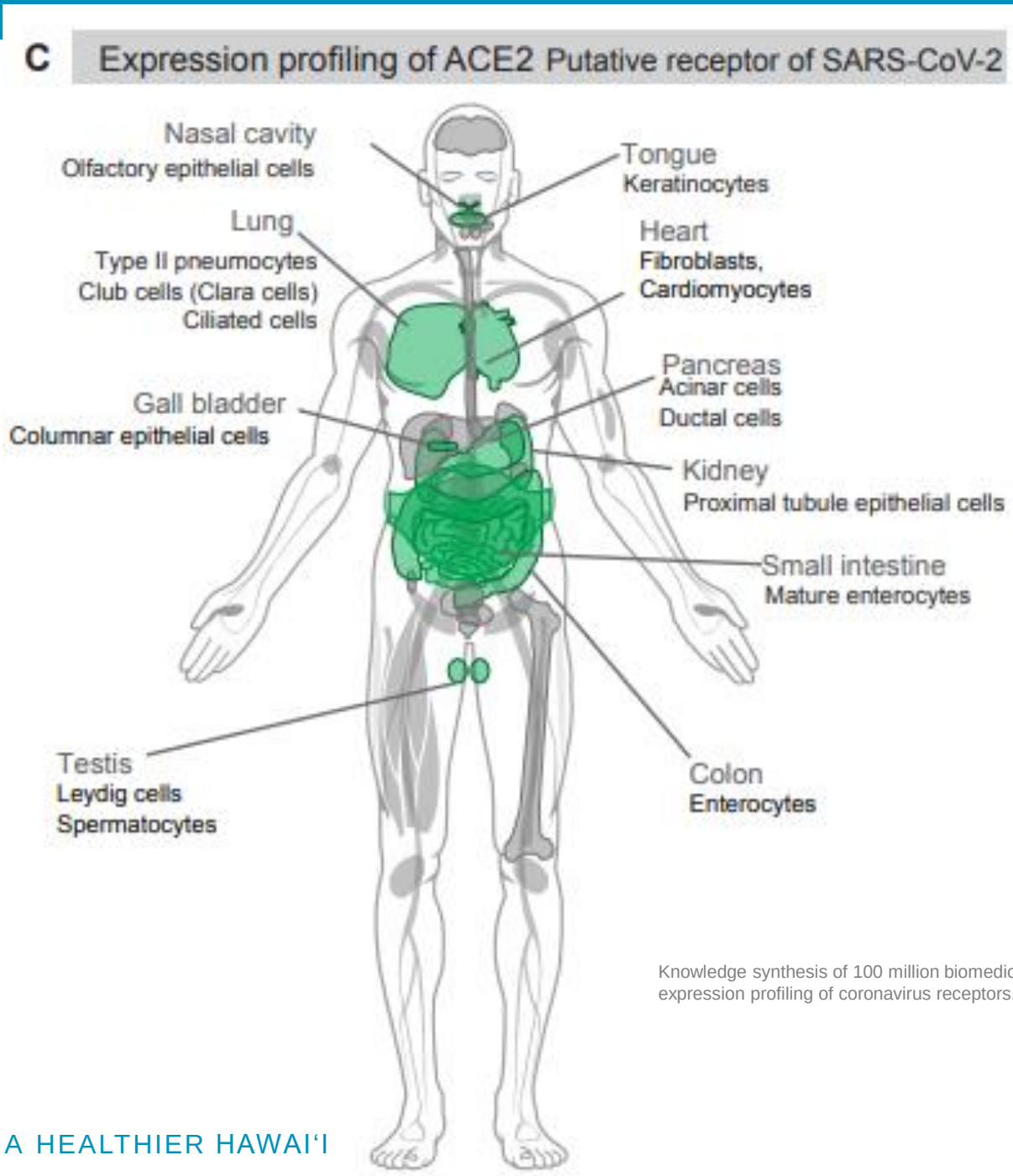
- 40% of patients had reduced exercise capacity after three months
- 1/3 had X-ray abnormalities at 6 months, correlating with impaired diffusion capacity
- Fifteen years later, 5% of patients had residual lung changes CT scan

Following MERS_CoV outbreak in 2012:

- 1/3 of the patients had lung fibrosis on CT six weeks later

What do we know about the experience of COVID-19 survivors? How big will this problem be?

- 2/3 of patients hospitalized in the US have not returned to baseline three weeks after discharge
- 1/3 of symptomatic, non-hospitalized Americans have not returned to baseline three weeks after diagnosis
- Close to 90% of patients hospitalized in Italy have not returned to baseline 3 months after discharge
- Even among young patients with no co-morbidities 20% have symptoms longer than two to three weeks
- The British Medical Journal estimates that about 10% of all patients will have persistent symptoms



Knowledge synthesis of 100 million biomedical documents 5 augments the deep expression profiling of coronavirus receptors. AJ Venkatakrishnan, et al.

eLife SHORT REPORT

A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm

Michael R Garvin[1], Christiane Alvarez[1], J Izaak Miller[1], Erica T Prates[1], Angelica M Walker[1,2], B Kirtley Amos[3], Alan E Mast[4], Amy Justice[5], Bruce Aronow[6,7], Daniel Jacobson[1,2,8]*

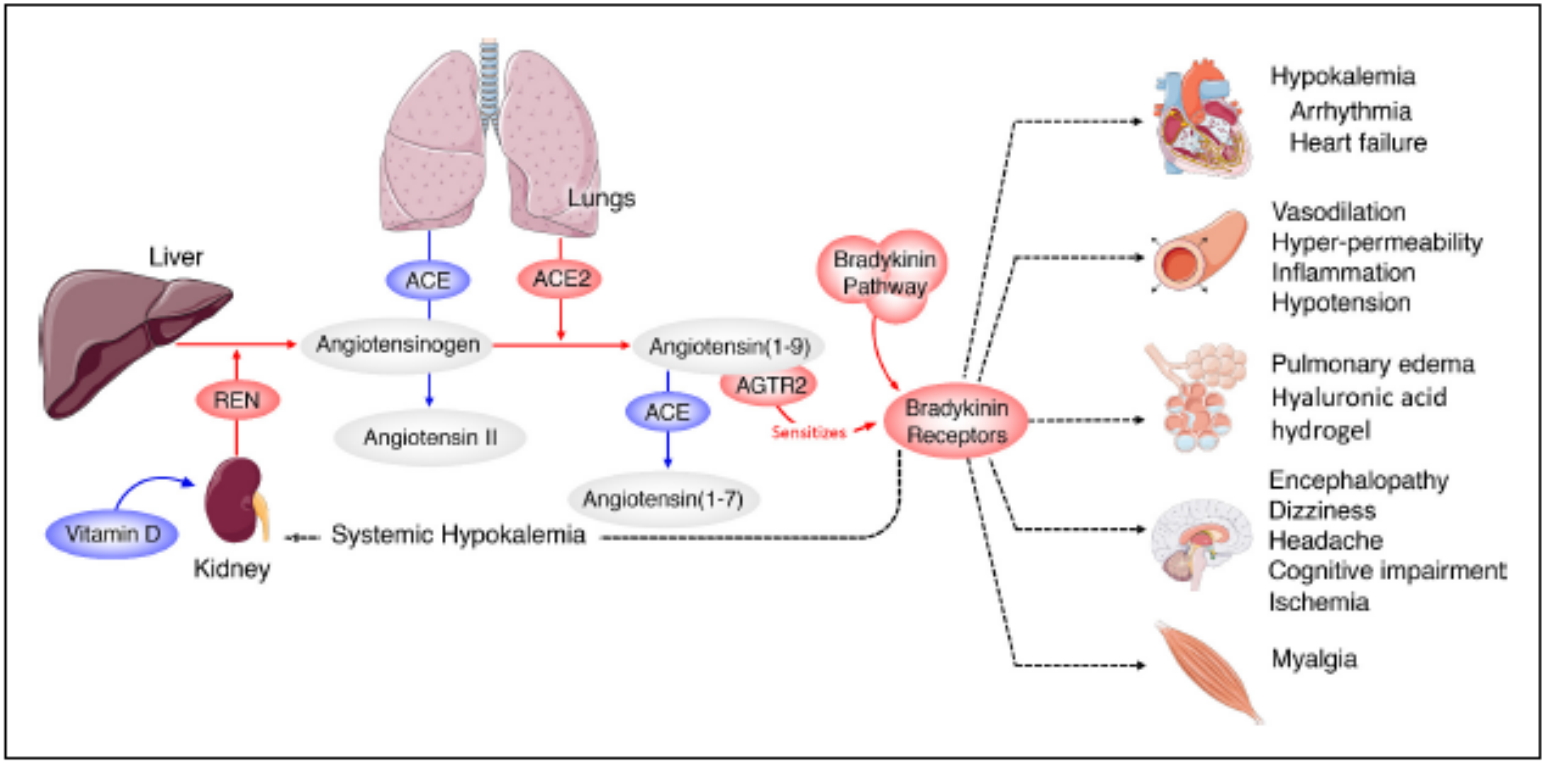
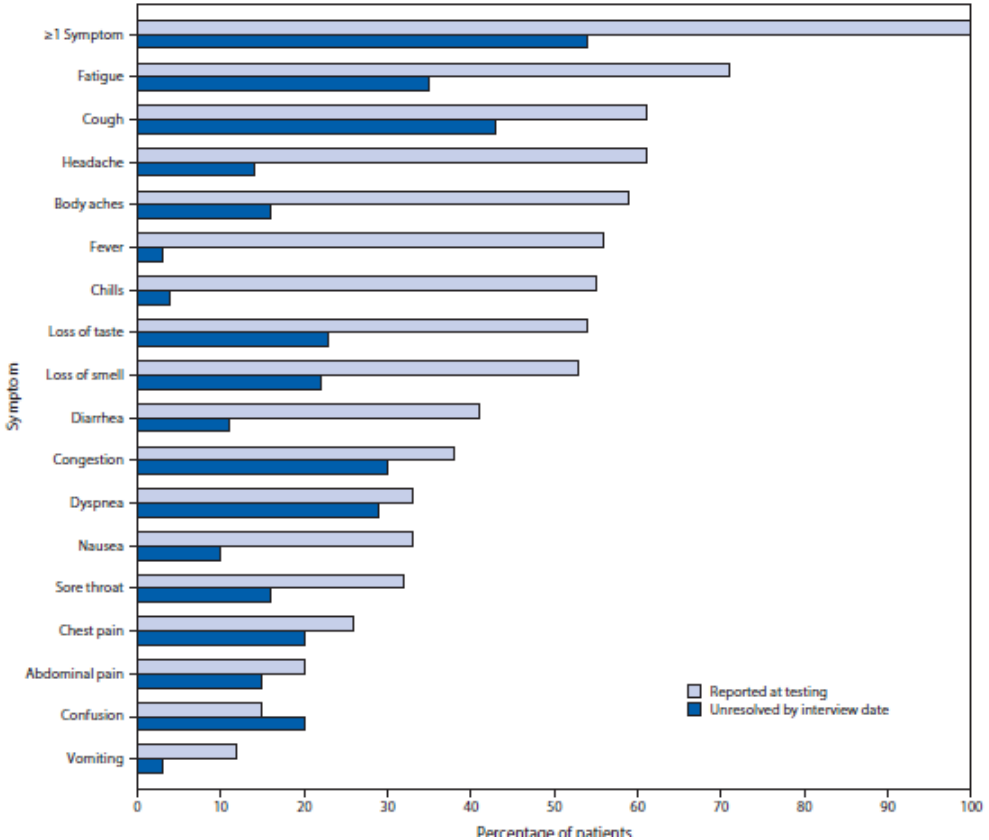


Figure 4. Systemic-level effects of critically imbalanced RAS and BK pathways. The gene expression patterns from COVID BAL samples reveal a RAS that is skewed toward low levels of ACE that result in higher levels of Ang_{1-9} and BK. High levels of ACE normally present in the lungs are responsible for generating system-wide angiotensin-derived peptides. As detailed in ***Figure 2***, the Bradykinin-Storm is likely to affect major organs that are regulated by angiotensin derivatives. These include altered electrolyte balance from affected kidney and heart tissue, arrhythmia in dysregulated cardiac tissue, neurological disruptions in the brain, myalgia in muscles and severe alterations in oxygen uptake in the lung itself. Red colors indicate upregulation and blue downregulation.

What are patients experiencing?

