LONG COVID
“Pain that lingers”

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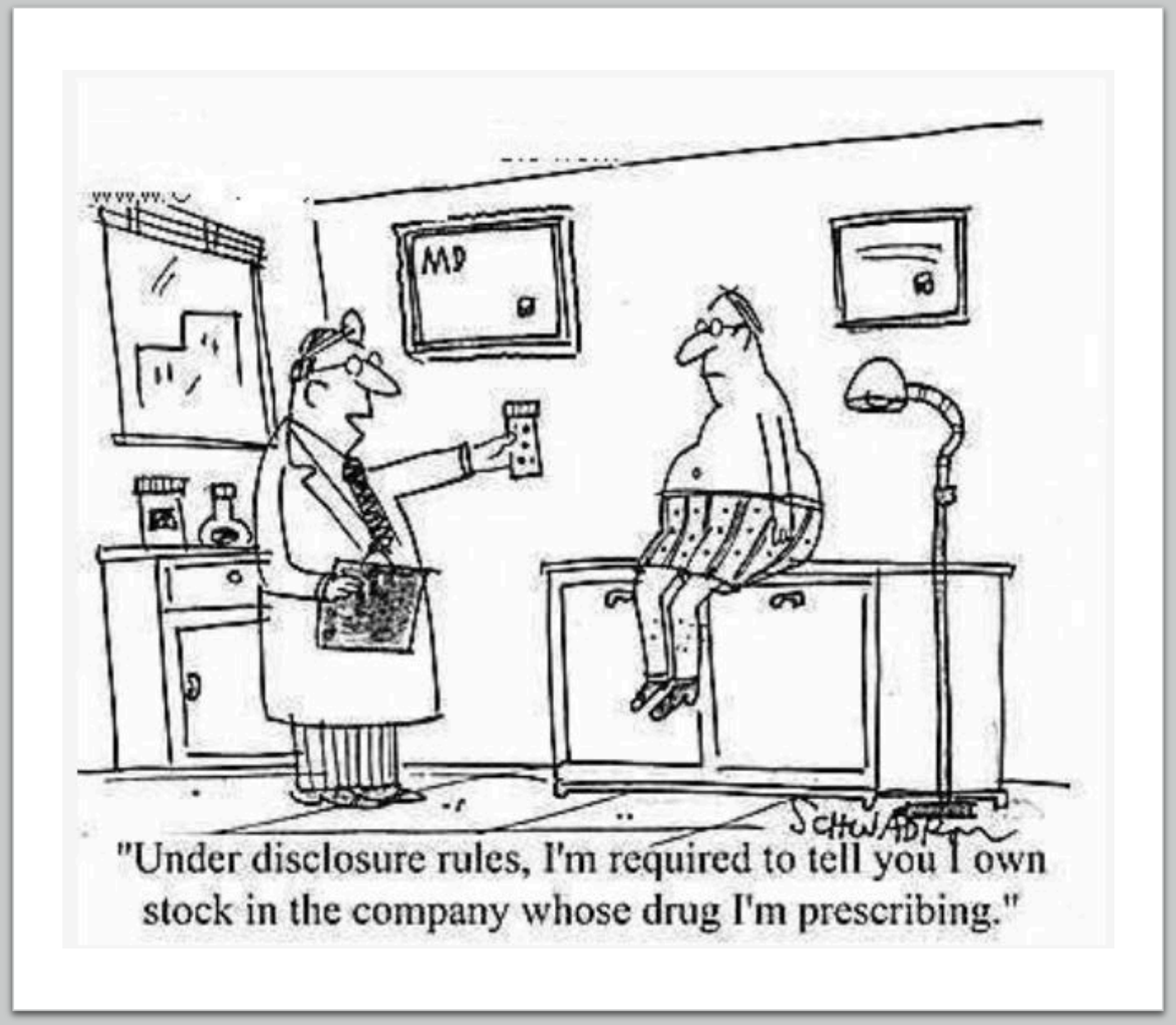
Stilwell OK


In memory of many,
in honor of all.
Let us take time today to honor the lives we have lost to COVID-19.
Today, and every day, we remember our beloved friends, family members, and neighbors.

DISCLOSURES

- NONE



OBJECTIVES

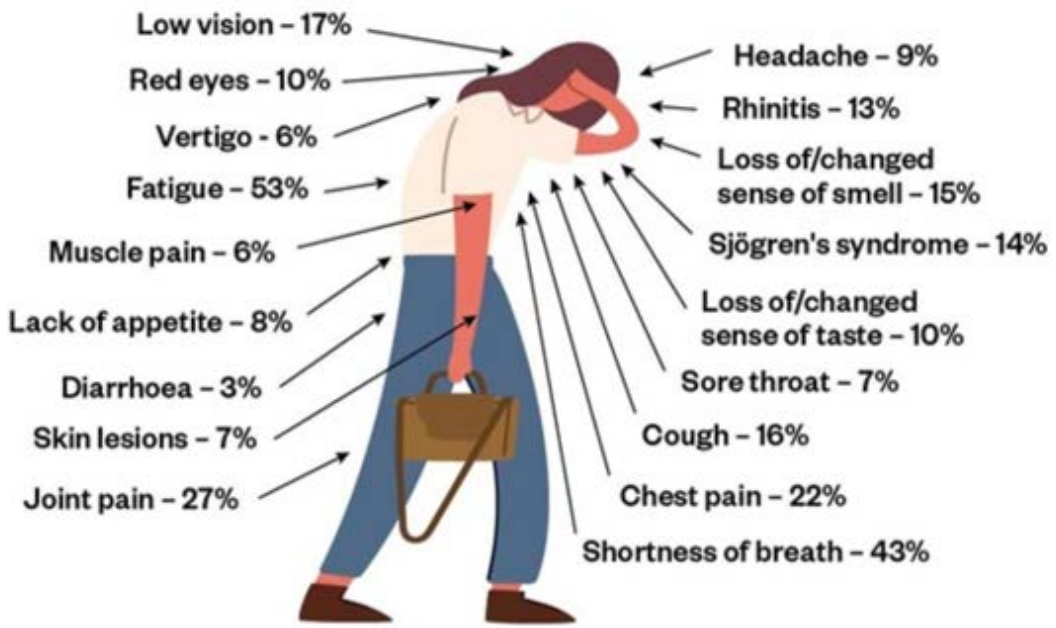
- Background of Long COVID
- Overview of Long COVID
- Epidemiology of Long COVID
- Pathophysiology of Long COVID
- Clinical manifestations of Long COVID
- Management Considerations of Long COVID
- Future Directions

WHERE THE KNOWN MEETS THE UNKNOWN IS WHERE SCIENCE BEGINS

https://www.scientificamerican.com/article/rumsfelds-wisdom/

INTRODUCTION

- Widespread perception - people either die, get admitted to hospital or recover after 2 weeks
- Distinct pathway of ongoing effects for some people
- Urgent need to better understand the symptom journey and the clinical risks that underlie



Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA.* 2020

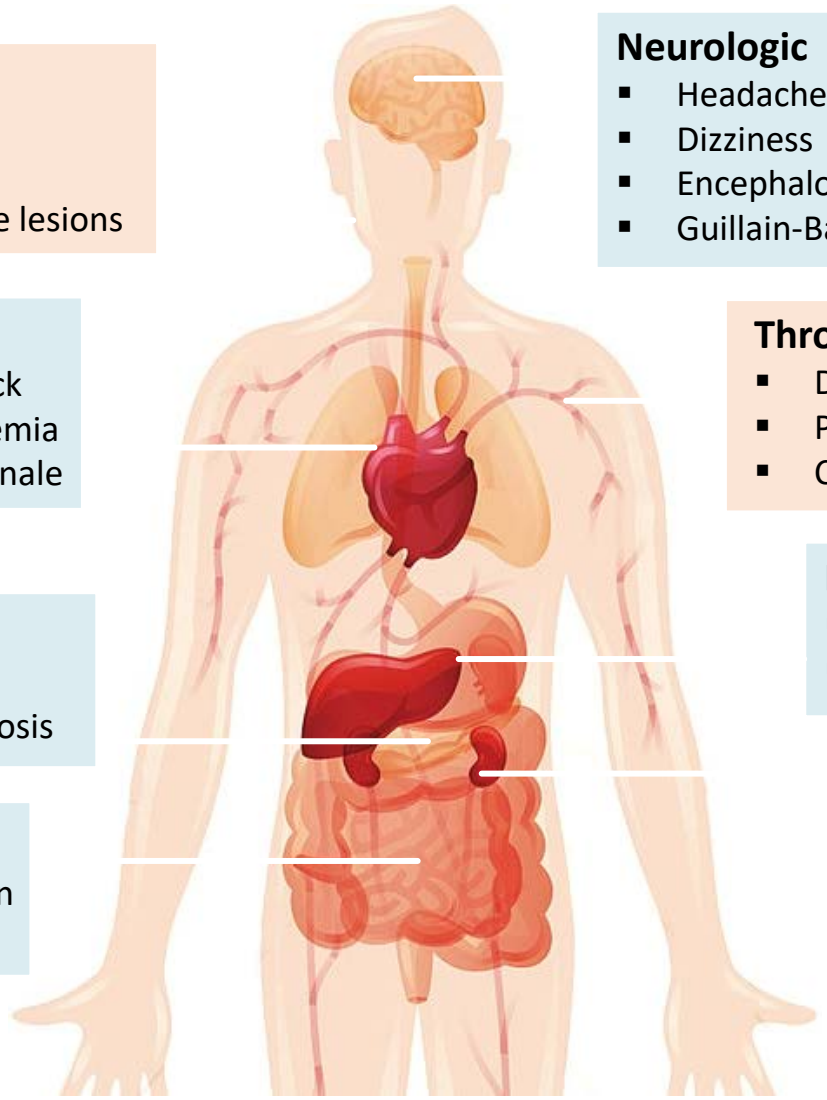
EXTRAPULMONARY MANIFESTATIONS OF COVID-19

Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis



Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

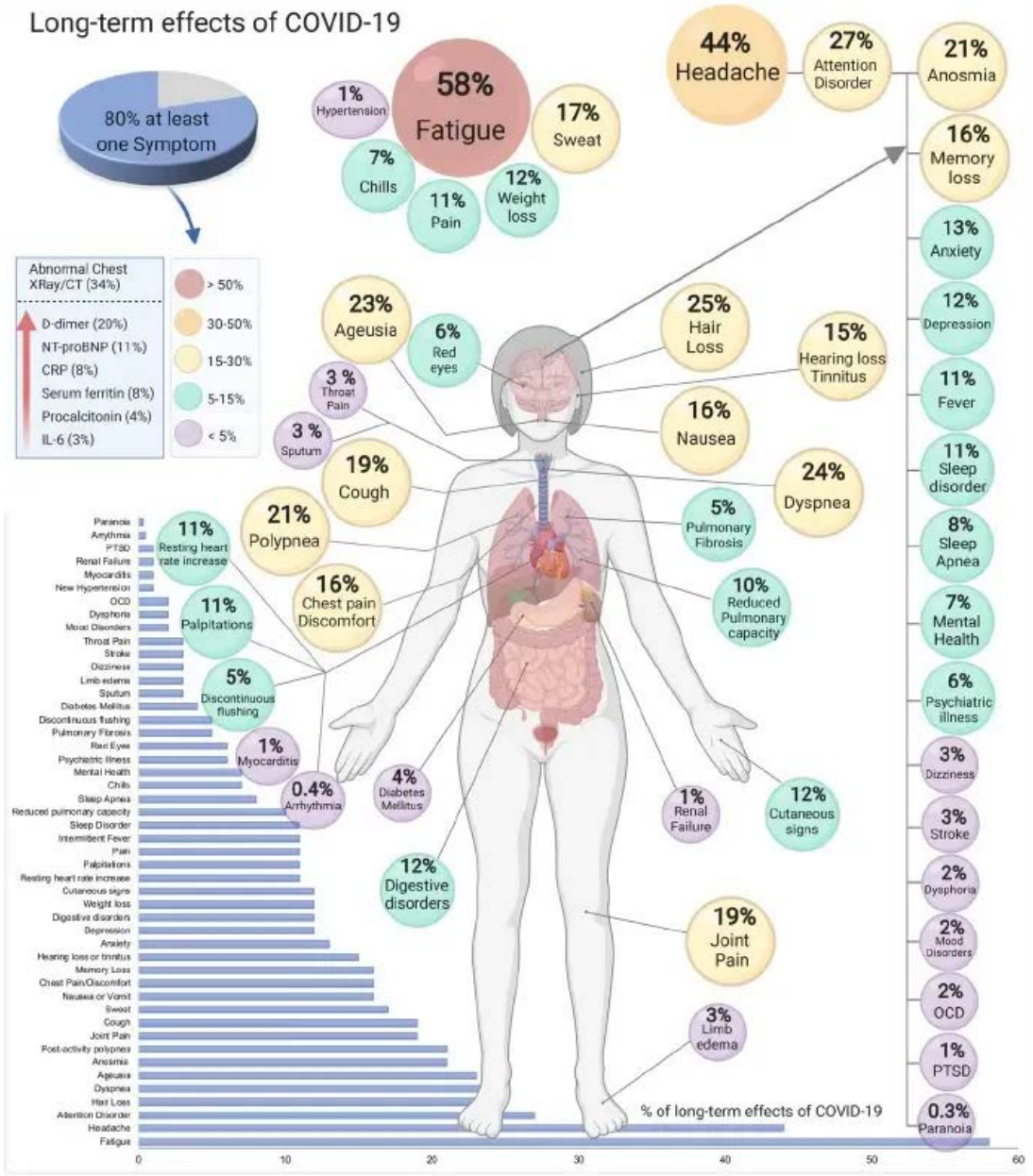
Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta A. et. al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020

Slide credit: clinicaloptions.com

WHICH OF THESE RETURN OR LAST?

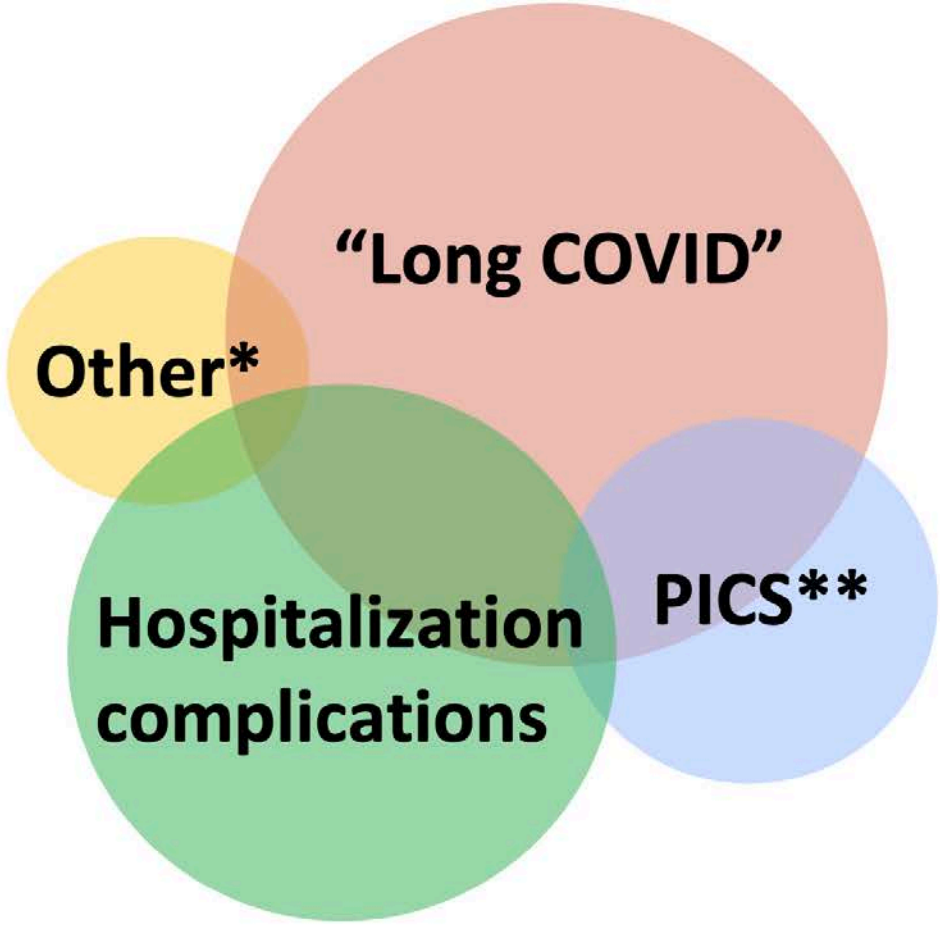
- Most people with COVID-19 will recover fully from their symptoms
- Number of people experience ongoing distressing physical symptoms
- 1 in 20 can be ill for at least 8 weeks and one in 45 for 12 weeks or more
- All ages from all backgrounds can be affected



https://covid.joinzoe.com/post/long-covid

Lopez-Leon S. et. al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv* [Preprint]. 2021 Jan 30

POST-ACUTE EFFECTS OF COVID-19
HETEROGENEOUS, OVERLAPPING, HARD TO DEFINE



*Multisystem inflammatory disorder, Guillain-Barre, among others
**Post-Intensive Care Syndrome

PEOPLE.COM › HEALTH

Gwyneth Paltrow Says Her Long-Haul COVID Symptoms Have Been 'Pretty Wild'

Paltrow, who tested positive for COVID-19 last year, said she's getting "better and better"

PUBLIC HEALTH

COVID long-haulers: Questions patients have about symptoms

APR 15, 2021

Sara Berg
Senior News Writer

PRINT PAGE

INSIDER

COVID long-haulers are killing themselves as symptoms become too painful to bear - but support groups offer relief

Cheryl Teh
Thu, April 15, 2021, 10:29 PM · 7 min read

Home / News / Health News

Long COVID Sufferers Are Seeking Disability Benefits. Will They Change the System?

People who are ill and unable to work long after a positive test for COVID-19 could help overhaul the delivery of disability benefits in the U.S.

By Chelsea Cirruzzo | April 15, 2021, at 6:15 a.m.

NORTH CAROLINA

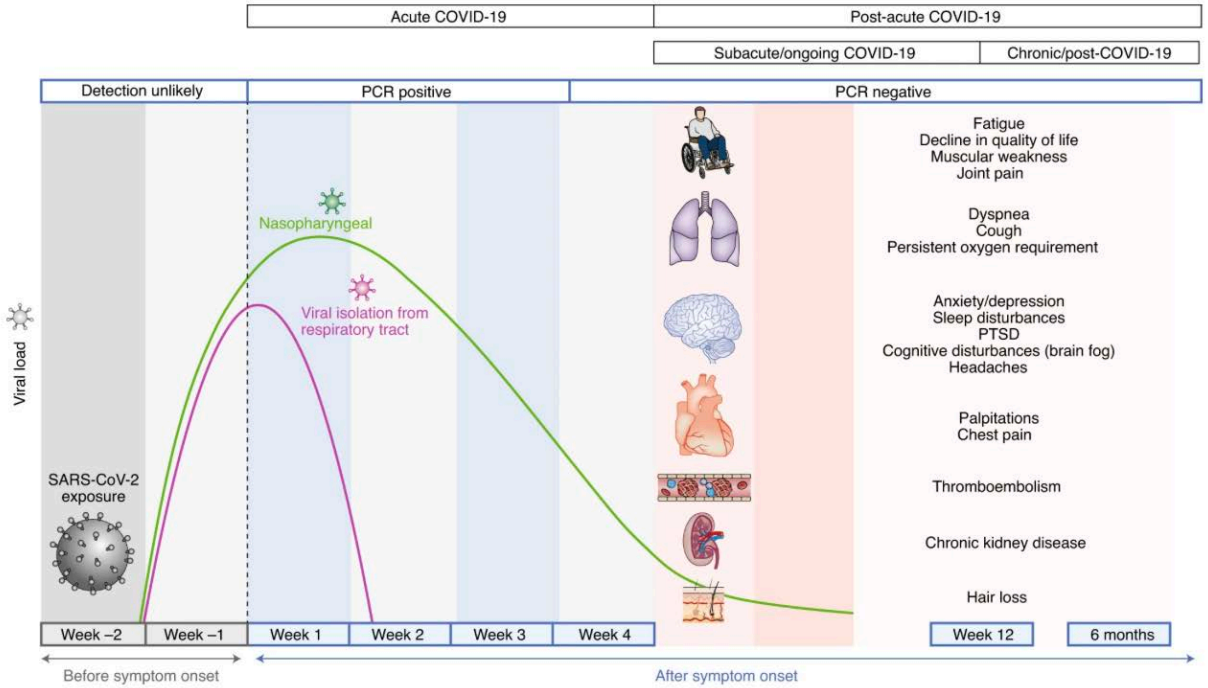
NC woman wrote her own obituary before dying from 'long haul' COVID

BY LAUREN LINDSTROM

APRIL 16, 2021 08:43 AM, UPDATED APRIL 16, 2021 12:03 PM

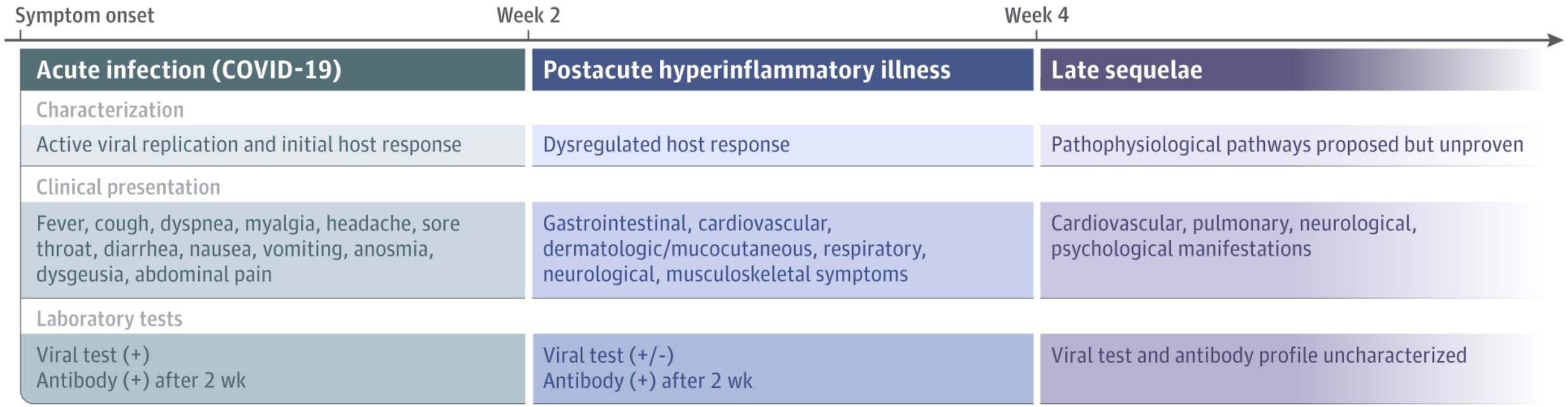
TIMELINE OF POST-ACUTE COVID-19

- Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms
- Beyond 4 weeks, replication-competent SARS-CoV-2 has not been isolated
- Post-acute COVID-19 - “Persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms”



Nalbandian A. et. Post-acute COVID-19 syndrome. *Nat Med*. 2021 Apr 27

PROPOSED FRAMEWORK AND TIMELINE OF THE SPECTRUM OF DISEASE DUE TO SARS-COV-2 INFECTION



The population-based framework refers to the fact that these illnesses are observed at the population level and not necessarily in any given individual

Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. *JAMA.* 2020

EPIDEMIOLOGY

Table 1 | Findings from clinical studies on the prevalence of post-acute COVID-19 syndrome

	Carfi et al.[3]	Halpin et al.[24]	Carvalho-Schneider et al.[21]	Chopra et al.[20]	Arnold et al.[22]	Moreno-Pérez et al.[23]	Moreno-Pérez et al.[23]	Garrigues et al.[26]	Huang et al.[5]
Site	Italy	United Kingdom	France	United States	United Kingdom	Spain	Spain	France	China
Number of participants	143	100	150	488	110	277	277	120	1,733
Follow-up									
Duration	2 months post-symptom onset	1–2 months post-discharge	2 months post-symptom onset	2 months post-discharge	3 months post-symptom onset	2–3 months post-COVID-19 onset	4 months post-COVID-19 onset	3–4 months post-admission	6 months post-symptom onset
Mode of follow-up evaluation	In person	Telephone survey	Telephone survey	Telephone survey	In person	In person	In person	Telephone survey	In person
Baseline characteristics									
Age (years)	Mean (s.d.) = 56.5 (14.6)	Median (ward/ICU) = 70.5/58.5	Mean (s.d.) = 45 (15)	NR	Median (IQR) = 60 (44–76)	Median (IQR) = 56 (42–67.5)	Median (IQR) = 56 (42–67.5)	Mean (s.d.) = 63.2 (15.7)	Median (IQR) = 57 (47–65)
Female (%)	37.1	46	56	NR	38.2	47.3	47.3	37.5	48
Acute COVID-19 features									
Oxygen therapy requirement (%)	53.8	78			75.4				75
Non-invasive ventilation (%)	14.7	30							6
Invasive ventilation (%)	4.9	1							1
ICU care (%)	12.6	32	0		16.4	8.7	8.7	20	4
Post-acute COVID-19									
≥1 symptom (%)	87.4		66	32.6	74	50.9			76
≥3 symptoms (%)	55.2								
General sequelae									
Fatigue (%)	53.1	64	40		39	34.8		55	63
Joint pain (%)	27.3		16.3		4.5	19.6			9
Muscular pain (%)						19.6			2
Fever (%)	0		0		0.9	0			0.1
Respiratory sequelae									
Dyspnea (%)	43.4	40	30	22.9	39	34.4	11.1	41.7	23
Cough (%)	~15			15.4	11.8	21.3	2.1	16.7	
Cardiovascular sequelae									
Chest pain (%)	21.7		13.1		12.7			10.8	5
Palpitations (%)			10.9						9
Neuropsychiatric sequelae									
Anxiety/depression (%)									23
Sleep disturbances (%)					24			30.8	26
PTSD (%)		31							
Loss of taste/smell (%)	~15		22.7	13.1	11.8	21.4		10.8–13.3	7–11
Headache (%)	~10				1.8	17.8	5.4		2
Gastrointestinal sequelae									
Diarrhea (%)					0.9	10.5			~5
Dermatologic sequelae									
Hair loss (%)								20	22
Skin rash (%)									3
Quality of life									
Scale	EuroQol visual analog scale	EQ-5D-5L			SF-36	EuroQol visual analog scale		EQ-5D-5L	EuroQol visual analog scale
Decline (percentage of patients reporting or yes/no)	44.1	Yes			Yes	Yes		Yes	Yes

IQR, interquartile range; NR, not reported; s.d., standard deviation; SF-36, 36-Item Short Form Survey.

