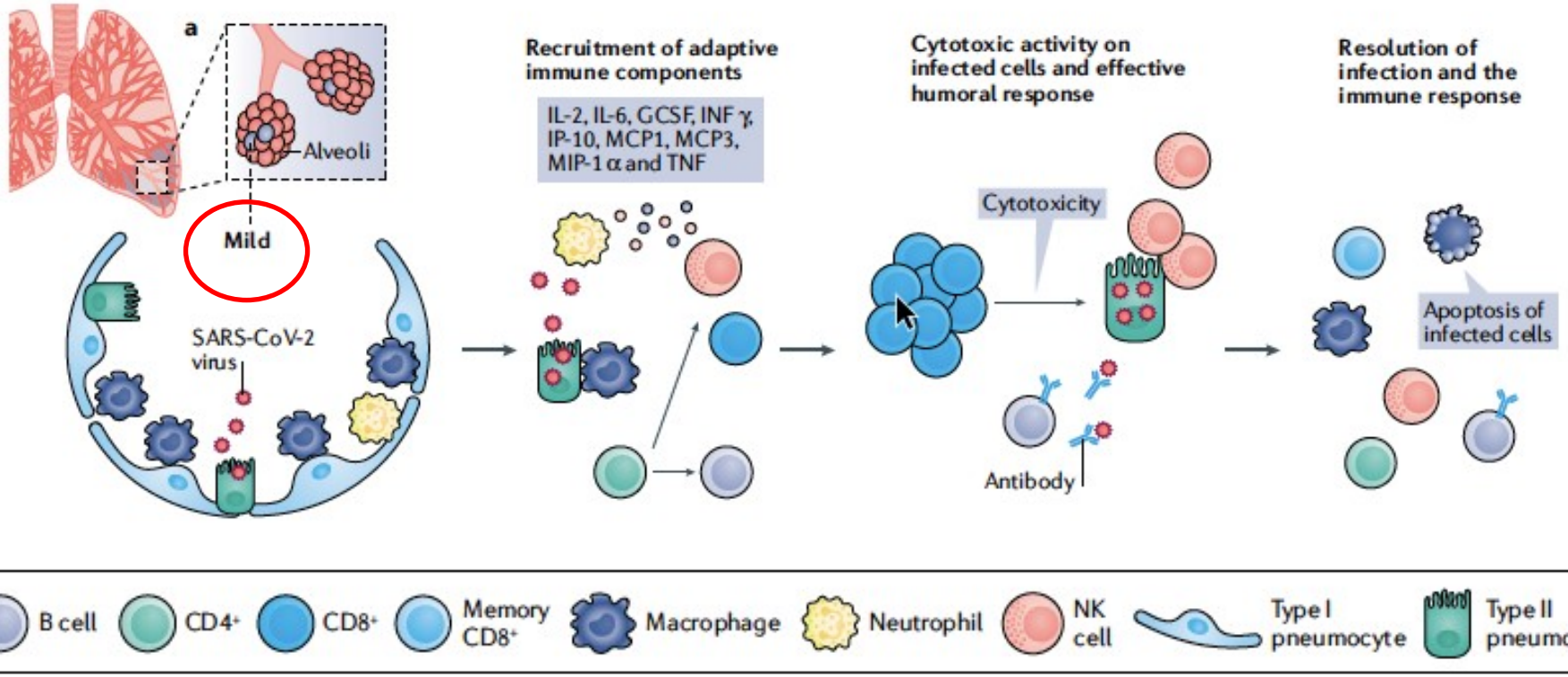
UNIVERSITÀ
DI SIENA
1240

Gli esiti sistemici da COVID 19

Ranuccio Nuti
Professore Emerito di Medicina Interna
Università degli Studi di Siena

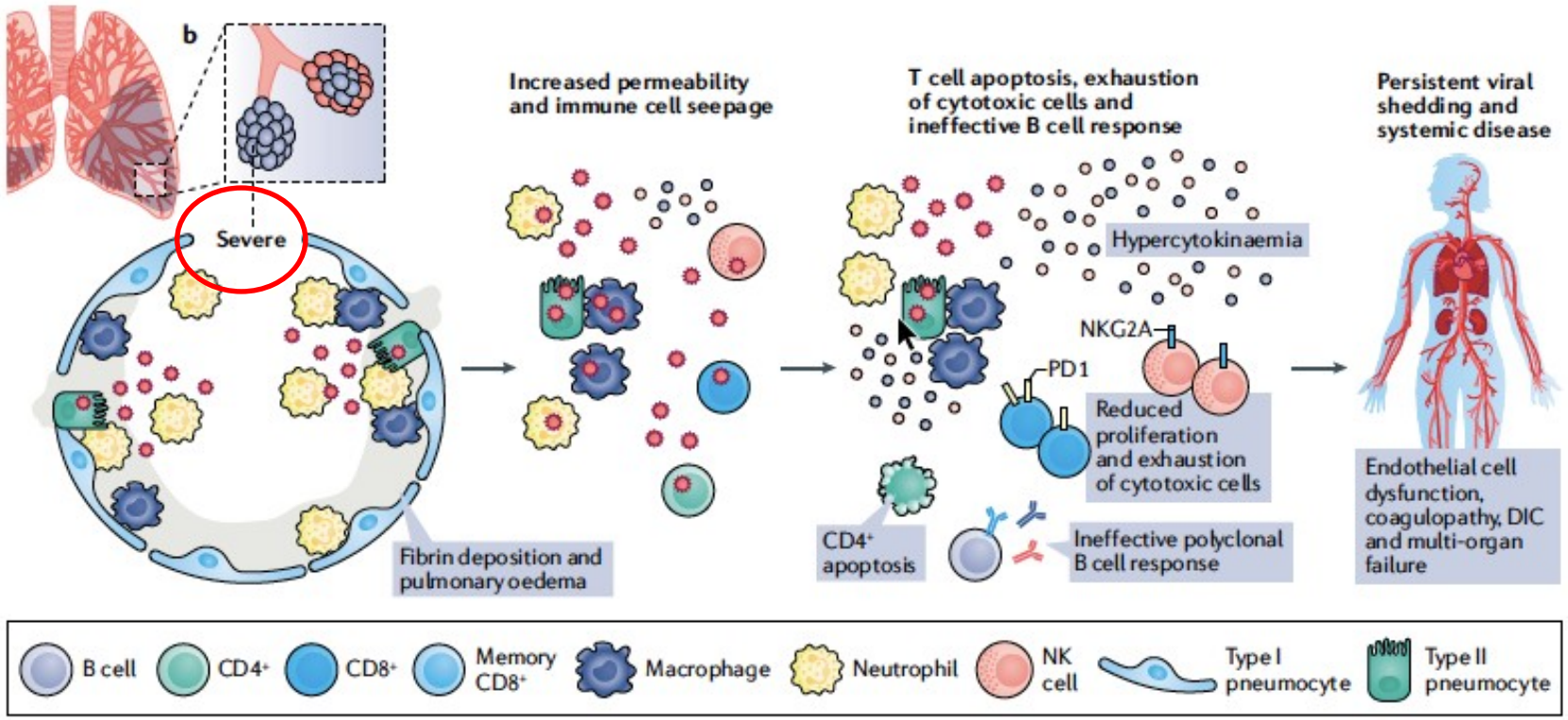
Pathogenesis and outcomes of COVID-19



Infection of the lungs induces the death of type II pneumocytes. Macrophages and neutrophils elicit a specific innate immune response to eradicate the pathogen and kill virus-infected cells. The increase in pro-inflammatory cytokines within the lung leads to the recruitment of leukocytes. IL-2, IL-6, GCSF, IFNγ, IP-10), MCP1 and 3, MIP-1α and TNF) stimulate the adaptive immune response. Infiltration of lymphocytes (CD4+ and CD8+ T cells) and natural killer (NK) cells is required to ensure an optimal defence response against SARS-CoV-2. CD4+ T cells mediate antibody production by B cells and enhance effector CD8+ T cell and NK responses during infections.

This orchestrated immune response leads to viral eradication and resolution of the disease. In these patients, coronavirus disease 2019 (COVID-19) seems to manifest as a mild disease with symptoms similar to the common flu that resolve spontaneously.