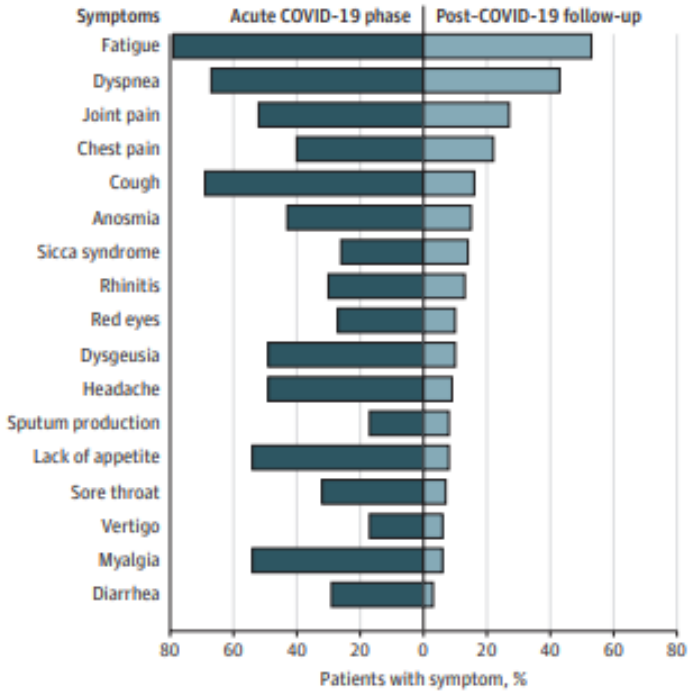
3 weeks out: Morbidity and Mortality Weekly Report

FIGURE. Self-reported symptoms at the time of positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) testing results and unresolved symptoms 14–21 days later among outpatients (N = 274)* — 14 academic health care systems,† United States, March–June 2020



6 weeks out:

Figure. COVID-19–Related Symptoms



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)-related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

M Tenforde, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020 MMWR / July 31, 2020 / Vol. 69 / No. 30

B Saloner, K Parish, J Ward, G DiLaura, S Dolovich,. Persistent Symptoms in PatientsAfterAcuteCOVID-19. Published Online: July 9, 2020. doi:10.1001/jama.2020.12603

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PULMONARY PROBLEMS

- Cough, dyspnea, and chest pain are common
- Reactive airway disease can contribute to cough and dyspnea
- Pulmonary fibrosis can be seen on imaging
- PE and Chronic Thromboembolic Pulmonary Hypertension
- Tracheal stenosis had been reported after prolonged intubation
- Spontaneous pneumothorax should be suspected when symptoms suggest

Pulmonary Problems

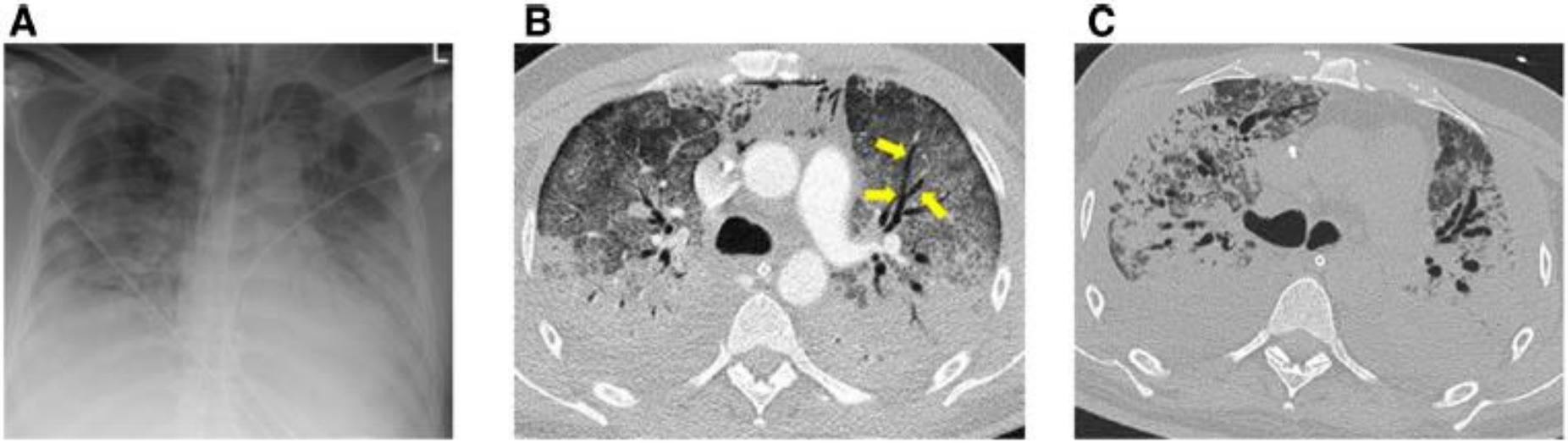
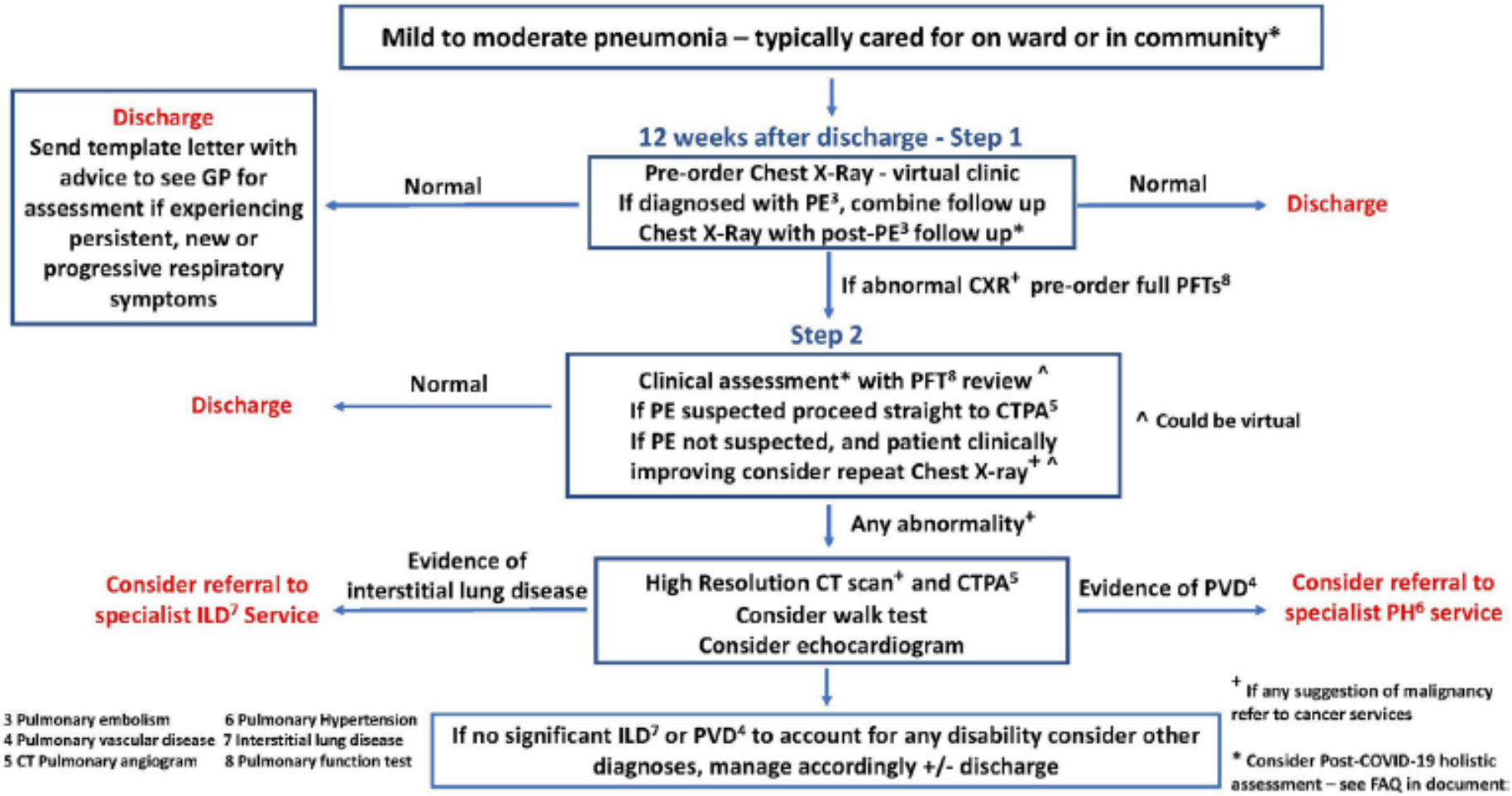


Figure 1 (A) Plain chest radiograph in a male patient with COVID-19 pneumonia referred for extracorporeal membrane oxygenation support. (B) CT images showing broadly symmetrical air space opacification with dependent dense parenchymal opacification and extensive ground-glass opacification with thickened interlobular and intralobular septa (the 'crazy-paving' pattern) in the non-dependent lung. Note that the airways are conspicuous against the ground-glass opacification but, importantly, taper normally (arrows) and have smooth walls. (C) CT performed 10 days later

George PM, Barratt SL, Condliffe R, et al.. Thorax Epub ahead of print: 08.24.20 doi:10.1136/thoraxjnl-2020-215314

PULMONARY


Mild to moderate pneumonia – typically cared for on ward or in community*
12 weeks after discharge - Step 1
Pre-order Chest X-Ray - virtual clinic
If diagnosed with PE[3], combine follow up Chest X-Ray with post-PE[3] follow up*
Normal
Discharge
Send template letter with advice to see GP for assessment if experiencing persistent, new or progressive respiratory symptoms
Normal
Discharge
If abnormal CXR+ pre-order full PFTs[8]
Step 2
Clinical assessment* with PFT[8] review ^
If PE suspected proceed straight to CTPA[5]
If PE not suspected, and patient clinically improving consider repeat Chest X-ray+ ^
^ Could be virtual
Normal
Discharge
Any abnormality+
High Resolution CT scan+ and CTPA[5]
Consider walk test
Consider echocardiogram
Evidence of interstitial lung disease
Consider referral to specialist ILD[7] Service
Evidence of PVD[4]
Consider referral to specialist PH[6] service
If no significant ILD[7] or PVD[4] to account for any disability consider other diagnoses, manage accordingly +/- discharge
3 Pulmonary embolism
4 Pulmonary vascular disease
5 CT Pulmonary angiogram
6 Pulmonary Hypertension
7 Interstitial lung disease
8 Pulmonary function test
+ If any suggestion of malignancy refer to cancer services
* Consider Post-COVID-19 holistic assessment – see FAQ in document

CARDIAC PROBLEMS

- Palpitations are common, mostly sinus tachycardia
- New atrial fibrillation is seen
- Myocarditis can be seen in ICU, but studies of residual MRI abnormalities in survivors are small and uncontrolled
- Personal communication tells me subclinical myocarditis has not been observed in a large Boston cohort
- Others with no prior heart disease developed post viral heart failure
- Deconditioning is a major problem

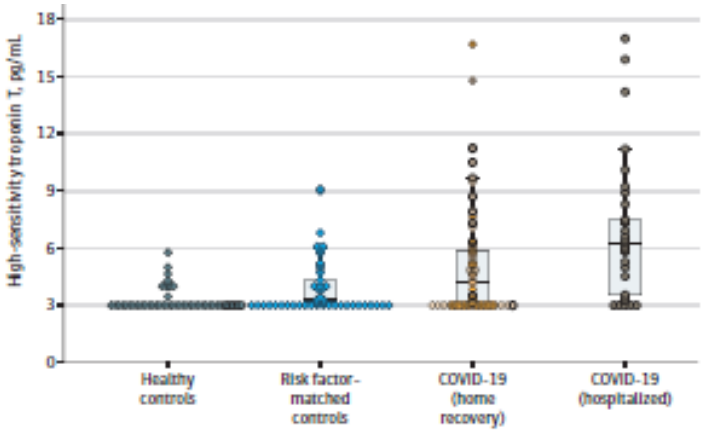
JAMA Cardiology | Original Investigation

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jedrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

Table 2. Results of the Receiver Operating Characteristic Curve Analyses

	COVID-19 vs healthy controls		COVID-19 vs risk factor–matched controls	
Characteristic	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value
Native T1	0.86 (0.80-0.92)	<.001	0.76 (0.69-0.83)	<.001
Native T2	0.84 (0.78-0.91)	<.001	0.79 (0.73-0.85)	<.001
LVEF	0.70 (0.62-0.79)	<.001	0.62 (0.52-0.71)	.01
LVEDV index	0.65 (0.56-0.73)	.001	0.67 (0.58-0.75)	<.001
LV mass index	0.60 (0.49-0.70)	.07	0.63 (0.54-0.71)	<.001
RVEF	0.74 (0.66-0.83)	.001	0.61 (0.52-0.70)	.02
hsTnT	0.79 (0.72-0.86)	<.001	0.72 (0.57-0.76)	<.001
NT-proBNP	0.56 (0.46-0.65)	.21	0.52 (0.44-0.61)	.58
High-sensitivity CRP	0.54 (0.44-0.64)	.48	0.60 (0.52-0.76)	.05



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GLOBAL PROBLEMS

- Fatigue, fever, chills, headache, diaphoresis, arthralgia, malaise, are common.
- “Brain fog,” impaired cognition, concentration, balance, and ocular function are well documented. Long term neurologic inflammation has been suggested.
- Myalgic encephalomyelitis / chronic fatigue syndrome
- Loss of olfactory senses
- Diarrhea
- Relapsing course
- Coagulopathy? COVID toes
- Post Intensive Care Syndrome, including Critical Illness Polyneuropathy and Critical Illness Myopathy may require prolonged rehabilitation services.
- Autonomic dysregulation. Postural Orthostatic Tachycardia Syndrome.