EPIDEMIOLOGY

- Studies - early evidence to aid identification of people at high risk for post-acute COVID-19

- Severity of illness during acute COVID-19 has been significantly associated with
  - Presence or persistence of symptoms
  - Reduction in health-related quality of life scores
  - Pulmonary function abnormalities
  - Radiographic abnormalities in the post-acute COVID-19 setting

Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Arnold, D. T. et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*
Halpin, S. J. et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J. Med. Virol*

EPIDEMIOLOGY

- Additional associations factors
  - Pre-existing respiratory disease
  - Higher body mass index
  - Older age
  - Black, Asian and minority ethnic (BAME)
  - Dyspnea at 4–8 weeks follow-up

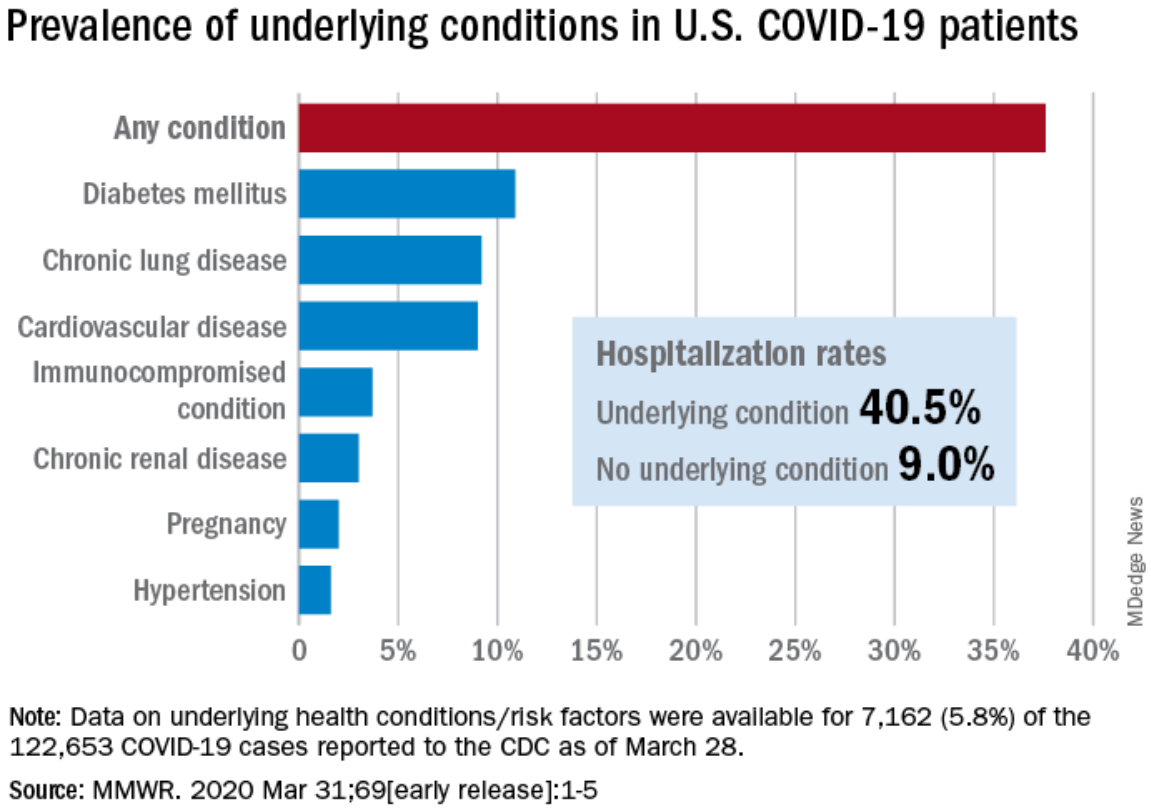
- Women more likely to experience fatigue and anxiety/depression at 6 months follow-up

Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Lee, A. M. et al. Stress and psychological distress among SARS survivors 1 year after the outbreak. *Can. J. Psychiatry*

EPIDEMIOLOGY

- Comorbidities, well-recognized determinants of increased severity and mortality related to acute COVID-19
  - Diabetes
  - Obesity
  - Chronic cardiovascular or kidney disease
  - Cancer
  - Organ transplant recipients

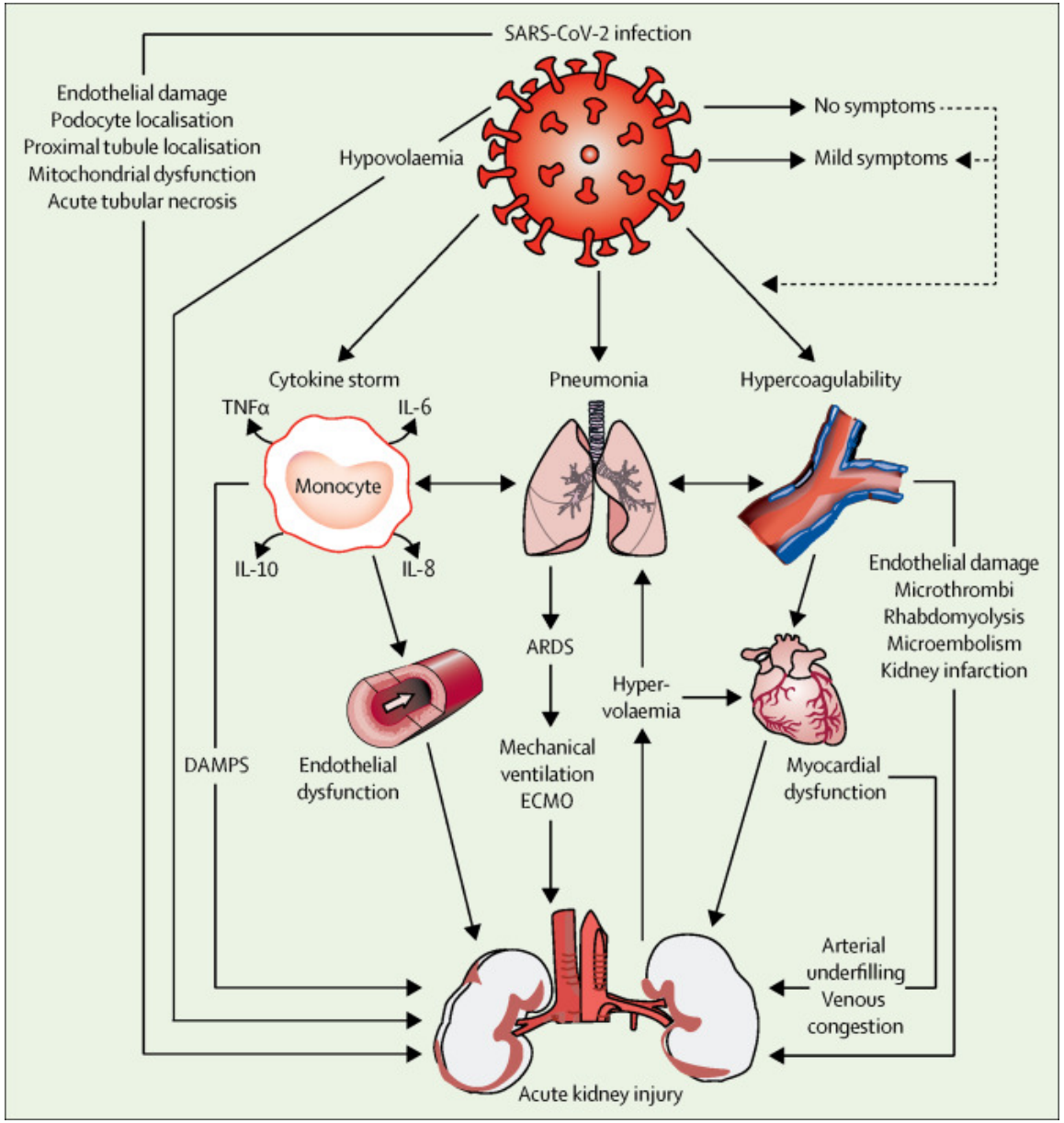
- Association with post-acute COVID-19 outcomes in those who have recovered remains to be determined



Gupta, A. et al. Extrapulmonary manifestations of COVID-19. *Nat. Med*
Williamson, E. J. et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*

PATHOPHYSIOLOGY

- Predominant pathophysiologic mechanisms of acute COVID-19 include the following:
  - Direct viral toxicity
  - Endothelial damage
  - Microvascular injury
  - Immune system dysregulation and stimulation of a hyperinflammatory state
  - Hypercoagulability with resultant in situ thrombosis and macrothrombosis
  - Maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway



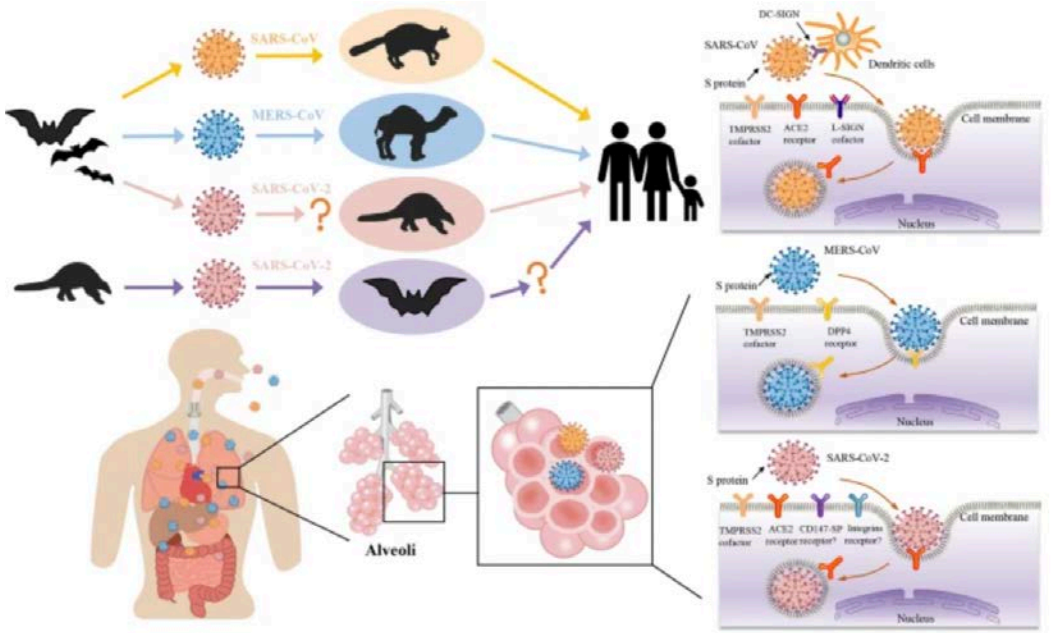
Gupta, A. et al. Extrapulmonary manifestations of COVID-19. *Nat. Med*
Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med*. 2020

PATHOPHYSIOLOGY

- Overlap of post-acute COVID-19 sequelae of with those of SARS and MERS may be explained by phylogenetic similarities between responsible pathogenic coronaviruses

- Overlap of genomic sequence identity of SARS-CoV-2
  - 79% with SARS-CoV-1
  - 50% with MERS-CoV

- SARS-CoV-1 and SARS-CoV-2 share same host cell receptor ACE2



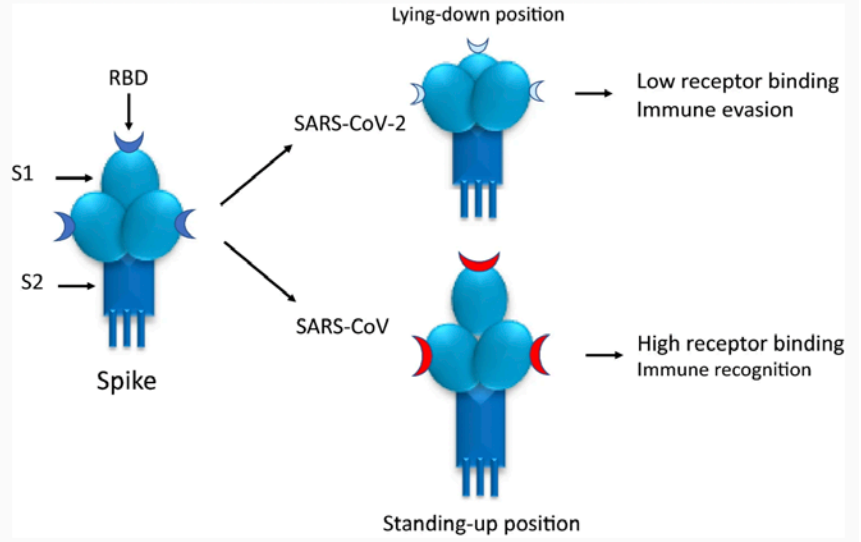
Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*

Hu, B., Guo, H., Zhou, P. & Shi, Z.-L.Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.*

Zhu, Z., Lian, X., Su, X. *et al.* From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. *Respir Res*

PATHOPHYSIOLOGY

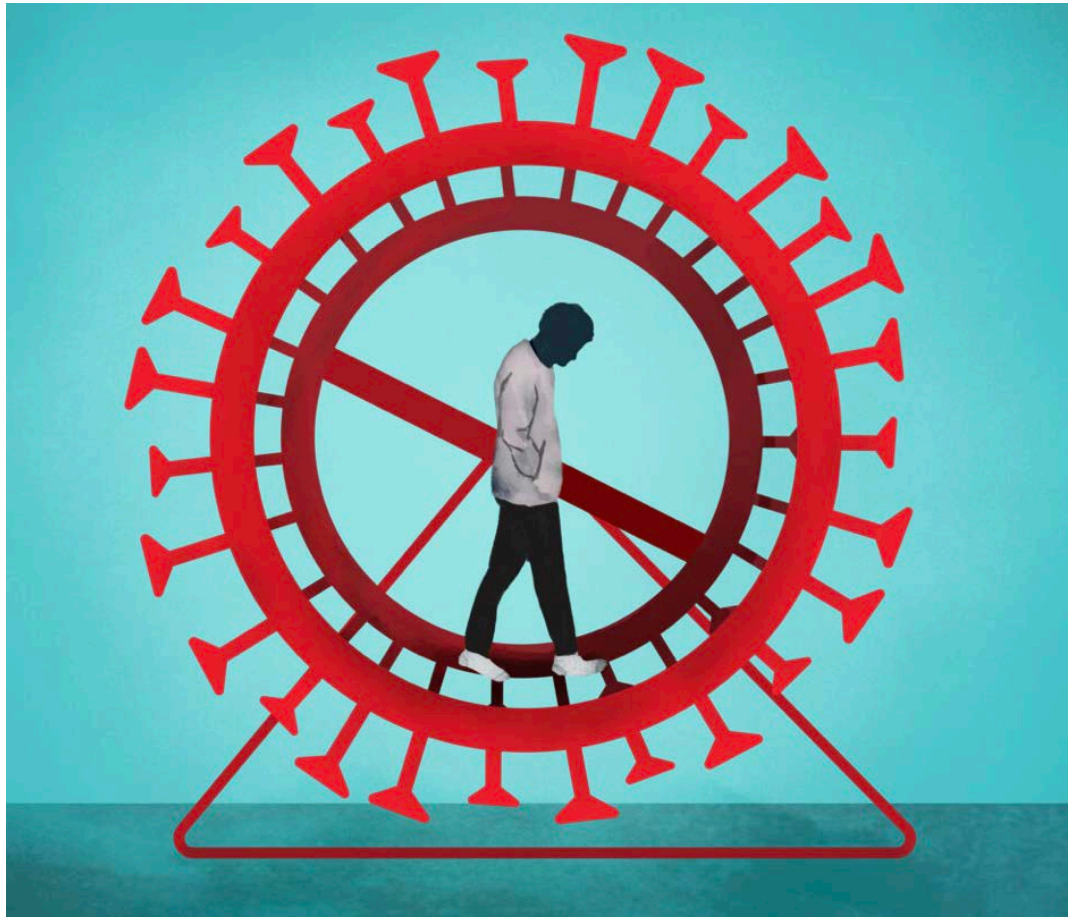
- Mechanisms probably contributed to more effective and widespread transmission of SARS-CoV-2
  - Higher affinity of SARS-CoV-2 for ACE2 compared with SARS-CoV-1
  - Spike gene in SARS-CoV-2 has 73% amino acid similarity with SARS-CoV-1 in receptor-binding domain of spike protein
  - Additional S1–S2 cleavage site in SARS-CoV-2 enables more effective cleavage by host proteases and facilitates more effective binding



Shang, J. et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature*
Wrobel, A. G. et al. SARS-CoV-2 and bat RaTG13 spike glycoprotein structures inform on virus evolution and furin-cleavage effects. *Nat. Struct. Mol. Biol.*
Rossi, G.A., Sacco, O., Mancino, E. *et al.* Differences and similarities between SARS-CoV and SARS-CoV-2: spike receptor-binding domain recognition and host cell infection with support of cellular serine proteases. *Infection*

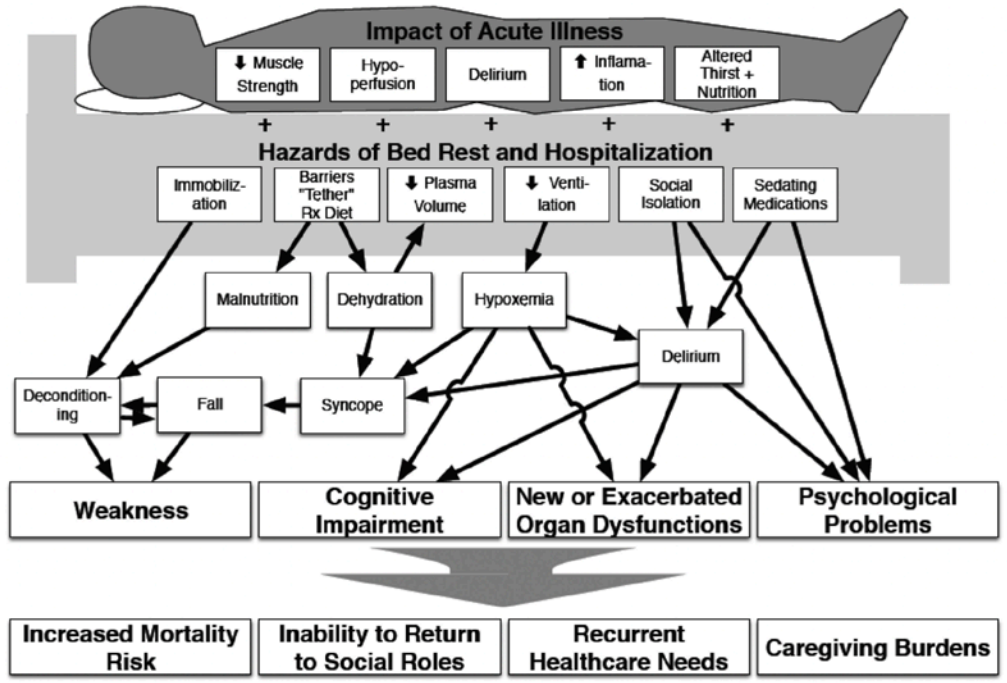
PATHOPHYSIOLOGY

- Potential mechanisms contributing to pathophysiology of post-acute COVID-19 include
  - Virus-specific pathophysiologic changes
  - Immunologic aberrations and inflammatory damage in response to acute infection
  - Expected sequelae of post-critical illness



POST-INTENSIVE CARE SYNDROME

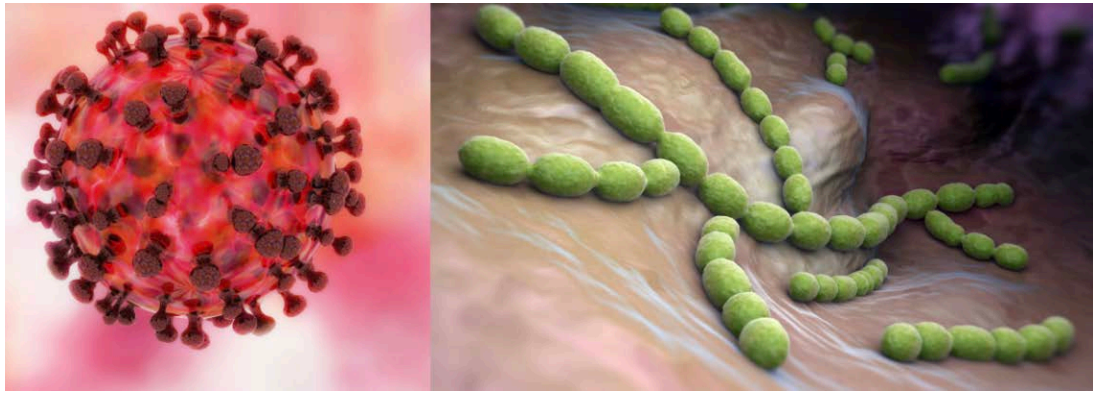
- Well recognized
- Includes new or worsening abnormalities in physical, cognitive and psychiatric domains after critical illness
- Multifactorial
  - Microvascular ischemia and injury
  - Immobility and metabolic alterations during critical illness



Needham, D. M. et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. *Am. J. Respir. Crit. Care*
Pandharipande, P. P. et al. Long-term cognitive impairment after critical illness*. N. Engl. J. Med.*
Inoue, S. et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. *Acute Med. Surg.*
Kress, J. P. & Hall, J. B. ICU-acquired weakness and recovery from critical illness. *N. Engl. J. Med.*

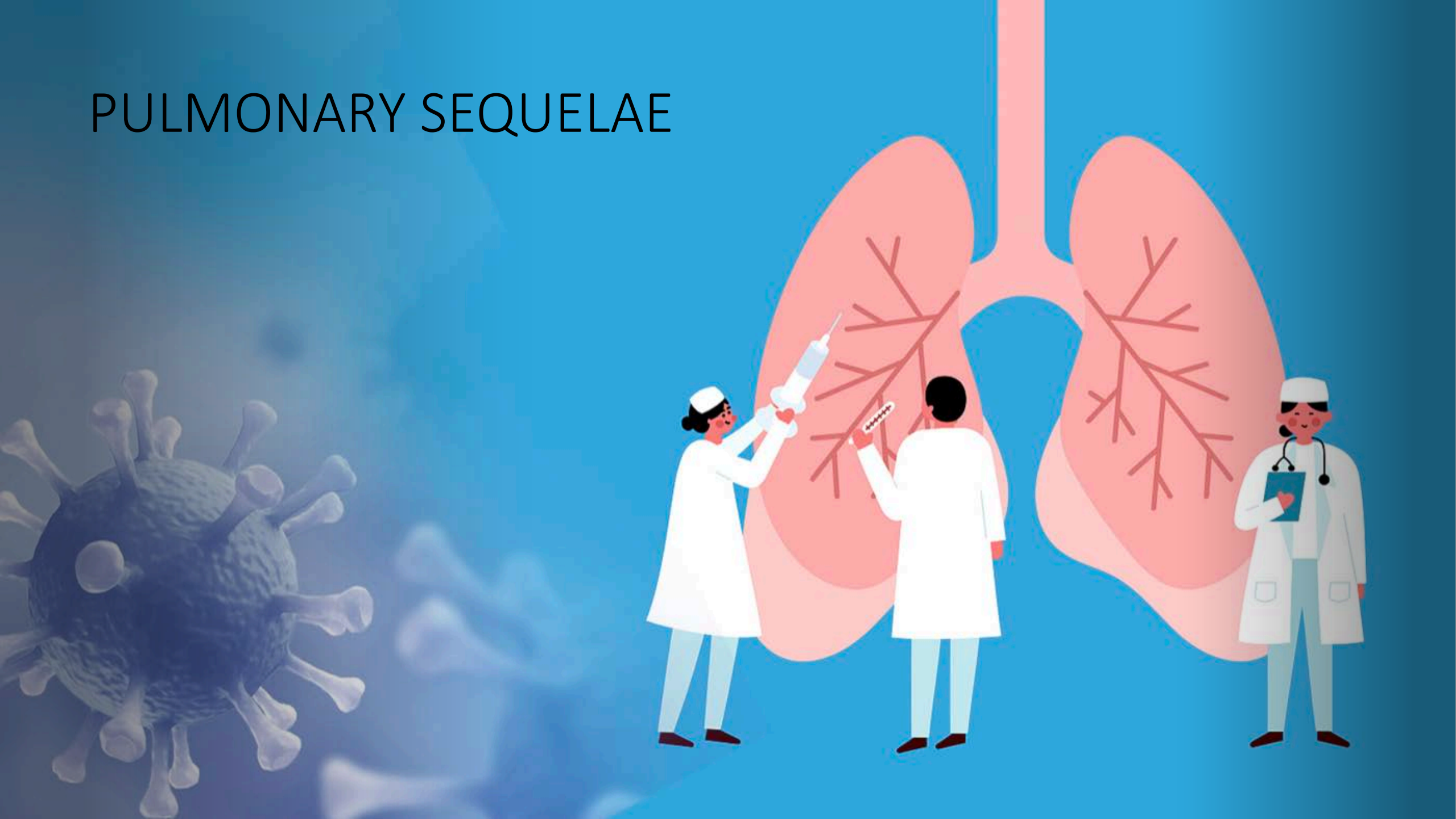
SECONDARY INFECTIONS

- 25–30% SARS survivors experience secondary infections
- Survivors of acute COVID-19 may be at increased risk of infections with bacterial, fungal or other pathogens
- Secondary infections do not explain persistent and prolonged sequelae of post-acute COVID-19



Zahariadis, G. et al. Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: variable incidence of atypical bacteria coinfection based on diagnostic assays. *Can. Respir. J.*
Zheng, Z., Chen, R. & Li, Y. The clinical characteristics of secondary infections of lower respiratory tract in severe acute respiratory syndrome. *Chin. J. Respir. Crit. Care Med.*
Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*
Lescure, F. X. et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect. Dis.*
Zhou, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*

PULMONARY SEQUELAE



EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- Spectrum of pulmonary manifestations
  - Dyspnea with or without chronic oxygen dependence
  - Difficult ventilator weaning
  - Fibrotic lung damage

- Dyspnea most common persistent symptom - 42–66% prevalence at 60–100 days follow-up

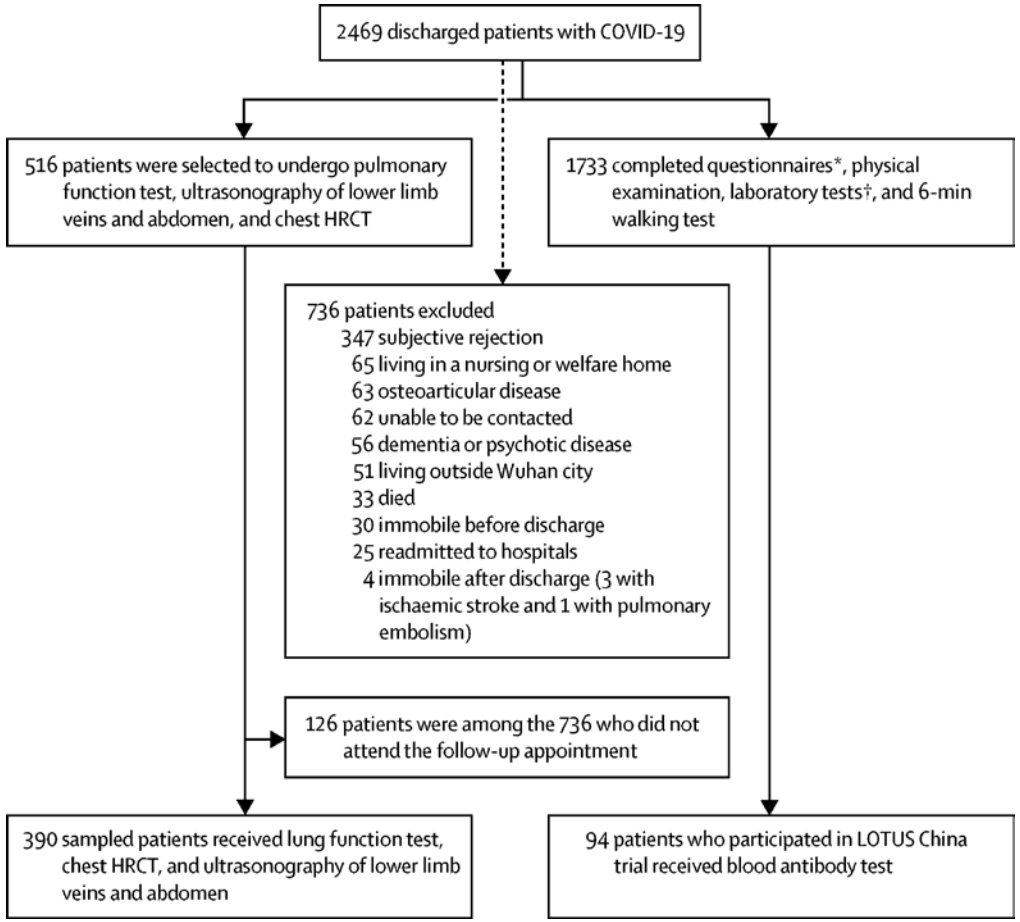
- Reduction in diffusion capacity most commonly reported physiologic impairment in post-acute COVID-19, with significant decrement directly related to severity of acute illness