Pathogenesis and outcomes of COVID-19

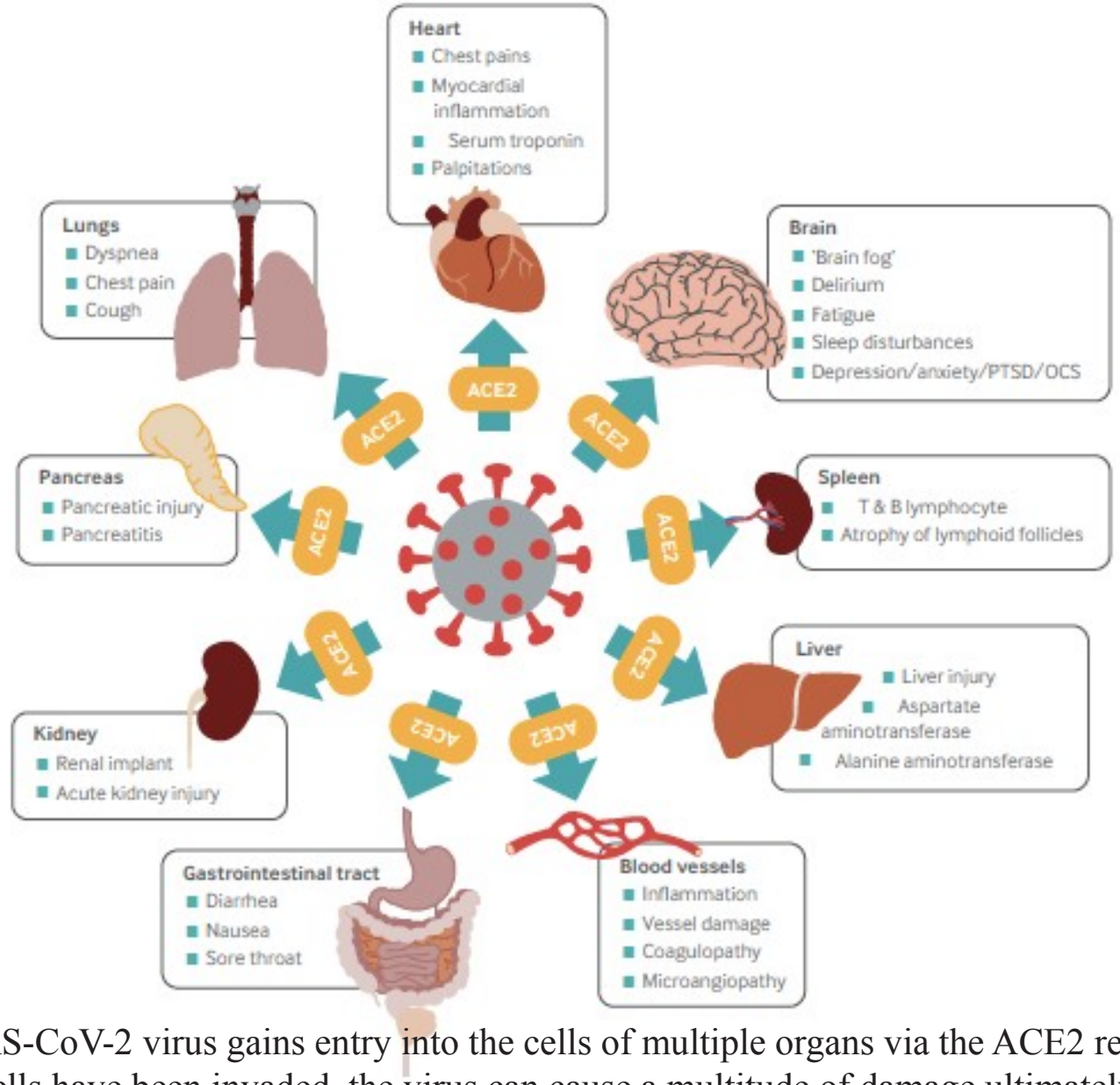


For possibly individual predisposition or differences in viral loads during primary SARS-CoV-2 infection, some patients experience more severe disease. In the absence of robust CD4+ T cell activation, B cells generate a polyclonal antibody response that may be ineffective in neutralizing SARS-CoV-2.

Increased numbers of exhausted T cells that express high levels of programmed cell death protein 1 (PD1), suggest decreased proliferation and activity of CD8+ T cells. Similarly, NK cells exhibit increased levels of the inhibitory CD94–NK group 2 member A (NKG2A). Impaired cytotoxic activity results in persistent viral shedding that amplifies macrophage and neutrophil activation, leading to the massive production of cytokines.

In these patients, COVID-19 manifests as a severe disease, consisting of advanced pneumonia and acute respiratory distress syndrome. The generation of excess cytokines and persistent viral infection leads to systemic vascular damage, disseminated intravascular coagulation (DIC) and the failure of vital organs, including the kidney and the heart.

Multi-organ complications of Covid-19 and long Covid.



The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms. Crook H.. et al. 2021

We are reviewing these guidelines as new evidence, policy and practice emerges: give us your feedback.

COVID-19 rapid guideline: managing the long-term effects of COVID-19

NICE guideline [NG188] Published: 18 December 2020

This guideline has been developed jointly by NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP).

To develop the recommendations, we have used the following clinical definitions for the initial illness and long COVID at different times:

- **Acute COVID-19**: signs and symptoms of COVID-19 for up to 4 weeks.
- **Ongoing symptomatic COVID-19**: signs and symptoms of COVID-19 from 4 to 12 weeks.
- **Post-COVID-19 syndrome**: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

Acute COVID-19

Signs and symptoms of COVID-19 for up to 4 weeks.

Ongoing symptomatic COVID-19

Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.

Post-COVID-19 syndrome

Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

Long COVID

In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

Common symptoms of ongoing symptomatic COVID-19 and post-COVID-19 syndrome

Symptoms after acute COVID-19 are highly variable and wide ranging. The most commonly reported symptoms include (but are not limited to) the following.

Respiratory symptoms

- Breathlessness
- Cough

Cardiovascular symptoms

- Chest tightness
- Chest pain
- Palpitations

Generalised symptoms

- Fatigue
- Fever
- Pain

Neurological symptoms

- Cognitive impairment ('brain fog', loss of concentration or memory issues)
- Headache
- Sleep disturbance
- Peripheral neuropathy symptoms (pins and needles and numbness)
- Dizziness
- Delirium (in older populations)

Common symptoms of ongoing symptomatic COVID-19 and post-COVID-19 syndrome

Gastrointestinal symptoms

- Abdominal pain
- Nausea
- Diarrhoea
- Anorexia and reduced appetite (in older populations)

Musculoskeletal symptoms

- Joint pain
- Muscle pain

Psychological/psychiatric symptoms

- Symptoms of depression
- Symptoms of anxiety

Ear, nose and throat symptoms

- Tinnitus
- Earache
- Sore throat
- Dizziness
- Loss of taste and/or smell

Dermatological

- Skin rashes

> EClinicalMedicine. 2021 Aug;38:101019. doi: 10.1016/j.eclinm.2021.101019. Epub 2021 Jul 15.

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

Hannah E Davis [1], Gina S Assaf [1], Lisa McCorkell [1], Hannah Wei [1], Ryan J Low [1 2], Yochai Re'em [1 3], Signe Redfield [1], Jared P Austin [1 4], Athena Akrami [1 2]

Public discourse on COVID-19 has largely centered around those with severe or fatal illness. As prevention efforts have focused on minimizing mortality, the morbidity of COVID-19 illness has been underappreciated.