Cerebral Micro-Structural Changes in COVID-19 Patients – An MRI-based 3-month Follow-up Study

Yiping Lu, MD[a,1], Xuanxuan Li, MD[a,1], Daoying Geng, MD, Prof[a,1], Nan Mei, MD[a,1], Pu-Yeh Wu, PhD[b], Chu-Chung Huang, PhD[c], Tianye Jia, PhD[d], Yajing Zhao, MD[a], Dongdong Wang, MD[a], Anling Xiao, MD, Prof[e,**], Bo Yin, PhD, Prof[a,*]

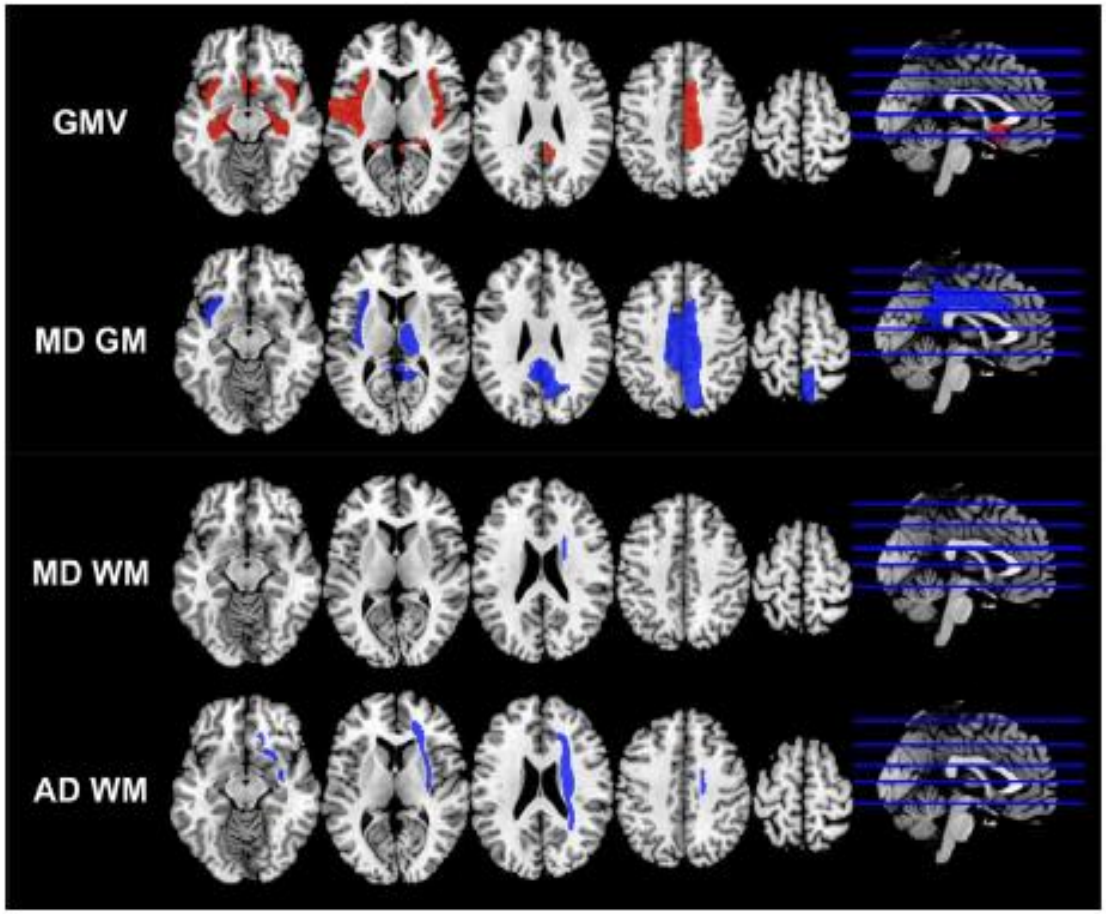


Figure 2. The regions with statistically significant differences in the volumes and diffusion indices of the COVID-19 group compared with the control group. The regions with relative higher mean values in the COVID-19 group were marked as red, and the regions with relative lower mean values in the COVID-19 group were marked as blue. GMV: gray matter volume; MD GM: mean diffusivity of gray matter; MD WM: mean diffusivity of white matter; AD WM: axial diffusivity of white matter.

PSYCHOLOGICAL

- PTSD, anxiety, guilt, and depression are expected consequences of COVID-19
- Mental health complications are strongly correlated with social determinants of health
- Support networks are springing up on social media for Long Haul COVID Fighters:
  - COVID-19 Survivor Corps, etc.
- Acknowledge, support, treat when clearly indicating, avoiding overtreating
  - “Medicalization”

SOCIAL/FINANCIAL/OCCUPATIONAL

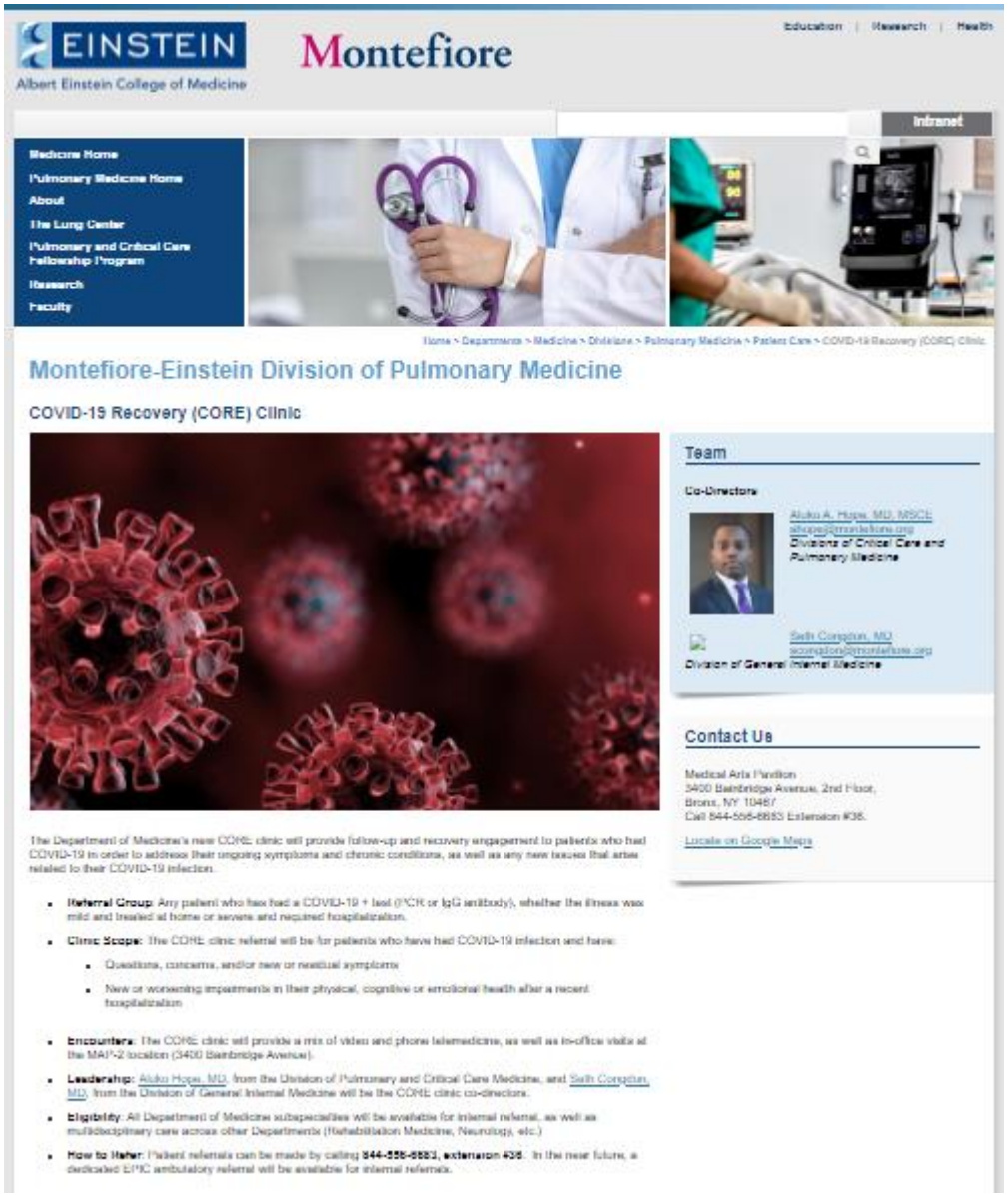
- COVID-19 patients face societal discrimination, loss of income, loss of insurance, and significant disruption of employment.

FINAL QUESTION

- **How can we show our COVID-19 survivors that we care?**

- Should HHP create a Covid-19 Survivor Recovery Program?

- How should that be organized? Funded? Staffed?



COVID-19: Clinical-Pathologic Correlations and What Post-Mortem Findings Tell Us

Owen Chan, MD, PhD
Pathology, Pan Pacific Pathologists
Laboratory Medical Director, Pali Momi Medical Center, Clinical Labs of Hawai‘i

COVID-19

What are the clinical characteristics of ill patients?

Clinical Characteristics of COVID-19: Meta-analysis

Outcomes		Critical illness		
		No. reports	No. patients	Prevalence% (95%CI)
Clinical symptoms				
Fever		6	364	80.8 (41.1–100.0)
Cough	Respiratory	6	364	65.6 (51.7–78.2)
Sore throat	Respiratory	3	245	16.7 (0.0–53.2)
Increased sputum production	Respiratory	3	222	32.1 (15.6–51.0)
Shortness of breath	Respiratory	6	364	49.2 (21.5–77.2)
Myalgia	Musculoskeletal	5	351	17.6 (8.2–29.5)
Fatigue	Musculoskeletal	4	299	41.2 (5.2–84.0)
Diarrhea	Gastrointestinal	4	234	7.6 (0.0–24.0)
Headache	Neurologic	4	274	11.3 (0.1–33.9)

Affects multiple systems

J Infect. 2020 Jun;80(6):656-665.

Clinical Characteristics of COVID-19: Meta-analysis

Outcomes	Critical illness		
	No. reports	No. patients	Prevalence% (95%CI)
Laboratory findings			
Leucocytes (↑)	2	186	27.7 (0.0–100.0)
Leucocytes (↓)	3	216	33.7 (0.00–95.7)
Lymphocytes (↓)	3	203	81.5 (18.9–100.0)
Platelets (↓)	2	169	32.3 (0.0–100.0)
Aspartate aminotransferase (↑)	2	155	46.1 (0.0–100.0)
Creatinine (↑)	2	151	6.4 (0.0, 100.0)
Creatine kinase (↑)	2	134	28.6 (0.0–100.0)
Lactate dehydrogenase (↑)	3	173	62.7 (55.7–100.0)
C-reactive protein (↑)	2	171	40.3 (0.0–100.0)
D-dimer (↑)	2	109	59.6 (50.2–68.7)
Procalcitonin (↑)	3	165	35.7 (0.0–100.0)
Chest CT findings			
Bilateral pneumonia	2	186	91.0 (0.0–100)
Complications			
ARDS	4	315	38.2 (3.2–83.0)
Cardiac failure	4	155	17.1 (1.5–42.2)
Shock	3	222	17.4 (0.0, 61.5)
Renal insufficiency	5	328	9.8 (0.1–28.7)

ARDS=Acute Respiratory Distress Syndrome.

Hematologic

Hepatic

Pulmonary

Cardiovascular

Renal

Affects multiple systems

J Infect. 2020 Jun;80(6):656-665.

COVID-19 Mortality

Overall Hospital:	**15-20%**
ICU admission:	**40%**

Age and Mortality

<40 yrs:	**<5%**
70-79 yrs:	**35%**
80-89 yrs:	**>60%**

JAMA. 2020 Aug 25;324(8):782-793

COVID-19: Comorbidities and Mortality

Table 1 Leading comorbidities among COVID-19 deaths in NY, USA

Comorbidities	Death %
Hypertension	55.4%
Diabetes	37.3%
Hyperlipidemia	18.5%
Coronary artery disease	12.4%
Renal disease	11.0%
Dementia	9.1%
COPD	8.3%
Cancer	8.1%
Atrial fibrillation	7.1%
Heart failure	7.1%

Data reported by hospitals, nursing homes, and other health facilities to the New York State Department of Health, as of April 6, 2020 [26]

SN Compr Clin Med. 2020 Jun 25:1-8

Comorbidities with greatest associated mortality:

- **Cardiovascular disease**
- **Diabetes**
- **Renal disease**

COVID-19 Mortality

What can we learn from post-mortem studies?

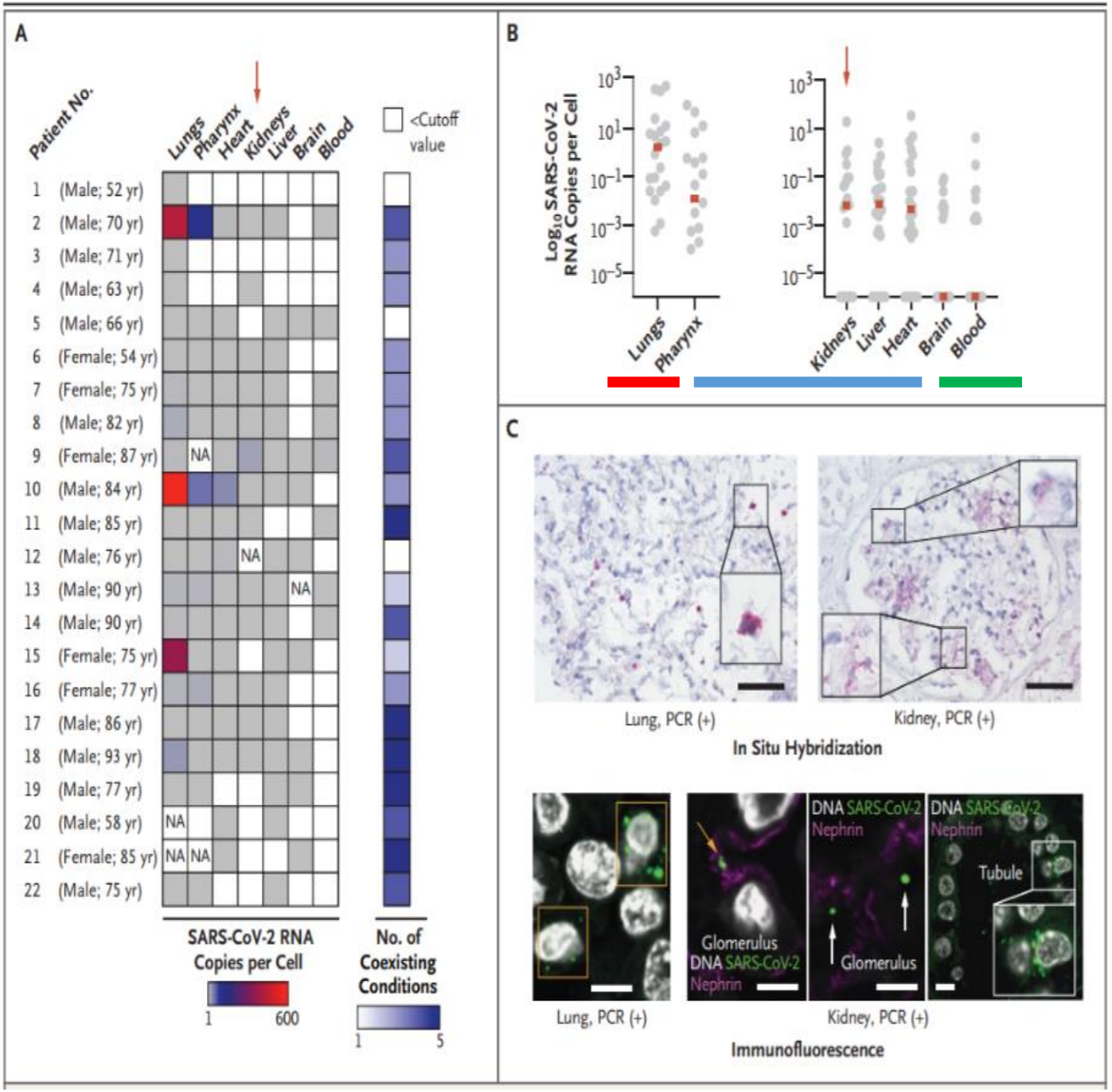
- **Cause of death**
- **Pathobiology of COVID-19**