- Less common, hospitalized COVID-19 survivors to have restrictive pulmonary physiology at 3 and 6 months

Carfi, A., Bernabei, R., Landi, F. & Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *J. Am. Med. Assoc*
Chopra, V., Flanders, S. A. & O'Malley, M. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann. Intern. Med*
Halpin, S. J. et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J. Med. Virol.*

PATHOLOGY AND PATHOPHYSIOLOGY

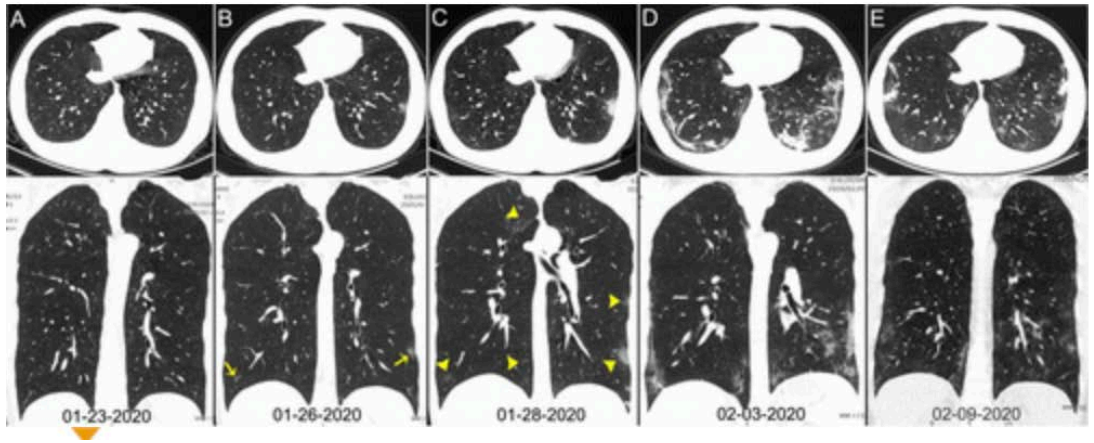
- 50% of 349 patients who underwent HRCT of the chest at 6 months had at least 1 abnormal pattern in the post-acute COVID-19 study
- Majority of abnormalities observed by CT were ground-glass opacities
- Long-term risks of chronic pulmonary embolism and consequent pulmonary hypertension are unknown at this time



Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*

PATHOLOGY AND PATHOPHYSIOLOGY

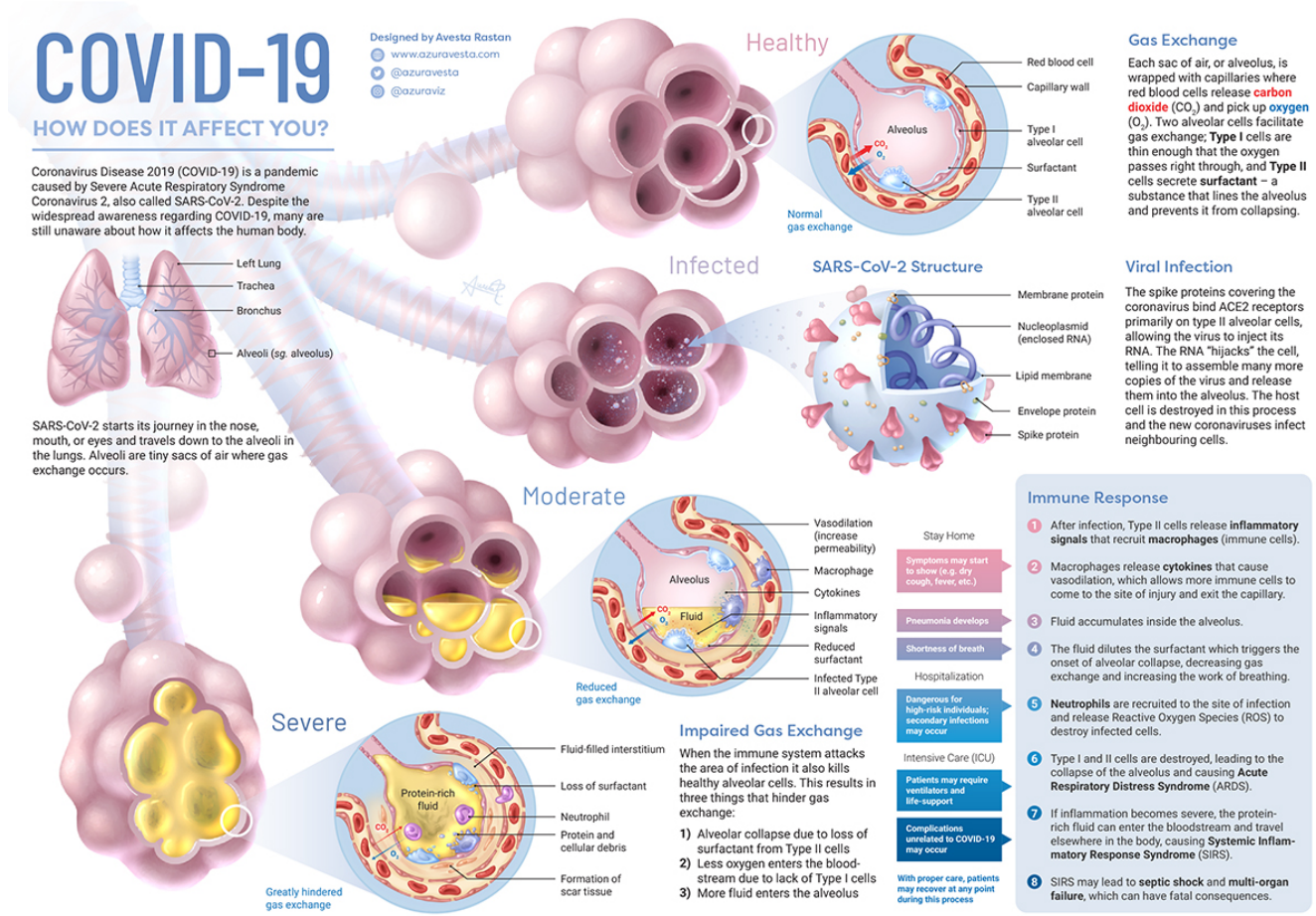
- Fibrotic changes on CT scans of chest
  - Reticulations or traction bronchiectasis
  - Observed 3 months after hospital discharge in approximately 25 and 65% of survivors in cohort studies of mild-to-moderate cases and mostly severe cases



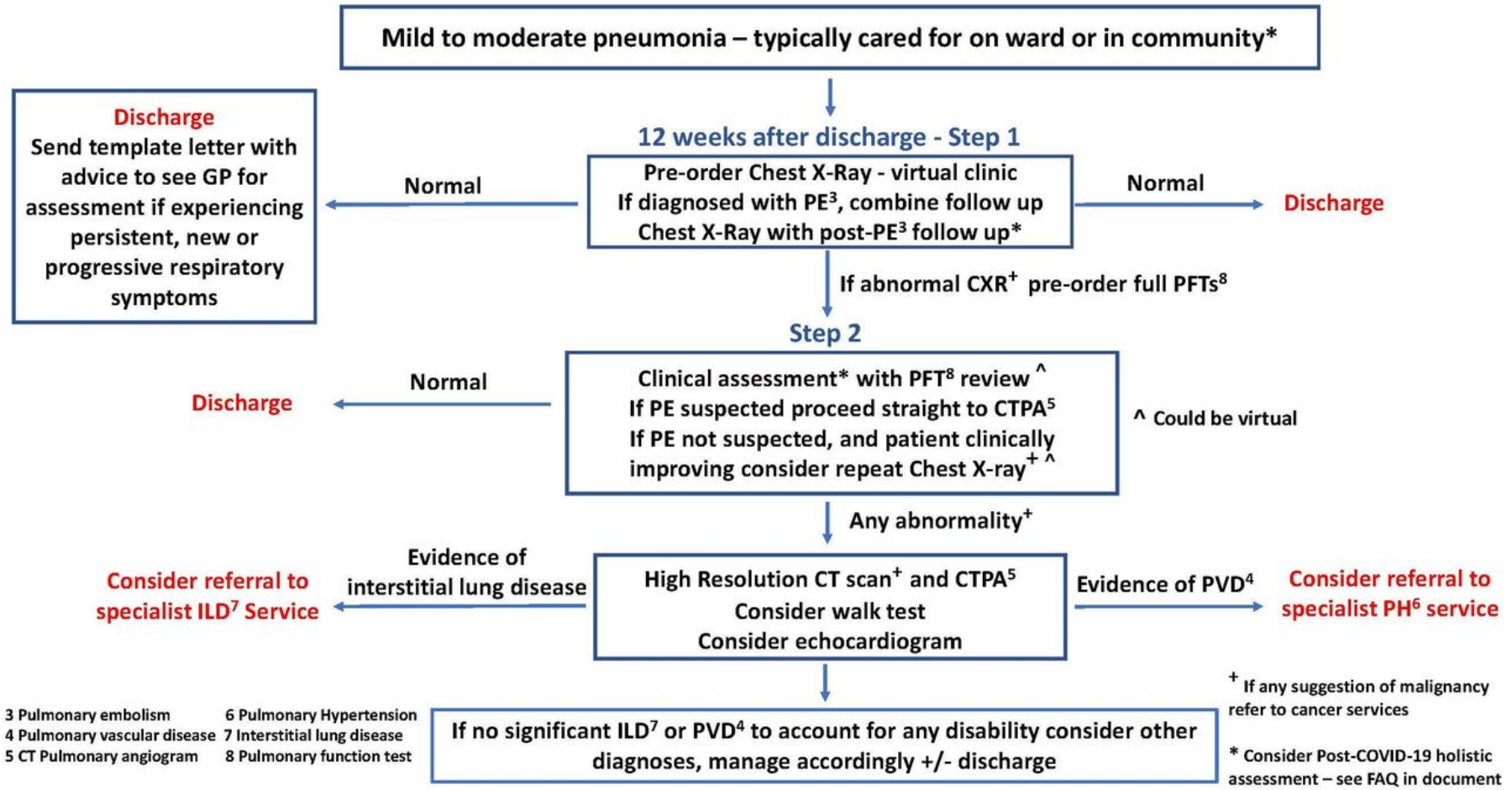
- Patients with greater severity of acute COVID-19 are at the highest risk for long-term pulmonary complications, including persistent diffusion impairment and radiographic pulmonary abnormalities

Zhao, Y. M. et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*
Shah, A. S. et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax*

PATHOLOGY AND PATHOPHYSIOLOGY

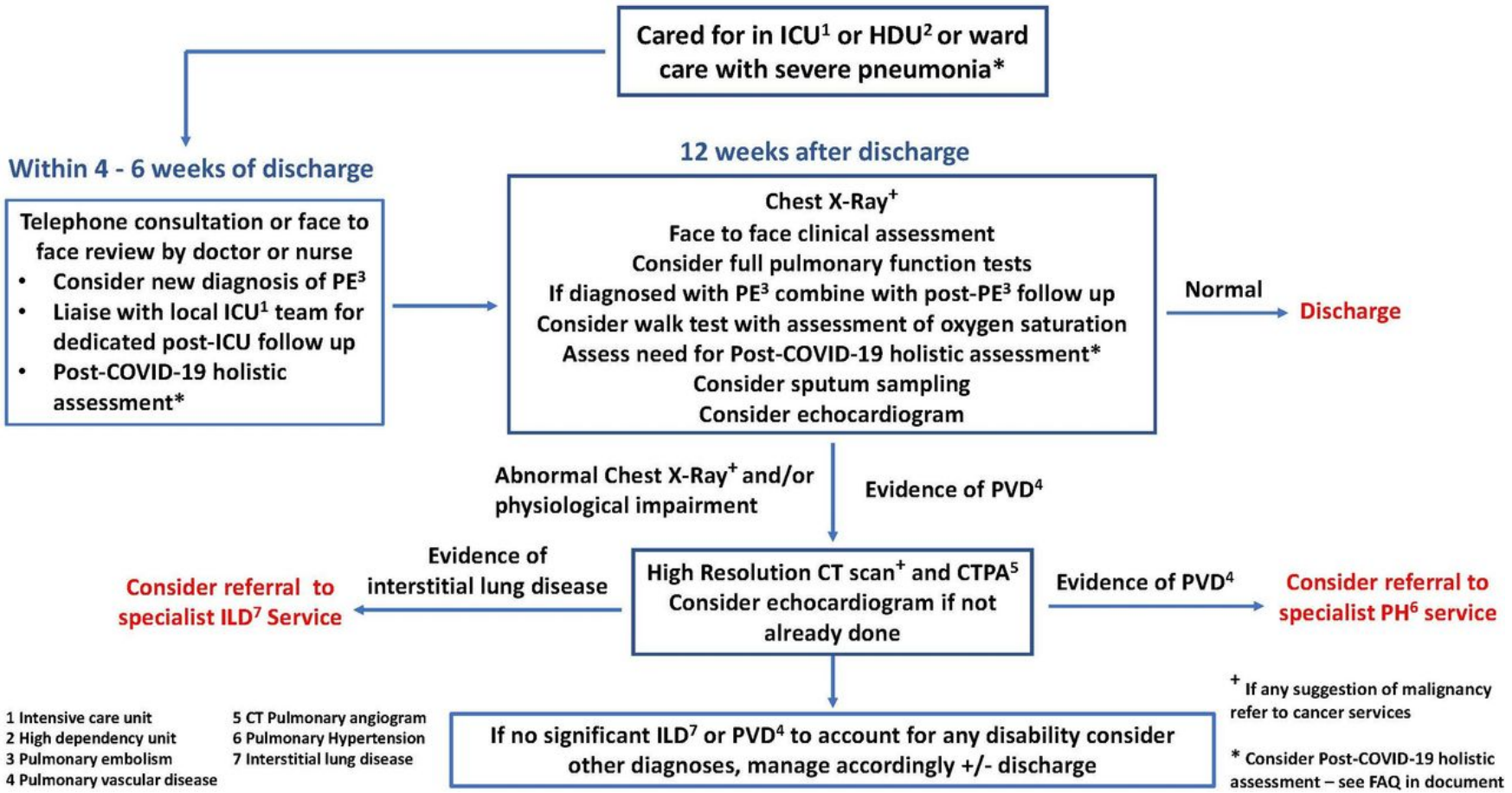


MANAGEMENT CONSIDERATIONS



George, P. M. et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*

MANAGEMENT CONSIDERATIONS

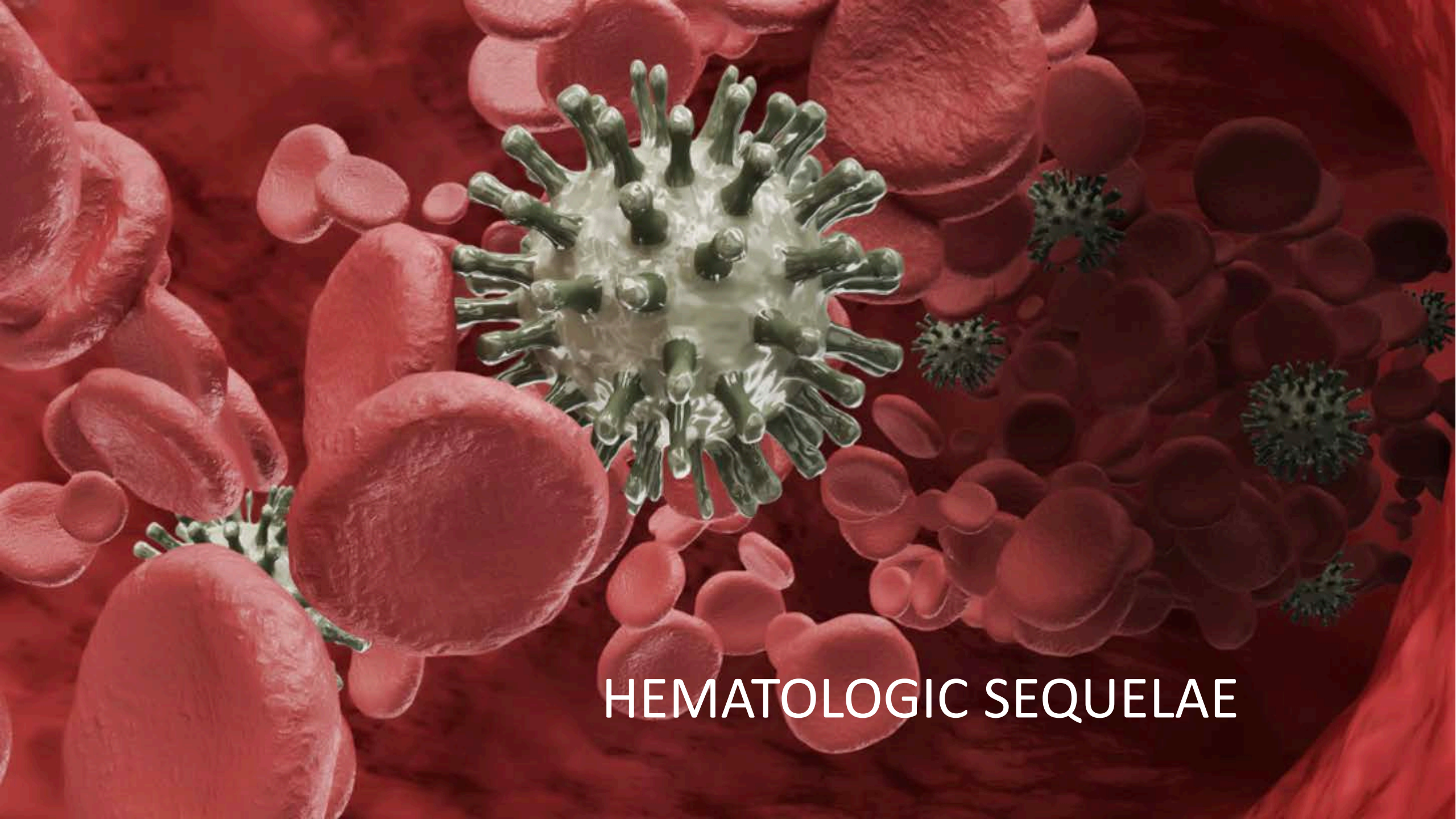


George, P. M. et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*

MANAGEMENT CONSIDERATIONS

- Treatment with corticosteroids may be beneficial in a subset of patients with post-COVID inflammatory lung disease
- Steroid use during acute COVID-19 not associated with diffusion impairment and radiographic abnormalities at 6 months follow-up in the post-acute COVID-19 study
- Lung transplantation has previously been performed for fibroproliferative lung disease after ARDS due to influenza A (H1N1) infection and COVID-19
- Clinical trials of antifibrotic therapies to prevent pulmonary fibrosis after COVID-19 underway

Myall, K. J. et al. Persistent post-COVID-19 inflammatory interstitial lung disease: an observational study of corticosteroid treatment. *Ann. Am. Thorac. Soc*
Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Chang, Y. et al. Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation*



HEMATOLOGIC SEQUELAE

EPIDEMIOLOGY

- Rate of venous thromboembolism (VTE) in post-acute COVID-19 setting - <5%

- A single-center report of 163 patients without post-discharge thromboprophylaxis suggested a 2.5% cumulative incidence of thrombosis at 30 days following discharge, with median duration to these events 23 days post-discharge

- This same study including other multiple studies have shown 3.7% cumulative incidence of bleeding at 30 days post-discharge, mostly related to mechanical falls

Patell, R. et al. Post-discharge thrombosis and hemorrhage in patients with COVID-19. *Blood*
Roberts, L. N. et al. Post-discharge venous thromboembolism following hospital admission with COVID-19. *Blood*
Salisbury, R. et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. *Blood Adv.*

EPIDEMIOLOGY

- Prospective study from Belgium at 6 weeks post-discharge follow-up assessed D-dimer levels and venous ultrasound in 102 patients
  - 8% received post-discharge thromboprophylaxis
  - Only one asymptomatic VTE event

- China study - No DVT in 390 participants, selected using a stratified sampling procedure to include those with a higher severity of acute COVID-19, who had ultrasonography of lower extremities

- Ongoing studies, such as CORONA-VTE, CISCO-19 and CORE-19, will help to establish more definitive rates of such complications

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Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Spyropoulos, A. C. et al. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J. Thromb. Haemost.*
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PATHOLOGY AND PATHOPHYSIOLOGY

- COVID-19-associated coagulopathy is consistent with a hyperinflammatory and hypercoagulable state
- Disproportionately high rates (20–30%) of thrombotic rather than bleeding complications in acute COVID-19
- Risk of thrombotic complications in post-acute COVID-19 phase probably linked to duration and severity of a hyperinflammatory state, although how long this persists is unknown

Pavoni, V. et al. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J. Thromb. Thrombolysis*
Chaudhary, R., Kreutz, R. P., Bliden, K. P., Tantry, U. S. & Gurbel, P. A. Personalizing antithrombotic therapy in COVID-19: role of thromboelastography and thromboelastometry. *Thromb. Haemost.*

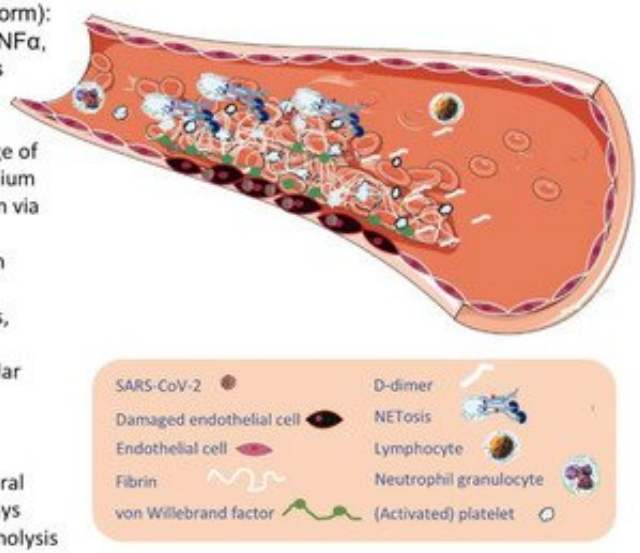
PATHOLOGY AND PATHOPHYSIOLOGY

Pathomechanism

Excessive immune response (cytokine storm): elevated IL-1, IL-6, TNFα, chemokine levels

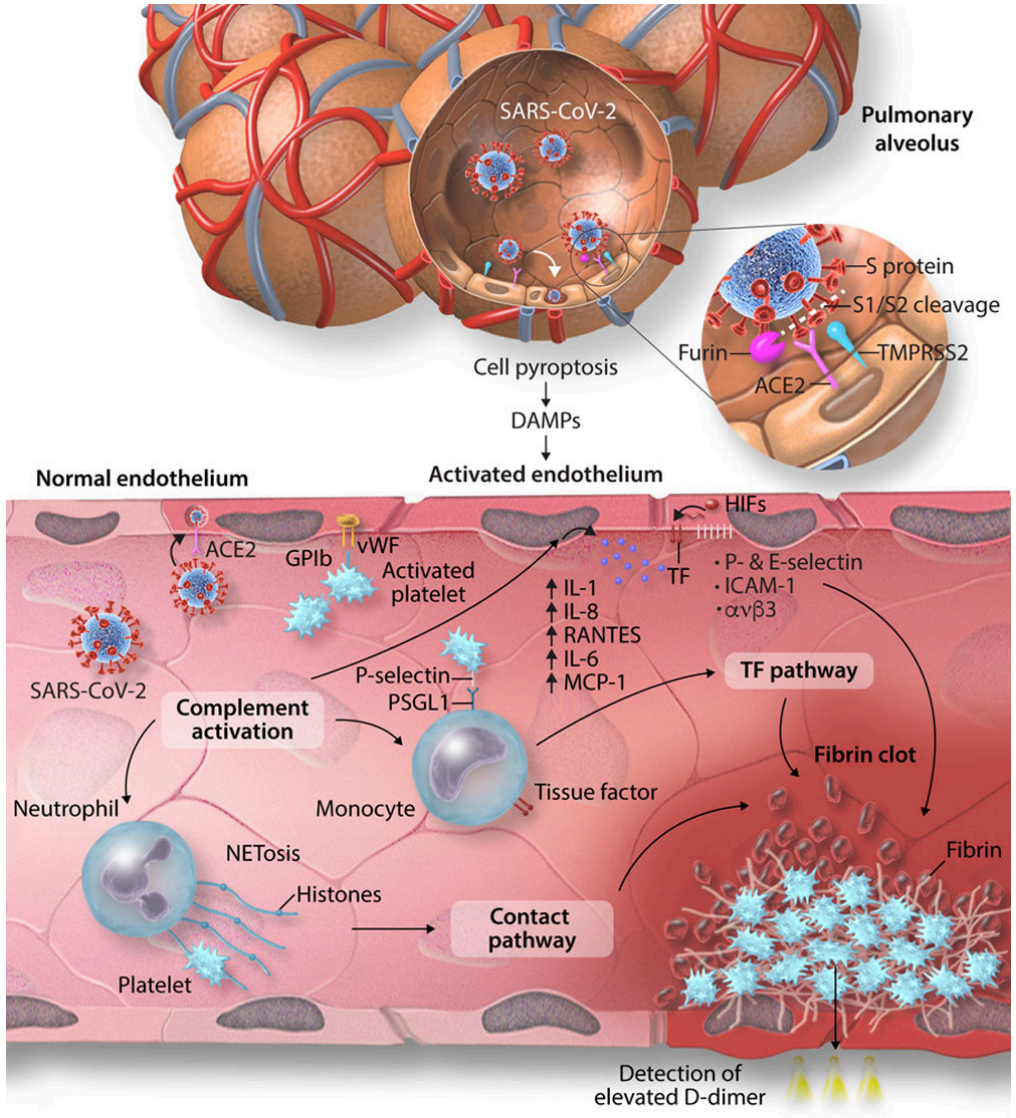
↓

- Activation and damage of the vascular endothelium
- Coagulation activation via multiple pathways ➔increased thrombin generation
- Activation of platelets, white blood cells
- Neutrophil extracellular trap formation
- Complement system activation
- Dysregulation of natural anticoagulant pathways
- Dysregulation of fibrinolysis



Laboratory findings

- Elevated D-dimer levels
- Increased FDP levels
- Slightly prolonged prothrombin time
- Thrombocytopenia, if present, is usually mild
- Elevated ferritin levels



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McFadyen JD, Stevens H, Peter K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. *Circ Res*. 2020