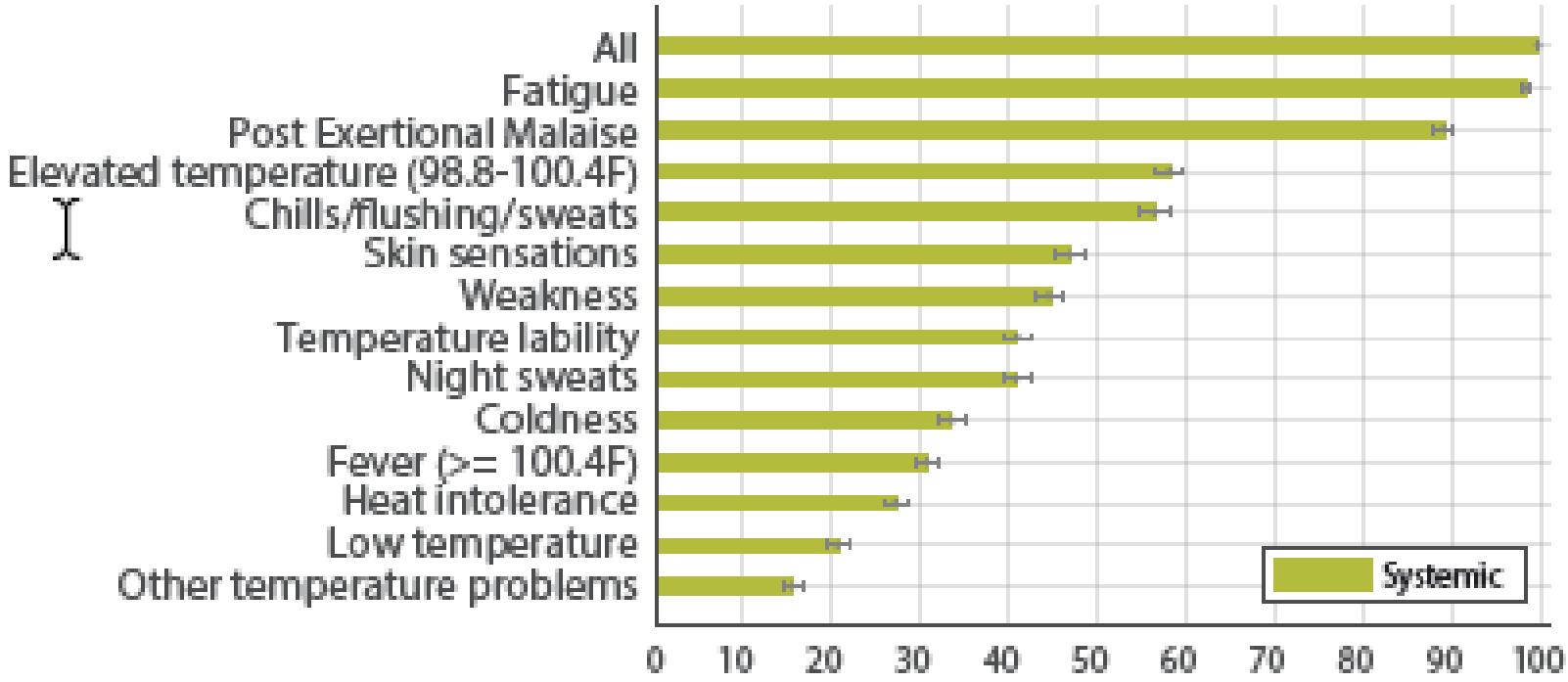
Recent studies show that a growing number of patients with COVID-19 will experience prolonged symptoms, the profile and timeline of which remains uncertain.

Early in the course of the pandemic, patients identified this trend, referring to themselves as “Long-Haulers” and the prolonged illness as “Long COVID”.

Davis E. et al. 2021

Symptom prevalence estimates
(non-neuropsychiatric symptoms).

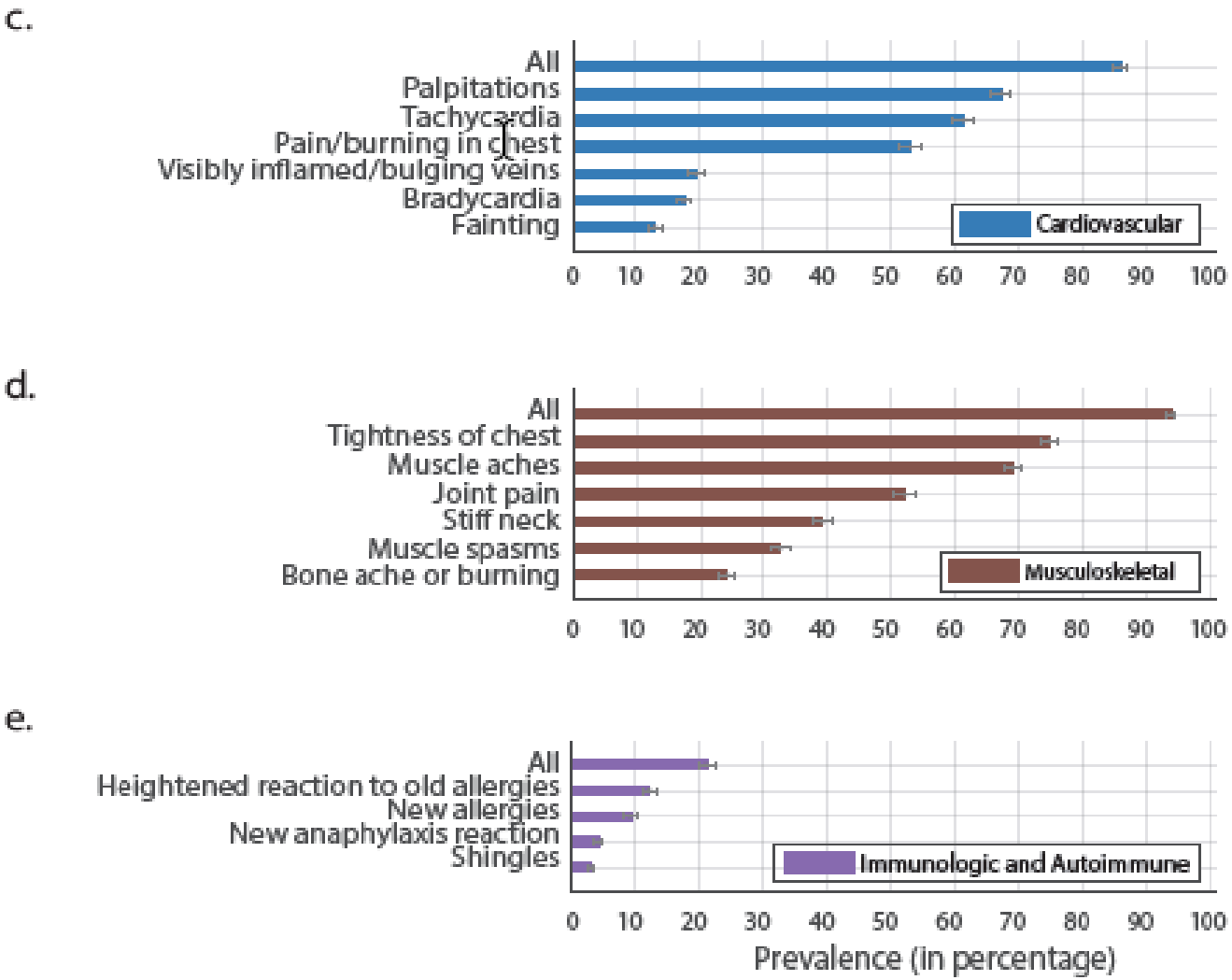
a.



Fatigue is a feeling of weariness, tiredness, or lack of energy.
"Fatigue". *MedlinePlus*. Retrieved April 30, 2020.

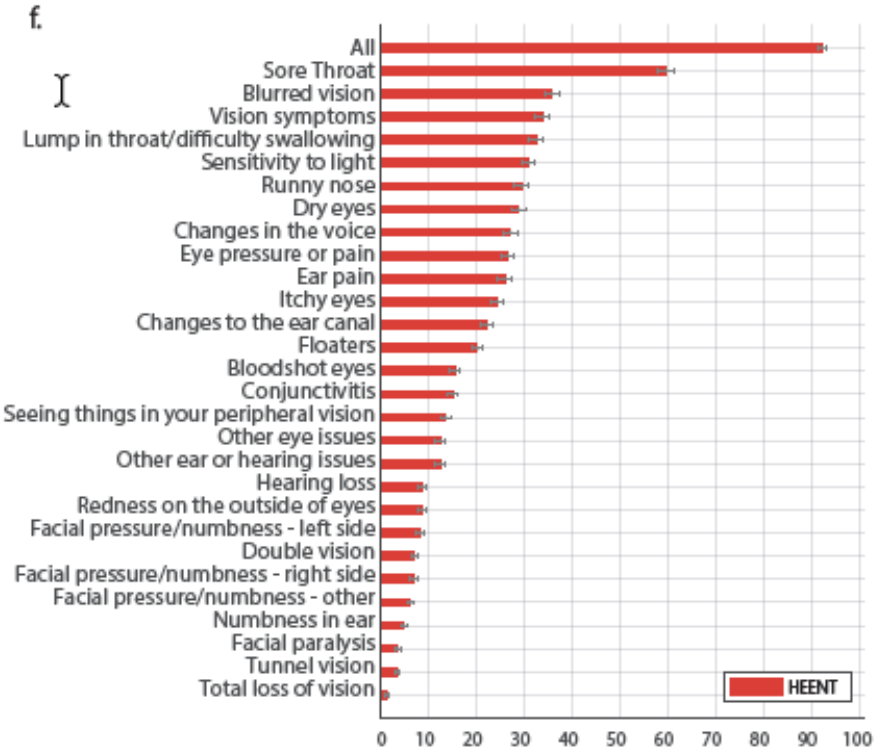
Davis E. et al. 2021

Symptom prevalence estimates
(non-neuropsychiatric symptoms).