COVID-19 Pathology

VIRAL TROPISM

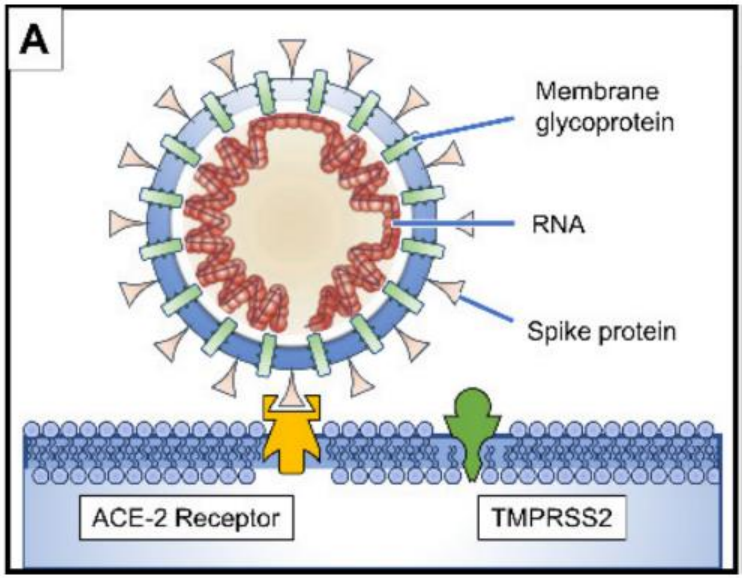
Autopsy Study of 22 COVID-19-infected Persons: VIRAL TROPISM

- **Multiorgan**
- **Lungs: Viral load tends to be greatest**
  - **Infects pneumocytes**
- **Kidneys: Virus infects glomerular epithelium, endothelium, and tubular cells**
- **Lung > Pharynx, Kidneys, Liver, Heart > Brain, Blood**



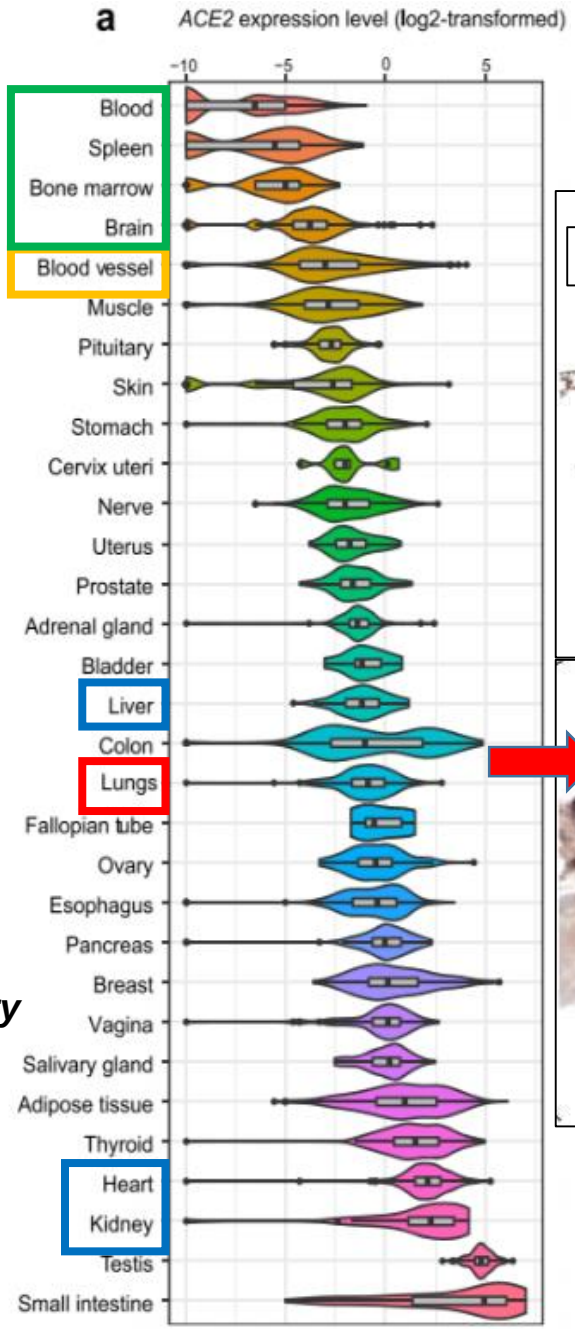
N Engl J Med. 2020 Aug 6;383(6):590-592.

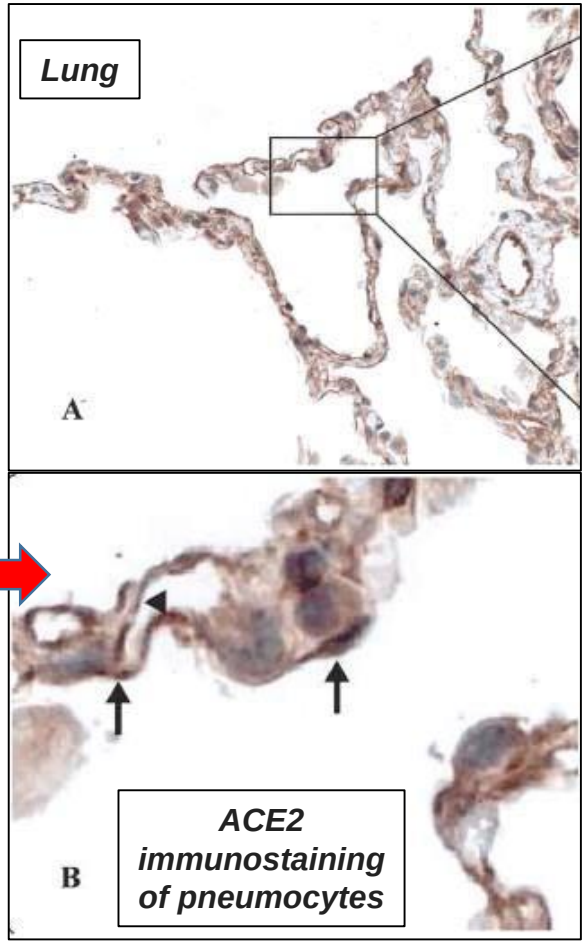
ACE2 Expression in the Body



Viral Entry into Cells

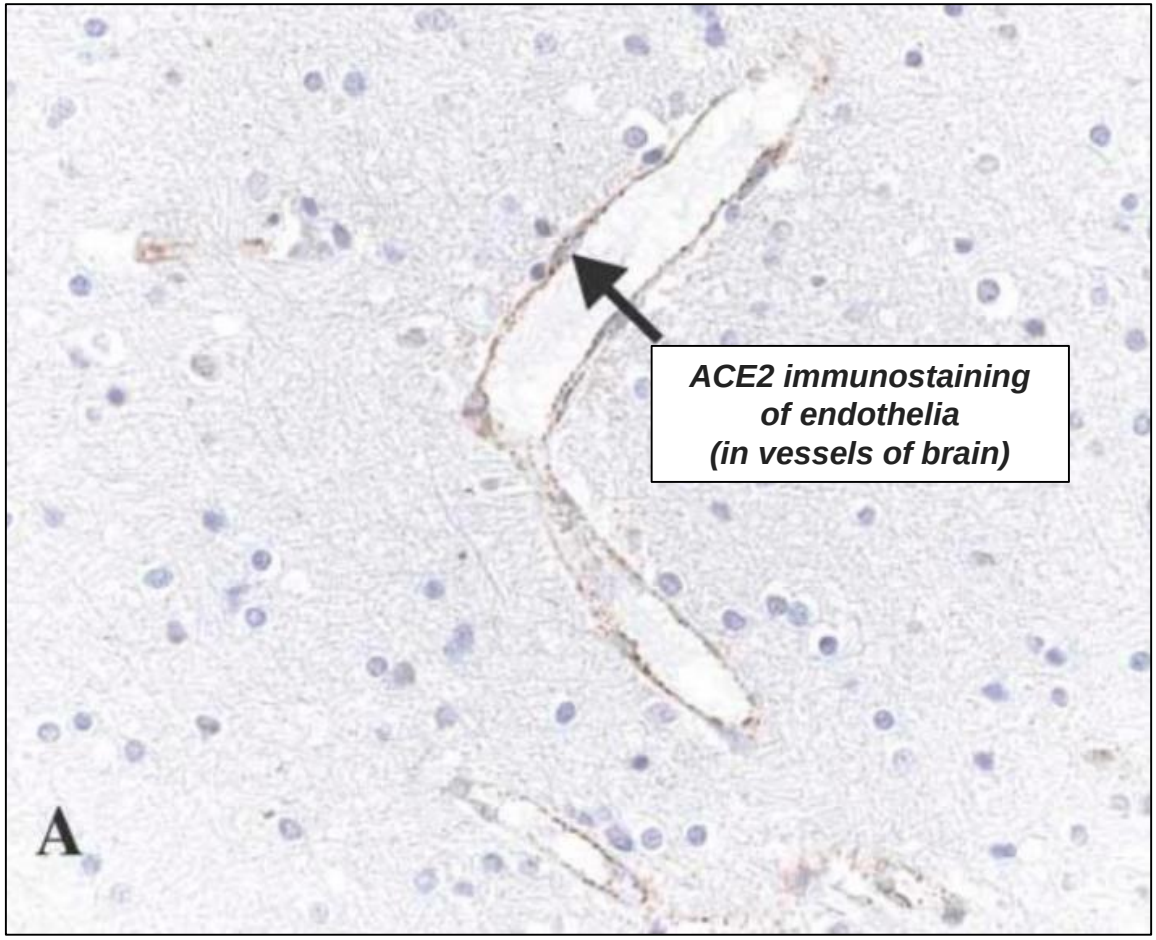
- ***Angiotensin-converting enzyme 2 (ACE2) – receptor for cell entry***
- ***Transmembrane serine protease 2 (TMPRSS2) – protease promotes entry***





Pathogens. 2020 Mar 20;9(3):231
Infect Dis Poverty. 2020 Apr 28;9(1):45
J Pathol. 2004 Jun;203(2):631-7

ACE2 Expression in the Body: Endothelial Cells



SARS-CoV-2
has an entry mechanism
to infect endothelia
(blood vessels).

J Pathol. 2004 Jun;203(2):631-7

COVID-19 Pathology

ENDOTHELIA

Autopsy Study of 3 COVID-19-infected Persons

Lancet. 2020 May 2;395(10234):1417-1418.

Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbid-

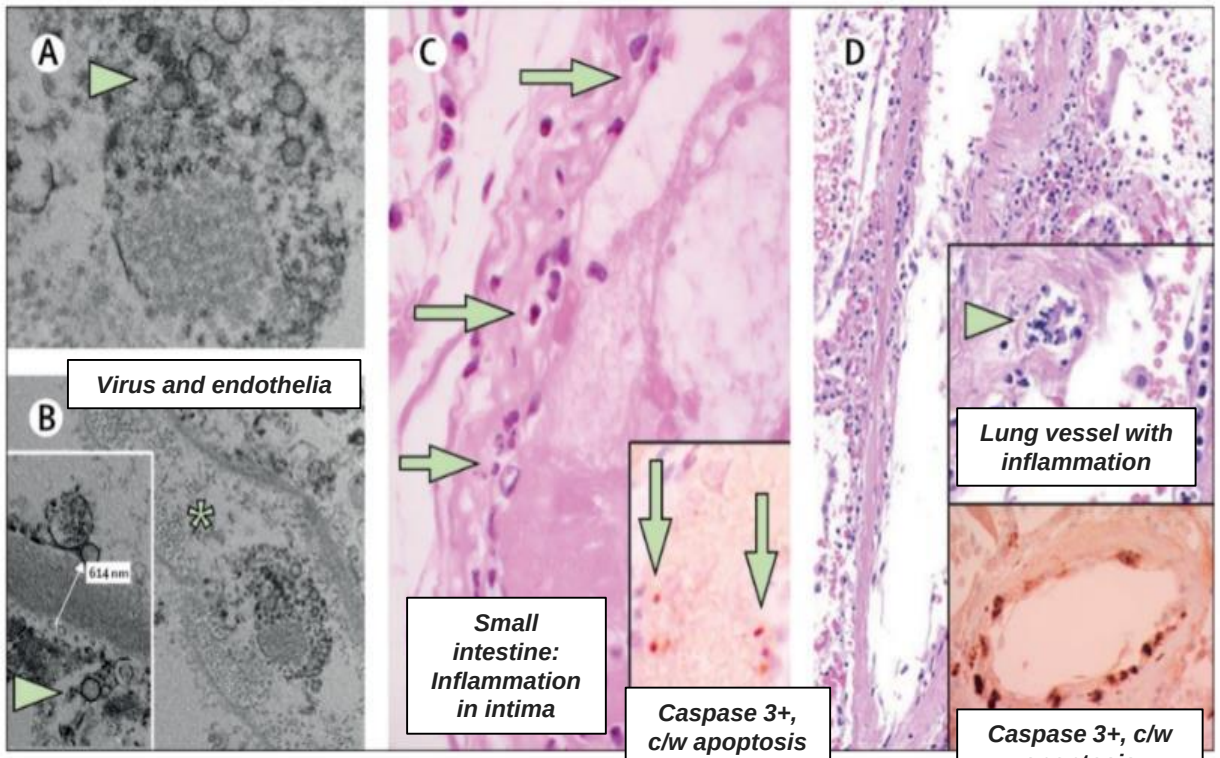
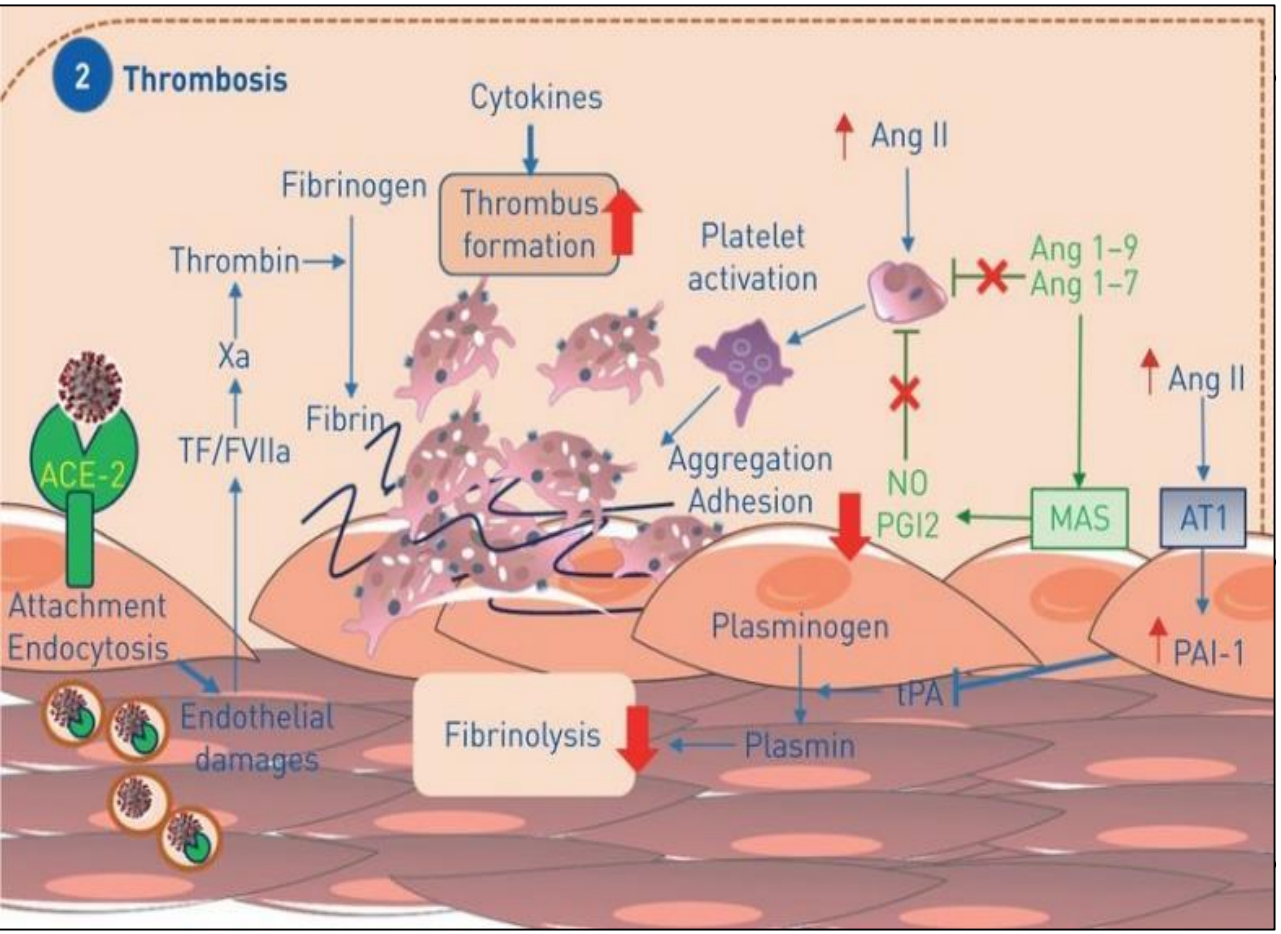


Figure: Pathology of endothelial cell dysfunction in COVID-19

- ***ACE2 is expressed in endothelia (found in blood vessels)***
- ***Endothelial cells can be infected by SARS-CoV-2 to cause endotheliitis.***

Hypothetical mechanism by which SARS-CoV-2 causes endothelial dysfunction



SARS-CoV-2 binds to ACE2 expressed on endothelial cells (of blood vessels)

Induces damage

Thrombus formation

Eur Respir J. 2020 Jul 30;56(1):2001634.

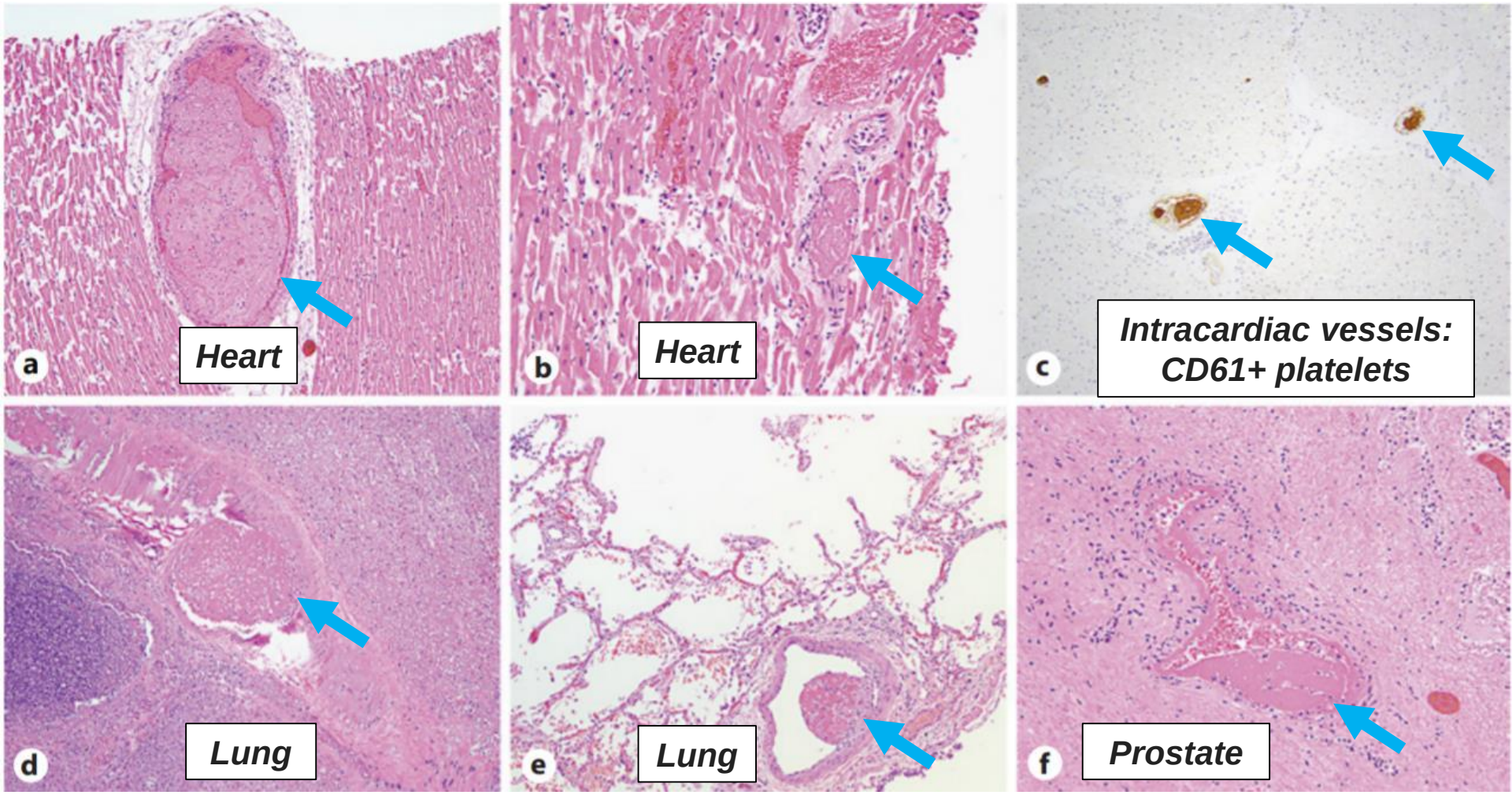
Autopsy Study of 32 COVID-19-infected Persons: THROMBI

- ***Macro and/or microscopic thrombi: 84%***
  - *Most in lung and heart*
- ***Elevated D-dimer: 69%***
- ***Prolonged coagulation factors***

Site	Thrombi ($n = 32$)	Thrombosis and coexisting organ infarction
Heart		
Intramyocardial small vessel thrombi	6 (19%)	1
Valve-associated thrombi	2 (6%)	
Lungs		
Small vessel thrombi	23 (72%)	3
Large vessel thrombi	11 (34%)	3
Both	9 (28%)	3
Trachea	4 (13%)	1
Thyroid	3 (9%)	0
Lymph node	3 (9%)	1
Bladder	2 (6%)	0
Kidney	2 (6%)	1
Prostate	2 (6%)	1
Esophageal varices	1 (3%)	0
Diaphragm	1 (3%)	0
Ovary	1 (3%)	0

Pathobiology. 2020 Sep 17:1-13.

Autopsy Study of 32 COVID-19-infected Persons: Multisystem Microscopic Thromboses



Pathobiology. 2020
Sep 17:1-13.

COVID-19 Pathology

RESPIRATORY

Autopsy Study of 32 COVID-19-infected Persons: LUNG

Table 4. Pathological characteristics of the lungs

Characteristics	DAD			
	none	exudative	proliferative	both
Patients	2 (6%)	3 (9%)	3 (9%)	24 (75%)
Alveolar neutrophils	1	2	2	11
Organizing pneumonia	0	2	3	8
Pulmonary edema	0	0	0	8
Combined lung weights, g[a]	1,630 (1,160–2,100)	1,917 (1,830–2,020)	2,050 (1,540–2,520)	1,804 (1,000–3,110)[b]
Duration of disease, days	18 (1–36)	9 (7–11)	35 (26–42)	20 (1–58)
Intubated	0	0	2 (67%)	13 (52%)
Length of intubation, days	NA	NA	31 (28–33)	15 (1–50)

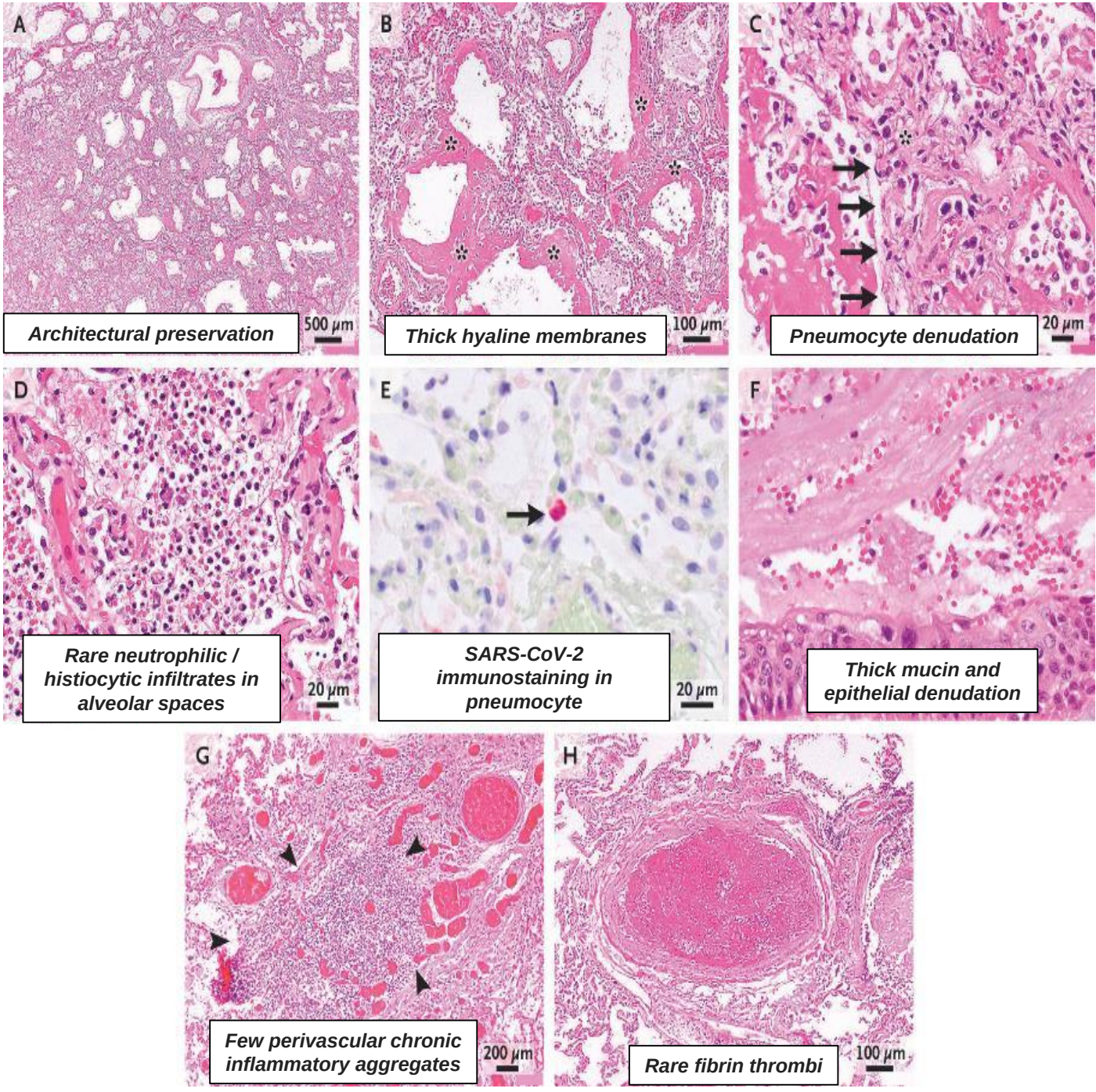
Data are presented as *n* (%) or mean (range). DAD, diffuse alveolar damage; NA, not applicable. [a] Reference range for combined lung weights in adults = 685–1,050 g. [b] Combined weight for the right lung and lung biopsy only cases are not applicable.