MANAGEMENT CONSIDERATIONS

- No conclusive evidence
- Extended post-hospital discharge up to 6 weeks and prolonged primary thromboprophylaxis up to 45 days in those managed as outpatients may have a more favorable risk–benefit ratio in COVID-19
- Elevated D-dimer levels in addition to comorbidities such as cancer and immobility, may help to risk stratify patients at highest risk of post-acute thrombosis
- Individual patient-level considerations for risk versus benefit should dictate recommendations at this time

Bajaj, N. S. et al. Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: a trial sequential and cumulative meta-analysis. *PLoS Med.*
Chiasakul, T. et al. Extended vs. standard-duration thromboprophylaxis in acutely ill medical patients: a systematic review and meta-analysis. *Thromb. Res.*
Bikdeli, B. et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J. Am. Coll. Cardiol.*

MANAGEMENT CONSIDERATIONS

- Direct oral anticoagulants and low-molecular-weight heparin preferred anticoagulation agents over vitamin K antagonists
- Therapeutic anticoagulation for those with imaging-confirmed VTE recommended for ≥3 months
- Role of antiplatelet agents such as aspirin as an alternative for thromboprophylaxis in COVID-19 not yet been defined and currently being investigated as a prolonged primary thromboprophylaxis strategy in outpatients
- Physical activity and ambulation should be recommended to all patients when appropriate

Bikdeli, B. et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J. Am. Coll. Cardiol.*
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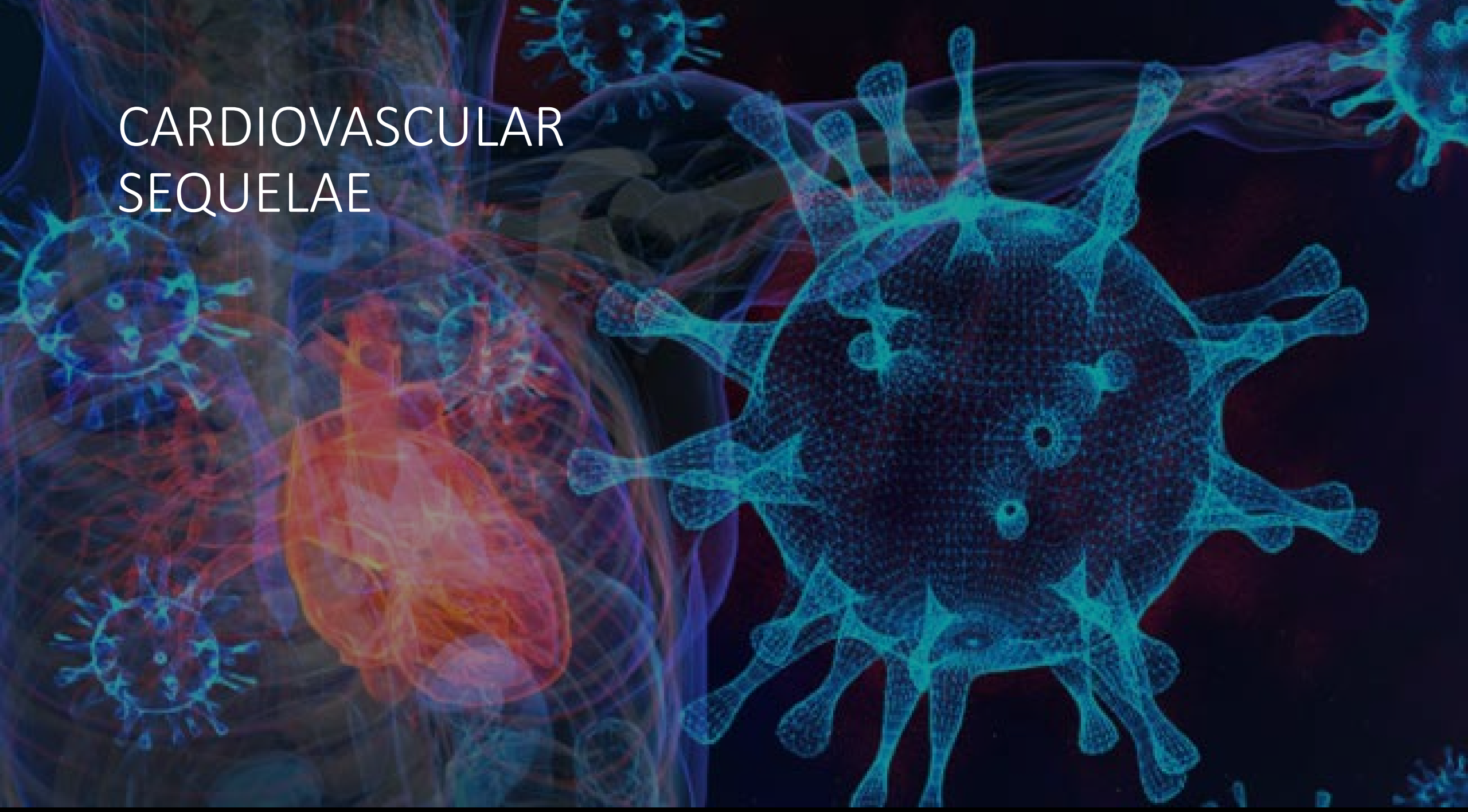
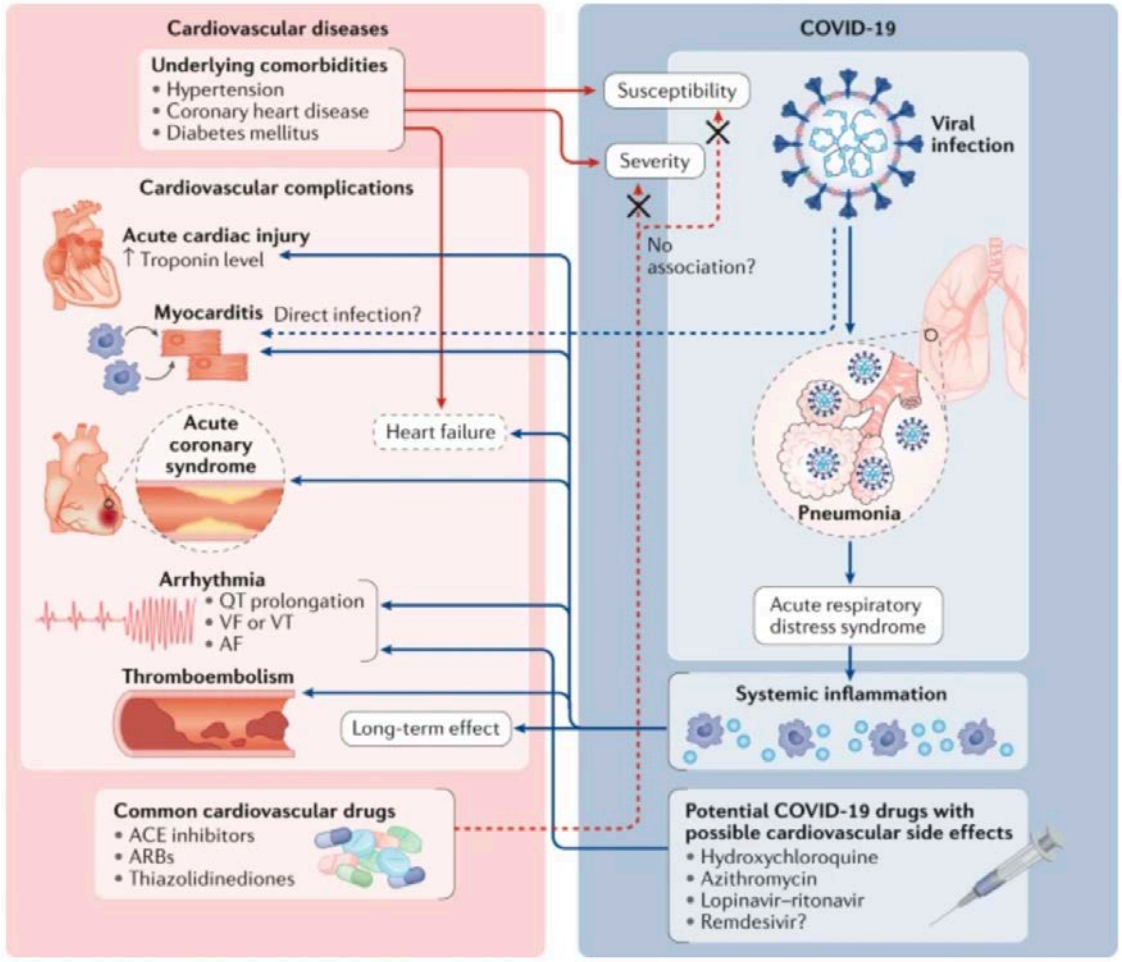
CARDIOVASCULAR SEQUELAE



EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- Chest pain reported in up to ~20% of COVID-19 survivors at 60 days follow-up
- Ongoing palpitations and chest pain reported in 9% and 5%, respectively, at 6 months follow-up
- Increased incidence of stress cardiomyopathy during COVID-19 pandemic compared with pre-pandemic periods (7.8% versus 1.5–1.8%, respectively), although mortality and re-hospitalization rates in these patients are similar



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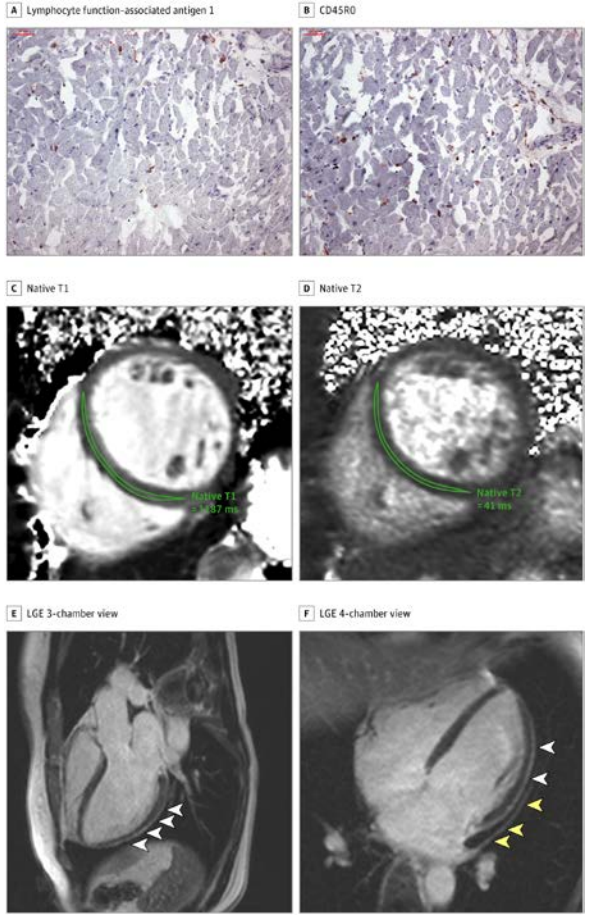
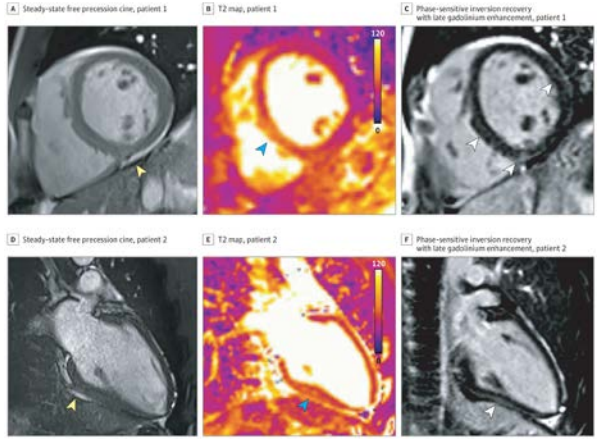
Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Jabri, A. et al. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. *JAMA Netw. Open*

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- Preliminary data with cardiac MRI - ongoing myocardial inflammation - rates as high as 60% more than 2 months after diagnosis of COVID-19

- In a study of 26 competitive college athletes with mild or asymptomatic SARS-CoV-2 infection, cardiac MRI revealed features diagnostic of myocarditis in 15% participants, and previous myocardial injury in 30.8% participants





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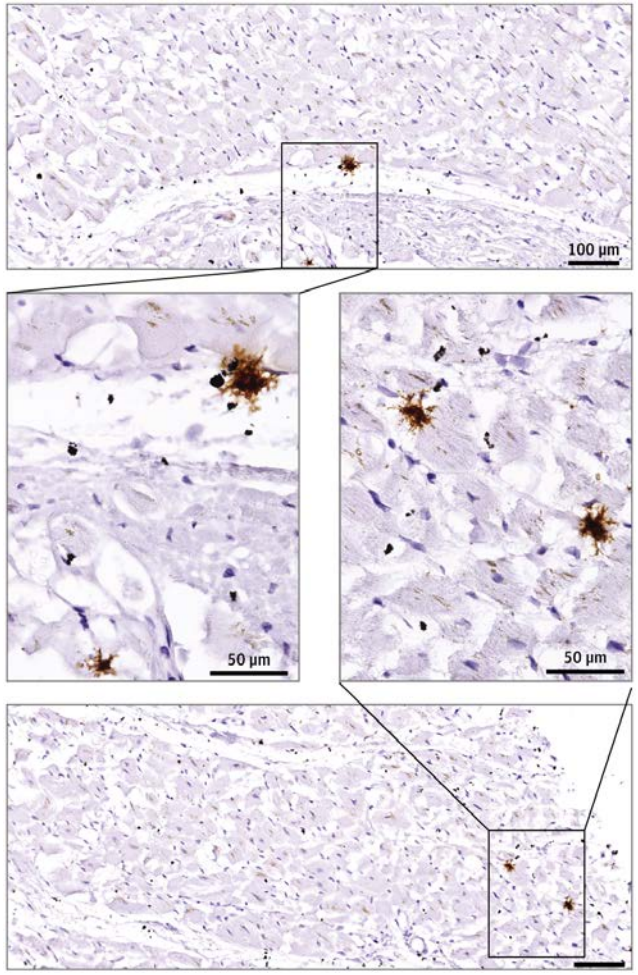
Rajpal, S. et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. *JAMA Cardiol.*

PATHOLOGY AND PATHOPHYSIOLOGY

- Mechanisms perpetuating cardiovascular sequelae in post-acute COVID-19 include
  - Direct viral invasion
  - Downregulation of ACE2
  - Inflammation and the immunologic response affecting structural integrity of myocardium, pericardium and conduction system

- Autopsy studies in 39 cases of COVID-19 detected virus in heart tissue of 62.5% of patients

- Subsequent inflammatory response may lead to cardiomyocyte death and fibro-fatty displacement of desmosomal proteins important for cell-to-cell adherence



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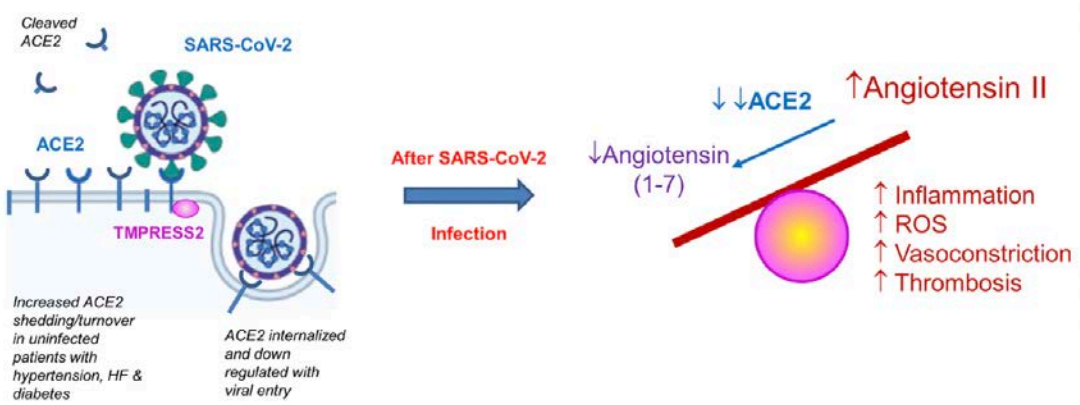
Gemayel, C., Pelliccia, A. & Thompson, P. D. Arrhythmogenic right ventricular cardiomyopathy. *J. Am. Coll. Cardiol.*
Siripanthong, B. et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*

PATHOLOGY AND PATHOPHYSIOLOGY

- Recovered patients may have persistently increased cardiometabolic demand, as observed in long-term evaluation of SARS survivors
- May be associated with reduced cardiac reserve, corticosteroid use and dysregulation of the renin–angiotensin–aldosterone system (RAAS)
- Myocardial fibrosis or scarring, and resultant cardiomyopathy from viral infection, can lead to re-entrant arrhythmias



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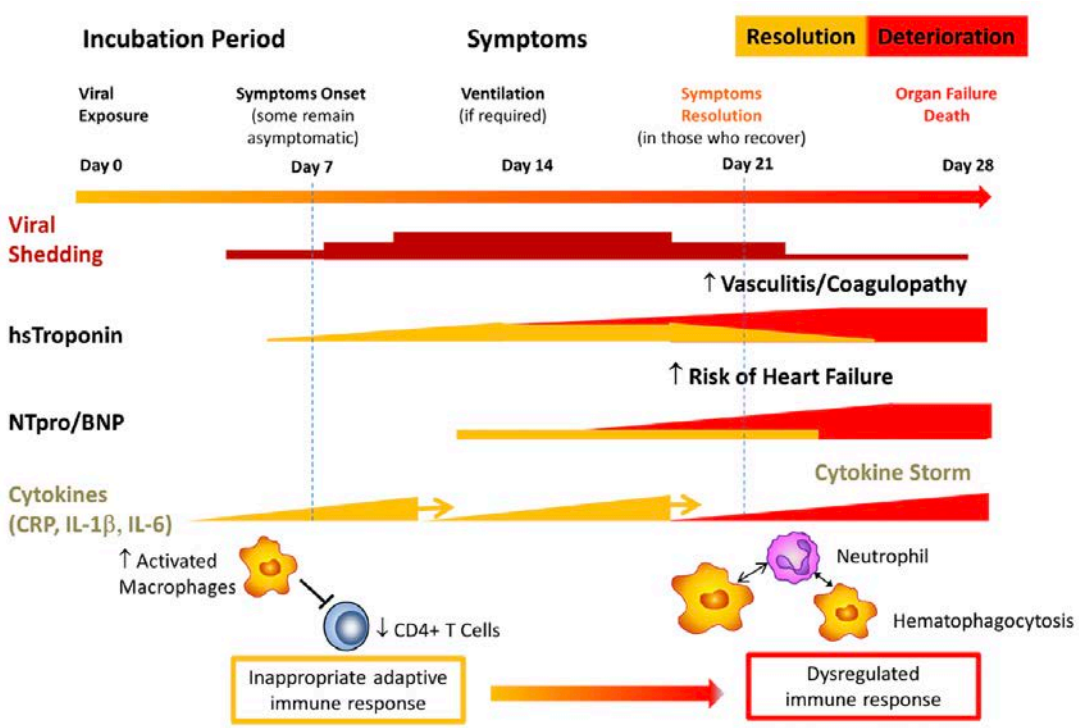
Liu, P. P., Blet, A., Smyth, D. & Li, H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*

PATHOLOGY AND PATHOPHYSIOLOGY

- COVID-19 may also perpetuate arrhythmias
  - Heightened catecholaminergic state due to cytokines such as IL-6, IL-1 and tumor necrosis factor-α
  - Prolonged ventricular action potentials by modulating cardiomyocyte ion channel expression

- Autonomic dysfunction after viral illness
  - Postural orthostatic tachycardia syndrome
  - Inappropriate sinus tachycardia
  - Result of adrenergic modulation



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Agarwal, A. K., Garg, R., Ritch, A. & Sarkar, P. Postural orthostatic tachycardia syndrome. *Postgrad. Med. J.*
Lau, S. T. et al. Tachycardia amongst subjects recovering from severe acute respiratory syndrome (SARS). *Int. J. Cardiol.*

POSTURAL TACHYCARDIA SYNDROME (POTS)

- Characterized by sustained heart rate increment of at least 30 beats/minute within 10 min of standing or head-up tilt in the absence of orthostatic hypotension
- Standing heart rate for all subjects is often greater than 120 beats/minute
- For individuals aged 12–19 years the required increment is at least 40 beats/minute
- Accompanied by symptoms of orthostatic intolerance
- > 6 months symptom duration

POTS ASSOCIATED SYMPTOMS

- Fatigue - most patients' chief complaint; many describe more fatigue than sleepiness, insomnia common
- Gastrointestinal - nausea, bloating, early satiety, constipation, diarrhea, motility disorders
- Urinary - increased frequency, urgency, incontinence, many dx with interstitial cystitis
- Pain - many diagnosed with fibromyalgia, small fiber neuropathy, hypermobile Ehlers-Danlos syndrome
- Migraine - extremely common (up to 90%)
- Cognitive - "brain fog"
- Psychiatric - anxiety, "hyperarousal," panic attacks
- Sleep - insomnia
- Allergic- skin flushing, hives, dermatographia, food and drug allergies (mast cell)

MANAGEMENT CONSIDERATIONS

- Serial clinical and imaging evaluation with electrocardiogram and echocardiogram at 4–12 weeks in patients with
  - Cardiovascular complications during acute infection
  - Persistent cardiac symptoms

- No evidence to support routine utilization of advanced cardiac imaging

- Competitive athletes with cardiovascular complications related to COVID-19
  - Avoid competitive sports or aerobic activity for 3–6 months until
    - Resolution of myocardial inflammation by cardiac MRI or
    - Troponin normalization

George, P. M. et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*
Desai, A. D., Boursiquot, B. C., Melki, L. & Wan, E. Y. Management of arrhythmias associated with COVID-19. *Curr. Cardiol. Rep.*
Hendren, N. S., Drazner, M. H., Bozkurt, B. & Cooper, L. T. Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation*
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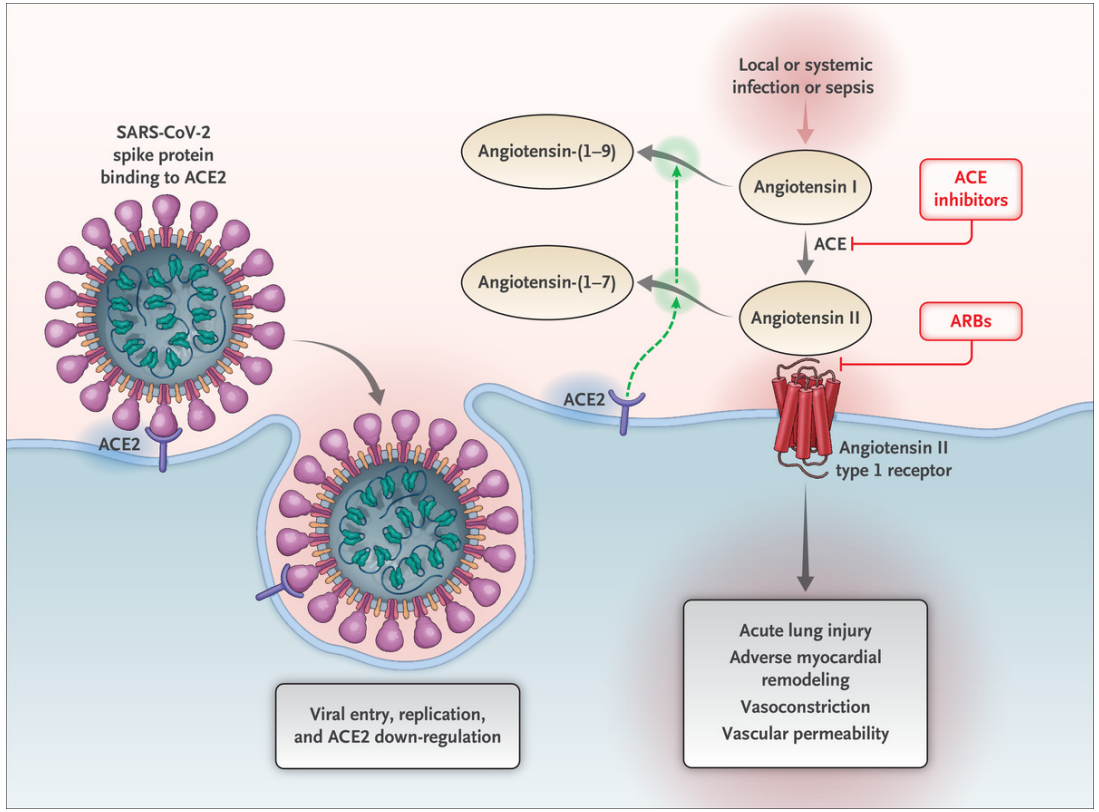
MANAGEMENT CONSIDERATIONS

- Use of RAAS inhibitors shown to be safe and should be continued in those with stable cardiovascular disease
- Abrupt cessation of RAAS inhibitors may be potentially harmful
- In patients with ventricular dysfunction, guideline-directed medical therapy should be initiated and optimized as tolerated



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Lopes, R. D. et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *J. Am. Med. Assoc.*

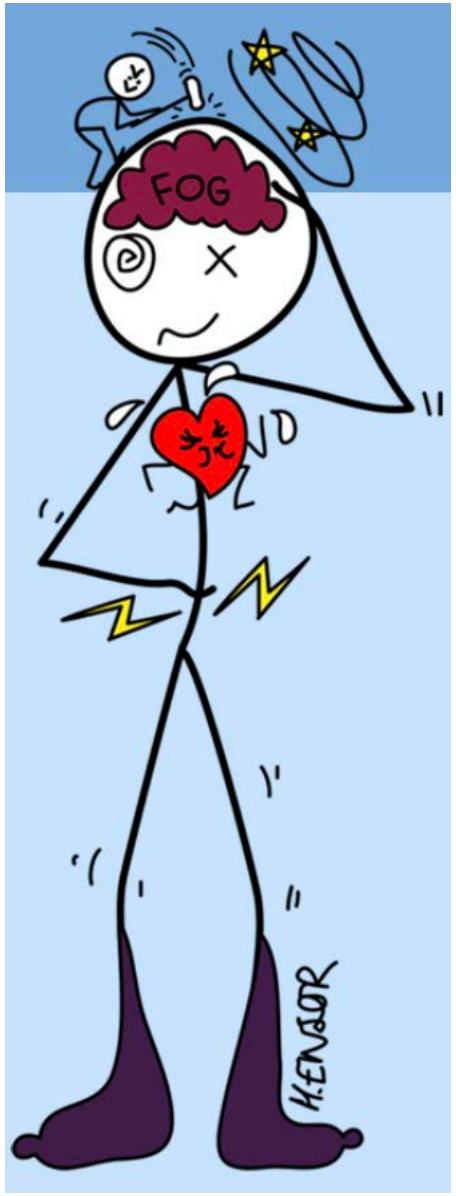
Vaduganathan, M. et al. Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *N. Engl. J. Med.* Guzik, T. J. et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res.*

Rey, J. R. et al. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. *Eur. J. Heart Fail.*

MANAGEMENT CONSIDERATIONS

- Patients with postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia may benefit from a low-dose beta blocker for heart rate management and reducing adrenergic activity

- Attention warranted to use of drugs such as anti-arrhythmic agents in patients with fibrotic pulmonary changes after COVID-19



Raj, S. R. et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation*
Kociol, R. D. et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation*

NEUROPSYCHIATRIC SEQUELAE

CLINICAL MANIFESTATIONS

- Similar to chronic post-SARS syndrome
- COVID-19 survivors have reported a post-viral syndrome of
  - Chronic malaise
  - Diffuse myalgia
  - Depressive symptoms
  - Non-restorative sleep