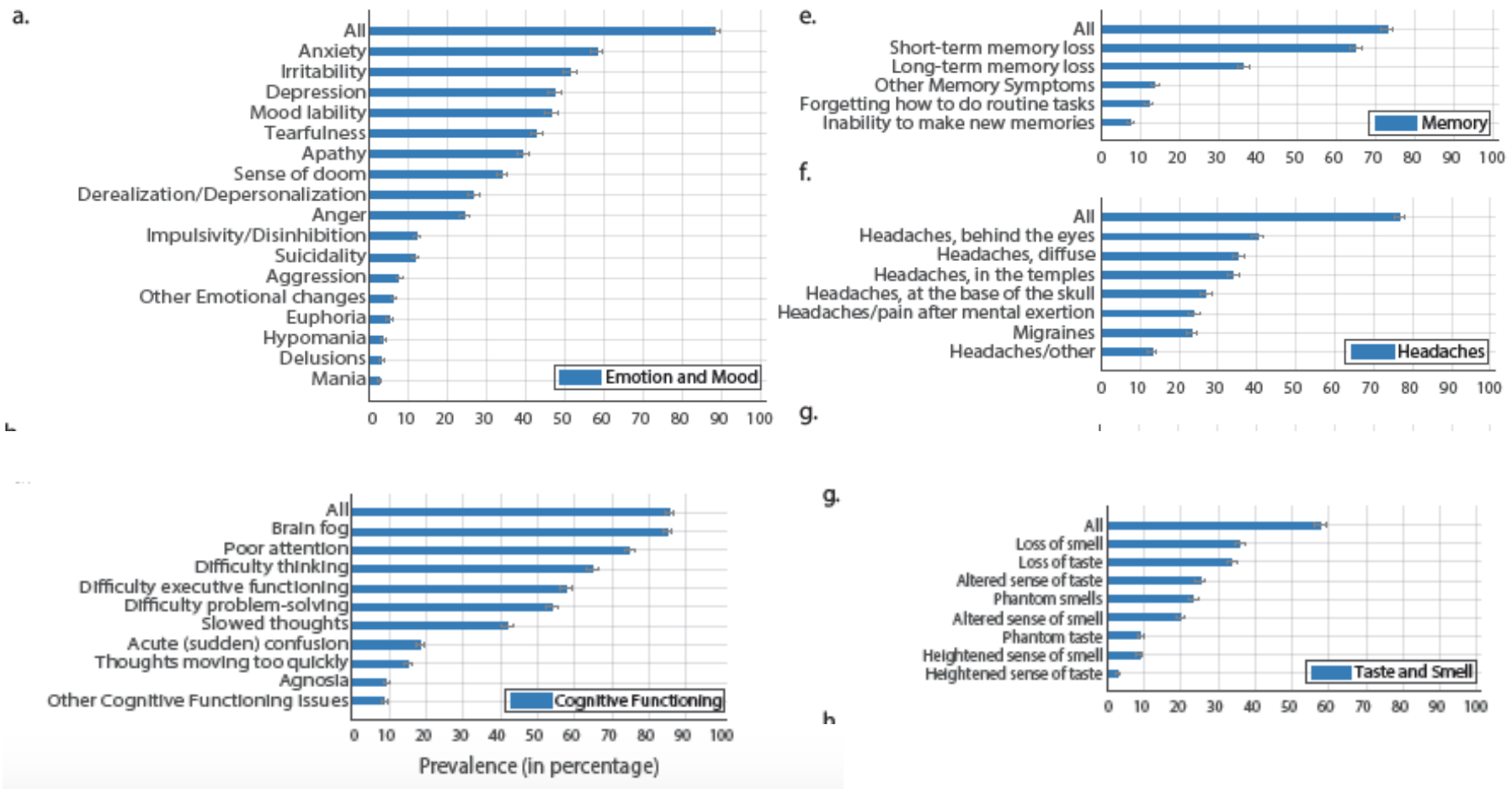
Davis E. et al. 2021

Symptom prevalence estimates (non-neuropsychiatric symptoms).