- ***Diffuse alveolar damage (DAD) in most decedents***
  - *Histologic correlate for acute respiratory distress syndrome (ARDS)*
  - *Formation of **hyaline membranes** (mix of proteinaceous exudate, surfactant from type II pneumocytes, cellular debris) along alveolar walls, which interfere with gas exchange*
  - *Can progress to organizing pneumonia and pulmonary fibrosis*

Pathobiology. 2020 Sep 17:1-13.

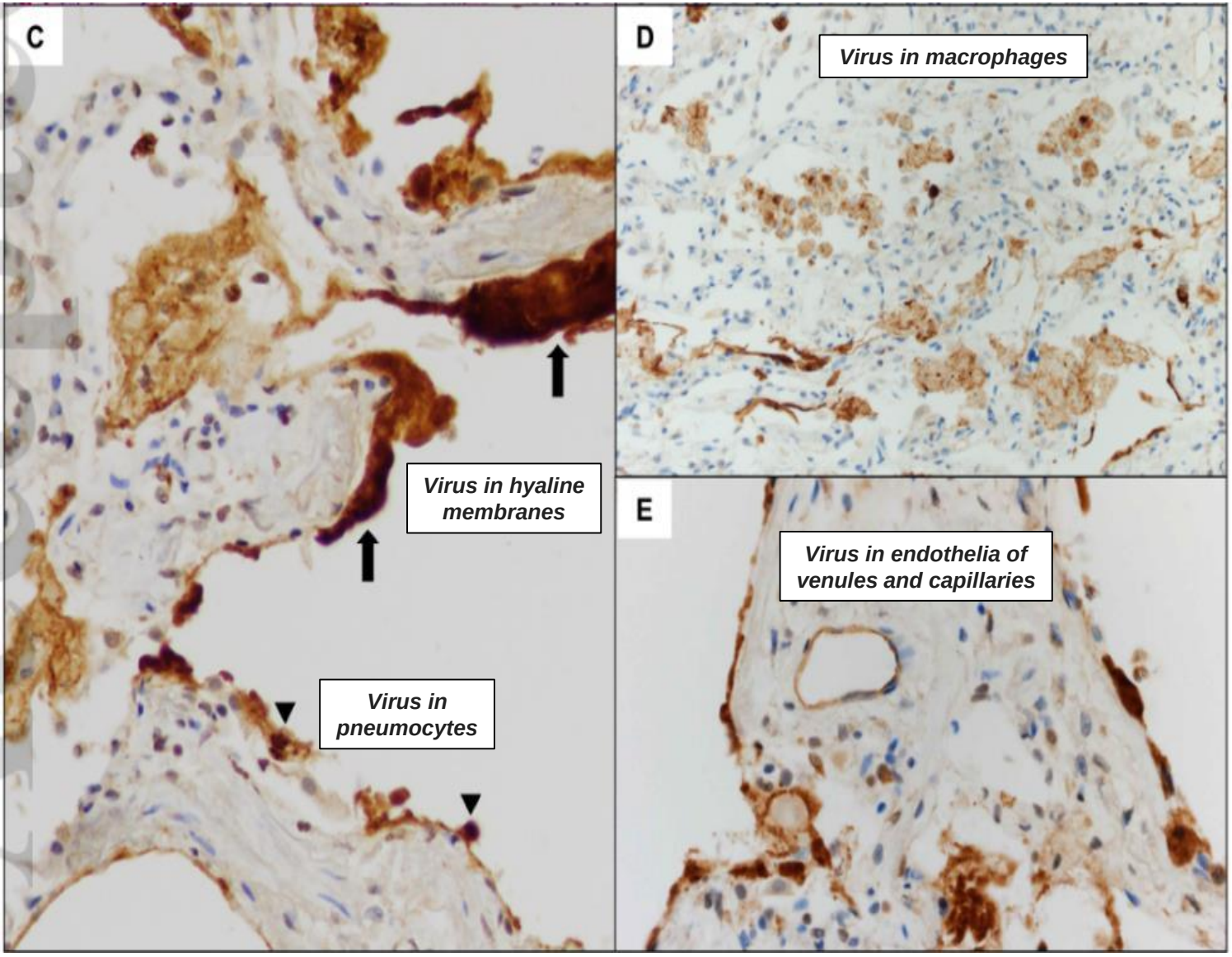
COVID-19 Infection: LUNG

Autopsy of 76 y.o. woman:
Diffuse alveolar damage with superimposed bronchopneumonia



N Engl J Med. 2020 Jul 23;383(4):380-387.

SARS-CoV-2 Infection in the LUNG: Immunohistochemistry

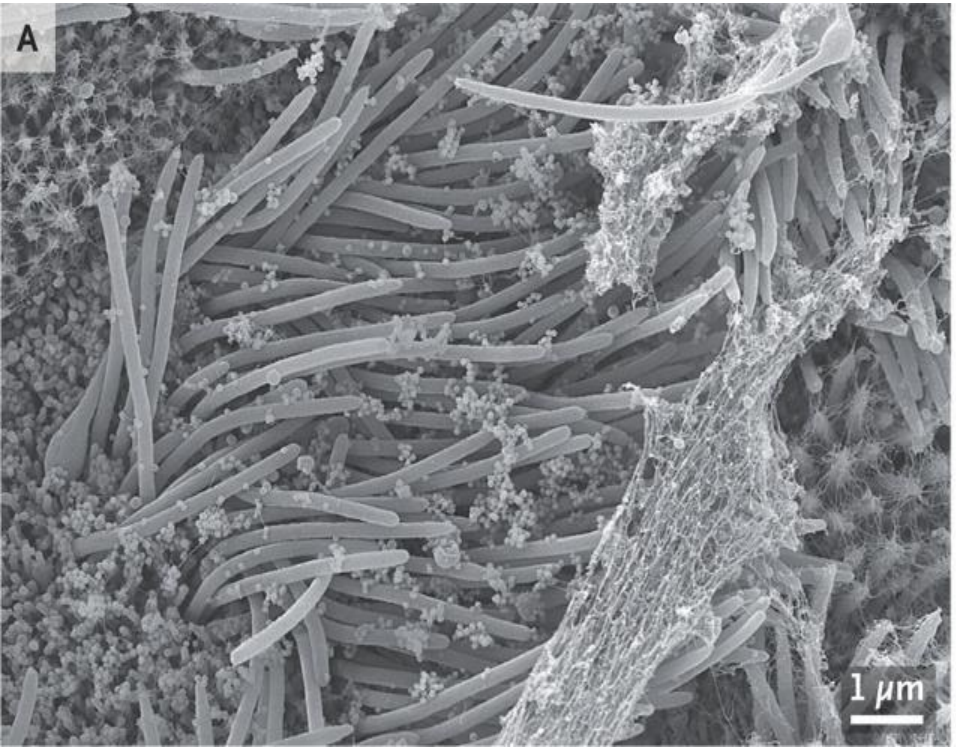


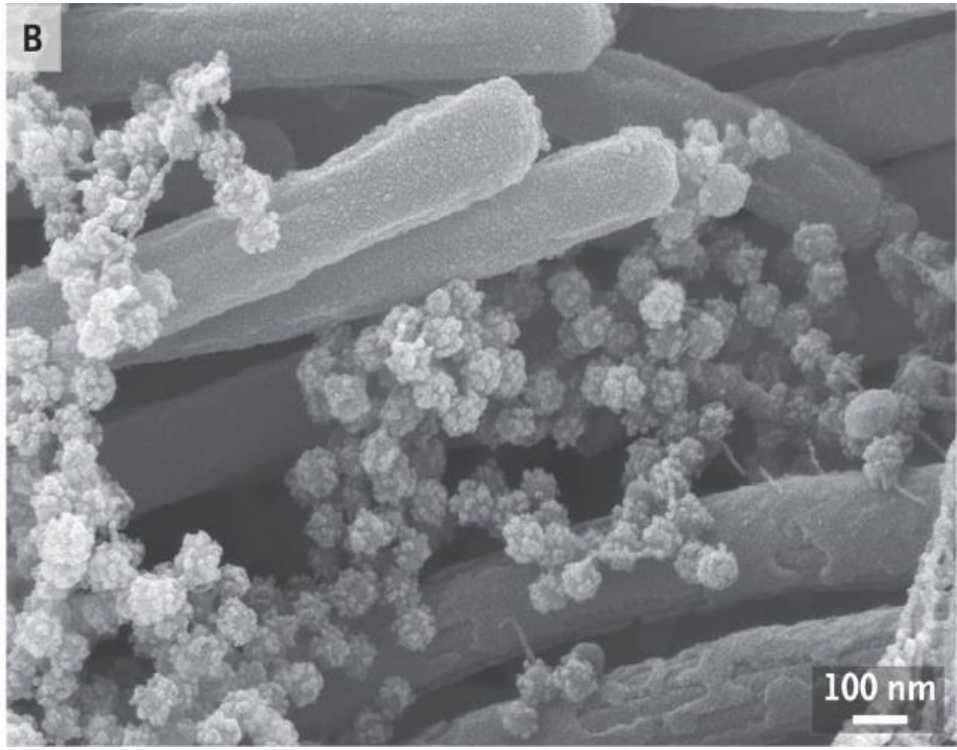
Virus detected in:

- Pneumocytes
- Hyaline membranes
- Macrophages
- Blood vessels

Histopathology. 2020 Jul 2:10.1111/his.14201.

SARS-CoV-2 Infection in the LUNG: Electron Microscopy





A) Infected ciliated cells with strands of mucus attached to the cilia tips.

B) SARS-CoV-2 virions produced by human airway epithelial cells.
Virus production was ~3×10^6 plaque-forming units per culture, a finding consistent with a high number of virions produced and released per cell.

SARS-CoV-2 directly infects pneumocytes.

N Engl J Med. 2020 Sep 3;383(10):969

COVID-19 Pathology

CARDIOVASCULAR

Autopsy Study of 32 COVID-19-infected Persons: CARDIOVASCULAR

- ***Co-morbidities present in most***
  - *Hypertension*
  - *Coronary artery disease*
  - *Chronic heart failure*
- ***Pathologic findings were related to the co-morbidities.***
- ***No myocarditis***

Features	Patients (n = 30)	Average
Clinical findings		
Coronary artery disease	10 (33%)	
Chronic heart failure	6 (20%)	
Hypertension	21 (70%)	
Troponin (I)[a]		3.7 (ng/mL)
Normal	6 (20%)	0.027 (ng/mL)
Elevated	23 (77%)	4.89 (ng/mL)
Pathologic findings		
Heart weight[b]		480 (g)
Normal weight	2 (6%)	350 (g)
Cardiomegaly	28 (93%)	490 (g)
Histologic features		
Atherosclerosis (>50% stenosis)	17 (57%)	
Myocyte hypertrophy	24 (80%)	
Myocyte ischemia	5 (17%)	
Interstitial fibrosis	20 (67%)	

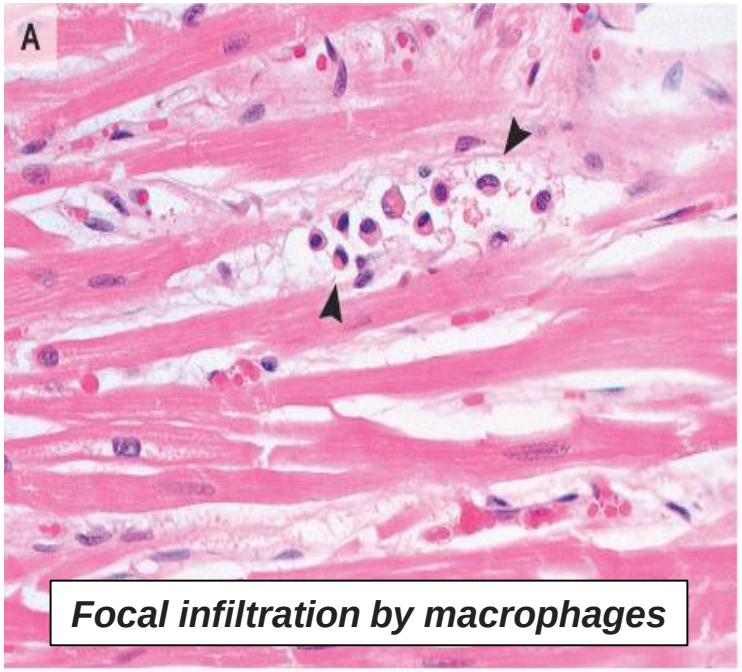
[a] Normal troponin-I: ≤0.04 ng/mL. [b] Normal heart weight: male 270–360 g, female 200–280 g.