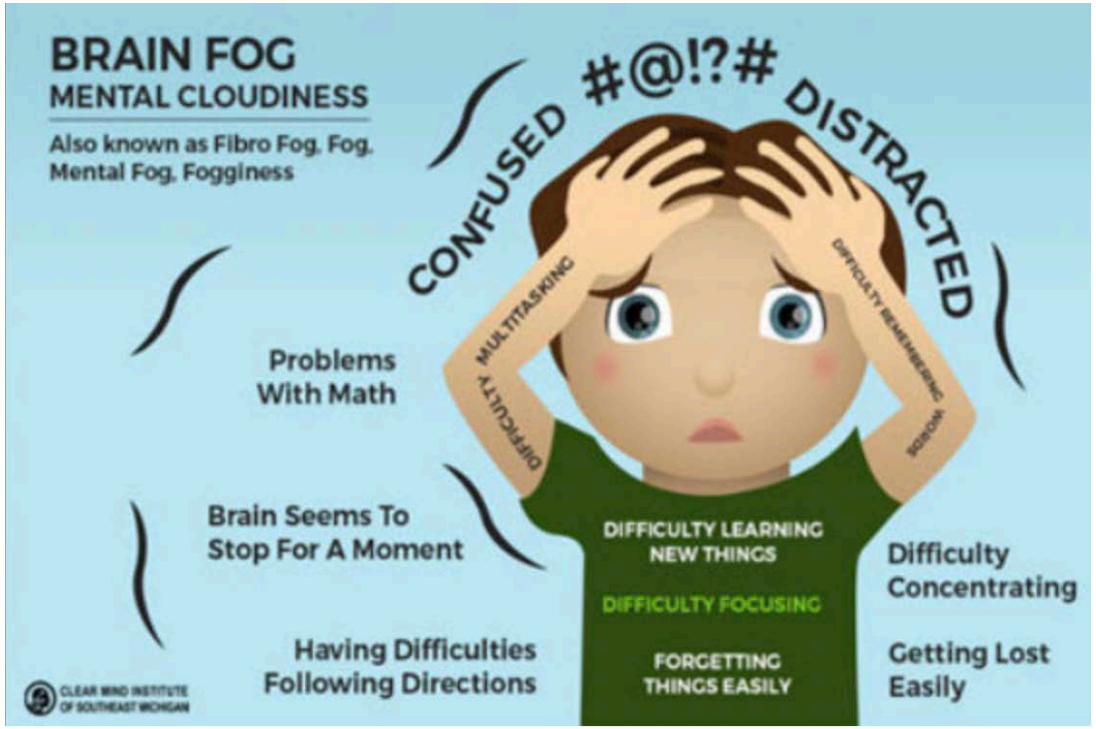
NEUROLOGIC COMPLICATIONS OF COVID-19

	SYMPTOMS OR SYNDROMES	RELATION TO DISEASE COURSE	FREQUENCY
Neurologic symptoms of COVID-19	Anosmia, dysgeusia, headache, dizziness, paresthesias	Early	Common
Neurologic complications of severe COVID-19	Encephalopathy, Stroke, ANE, seizures	Late	Common in severe disease
Direct involvement of CNS with SARS CoV-2	Meningoencephalitis	Unknown	Rare
Para-infectious and Post-infectious complications of SARS Cov-2	GBS, Miller Fisher syndrome, ADEM	7 to 10 days after onset	Unknown
COVID-19 in patients with existing neurologic illness	MS, MG, Epilepsy, Dementia, PD	N/A	Unknown

Fauci, A. International AIDS conference.
Nordvig, A. S. et al. Potential neurological manifestations of COVID-19. *Neurol. Clin. Pract.*

CLINICAL MANIFESTATIONS

- Other post-acute manifestations of COVID-19 include
  - Migraine-like headaches often refractory to traditional analgesics
  - Late-onset headaches ascribed to high cytokine levels
  - Loss of taste and smell
  - Cognitive impairment with or without fluctuations, including brain fog



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Arnold, D. T. et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*

Pozo-Rosich, P. Headache & COVID-19: a short-term challenge with long-term insights. In *Proc. AHSAM 2020 Virtual Annual Scientific Meeting*

Heneka, M. T., Golenbock, D., Latz, E., Morgan, D. & Brown, R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res. Ther.*

Ritchie, K., Chan, D. & Watermeyer, T. The cognitive consequences of the COVID-19 epidemic: collateral damage? *Brain Commun.*

CLINICAL MANIFESTATIONS

- Individuals with COVID-19 experience a range of psychiatric symptoms persisting or presenting months after initial infection
  - PTSD
  - Depression
  - Anxiety
  - Insomnia
  - Obsessive compulsive symptomatology

- At 6 months follow up, anxiety, depression and sleep difficulties present in approximately 25% patients

- Incidence of first and recurrent psychiatric illness between 14 and 90 days of diagnosis about 18.1%

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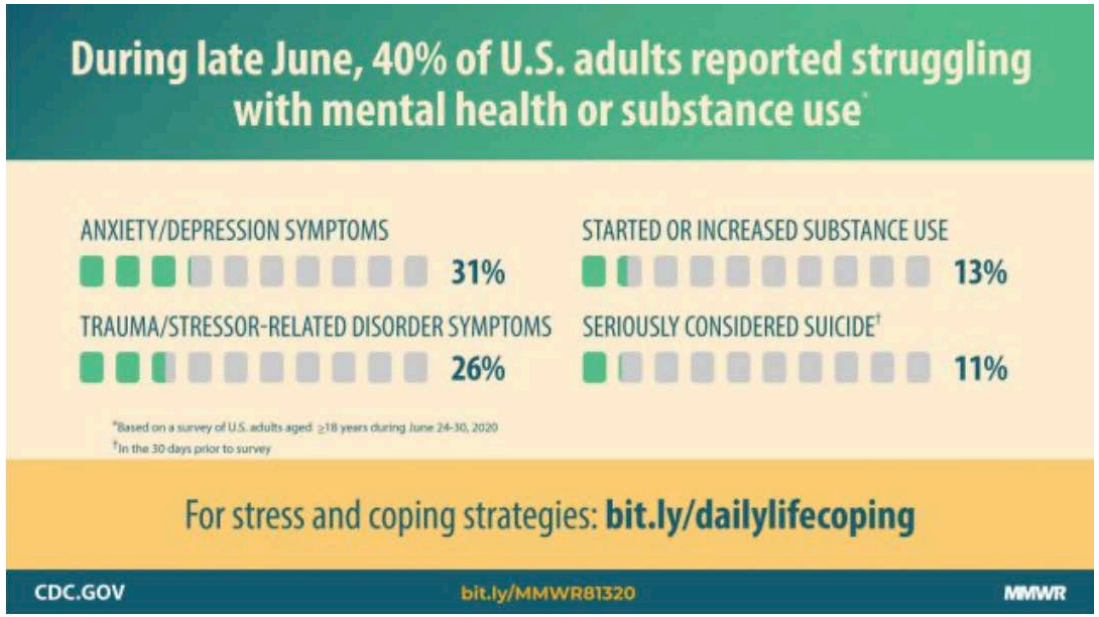
Rogers, J. P. et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*
Taquet, M., Luciano, S., Geddes, J. R. & Harrison, P. J. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*

CLINICAL MANIFESTATIONS

- 44,759 patients with no known previous psychiatric illness

- Probability of diagnosis of a new psychiatric illness within 90 days after COVID-19 diagnosis to be 5.8%
  - Anxiety disorder 4.7%
  - Mood disorder 2%
  - Insomnia 1.9%
  - Dementia (among those ≥65 years old) 1.6%

- Significantly higher than in matched control cohorts of patients diagnosed with influenza and other respiratory tract infections



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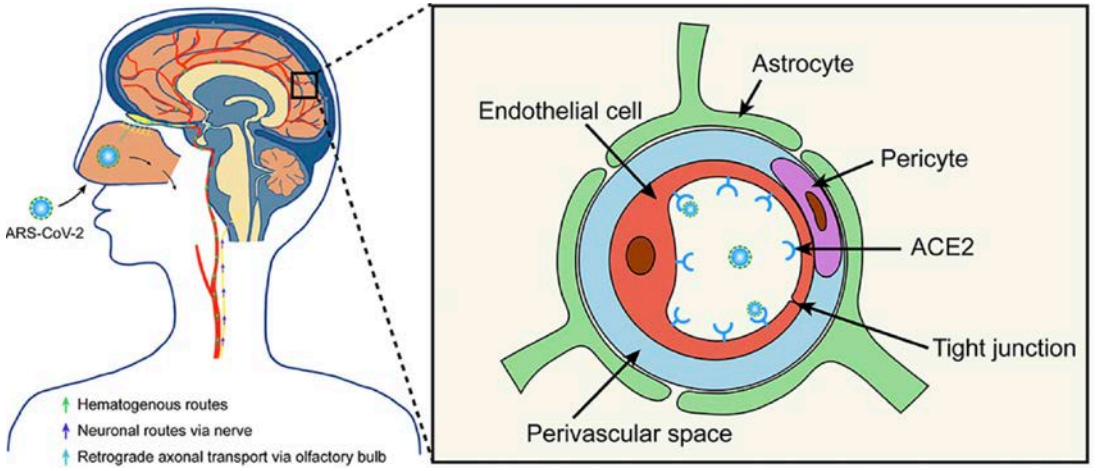
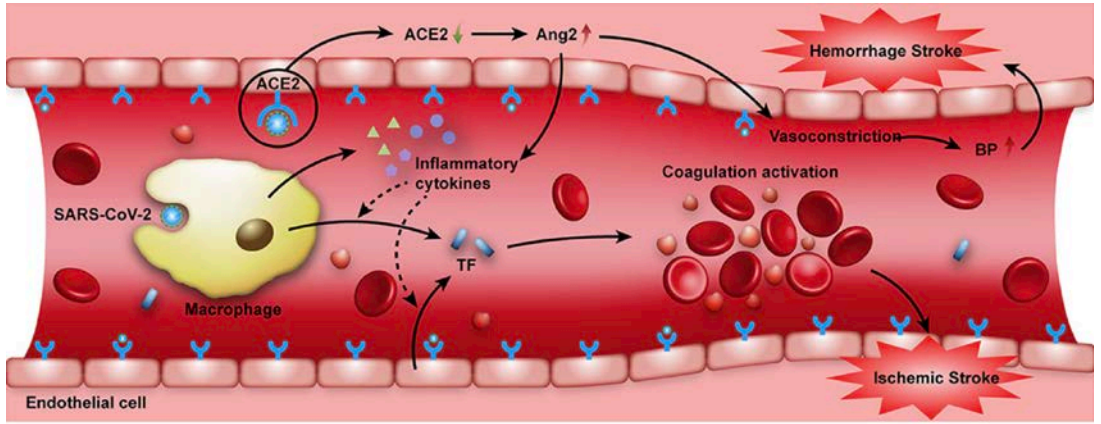
CLINICAL MANIFESTATIONS

- Lingering or permanent neurological deficits requiring extensive rehabilitation complications of acute COVID-19
  - Ischemic or hemorrhagic stroke
  - Hypoxic–anoxic damage
  - Posterior reversible encephalopathy syndrome
  - Acute disseminated myelitis

- Acute critical illness myopathy and neuropathies resulting during acute COVID-19 or from effect of neuromuscular blocking agents can leave residual symptoms persisting for weeks to months





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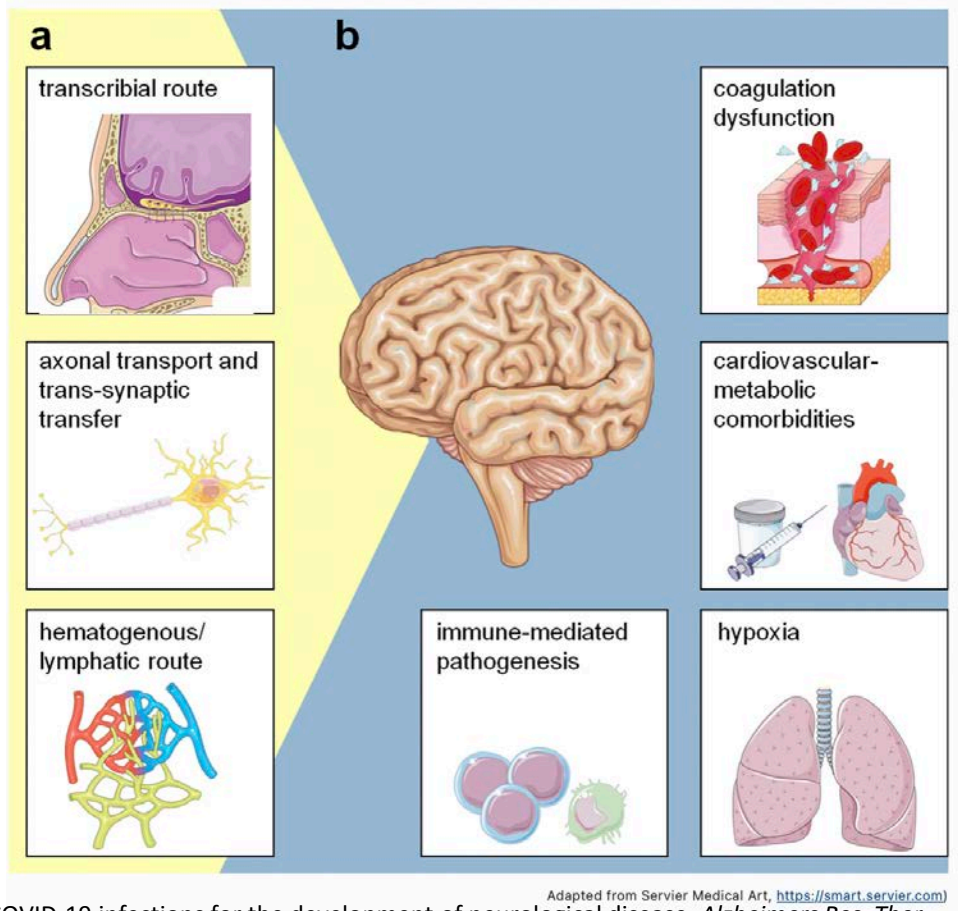
PATHOLOGY AND PATHOPHYSIOLOGY

- Mechanisms contributing to neuropathology in COVID-19
  - Direct viral infection
  - Severe systemic inflammation
  - Neuroinflammation
  - Microvascular thrombosis
  - Neurodegeneration

- No compelling evidence of SARS-CoV-2 infecting neurons



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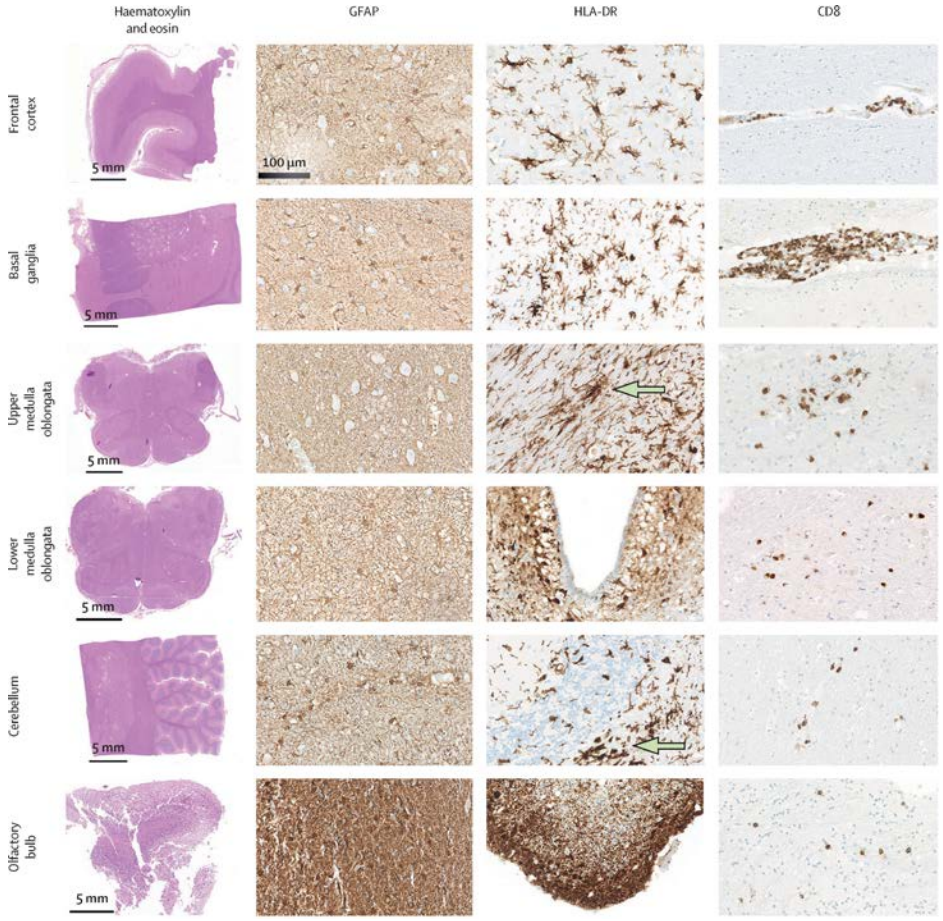
South, K. et al. Preceding infection and risk of stroke: an old concept revived by the COVID-19 pandemic. *Int J. Stroke* Desforges, M., Le Coupanec, A., Stodola, J. K., Meessen-Pinard, M. & Talbot, P. J. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.*

PATHOLOGY AND PATHOPHYSIOLOGY

- Autopsy series have shown that SARS-CoV-2 may cause changes in brain parenchyma and vessels
- Levels of immune activation directly correlate with cognitive–behavioral changes
- Persistent effects of COVID-19 may be due to
  - Inflammaging
  - Reduced ability to respond to new antigens
  - Accumulation of memory T cells



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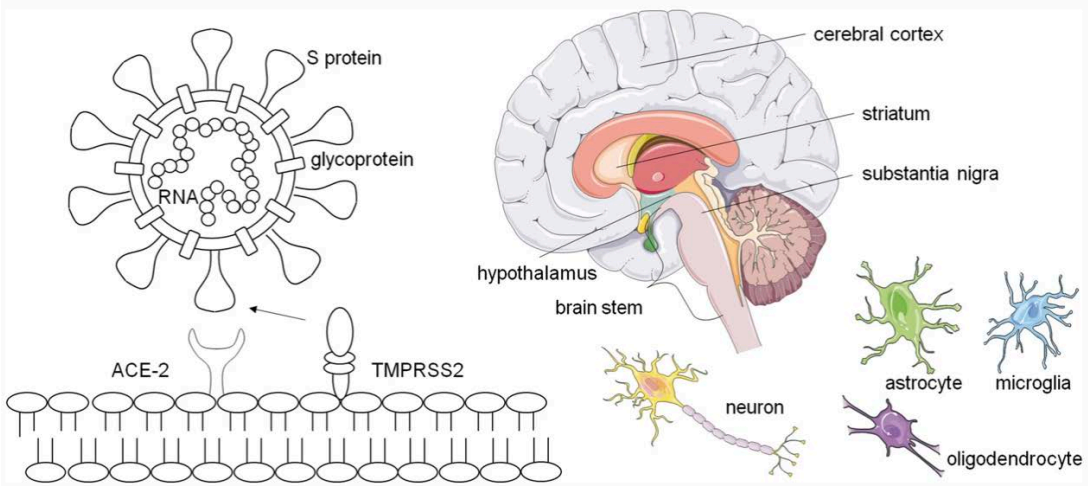
PATHOLOGY AND PATHOPHYSIOLOGY

- Other proposed mechanisms include
  - Dysfunctional lymphatic drainage from circumventricular organs
  - Viral invasion in extracellular spaces of olfactory epithelium
  - Passive diffusion and axonal transport through the olfactory complex

- Biomarkers of cerebral injury
  - Elevated peripheral blood levels of neurofilament light chain
  - In patients with COVID-19
  - More sustained increase in severe infections, suggesting possibility of more chronic neuronal injury



Adapted from Servier Medical Art, https://smart.servier.com)

Neurotropism of SARS-CoV-2. SARS-CoV-2 spike (S) proteins bind angiotensin-converting enzyme 2 (ACE-2) receptor of target cell. Cleavage of the S protein by type II transmembrane serine protease (TMPRSS2), facilitates viral entry. ACE-2 mRNA expression and double-positive ACE-2 + TMPRSS2 + cells have been identified, amongst others, on neurons and glial cells, in the cerebral cortex, striatum, hypothalamus, substantia nigra and brain stem, making the CNS potential direct targets of SARS-CoV-2 infection (

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Ameres, M. et al. Association of neuronal injury blood marker neurofilament light chain with mild-to-moderate COVID-19. *J. Neurol.*

PATHOLOGY AND PATHOPHYSIOLOGY

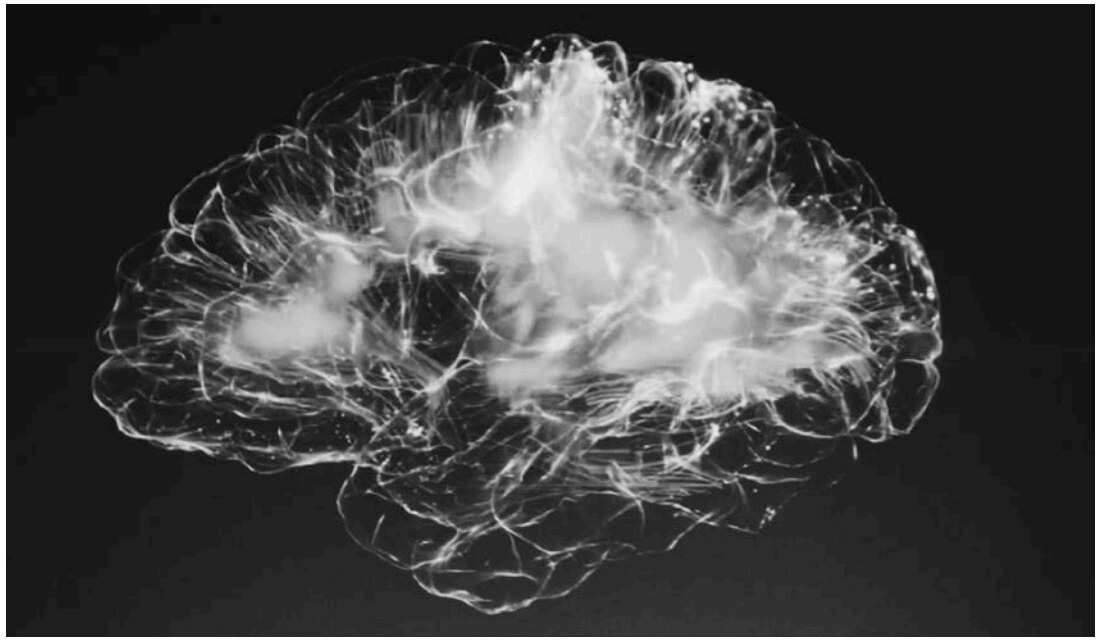
- Post-COVID brain fog in critically ill patients with COVID-19
  - Deconditioning
  - PTSD
  - Dysautonomia

- Long-term cognitive impairment well recognized in post-critical illness setting, occurring in 20–40% of patients discharged from an ICU

Kaseda, E. T. & Levine, A. J. Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors. *Clin. Neuropsychol.*
Novak, P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *eNeurologicalSci*
Miglis, M. G., Goodman, B. P., Chémali, K. R. & Stiles, L. Re: 'Post-COVID-19 chronic symptoms' by Davido et al. *Clin. Microbiol. Infect.*
Sakusic, A. & Rabinstein, A. A. Cognitive outcomes after critical illness. *Curr. Opin. Crit. Care*

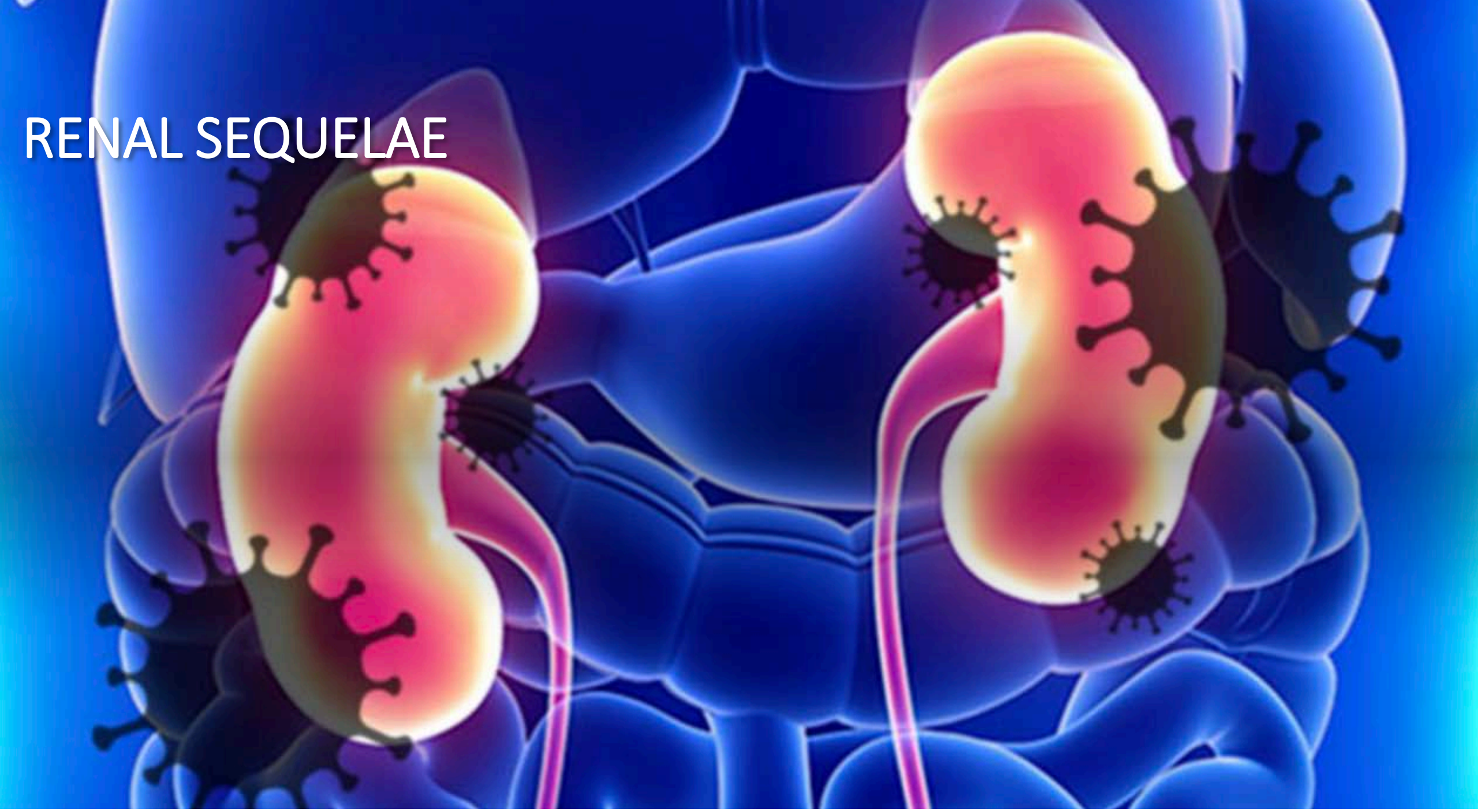
MANAGEMENT CONSIDERATIONS

- Standard therapies for neurologic complications such as headaches
- Imaging evaluation and referral to a specialist for refractory headache
- Neuropsychological evaluation in the post-acute illness setting in patients with cognitive impairment
- Standard screening tools to identify patients with anxiety, depression, sleep disturbances, PTSD, dysautonomia and fatigue