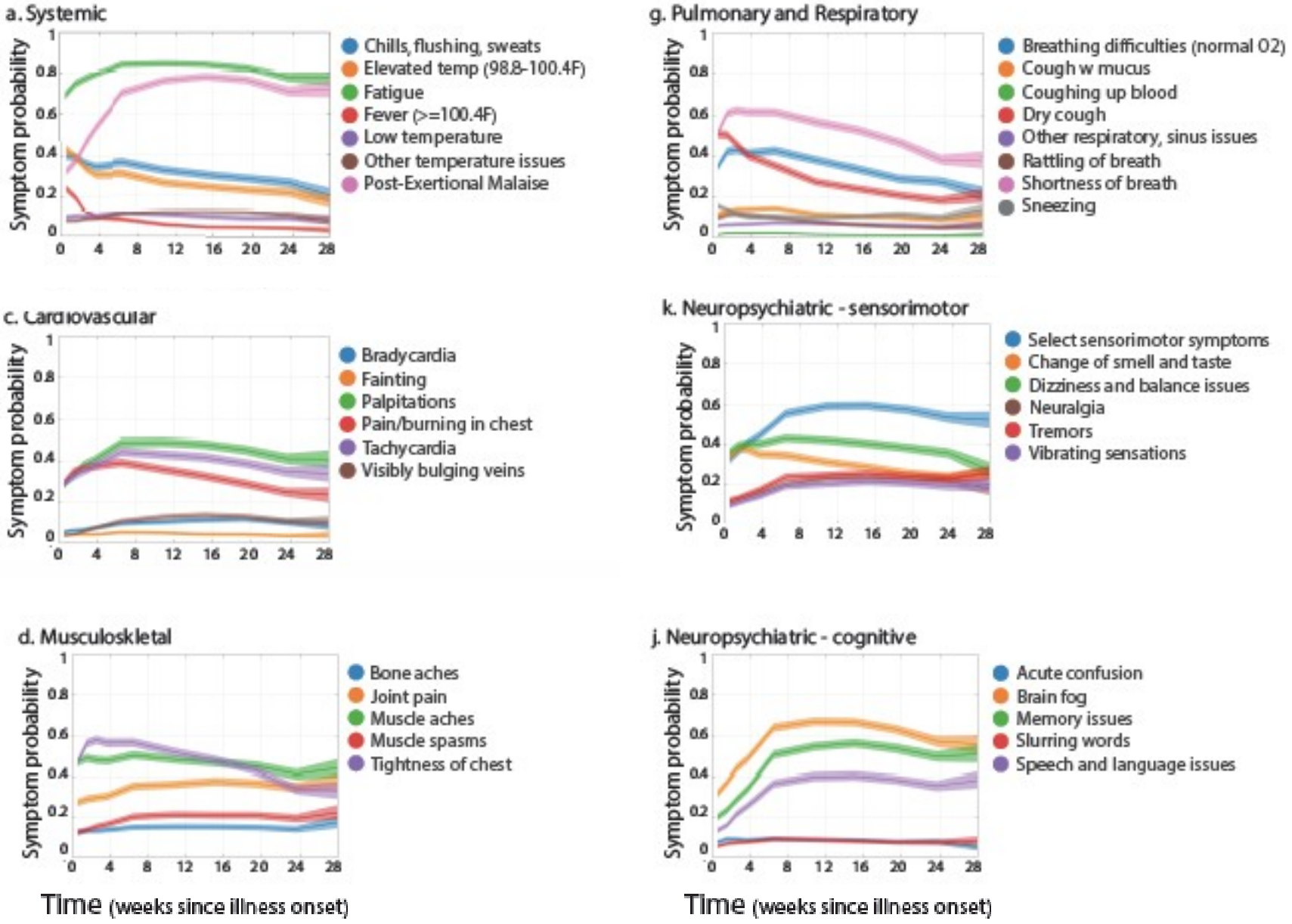
Davis E. et al. 2021

Symptom prevalence estimates for neuropsychiatric symptoms



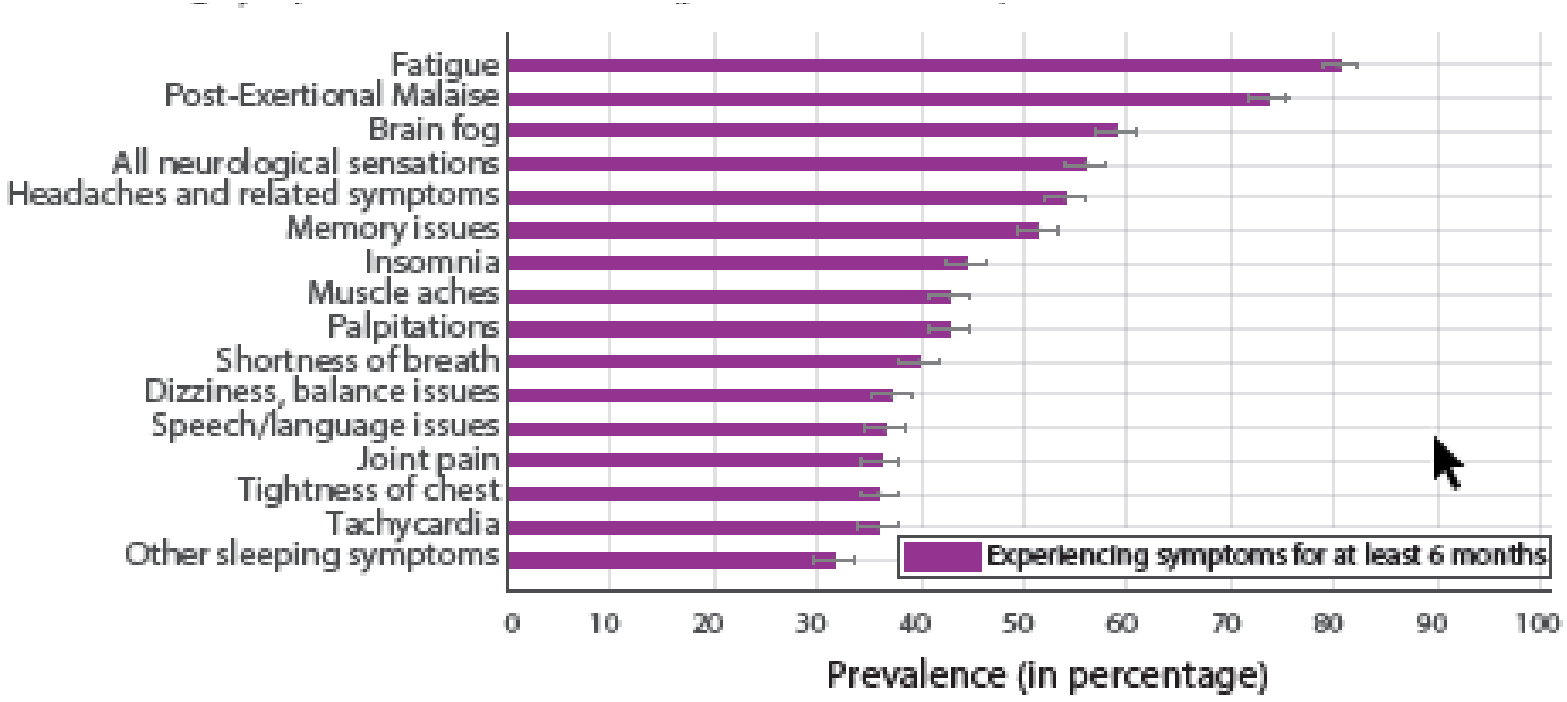
Davis E. et al. 2021

Symptom time courses



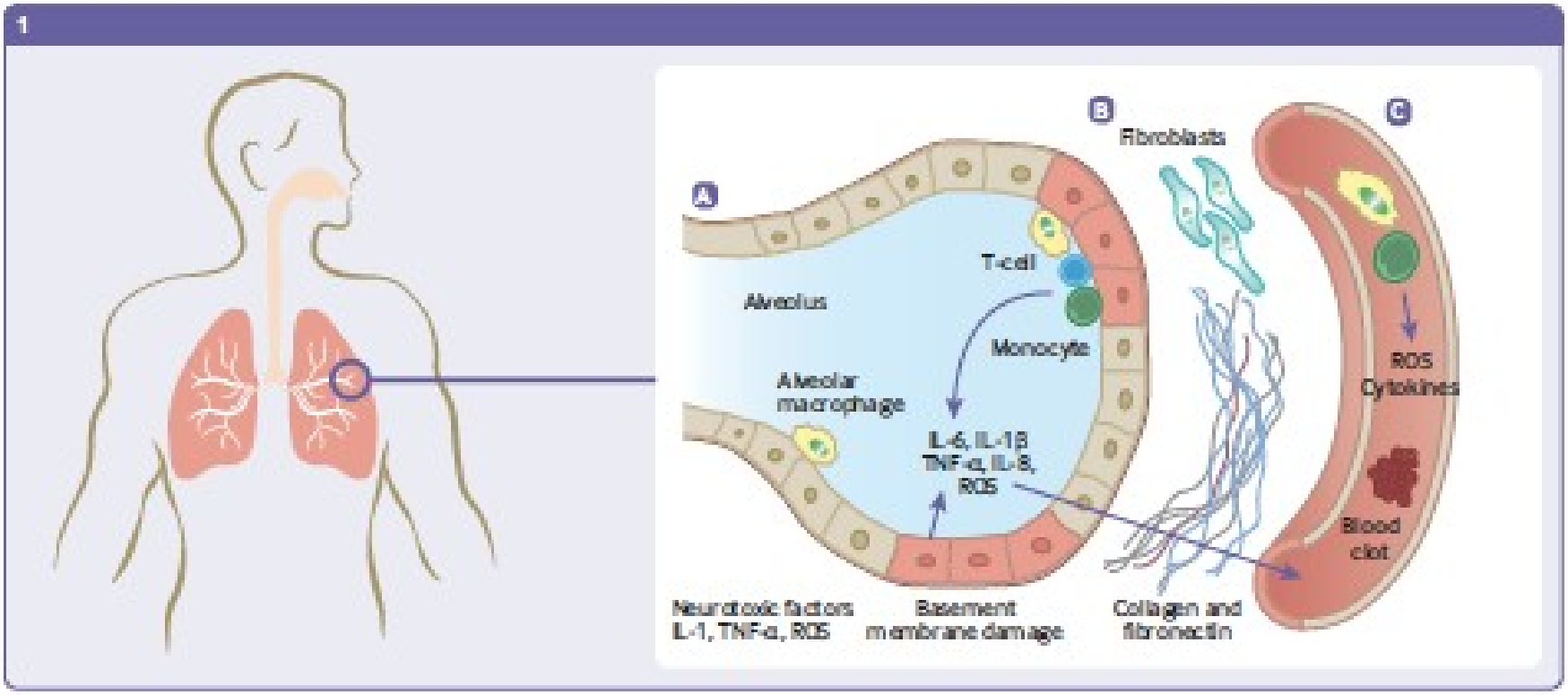
Davis E. et al. 2021

Remaining symptoms after 6 months
(prevalence >30%)