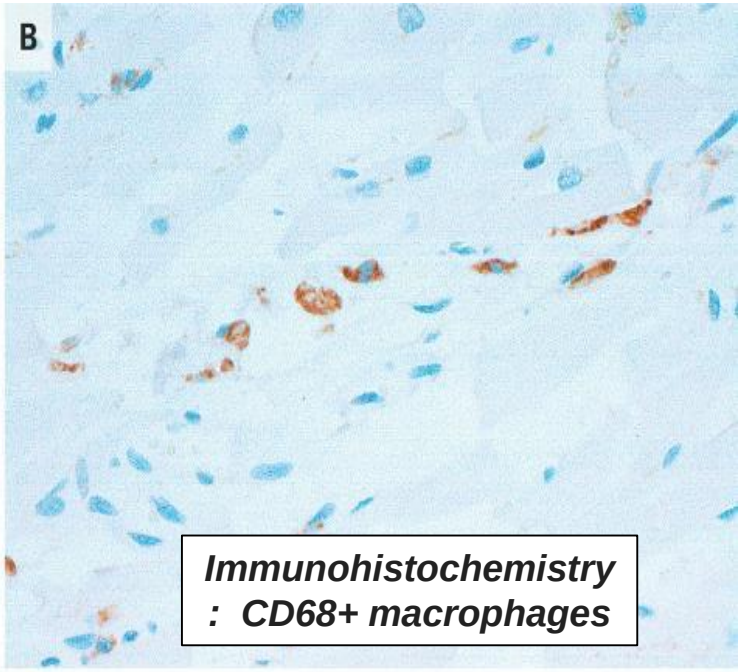
Pathobiology. 2020 Sep 17:1-13.

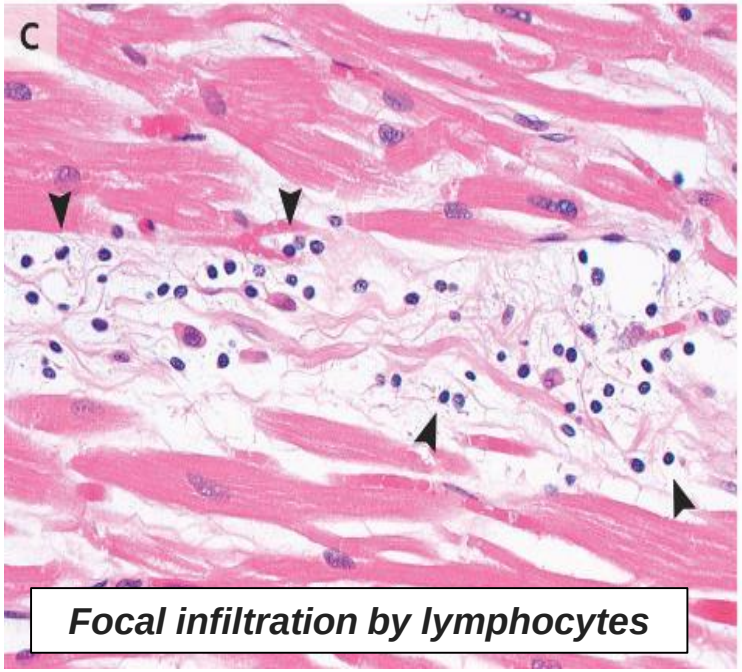
COVID-19 Infection: HEART

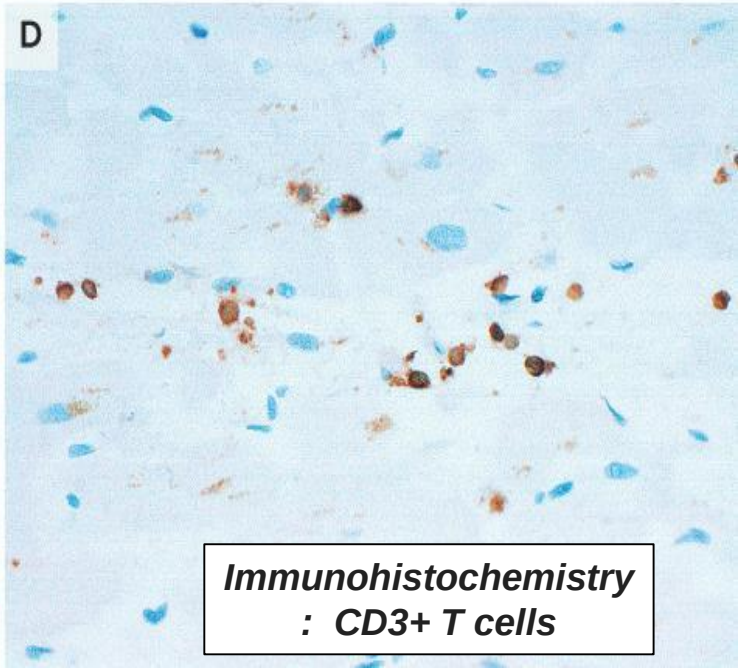
Autopsy of 76 y.o. woman:

- ***Focal myocardial inflammation***
- ***No myocardial injury***
- ***Not sufficient for a diagnosis of myocarditis***









N Engl J Med. 2020 Jul 23;383(4):380-387.

Autopsy Study of 39 COVID-19-infected Persons: CARDIOVASCULAR

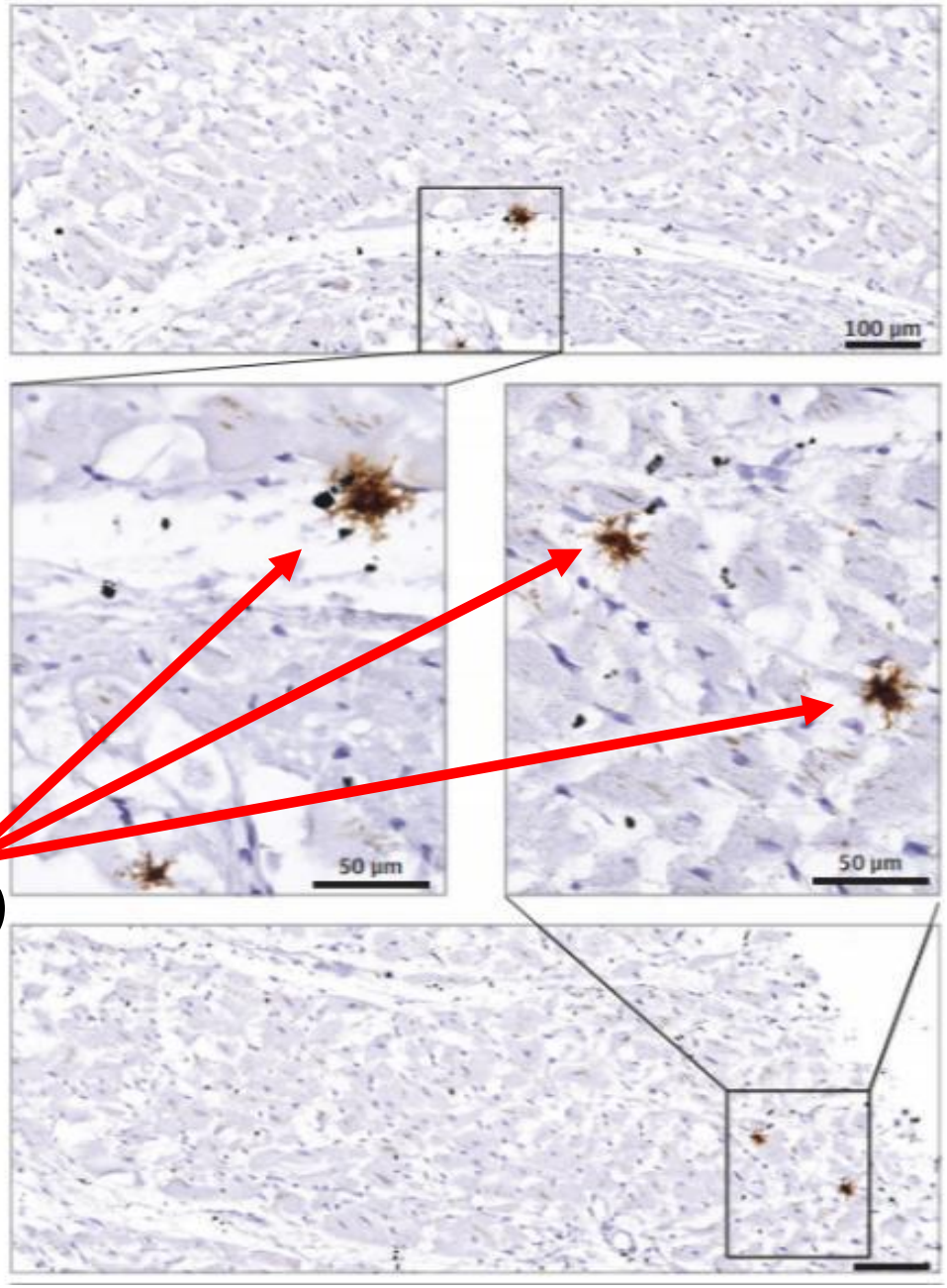
Methods

- *N=39 COVID-19+ autopsies (detected by NP swabbing)*
- *Conducted PCR on myocardial tissue for SARS-CoV-2*

Results

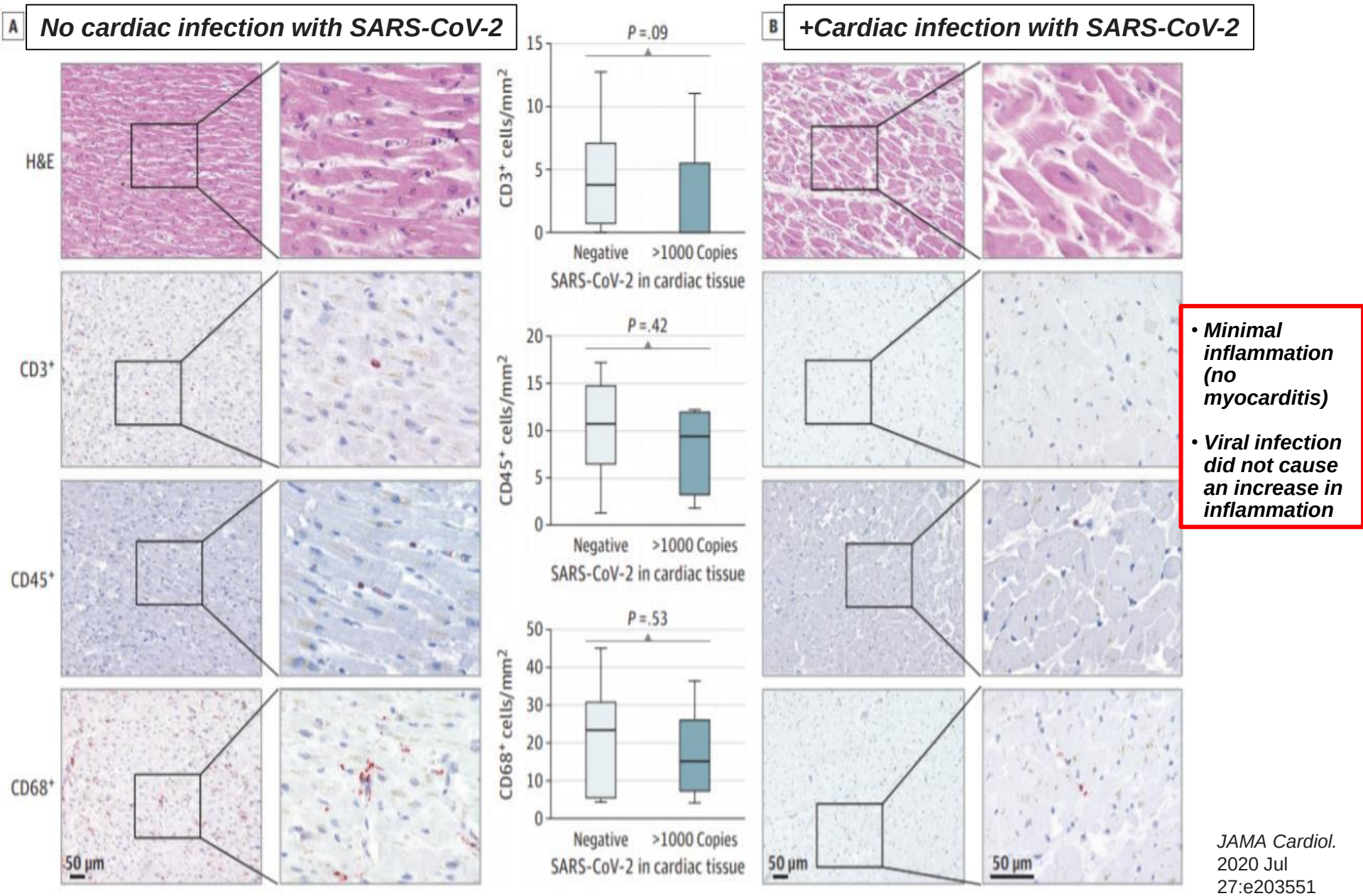
- ***Some cases have detectable virus by RT-PCR*:**
  in situ *hybridization showed that the infection involved interstitial cells (macrophages)*

- ***Infection did not occur in cardiac myocytes.***



JAMA Cardiol. 2020 Jul 27:e203551

Autopsy Study of 39 COVID-19-infected Persons: CARDIOVASCULAR



- ***Minimal inflammation (no myocarditis)***
- ***Viral infection did not cause an increase in inflammation***

JAMA Cardiol. 2020 Jul 27:e203551

COVID-19 Pathology

RENAL

Autopsy Study of 32 COVID-19-infected Persons: RENAL

- ***Co-morbidities present in most***
  - *Hypertension*
  - *Diabetes*
  - *Chronic kidney disease*
- ***Acute Changes***
  - *Acute tubular necrosis*
  - *Complement-mediated endothelial injury (up to 67%)*

Minimal inflammation

Feature	Patients ($n = 32$)	Notes
Clinical findings		
Diabetes/pre-diabetes	20 (63%)	
Hypertension	23 (72%)	
Obesity	10 (31%)	
Acute kidney injury	16 (53%)	$n = 30$[a]
Requiring renal replacement therapy	5 (17%)	$n = 30$[a]
Creatinine, mg/dL	Range: 0.66–9.61 ($n = 29$)	Mean 1.7
Proteinuria	9 (50%) ($n = 18$)	None quantitated
Pathologic findings ($n = 28$)[b]		
Diabetic nephropathy	14 (50%)	
Diffuse mesangial glomerulosclerosis	11 (39%)	
Nodular mesangial glomerulosclerosis	3 (11%)	
Other diagnoses		
Obesity related glomerulopathy	2	
Papillary Necrosis	2	
Thrombotic microangiopathy	2	
Atheroembolic disease	1	
Bilateral infarction	1	
Global glomerulosclerosis	5–95%	Mean 22.7%[b]
Interstitial fibrosis and tubular atrophy		
<25%	16 (57%)	
26–50%	7 (25%)	
>50%	5 (18%)	
Vascular sclerosis		
Mild	6 (21%)	
Moderate	10 (36%)	
Severe	12 (43%)	
C5b-9 immunohistochemical staining		
Cases in arterioles	67%	
Cases in glomeruli	21%	

[a] Two ESRD patients excluded. [b] Excludes ESRD and chest only autopsies.