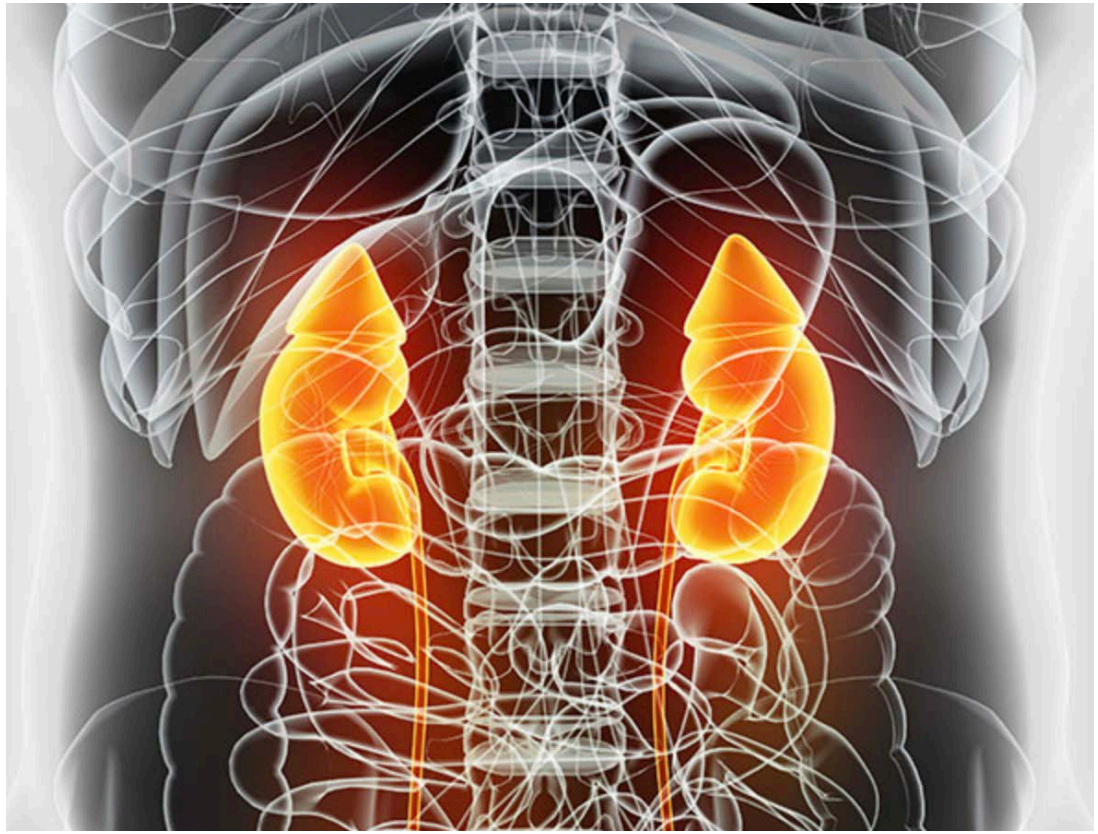
Do, T. P. et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology*
George, P. M. et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*
Kaseda, E. T. & Levine, A. J. Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors. *Clin. Neuropsychol.*

RENAL SEQUELAE



EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- In patients with acute COVID-19 severe acute kidney injury (AKI) requiring renal replacement therapy (RRT) occurs in
  - 5% of all hospitalized patients
  - 20–31% of critically ill
  - particularly among those with severe infections requiring mechanical ventilation



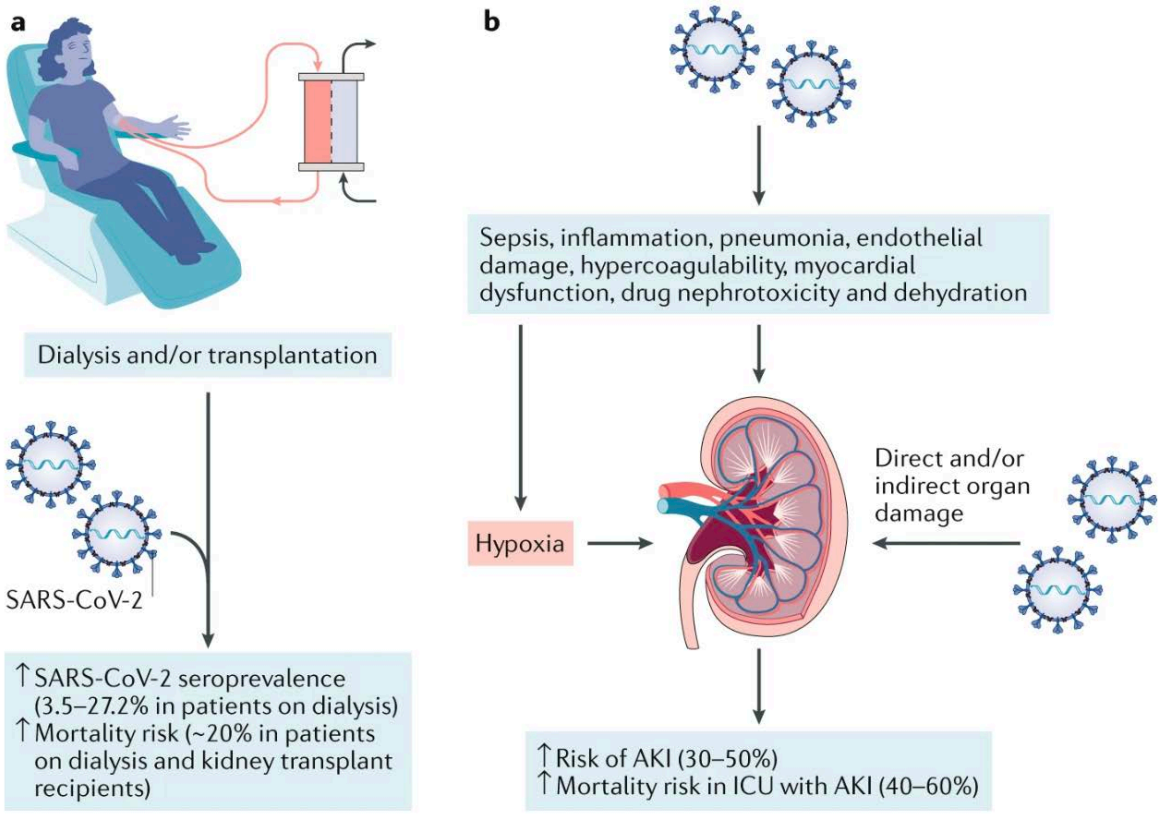
Robbins-Juarez, S. Y. et al. Outcomes for patients with COVID-19 and acute kidney injury: a systematic review and meta-analysis. *Kidney Int. Rep.*
Cummings, M. J. et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*
Gupta, S. et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern. Med.*
Stevens, J. S. et al. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. *PLoS ONE*

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- Early studies with short-term follow-up in patients requiring RRT
  - 27–64% dialysis independent by 28 days or ICU discharge
  - 35% patients with decreased estimated glomerular filtration rate at 6 months
  - 13% developed new-onset reduction of eGFR after documented normal renal function during acute COVID-19

- With adequate longer-term follow-up data, patients who require RRT for severe AKI experience
  - High mortality
  - Survival probability of 0.46 at 60 days
  - Renal recovery at 84% among survivors

From: The COVID-19 pandemic: consequences for nephrology

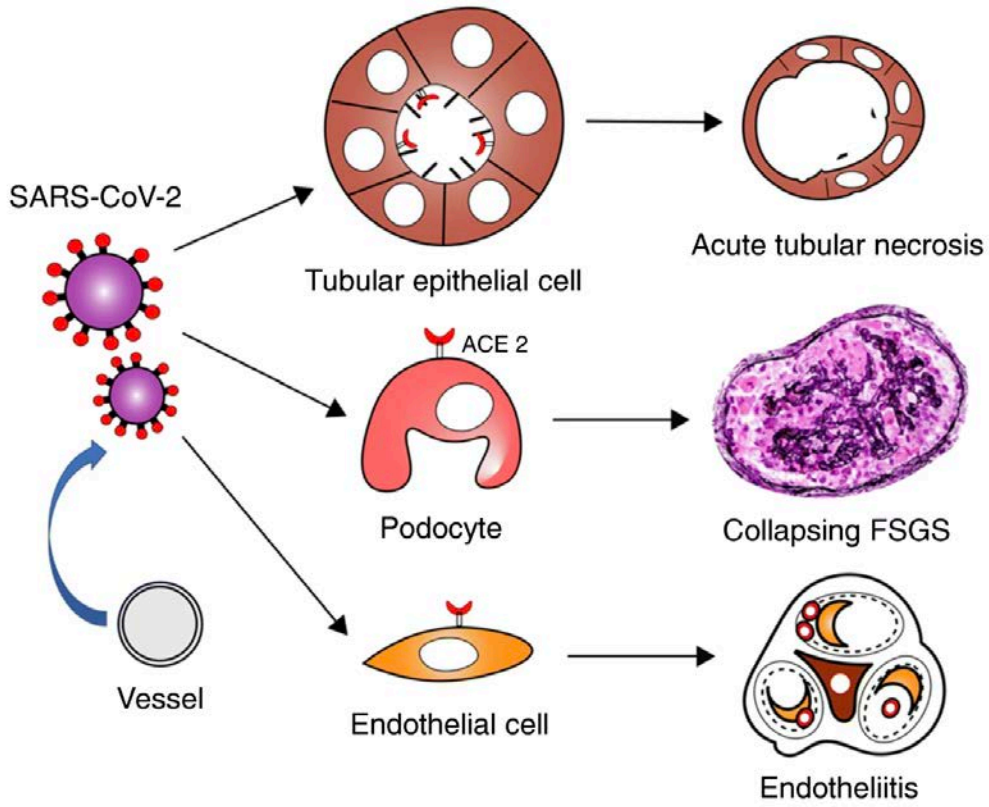


a | Patients on in-centre dialysis and kidney transplant recipients are at increased risk of community exposure to SARS-CoV-2 infection and COVID-19-associated mortality. **b** | Acute kidney injury (AKI) is also an important complication of severe COVID-19, likely as a consequence of multifactorial processes, and is associated with an increased risk of mortality. ICU, intensive care unit.

Gupta, S. et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern. Med.*
Wilbers, T. J. & Koning, M. V. Renal replacement therapy in critically ill patients with COVID-19: a retrospective study investigating mortality, renal recovery and filter lifetime. *J. Crit. Care*
Stevens, J. S. et al. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. *PLoS ONE*
Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*

PATHOLOGY AND PATHOPHYSIOLOGY

- SARS-CoV-2 has been isolated from renal tissue
- Acute tubular necrosis primary finding noted from renal biopsies and autopsies
- COVID-19-associated nephropathy (COVAN) characterized by
  - Collapsing variant of focal segmental glomerulosclerosis
  - Involution of glomerular tuft
  - Acute tubular injury
  - Thought to develop in response to interferon and chemokine activation



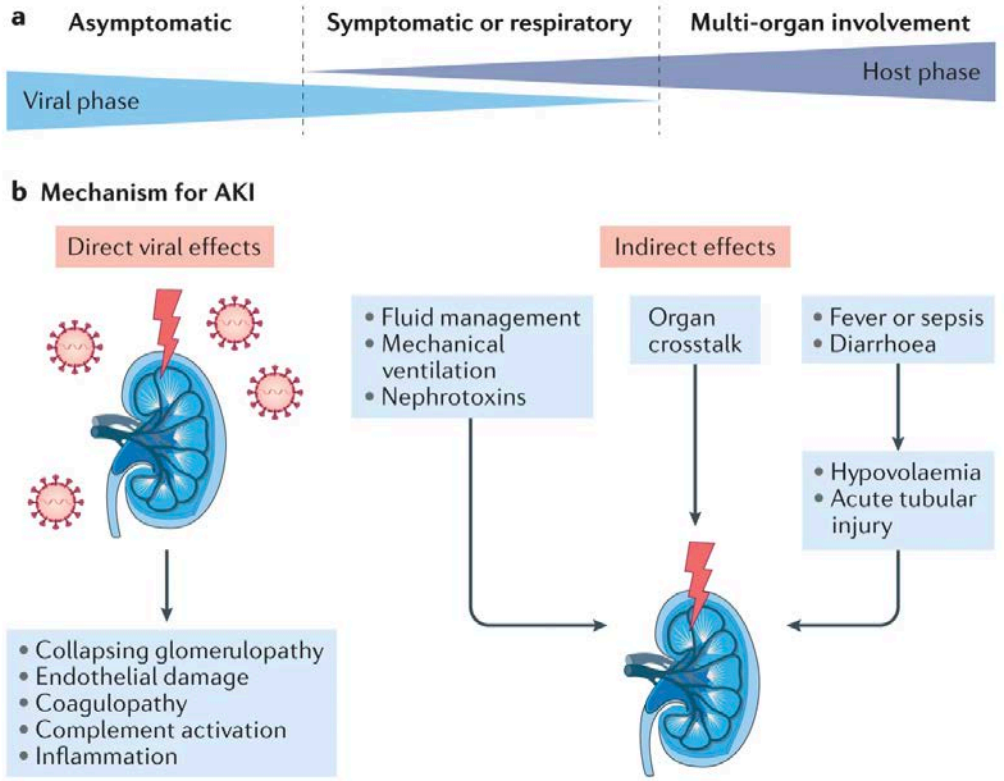
Schematic of histological features of renal complications in COVID-19. SARS-CoV-2 infects several kidney host cells using ACE2 and causes various types of damage. Each damage can cause AKI. Abbreviation: FSGS, Focal segmental glomerulosclerosis

Su, H. et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int.*
Kudose, S. et al. Kidney biopsy findings in patients with COVID-19. *J. Am. Soc. Nephrol.*
Sharma, P. et al. COVID-19-associated kidney injury: a case series of kidney biopsy findings. *J. Am. Soc. Nephrol.*
Golmai, P. et al. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. *J. Am. Soc. Nephrol.*
Santoriello, D. et al. Postmortem kidney pathology findings in patients with COVID-19. *J. Am. Soc. Nephrol.*

PATHOLOGY AND PATHOPHYSIOLOGY

- Association with *APOL1* risk alleles suggests that SARS-CoV-2 acts as a second hit in susceptible patients

- Thrombi in the renal microcirculation may also potentially contribute to the development of renal injury

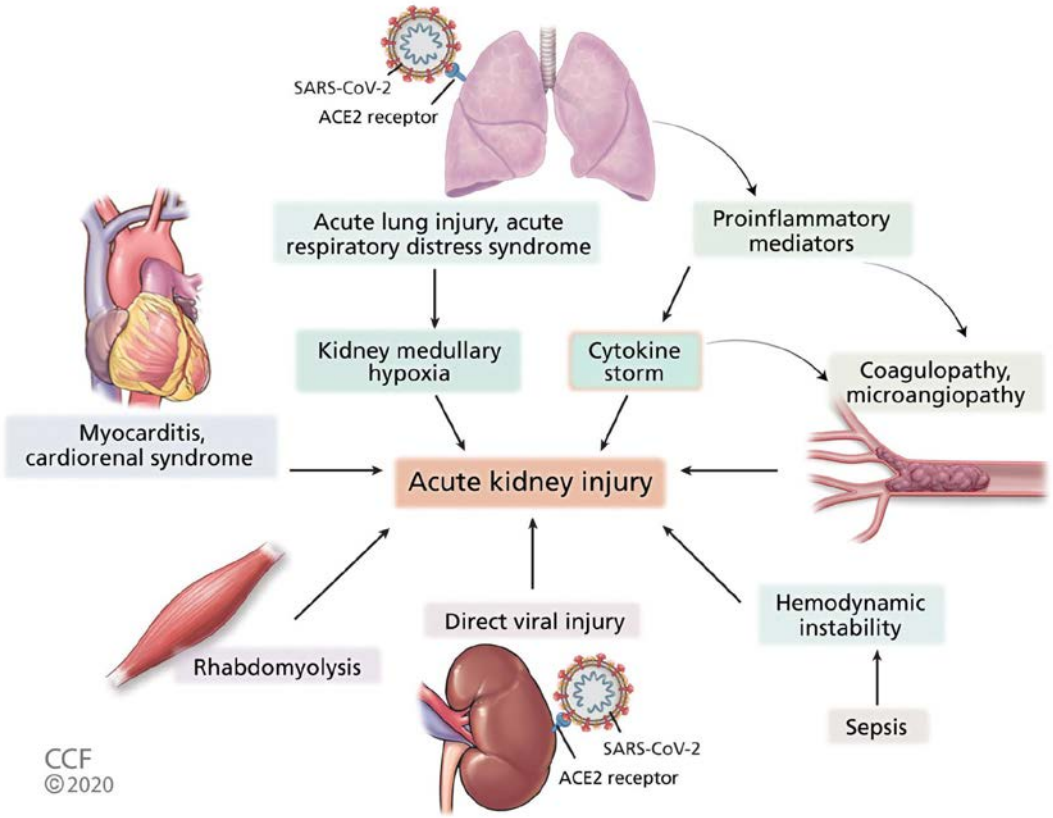


a,b | The pathogenesis of AKI in patients with COVID-19 (COVID-19 AKI) is likely multifactorial, involving both the direct effects of the SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19. AKI, acute kidney injury. Adapted from Acute Disease Quality Initiative 25, www.ADQI.org, CC BY 2.0 (https://creativecommons.org/licenses/by/2.0/).

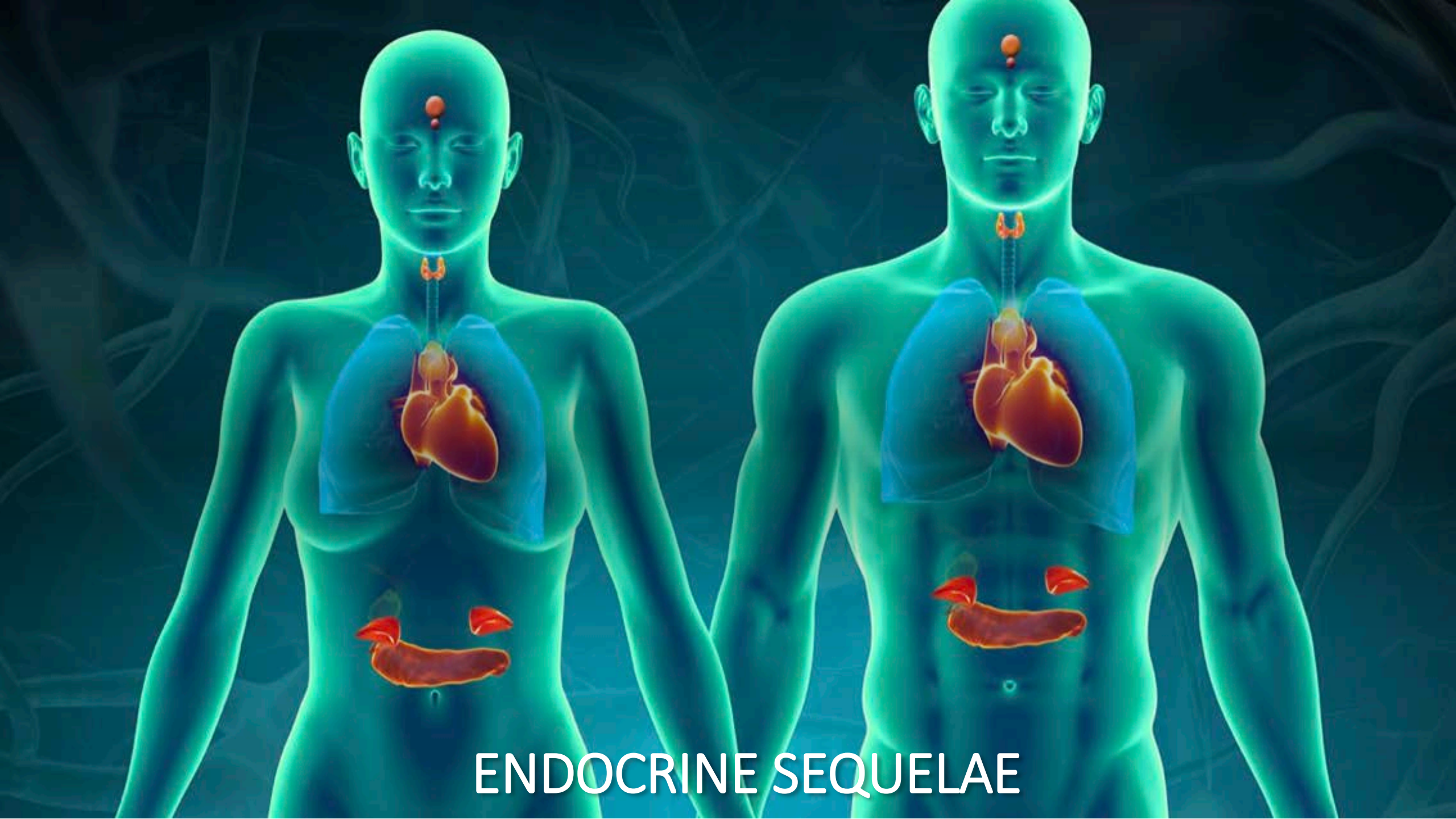
Velez, J. C. Q., Caza, T. & Larsen, C. P. COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19. *Nat. Rev. Nephrol.*
Jhaveri, K. D. et al. Thrombotic microangiopathy in a patient with COVID-19. *Kidney Int.*

MANAGEMENT CONSIDERATIONS

- Dialysis-dependent AKI at the time of discharge low
- Extent of the recovery of renal function remains to be seen
- COVID-19 survivors with persistent impaired renal function in post-acute infectious phase may benefit from early and close follow-up with a nephrologist in AKI survivor clinics

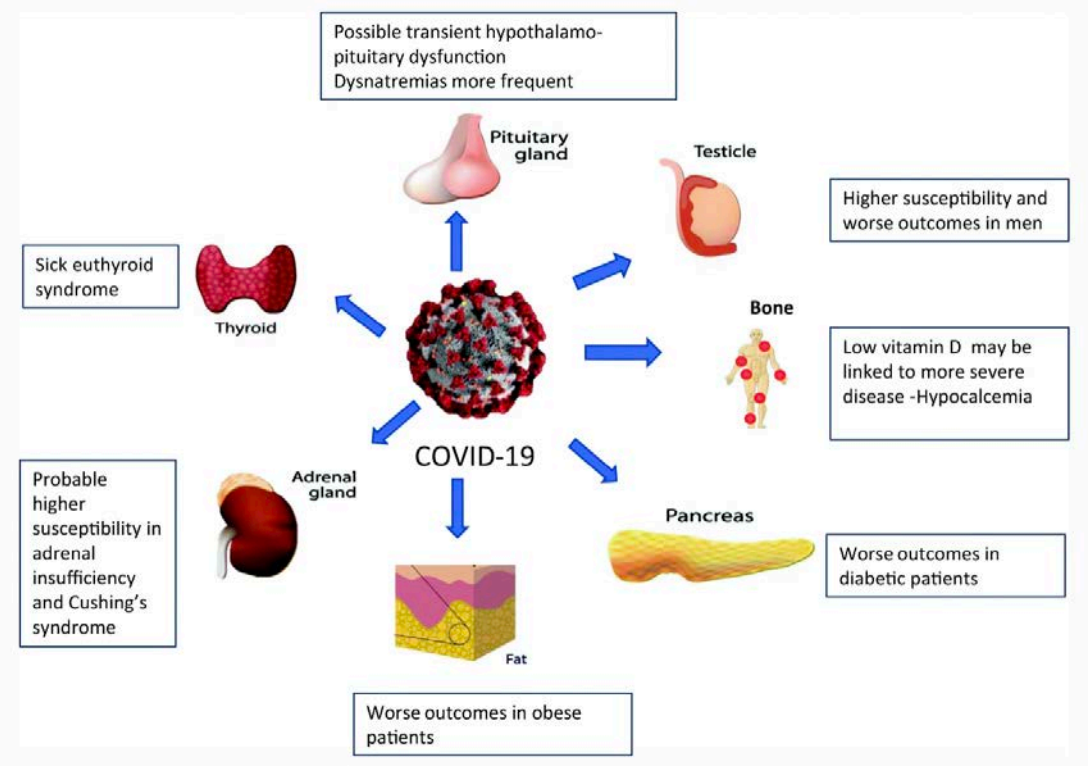


Meier, P., Bonfils, R. M., Vogt, B., Burnand, B. & Burnier, M. Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. *Clin. J. Am. Soc. Nephrol.*
Harel, Z. et al. Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. *Kidney Int.*


ENDOCRINE SEQUELAE

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

- Diabetic ketoacidosis (DKA) in patients without known diabetes mellitus weeks to months after resolution of COVID-19 symptoms
- Not yet known how long increased severity of pre-existing diabetes or predisposition to DKA persists after infection - will be addressed by international CoviDiab registry
- Subacute thyroiditis with clinical thyrotoxicosis has been reported weeks after resolution of respiratory symptoms
- COVID-19 may also potentiate latent thyroid autoimmunity manifesting as new-onset Hashimoto's thyroiditis or Graves' disease



Suwanwongse, K. & Shabarek, N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. *J. Med. Virol.*

Rubino, F. et al. New-onset diabetes in COVID-19. *N. Engl. J. Med.*

Ruggeri, R. M., Campenni, A., Siracusa, M., Frazzetto, G. & Gullo, D.Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones (Athens)*

Brancatella, A. et al. Subacute thyroiditis after SARS-COV-2 infection. *J. Clin. Endocrinol. Metab.*

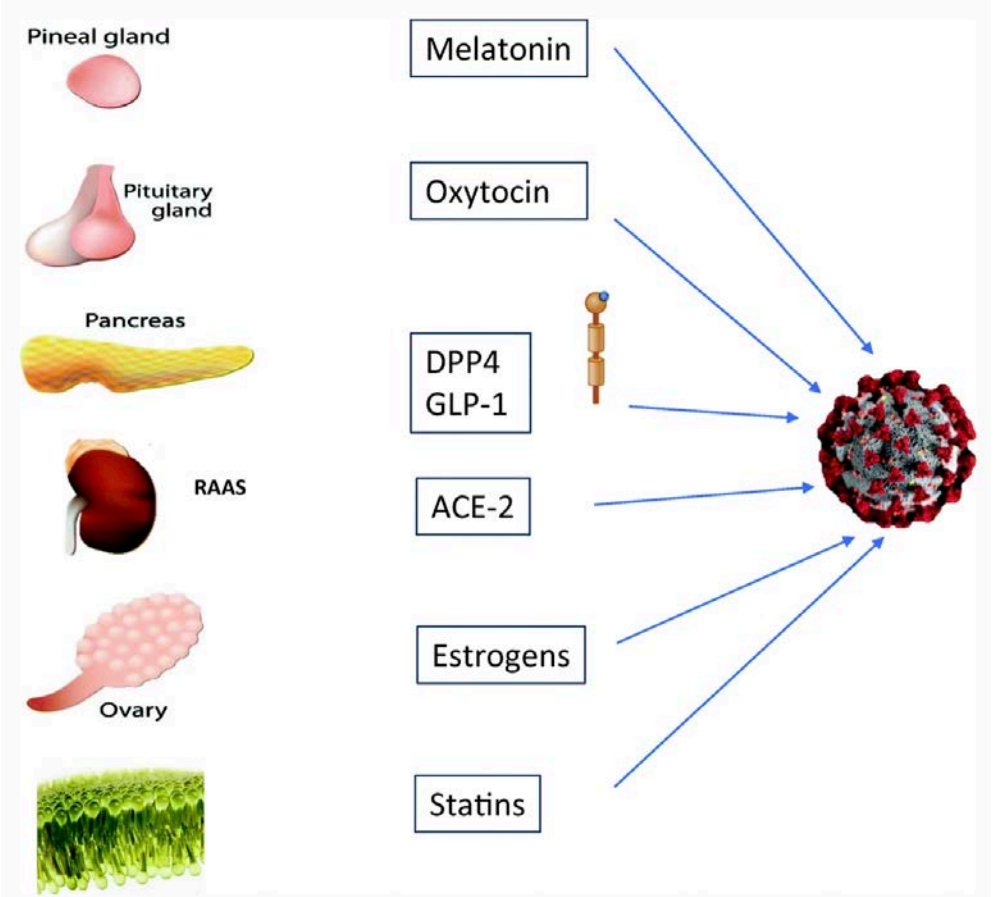
Tee, L. Y., Hajanto, S. & Rosario, B. H. COVID-19 complicated by Hashimoto's thyroiditis. *Singapore Med.* Mateu-Salat, M., Urgell, E. & Chico, A.SARS-COV-2 as a trigger for autoimmune disease: report of two cases of Graves' disease after COVID-19. *J. Endocrinol. Invest.*