Davis E. et al. 2021

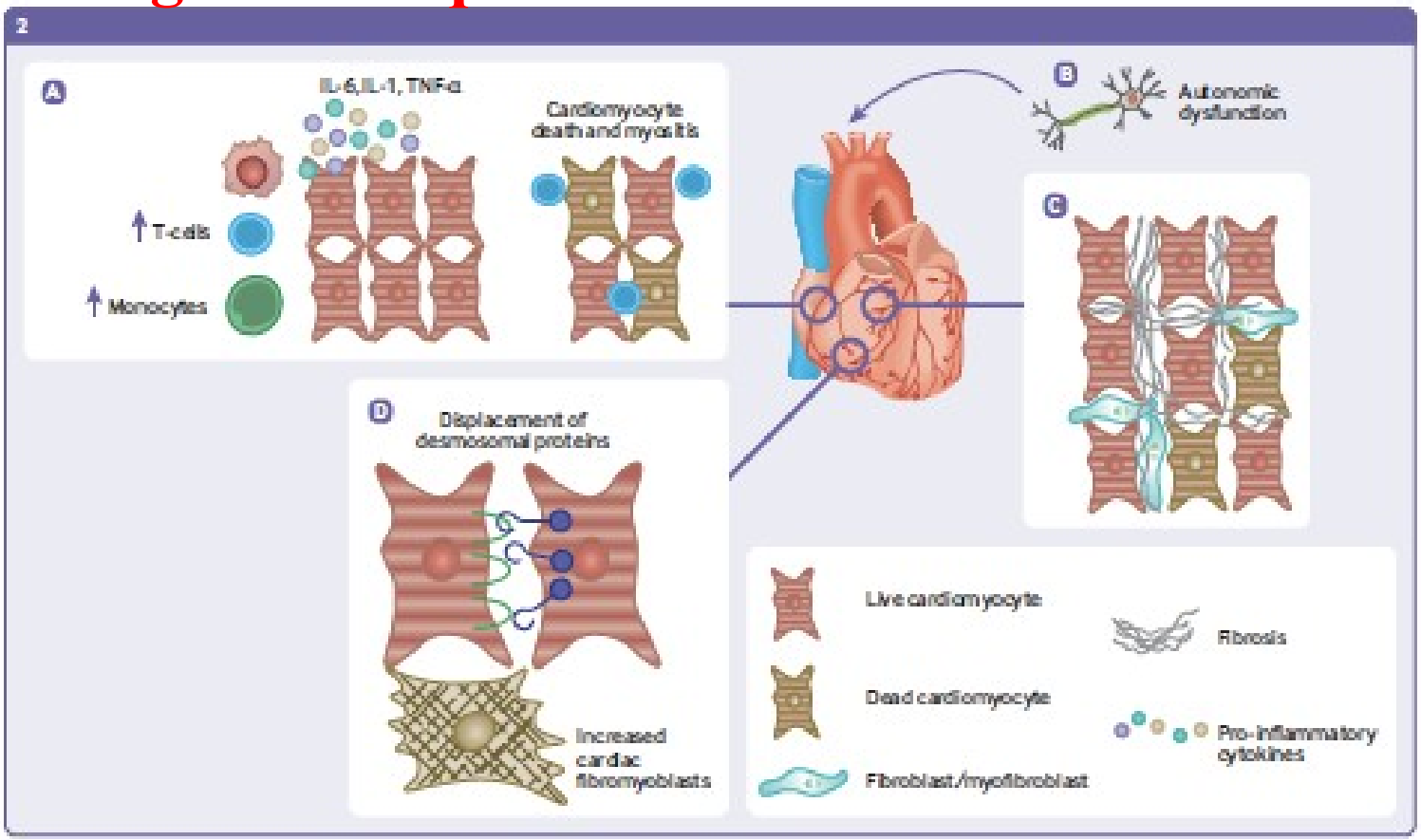
Long-term sequalae of covid-19: in the alveoli of the lungs



(A) Chronic inflammation results in the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS) which are released into the surrounding tissue and bloodstream.
(B) Endothelial damage triggers the activation of fibroblasts, which deposit collagen and fibronectin resulting in fibrotic changes.
(C) Endothelial injury, complement activation, platelet activation, and platelet-leukocyte interactions, release of pro-inflammatory cytokines, disruption of normal coagulant pathways, and hypoxia result in a prolonged hyperinflammatory and hypercoagulable state, increasing the risk of thrombosis.

Crook H.. et al. 2021

Long-term sequalae of covid-19: in the heart

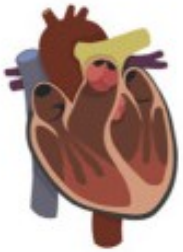


(A) Chronic inflammation of cardiomyocytes can result in myositis and cause cardiomyocytes death.
(B) Dysfunction of the afferent autonomic nervous system can cause complications such as postural orthostatic tachycardia syndrome.
(C) Prolonged inflammation and cellular damage prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis.
(D) Fibrotic changes are accompanied by an increase in cardiac fibromyoblasts, while damage to desmosomal proteins results in reduced cell-to-cell adhesion.