Pathobiology. 2020 Sep 17:1-13.

COVID-19 Pathology

HEPATOCELLULAR

Autopsy Study of 32 COVID-19-infected Persons: Hepatocellular

- ***Co-morbidities present (61% of decedents)***
  - *Steatosis* *(secondary to obesity, diabetes, and/or hyperlipidemia)*
  - *Chronic liver disease* *(bridging fibrosis and/or cirrhosis)*

- ***No direct hepatocyte injury by SARS-CoV-2***

Pathobiology. 2020 Sep 17:1-13.

COVID-19 Pathology

CENTRAL NERVOUS SYSTEM

Autopsy Study of 4 COVID-19-infected Persons: BRAIN

Table 1. COVID-19 patient characteristics and neuropathological findings with RT-PCR and IHC results.

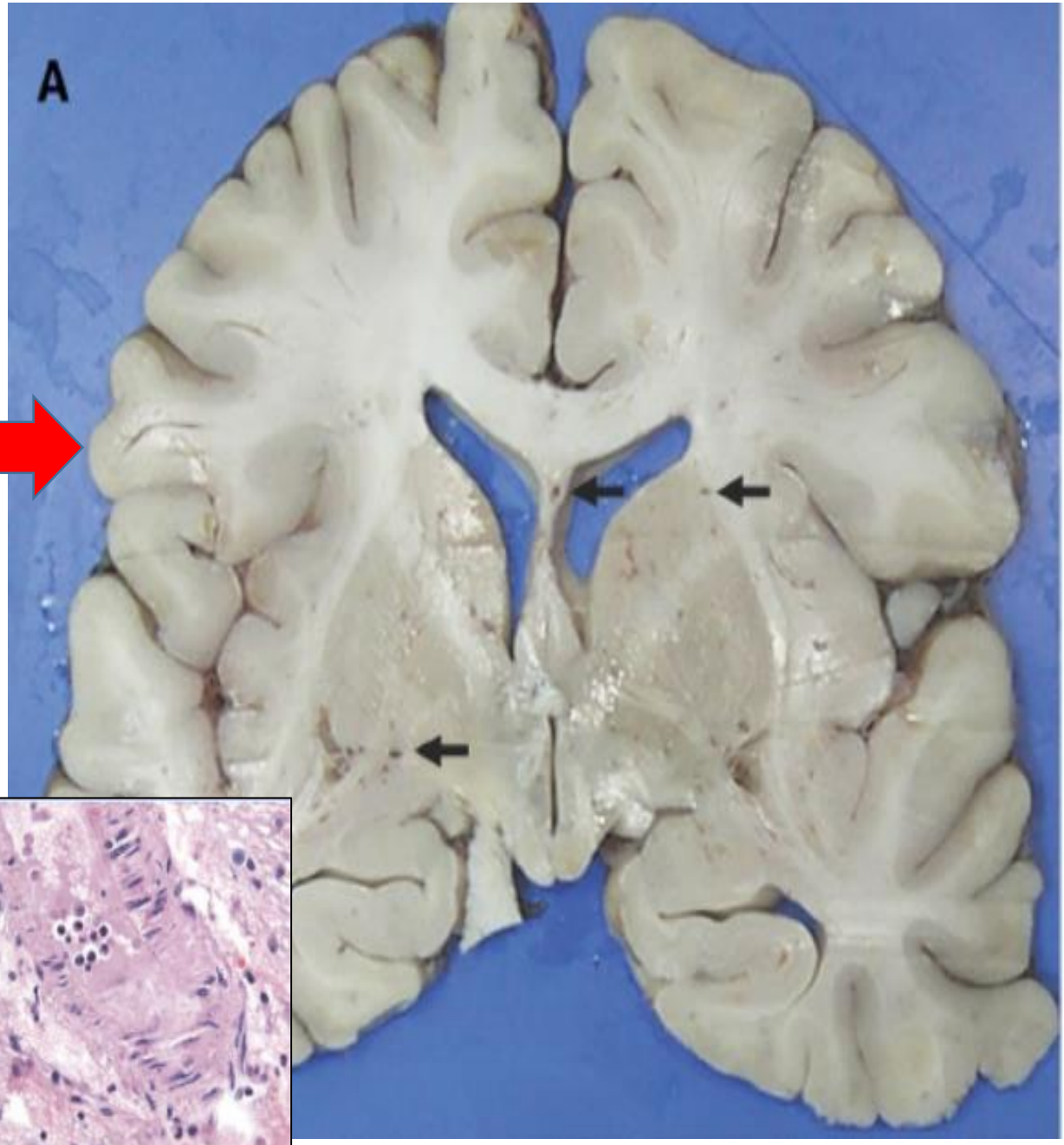
	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Female
Age (years)	63	82	38	90
Symptom-onset to death (days)	25	6	23	26
Death to autopsy (days)	7	6	10	5
Treatment at ICU (days)	2	0	14	0
Medical history	HTN, Gout, CKD with one functional kidney, Smoker	SSS with pacemaker, CAD with MI, PAD, Stroke, DM2, COPD, CRC, CKD	Obesity, HTN, DM2 with retinopathy & polyneuropathy, Recurrent cellulitis, Smoker	HTN, SSS with pacemaker, Asthma/ COPD, AD, Osteoporosis, Spinal stenosis, Recurrent lung infections
Blood group	A RhD+	A RhD+	A RhD+	N/A
HLA-type	N/A	N/A	HLA-DRB1	N/A
Neurologic symptoms	Ageusia, delirium during ICU stay	Non reported	Delirium, unconsciousness	Delirium, unconsciousness
Neuropathologic findings	Hypoxic injury (mild), mild perivascular degeneration and scattered inflammatory cells	Hypoxic injury (mild), perivascular degeneration, lacunar infarctions (old)	Severe hypoxic injury, vasculopathy with perivascular hemorrhage and degeneration, white matter lesions, PD	Hypoxic injury, perivascular degeneration, 2 tiny foci with some axonal spheroids, AD (Braak 5, CERAD Moderate), CAA, Limbic predominant DLB

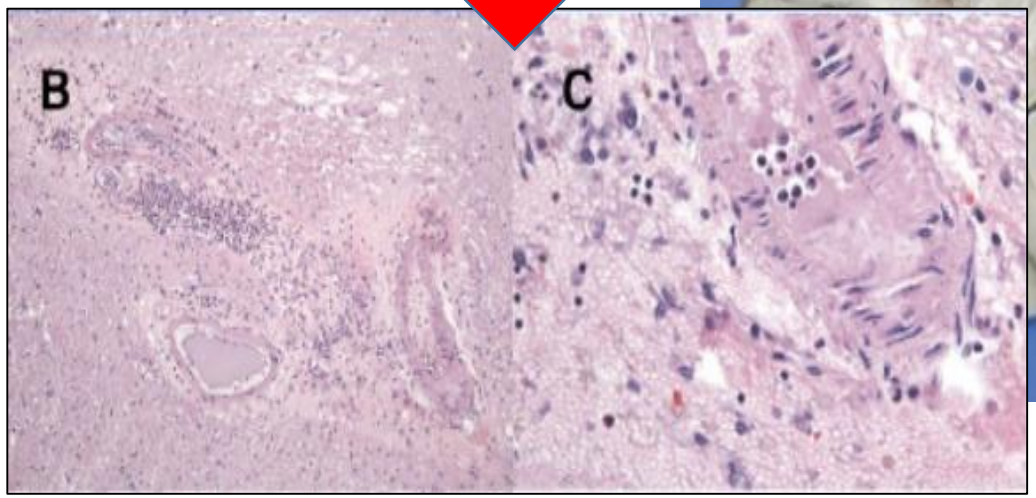
- **Various hypoxia-associated neuropathological features**
- **No evidence of viral neurotropism or encephalitis**

Brain Pathol. 2020 Aug 6:10.1111/bpa.12889.

Autopsy Study of 4 COVID-19-infected Persons: BRAIN

- Microhemorrhages in the white matter and deep gray matter
- Perivascular inflammation and perivascular hemorrhage, but very few inflammatory cells in the surrounding brain areas.





Brain Pathol. 2020 Aug 6:10.1111/bpa.12889.

Autopsy Study of 18 COVID-19-infected Persons: BRAIN

- *All had histologic evidence of acute hypoxic ischemic damage*
- *qRT-PCR of brain tissue were either equivocal or did not detect the virus*
- *Immunohistochemical analyses of brain tissue did not detect the virus.*
- *No encephalitis*

N Engl J Med. 2020 Sep 3;383(10):989-992.

Table 1. Gross Findings and Results of Histologic Analysis to Detect SARS-CoV-2.*

Patient No.	Days from Symptom Onset to Death	Hours from Death to Autopsy	Gross Inspection		Histologic Analysis
			Brain Volume	Observations	
			grams		
1	20	52	1290	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis
2	6	32	1460	Moderate atherosclerosis	Acute hypoxic ischemic damage
3	12	21	1210	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
4	6	36	1150	Moderate-to-severe atherosclerosis, pale substantia nigra and locus coeruleus	Acute hypoxic ischemic damage, moderate arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
5	9	40	1460	No gross abnormalities	Acute hypoxic ischemic damage
6	0	77	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal leptomeningeal chronic inflammation
7	2	54	1300	Moderate atherosclerosis, cortical atrophy	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Alzheimer's disease
8	2	32	1350	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, moderate arteriolosclerosis
9	23	23	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis
10	7	21	1120	Moderate atherosclerosis, anaplastic astrocytoma tumor resection cavity	Acute hypoxic ischemic damage, recurrent or residual anaplastic astrocytoma
11	26	41	1090	No gross abnormalities	Acute hypoxic ischemic damage, Alzheimer's type II astrocytosis
12	6	45	1130	Mild atherosclerosis, pale substantia nigra	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
13	12	61	1300	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis, focal perivascular chronic inflammation, Alzheimer's type II astrocytosis
14	0	102	1650	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis
15	8	20	1530	Moderate atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis, Alzheimer's type II astrocytosis
16	32	31	1150	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
17	7	25	1300	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal perivascular chronic inflammation, pathological features of Alzheimer's disease
18	9	26	1350	Mild atherosclerosis	Acute hypoxic ischemic damage, single microglial nodule, Alzheimer's type II astrocytosis

* The results of immunohistochemical analysis to detect SARS-CoV-2 were negative in all the patients.

Summary:

- *Patients with COVID-19 have a variety of clinical findings*
  - *Especially involving the respiratory system*

- *SARS-CoV-2 has multiorgan tropism*
  - *Lung >> Pharynx, Kidneys, Liver, Heart >> Brain, Blood*

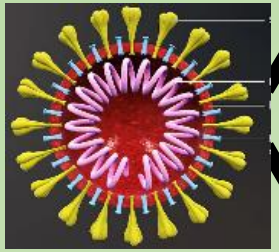
- *Autopsies show two patterns of injury*
  - *Chronic (co-morbidities, not caused by the virus)*
  - *Acute*
    - *Widespread thrombi*
    - *Direct injury in lung, due to SARS-CoV-2 / diffuse alveolar damage*
    - *Prominent inflammation is not observed in kidneys, liver, heart, brain*

Hypothesis

Pathologic Findings

Clinical Findings

Infection causing direct injury



Endothelia

Pulmonary

Thrombus formation

CNS

Cardiovascular

Hepatocellular

GI

Renal

Co-morbidities

DEATH

Q&A

HAWAIʻI PACIFIC HEALTH | HAWAIʻI HEALTH PARTNERS

CREATING A HEALTHIER HAWAIʻI

Save the Date! HHP 7th Annual Membership Meeting

- Saturday, November 7, 2020
  - 8:00 a.m. to 12:30 p.m.

- Physician Planning Committee

- Virtual meeting
- Community giveback project
  - Blood Bank of Hawai‘i
  - Hawai‘i Food Bank
  - Aloha United Way
  - Child & Family Services

- Details & updates forthcoming:
  - HHP website under “For Providers/Events Calendar”
  - HPH eConnect, “Hawai‘i Health Partners” channel
  - Emailed via Info@hawaiihealthpartners.org

Thank you!

- A recording of the meeting will be available afterwards.
- Unanswered question?
  - Contact us at Covid19Bulletin@hawaiipacifichealth.org

HAWAIʻI PACIFIC HEALTH | HAWAIʻI HEALTH PARTNERS

CREATING A HEALTHIER HAWAIʻI