PATHOLOGY AND PATHOPHYSIOLOGY

- Consequences of
  - Direct viral injury
  - Immunological and inflammatory damage
  - Iatrogenic complications

- Pre-existing diabetes may first become apparent during acute phase of COVID-19 and can generally be treated long term with agents other than insulin, even if initially associated with DKA

- No concrete evidence of lasting damage to pancreatic β cells



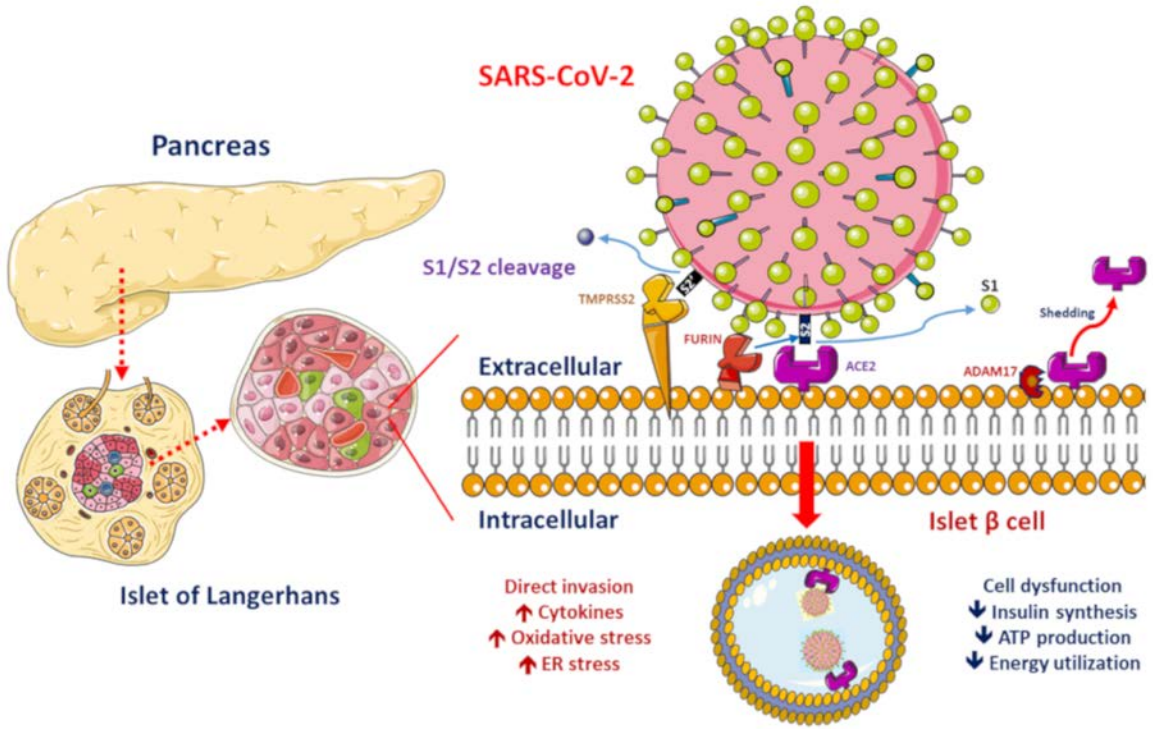
Possible endocrine and metabolic targets that have been considered for COVID-19 therapy. Different hormones and drugs have been included as possible targets for COVI-19 including melatonin, oxytocin, DPP-4 (human dipeptidyl peptidase 4), ACE-2 (angiotensin converting enzyme-2), estrogens and statins

PATHOLOGY AND PATHOPHYSIOLOGY

- Primary deficit in insulin production mediated by
  - Inflammation
  - Infection stress response
  - Peripheral insulin resistance

- No evidence that COVID-19-associated diabetes can be reversed after the acute phase, nor that its outcomes differ in COVID-19 long haulers

- COVID-19 also presents risk factors for bone demineralization related to
  - Systemic inflammation
  - Immobilization
  - Exposure to corticosteroids
  - Vitamin D insufficiency
  - Interruption of antiresorptive or anabolic agents for osteoporosis



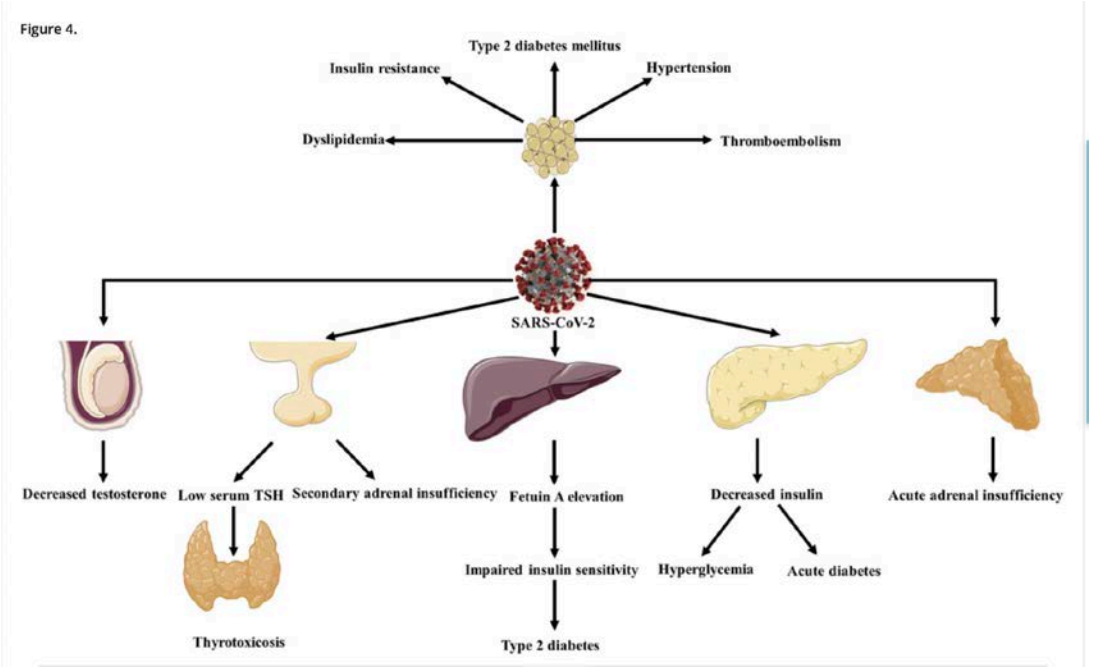
Gentile, S., Strollo, F., Mambro, A. & Ceriello, A.COVID-19, ketoacidosis and new-onset diabetes: are there possible cause and effect relationships among them? *Diabetes Obes. Metab.*
Yang, J. K., Lin, S. S., Ji, X. J. & Guo, L. M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol.*
Salvio, G. et al. Bone metabolism in SARS-CoV-2 disease: possible osteoimmunology and gender implications. *Clin. Rev. Bone Miner. Metab.*
Liao Y-H, Zheng J-Q, Zheng C-M, Lu K-C, Chao Y-C. Novel Molecular Evidence Related to COVID-19 in Patients with Diabetes Mellitus. *Journal of Clinical Medicine*. 2020

MANAGEMENT CONSIDERATIONS

- Serologic testing for type 1 diabetes-associated autoantibodies and repeat post-prandial C-peptide measurements should be obtained at follow-up in patients with newly diagnosed diabetes mellitus in absence of traditional risk factors for type 2 diabetes

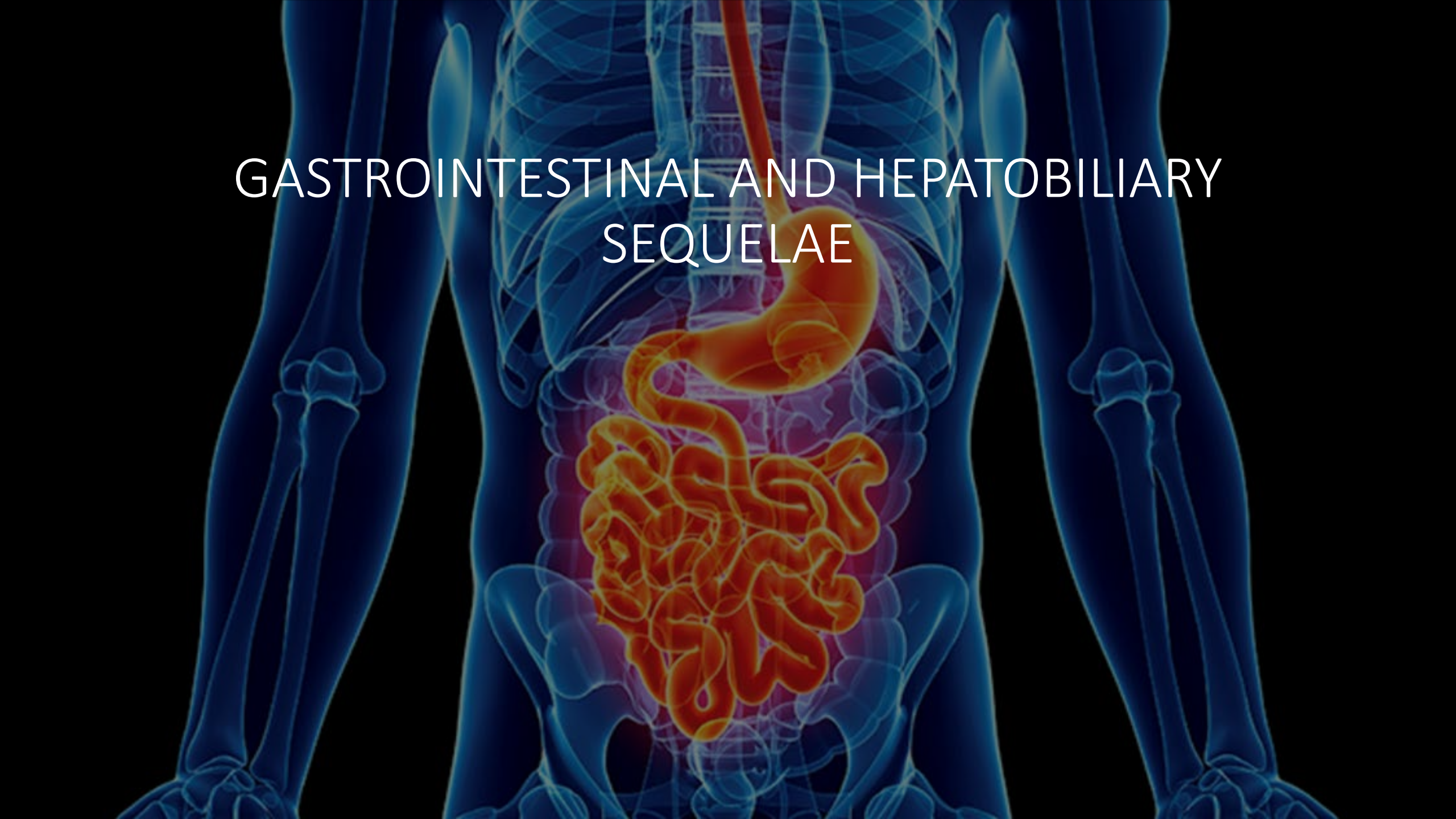
- It is reasonable to treat patients with such risk factors akin to ketosis-prone type 2 diabetes

- Incident hyperthyroidism due to SARS-CoV-2-related destructive thyroiditis can be treated with corticosteroids but new-onset Graves' disease should also be ruled out



DiMeglio, L. A., Evans-Molina, C. & Oram, R. A. Type 1 diabetes. *Lancet*
Ruggeri, R. M., Campenni, A., Siracusa, M., Frazzetto, G. & Gullo, D.Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones (Athens)*

GASTROINTESTINAL AND HEPATOBILIARY SEQUELAE



CLINICAL MANIFESTATIONS

- Significant gastrointestinal and hepatobiliary sequelae have not been reported in COVID-19 survivors

- Prolonged viral fecal shedding occurs in COVID-19, with viral ribonucleic acid detectable for mean of
  - 28 days after onset of SARS-CoV-2 infection symptoms
  - 11 days after negative respiratory samples

- COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic infectious organisms and depletion of beneficial commensals

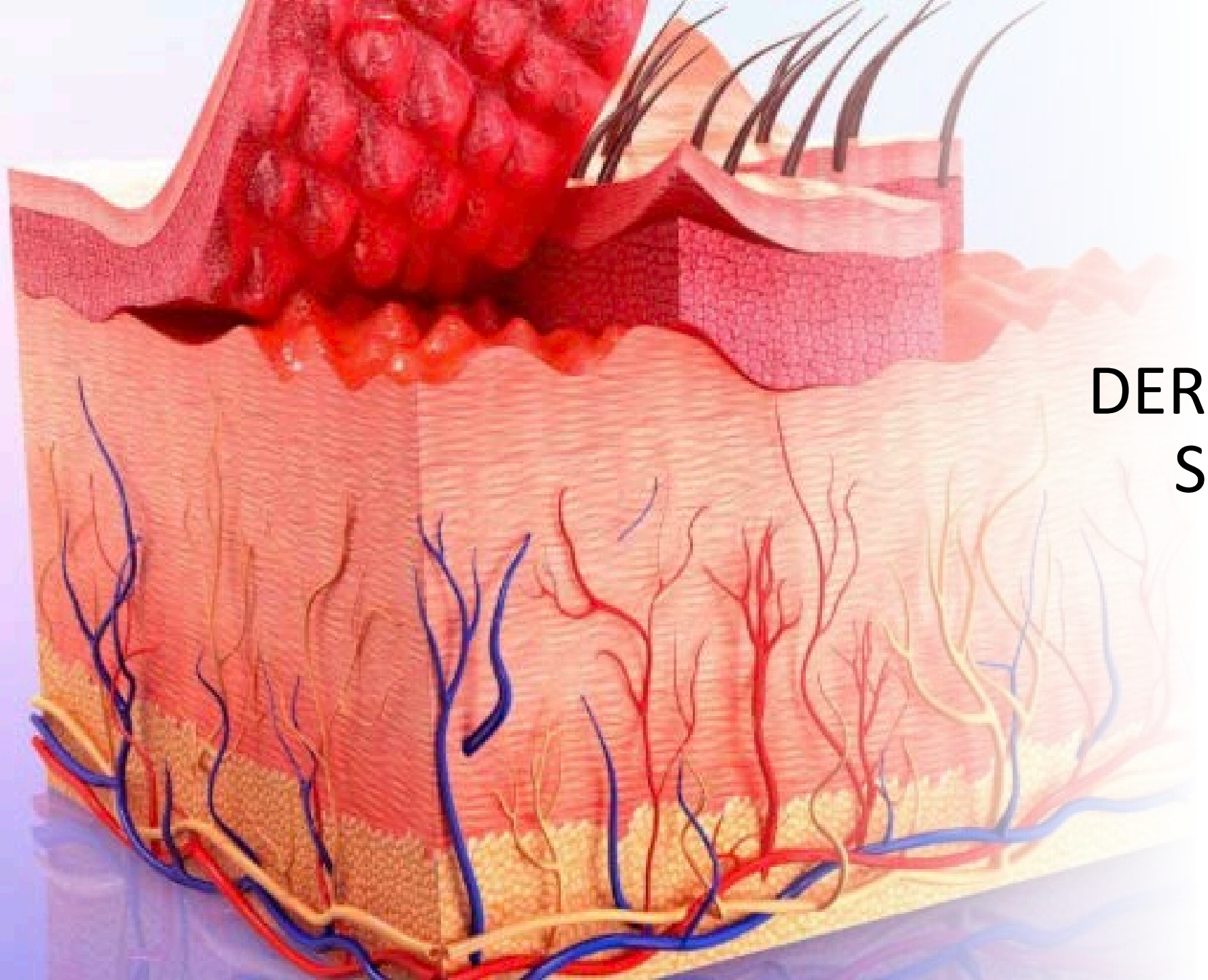
Cheung, K. S. et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology*
Wu, Y. et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol. Hepatol.*
Xiao, F. et al. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology*
Xu, Y. et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat. Med.*
Zuo, T. et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology*

CLINICAL MANIFESTATIONS

- *Faecalibacterium prausnitzii*, a butyrate-producing anaerobe typically associated with good health, has been inversely correlated with disease severity

- Long-term consequences of COVID-19 on the gastrointestinal system are being studied, including post-infectious irritable bowel syndrome and dyspepsia

Zuo, T. et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology*
Miquel, S. et al. *Faecalibacterium prausnitzii* and human intestinal health. *Curr. Opin. Microbiol.*



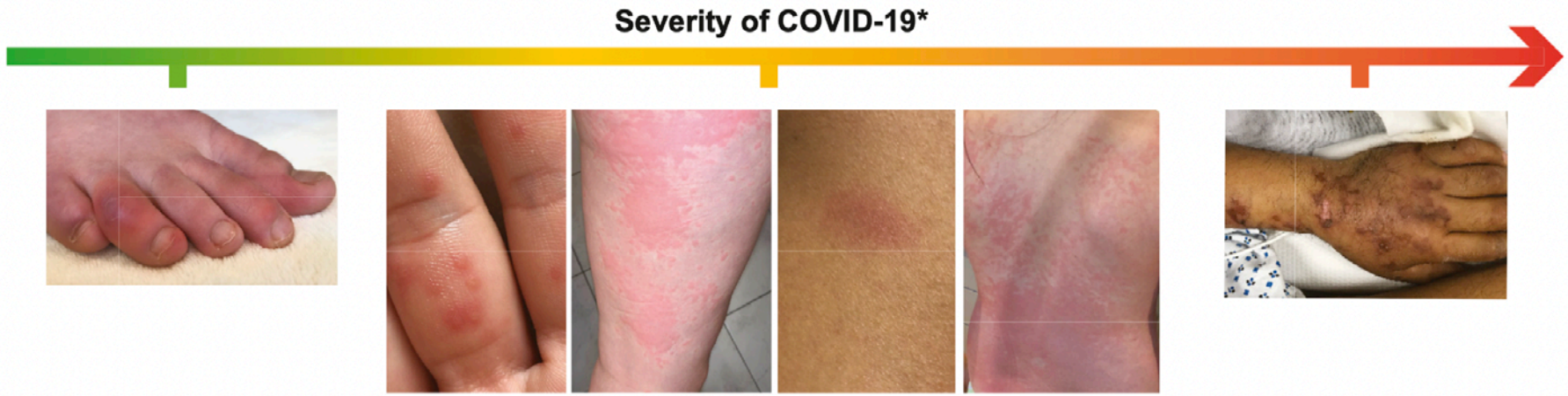
DERMATOLOGIC SEQUELAE

CLINICAL MANIFESTATIONS

- Dermatologic manifestations of COVID-19 to other acute COVID-19 symptoms occurred
  - After in 64%
  - Concurrent in 15%
  - Average latency from the time of upper respiratory symptoms to dermatologic findings of 7.9 days
- Only 3% of patients noted a skin rash at 6 months follow-up in the post-acute COVID-19 study
- Predominant dermatologic complaint
  - Hair loss
  - In approximately 20%
  - Possibly be attributed to telogen effluvium resulting from viral infection or a resultant stress response
- Ongoing investigations may provide insight into potential immune or inflammatory mechanisms of disease

Freeman, E. E. et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J. Am. Acad. Dermatol.*
Mirza, F. N., Malik, A. A., Omer, S. B. & Sethi, A. Dermatologic manifestations of COVID-19: a comprehensive systematic review. *Int. J. Dermatol.*
Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*
Garrigues, E. et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J. Infect.*
Genovese, G., Moltrasio, C., Berti, E. & Marzano, A. V.Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*

CLINICAL MANIFESTATIONS



Pernio

- Feet (84%) and hands (32%)
- Pain/burning (71%) and pruritus (36%)
- After other COVID-19 symptoms (49%)
- Fever (35%), cough (35%);19% asymptomatic
- 16% hospitalized

Vesicular/ Urticarial/ Macular Erythema/ Morbilliform

- Trunk and extremities
- Pruritus in 61-74%
- Typically after other COVID-19 symptoms (19%)
- Fever (65-74%), cough (52-66%), sore throat (39-50%), shortness of breath (28-45%)
- 22-45% hospitalized across groups

Retiform purpura

- Extremities and buttocks
- Often asymptomatic (73%)
- After other COVID -19 symptoms (91%)
- Fever (64%), cough (73%), and shortness of breath (73%)
- 100% hospitalized
- 82% with ARDS

*Severity calculated based on percentage of patients hospitalized for COVID-19

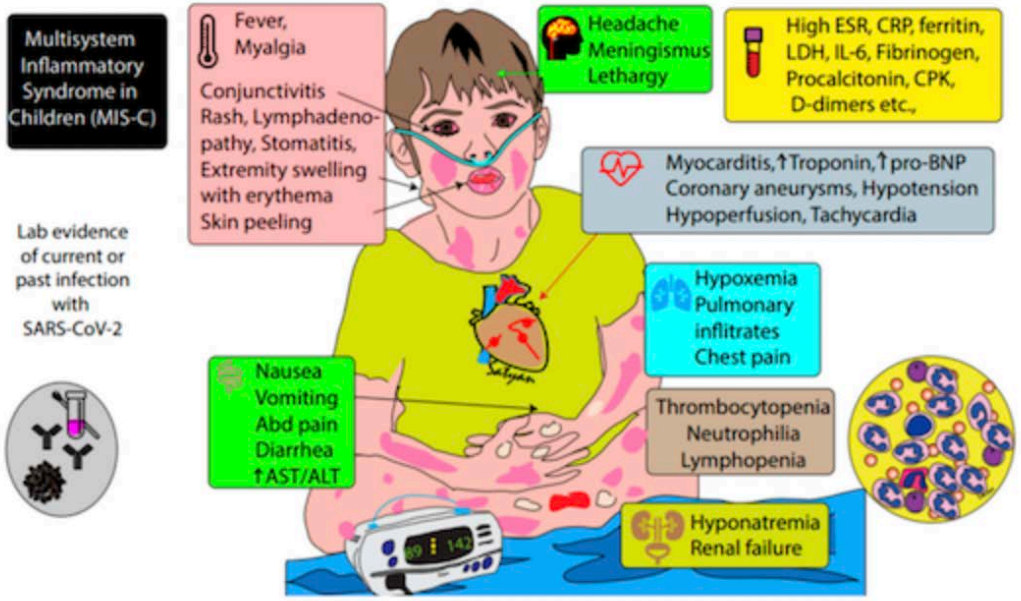
Freeman, E. E. et al. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J. Am. Acad. Dermatol*.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

- Defined by the presence of the following symptoms in people <21 years old (or ≤19 years old per the World Health Organization definition)
  - Fever
  - Elevated inflammatory markers
  - Multiple organ dysfunction
  - Current or recent SARS-CoV-2 infection
  - Exclusion of other plausible diagnoses

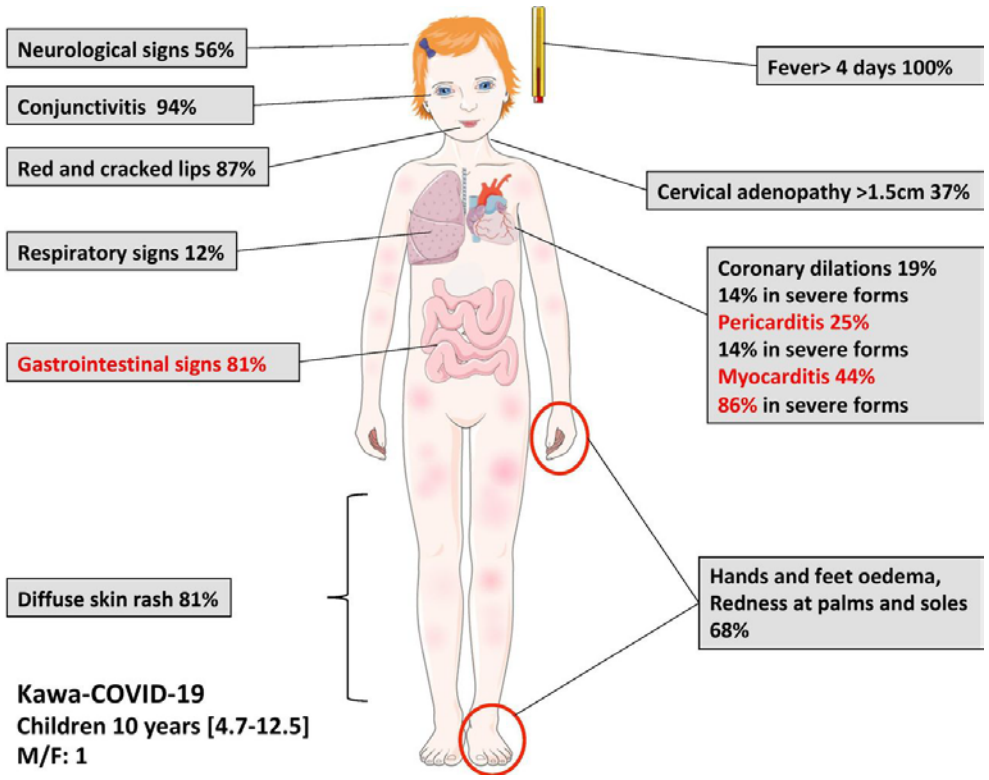
- Clinical presentations of MIS-C include fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, hypotension and cardiovascular and neurologic compromise



Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) (Centers for Disease Control and Prevention, 2020)
Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19 (World Health Organization, 2020)
Jiang, L. et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect. Dis.*
Henderson, L. A. et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. *Arthritis Rheumatol.*

CLINICAL MANIFESTATIONS

- Overlapping features noted with Kawasaki disease - an acute pediatric medium-vessel vasculitis
- However, comparison of Kawasaki disease and MIS-C cohorts demonstrates distinctive epidemiologic and clinical characteristics
- 80% of Kawasaki disease cases in children <5 years of age and primarily of Asian descent
- Patients with MIS-C typically >7 years, encompass a broader age range; African, Afro-Caribbean or Hispanic origin



Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (PIMS)—Guidance for Clinicians(Royal College of Paediatrics and Child Health, 2020)
Rowley, A. H. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat. Rev. Immunol.*
Schupper, A. J., Yaeger, K. A. & Morgenstern, P. F. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nerv. Syst.*
Lin, J. E. et al. Neurological issues in children with COVID-19. *Neurosci. Lett.*