Crook H.. et al. 2021

COVID-19 and the cardiovascular system

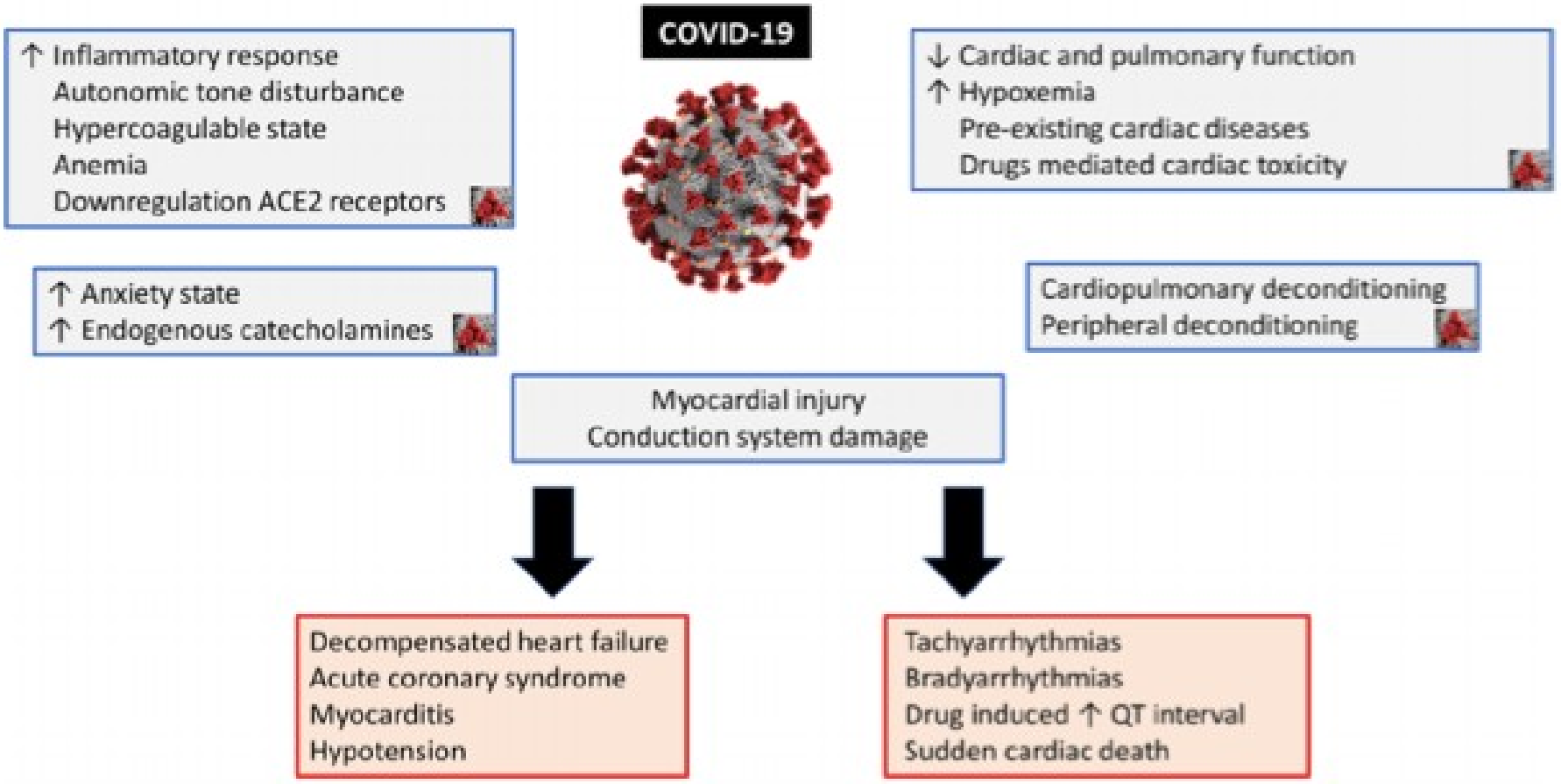
COVID-19



Risks

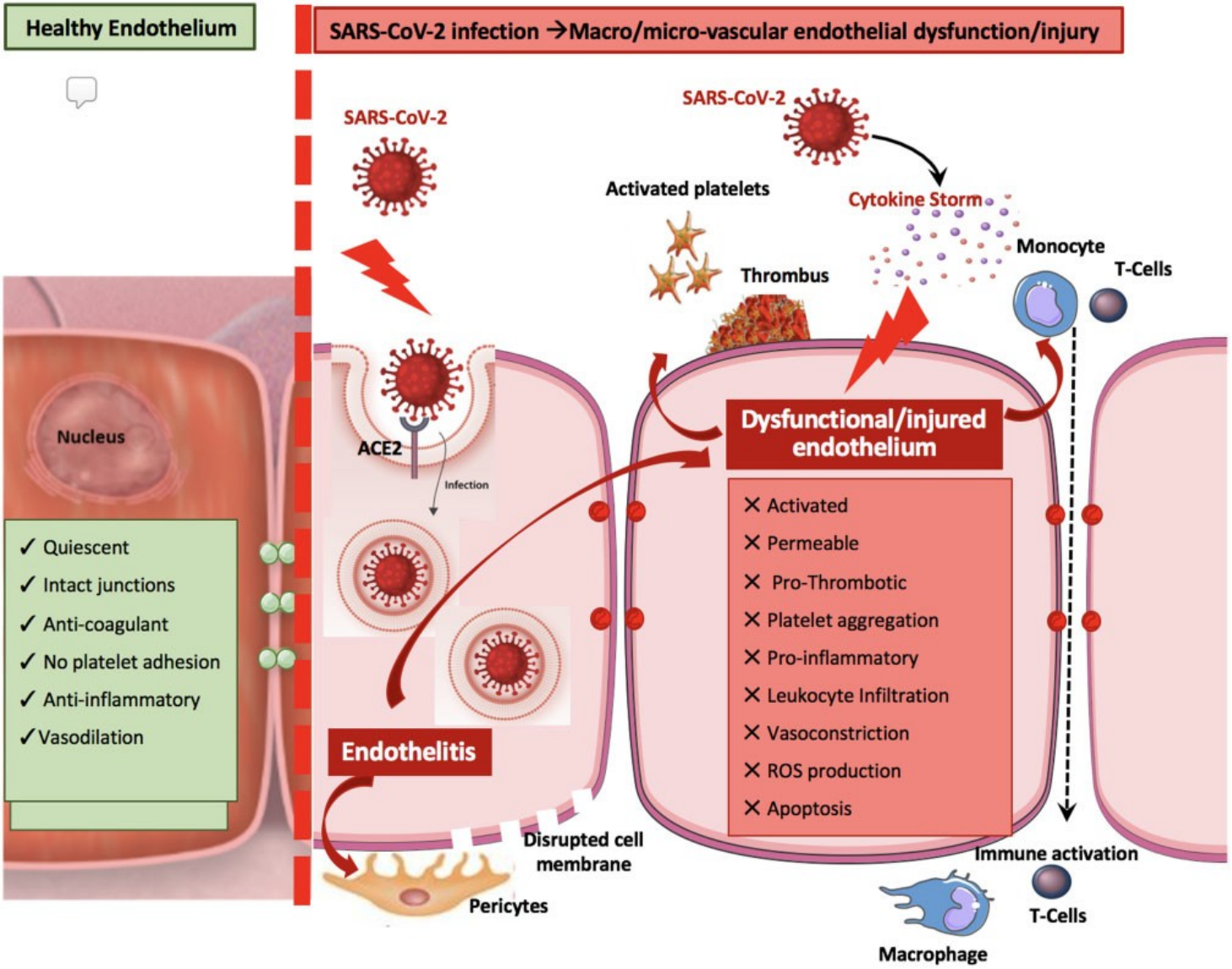
- Older Age
- Comorbidities - CVD, lung, renal, diabetes
- Systemic Inflammation
- Coagulation Abnormalities
- Severe Illness and Multiorgan Dysfunction
- Immobility

Mechanisms and consequences of COVID−19 myocardial damage. COVID−19, coronavirus diseas



Kochi A. et al. 2020

Endothelial dysregulation by SARS-CoV-2.



Evans PC. et al. 2020

Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science

The Working Group on Atherosclerosis and Vascular Biology together with the Council of Basic Cardiovascular Science of the European Society of Cardiology provide a Position Statement on the importance of the endothelium in the underlying pathophysiology behind the clinical presentation in COVID-19 and identify key questions for future research to address.

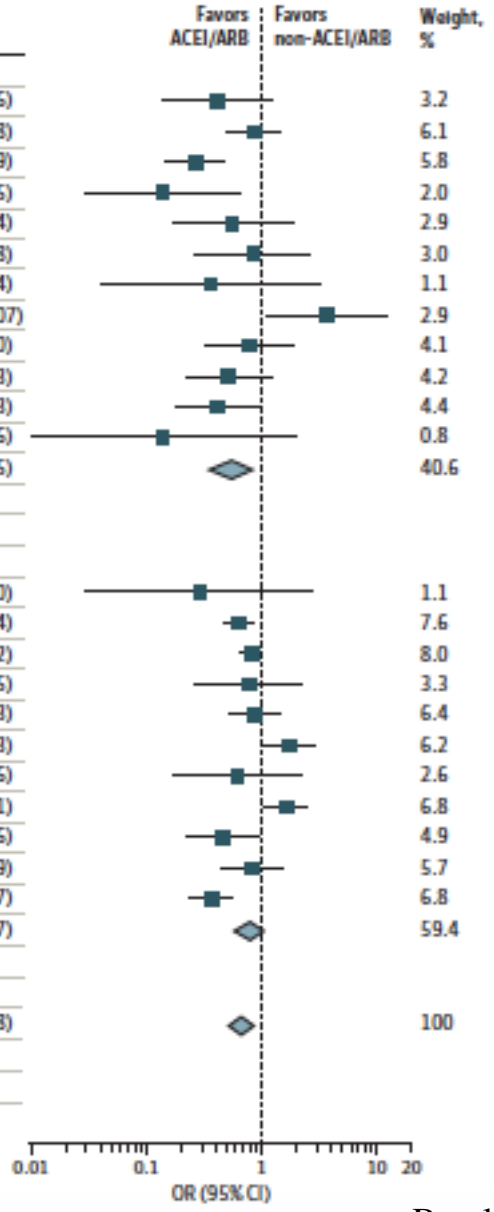
We propose that endothelial biomarkers and tests of function should be evaluated for their usefulness in the risk stratification of COVID-19 patients.

A better understanding of the effects of SARS-CoV-2 on endothelial biology in both the micro- and macrovasculature is required, and endothelial function testing should be considered in the follow-up of convalescent COVID-19 patients for early detection of long-term cardiovascular complications.

Evans PC. Et al. 2020

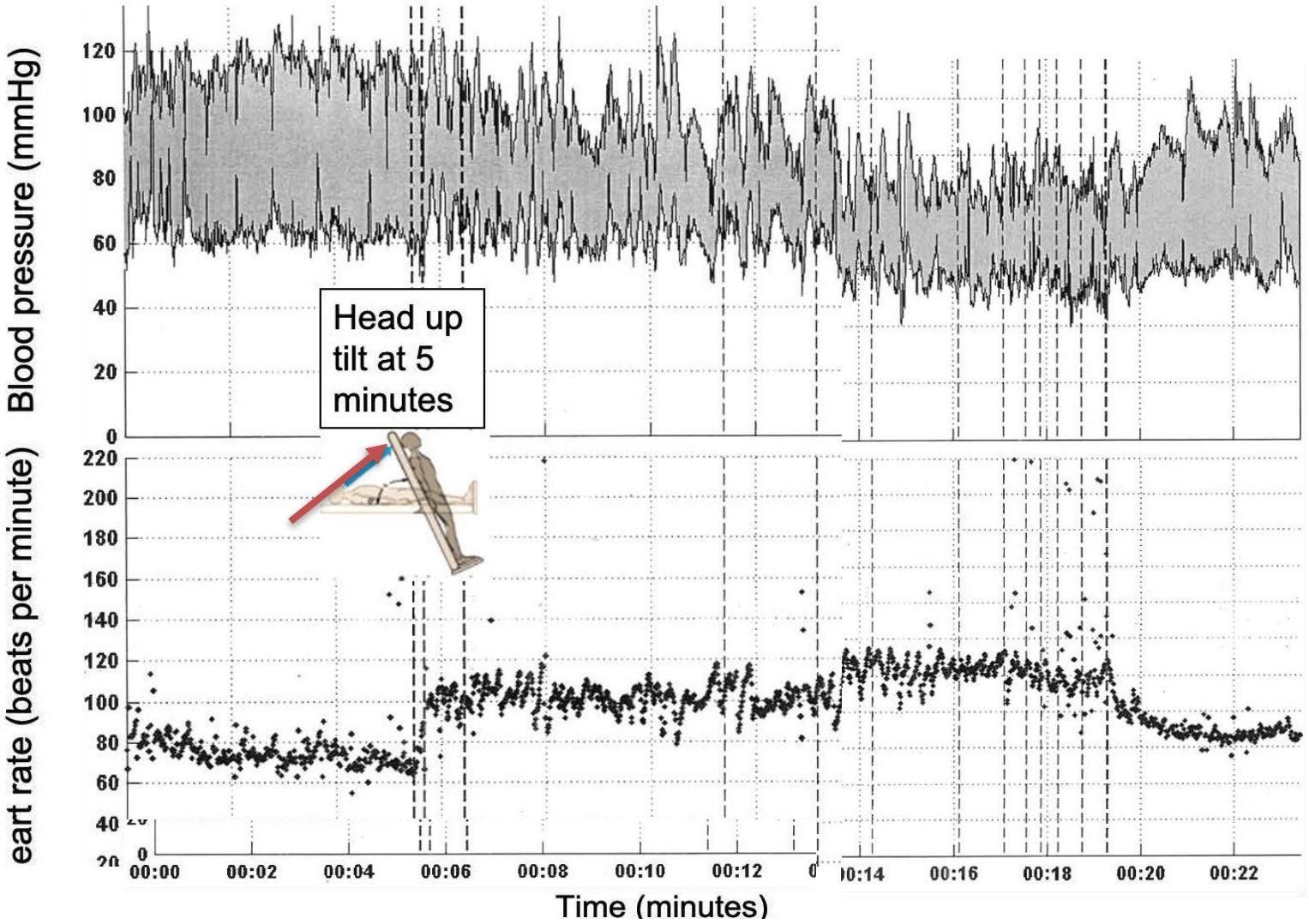
Subgroup Analysis of Adjusted Mortality and Severe Adverse Events Among Patients Who Did and Did Not Receive ACEIs or ARBs