CLINICAL MANIFESTATIONS

- Comparable incidence of coronary artery aneurysm and dilation among MIS-C and Kawasaki disease 20 and 25%, respectively
- Neurological complications of MIS-C, such as headache, altered mental status, encephalopathy, cranial nerve palsies, stroke, seizure, reduced reflexes, and muscle weakness more frequent than in Kawasaki disease
- Pooled meta-analysis of MIS-C studies reported recovery in 91.1% and death in 3.5% of patients

MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C) VS KAWASAKI DISEASE

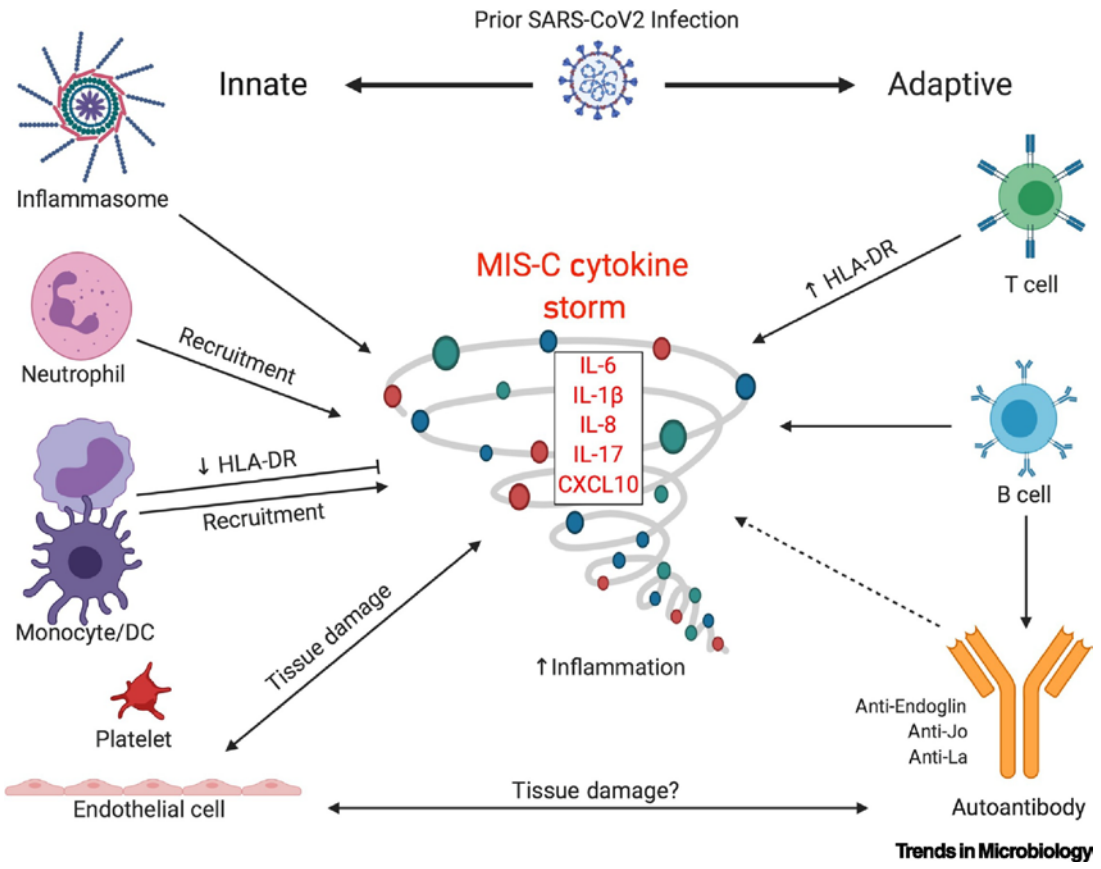
MIS-C	KAWASAKI DISEASE
Mean age 10-11 y	Mean age 2 y
Individuals with African heritage appear at highest risk	Asians at highest risk
Severe abdominal pain	Less severe GI complaints
Myocardial dysfunction/myocarditis	Coronary artery abnormalities (25%-60% in Kawasaki shock syndrome)
Acute kidney injury	Renal involvement very rare
NT-pro-BNP and troponin ↑↑	Not often reported (myocardial dysfunction less severe) but generally normal to mildly increased
Ferritin, triglycerides, and CRP ↑↑	Same, but less severe
Platelet count ↓ and normalizes with recovery	Marked thrombocytosis by day 10-14
Lymphopenia	Lymphopenia not described
Association with SARS-CoV2 infection (2-4 wk prior)	Specific etiology still unknown; no association with SARS CoV2

Abbreviations: CRP, C-reactive protein; GI, gastrointestinal; NT-proBNP, N-terminal-pro type b natriuretic peptide; SARS-CoV2, severe acute respiratory syndrome coronavirus.

Schupper, A. J., Yaeger, K. A. & Morgenstern, P. F. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nerv. Syst.*
Lin, J. E. et al. Neurological issues in children with COVID-19. *Neurosci. Lett.*

PATHOLOGY AND PATHOPHYSIOLOGY

- MIS-C may result from an aberrant acquired immune response rather than acute viral infection
- Pathophysiology of MIS-C similar in part to Kawasaki disease and toxic shock syndrome
- Possible mechanisms of injury related to
  - Immune complexes
  - Complement activation
  - Autoantibody formation through viral host mimicry
  - Massive cytokine release related to superantigen stimulation of T cells



Rowley, A. H. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat. Rev. Immunol.*

Nakra, N. A., Blumberg, D. A., Herrera-Guerra, A. & Lakshminrusimha, S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children (Basel)*

Jiang, L. et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect. Dis.*

MANAGEMENT CONSIDERATIONS

- Current recommendations include
  - Immunomodulatory therapy with intravenous immunoglobulin
  - Adjunctive glucocorticoids
  - Low-dose aspirin until coronary arteries are confirmed normal at least 4 weeks after diagnosis

- Therapeutic anticoagulation with enoxaparin or warfarin and low-dose aspirin is recommended in those with a coronary artery *z* score ≥ 10, documented thrombosis or an ejection fraction < 35%

- Studies such as the Best Available Treatment Study for Inflammatory Conditions Associated with COVID-19 are evaluating the optimal choice of immunomodulatory agents for treatment

Henderson, L. A. et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. *Arthritis Rheumatol.*

MANAGEMENT CONSIDERATIONS

- Serial echocardiographic assessment at intervals of 1–2 and 4–6 weeks after presentation

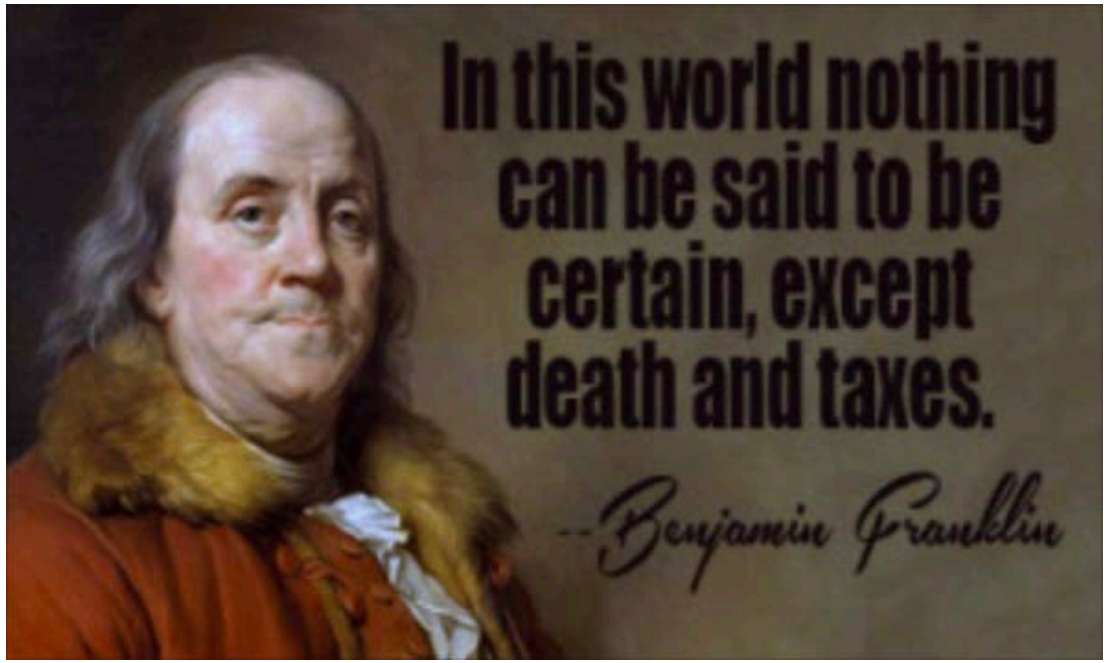
- Cardiac MRI may be indicated 2–6 months after diagnosis in those presenting with significant transient left ventricular dysfunction (ejection fraction < 50%) in acute phase or persistent dysfunction to assess for fibrosis and inflammation

- Serial electrocardiograms and consideration of an ambulatory cardiac monitor recommended at follow-up visits in patients with conduction abnormalities at diagnosis

McCrindle, B. W. et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*

POST-ACUTE SEQUALAE OF COVID-19:DEATH

- Review of databases of the US Department of Veterans Affairs
- To identify 6-month incident sequalae including diagnoses, medication use, and laboratory abnormalities in 30-day survivors of COVID-19
- Beyond the first 30 days of illness, people with COVID-19 exhibit higher risk of death and health resource utilization



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RACIAL AND ETHNIC CONSIDERATIONS

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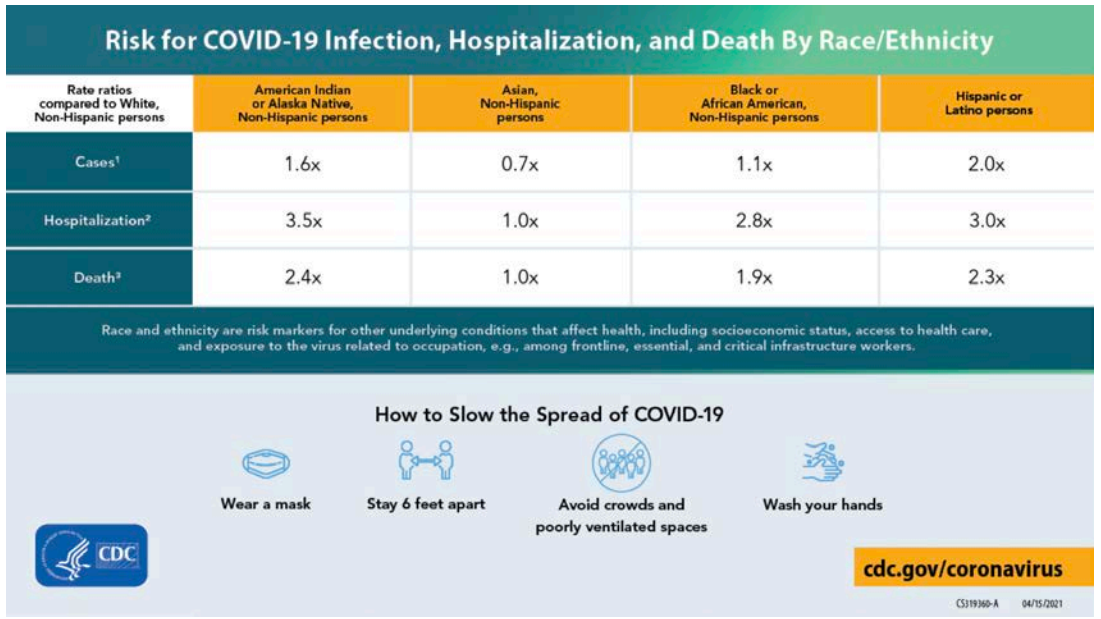
- Acute COVID-19 disproportionately affects communities of color
- Emerging data also suggest that COVAN may be the predominant pattern of renal injury in individuals of African descent
- MIS-C is also known to disproportionately affect children and adolescents of African, Afro-Caribbean or Hispanic ethnicity
- Larger studies are required to ascertain the association between sequelae of post-acute COVID-19 and race and ethnicity



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Yancy, C. W. COVID-19 and African Americans. *J. Am. Med. Assoc.*
Mackey, K. et al. Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: a systematic review. *Ann. Int. Med.*
Webb Hooper, M., Nápoles, A. M. & Pérez-Stable, E. J. COVID-19 and racial/ethnic disparities. *J. Am. Med. Assoc.*
Bunyavanich, S., Grant, C. & Vicencio, A. Racial/ethnic variation in nasal gene expression of transmembrane serine protease 2 (TMPRSS2). *J. Am. Med. Assoc.*

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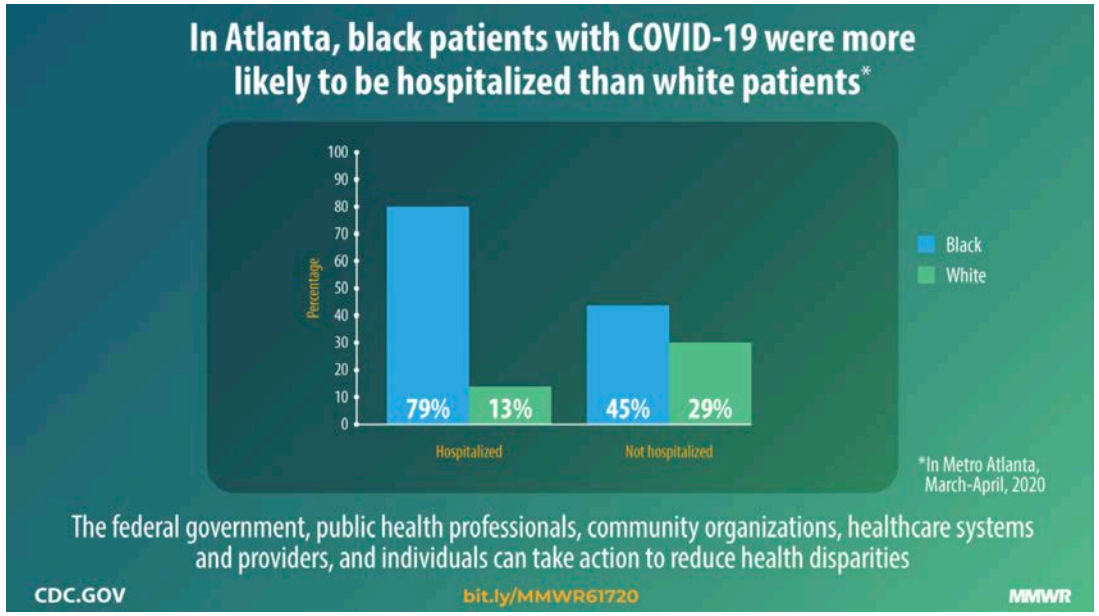


Velez, J. C. Q., Caza, T. & Larsen, C. P. COVAN is the new HIVAN: the re-emergence of collapsing glomerulopathy with COVID-19. *Nat. Rev. Nephrol.*
Henderson, L. A. et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. *Arthritis Rheumatol.*
Rowley, A. H. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat. Rev. Immunol.*

RACIAL AND ETHNIC CONSIDERATIONS

- These important differences may be related to multiple factors
  - Socioeconomic determinants
  - Racial/ethnic disparities
  - Plausible differences in the expression of factors involved in SARS-CoV-2 pathogenesis
  - Comorbidities

- Higher nasal epithelial expression of *TMPRSS2* has been reported in Black individuals compared with other self-reported races/ethnicities

- Ongoing and future studies integrate and analyze information along multiple axes to prevent inaccurate contextualization

Bunyavanich, S., Grant, C. & Vicencio, A. Racial/ethnic variation in nasal gene expression of transmembrane serine protease 2 (TMPRSS2). *J. Am. Med. Assoc.*

Chowkwanyun, M. & Reed, A. L. Racial health disparities and COVID-19—caution and context. *N. Engl. J. Med*.

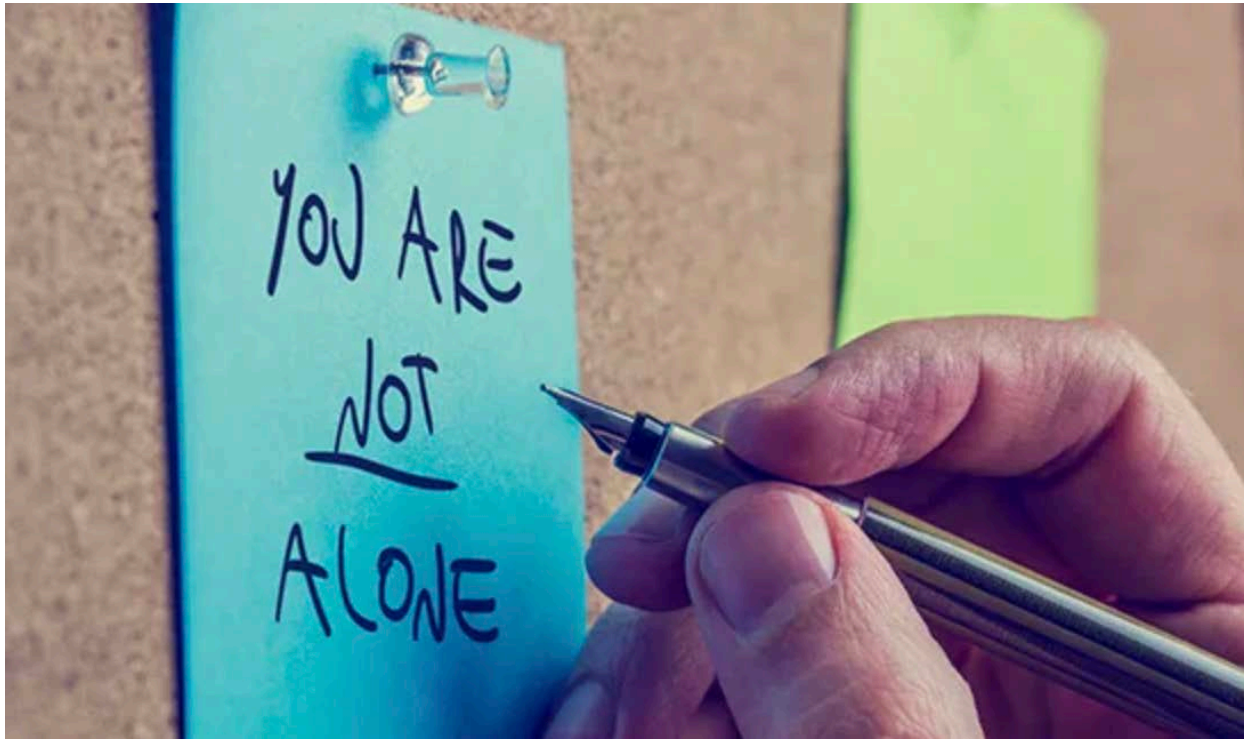
NUTRITION AND REHABILITATION

NUTRITION AND REHABILITATION CONSIDERATIONS

- Severe COVID-19, similar to other critical illnesses, causes catabolic muscle wasting, feeding difficulties and frailty - each associated with an increased likelihood of poor outcome
- Malnutrition noted in 26–45% of patients with COVID-19
- Protocols to provide nutritional support for patients continue to be refined
- All post-acute COVID-19 follow-up studies report significant deficits that incorporated assessments of health-related quality of life and functional capacity measures
- Early rehabilitation programs being evaluated in ongoing clinical studies
- Model COVID-19 rehabilitation units already routinely assessing acute COVID-19 survivors for swallowing function, nutritional status and measures of functional independence

PATIENT ADVOCACY GROUPS

- COVID Advocacy Exchange
  - https://www.covidadvocacyexchange.com
- The National Patient Advocate Foundation COVID Care Resource Center
  - https://www.patientadvocate.org/covidcare
- Long-haul COVID fighters Facebook groups
- Body Politic COVID-19 Support Group
  - https://www.wearebodypolitic.com/covid19
- Survivor Corps
  - https://www.survivorcorps.com/
- Patient-Led Research for COVID-19
  - patientresearchcovid19.com



PATIENT ADVOCACY GROUPS

- Surveys conducted by these groups have helped to identify persistent symptoms such as brain fog, fatigue and body aches as important components of post-acute COVID-19

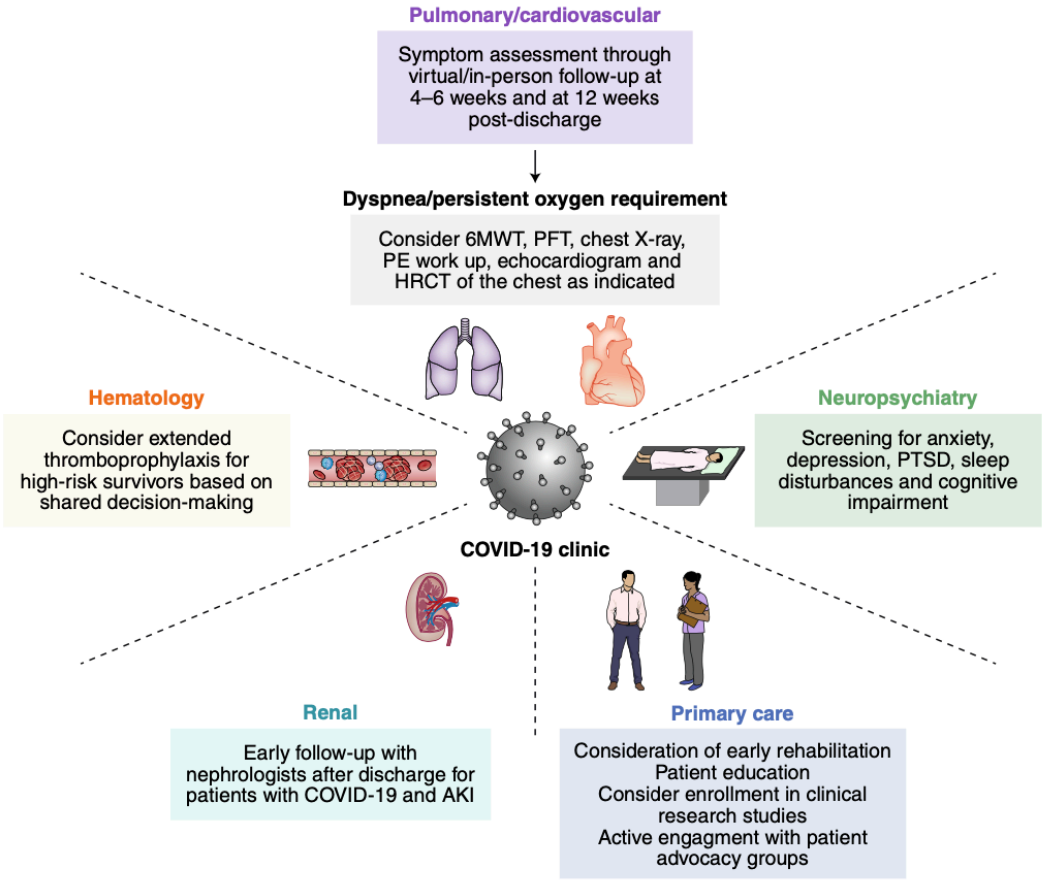
- Instrumental in highlighting the persistence of symptoms in patients with mild-to-moderate disease who did not require hospitalization

- Active engagement with these patient advocacy groups, many of whom identify themselves as long haulers, is crucial

- Dissemination of contact information and resources of these groups can occur at pharmacies, physician offices and in discharge summaries upon hospital discharge

CONCLUSIONS AND FUTURE DIRECTIONS

INTERDISCIPLINARY MANAGEMENT IN COVID-19 CLINICS



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FUTURE DIRECTIONS

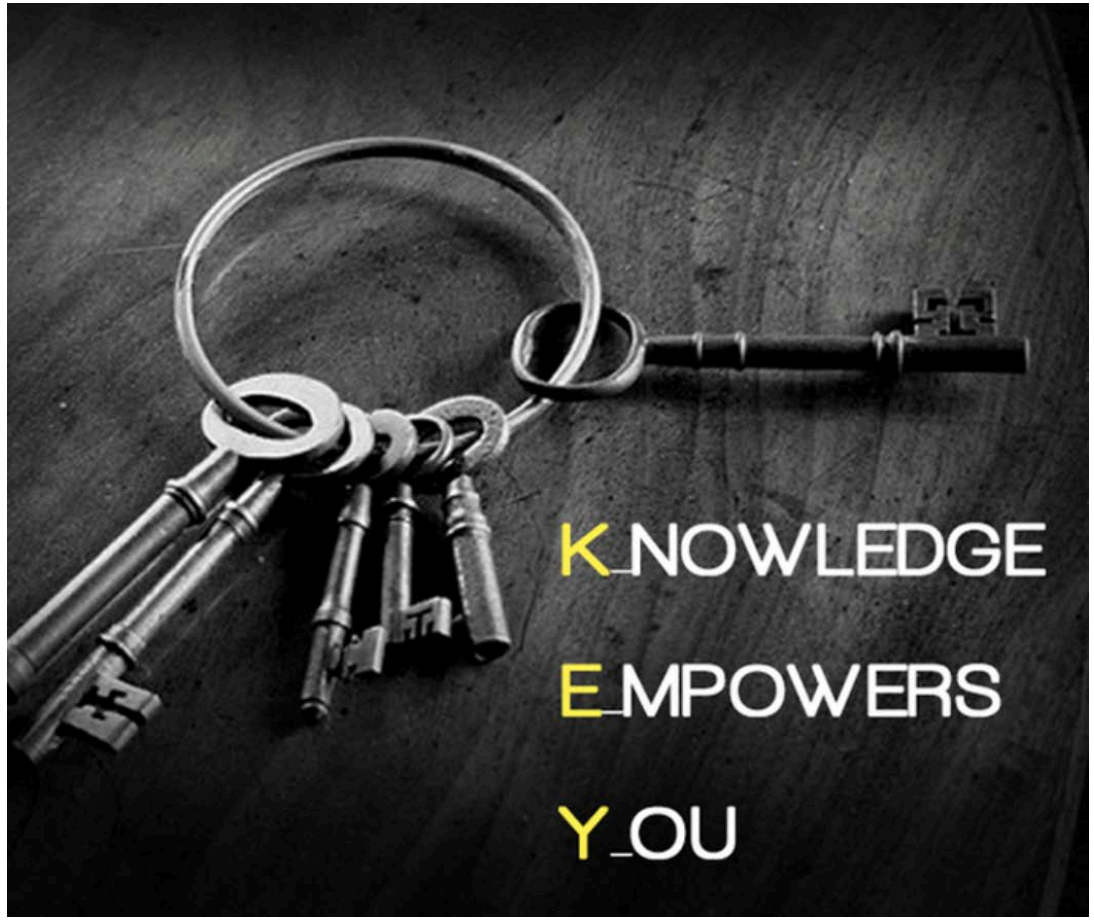
- Multi-organ sequelae of COVID-19 beyond acute phase of infection increasingly being appreciated

- Necessary active and future research needed to better understand natural history and pathophysiology

- Active and future clinical studies - including prospective cohorts and clinical trials - paramount to developing a robust knowledge database and informing clinical practice

ROLE OF HEALTHCARE PROVIDERS

- Recognition
- Carefully documentation
- Investigating and managing ongoing or new symptoms
- Follow-up of organ-specific complications that developed during acute illness
- Provide information in accessible formats
- Additional resources such as patient advocacy and support groups



THANK YOU