Source	log OR	SE	OR (95% CI)	Weight, %
Hypertension subgroup				
Conversano et al,[19] 2020	-0.8675	0.5605	0.42 (0.14-1.26)	3.2
Bravi et al,[7] 2020	-0.1393	0.2725	0.87 (0.51-1.48)	6.1
Chen et al,[23] 2020	-1.3093	0.2999	0.27 (0.15-0.49)	5.8
Chen et al,[24] 2020	-1.9661	0.7860	0.14 (0.03-0.65)	2.0
Felice et al,[9] 2020	-0.5798	0.6082	0.56 (0.17-1.84)	2.9
Gao et al,[28] 2020	-0.1625	0.5851	0.85 (0.27-2.68)	3.0
Matsuzawa et al,[44] 2020	-1.0217	1.1211	0.36 (0.04-3.24)	1.1
Selcuk et al,[5] 2020	1.2975	0.6087	3.66 (1.11-12.07)	2.9
Xu et al,[58] 2020	-0.2485	0.4546	0.78 (0.32-1.90)	4.1
Yuan et al,[60] 2020	-0.6539	0.4389	0.52 (0.22-1.23)	4.2
Zhang et al,[61] 2020	-0.8916	0.4200	0.41 (0.18-0.93)	4.4
Zhou et al[8] 2020	-1.9661	1.3465	0.14 (0.01-1.96)	0.8
Subtotal	NA	NA	0.55 (0.36-0.85)	40.6
Heterogeneity: $T^2=0.28$; $\chi^2=24.24$; df = 11; $P=.01$; $I^2=55.0\%$				
Test for overall effect: $z=2.69$; $P=.007$				
Mixed subgroup				
Bae et al,[20] 2020	-1.2379	1.1575	0.29 (0.03-2.80)	1.1
Bean et al,[21] 2020	-0.4620	0.1495	0.63 (0.47-0.84)	7.6
Fosbol et al,[27] 2020	-0.1985	0.1107	0.82 (0.66-1.02)	8.0
Gormez et al,[29] 2020	-0.2485	0.5413	0.78 (0.27-2.25)	3.3
Jung et al,[36] 2020	-0.1278	0.2492	0.88 (0.54-1.43)	6.4
Litaeuf et al,[40] 2020	0.5481	0.2696	1.73 (1.02-2.93)	6.2
Lopez-Otero et al,[42] 2020	-0.4780	0.6602	0.62 (0.17-2.26)	2.6
Mehta et al,[6] 2020	0.4947	0.2179	1.64 (1.07-2.51)	6.8
Mostaza et al,[46] 2020	-0.7765	0.3763	0.46 (0.22-0.96)	4.9
Shah et al,[54] 2020	-0.1985	0.3062	0.82 (0.45-1.49)	5.7
Zhou et al,[10] 2020	-0.9943	0.2209	0.37 (0.24-0.57)	6.8
Subtotal	NA	NA	0.79 (0.59-1.07)	59.4
Heterogeneity: $T^2=0.15$; $\chi^2=37.04$; df = 10; $P<.001$; $I^2=73.0\%$				
Test for overall effect: $z=1.54$; $P=.12$				
Total	NA	NA	0.68 (0.53-0.88)	100
Heterogeneity: $T^2=0.19$; $\chi^2=66.95$; df = 22; $P<.001$; $I^2=67.0\%$				
Test for overall effect: $z=3.01$; $P=.003$				
Test for subgroup differences: $\chi^2=1.78$; df = 1; $P=.18$; $I^2=43.9\%$				



Baral R.et al. 2021

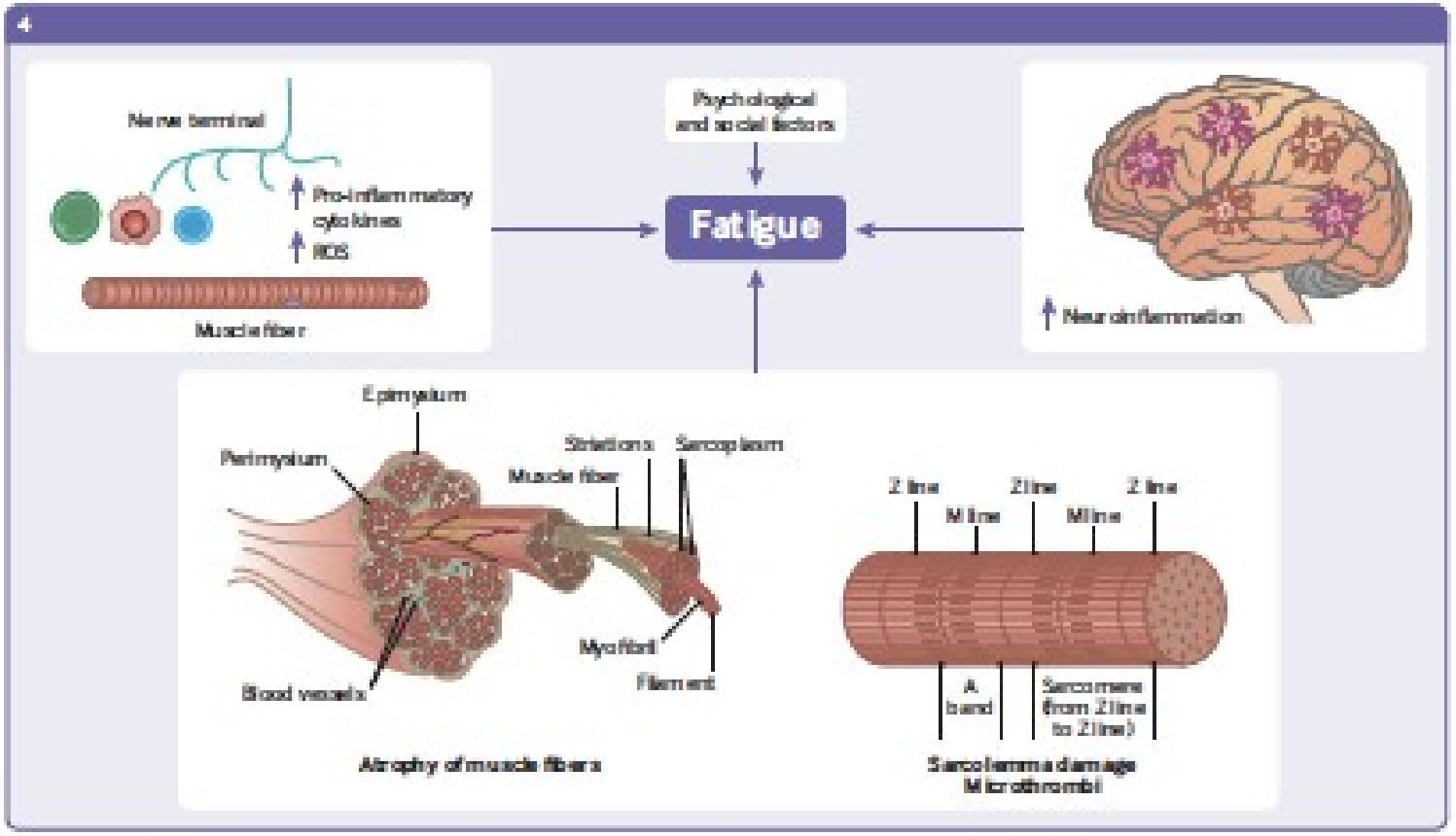
Autonomic dysfunction in ‘long COVID’



Continuous heart rate and blood pressure monitoring during a head-up tilt table test from an individual with long COVID and orthostatic intolerance following COVID-19 infection

Dani M. et al 2021

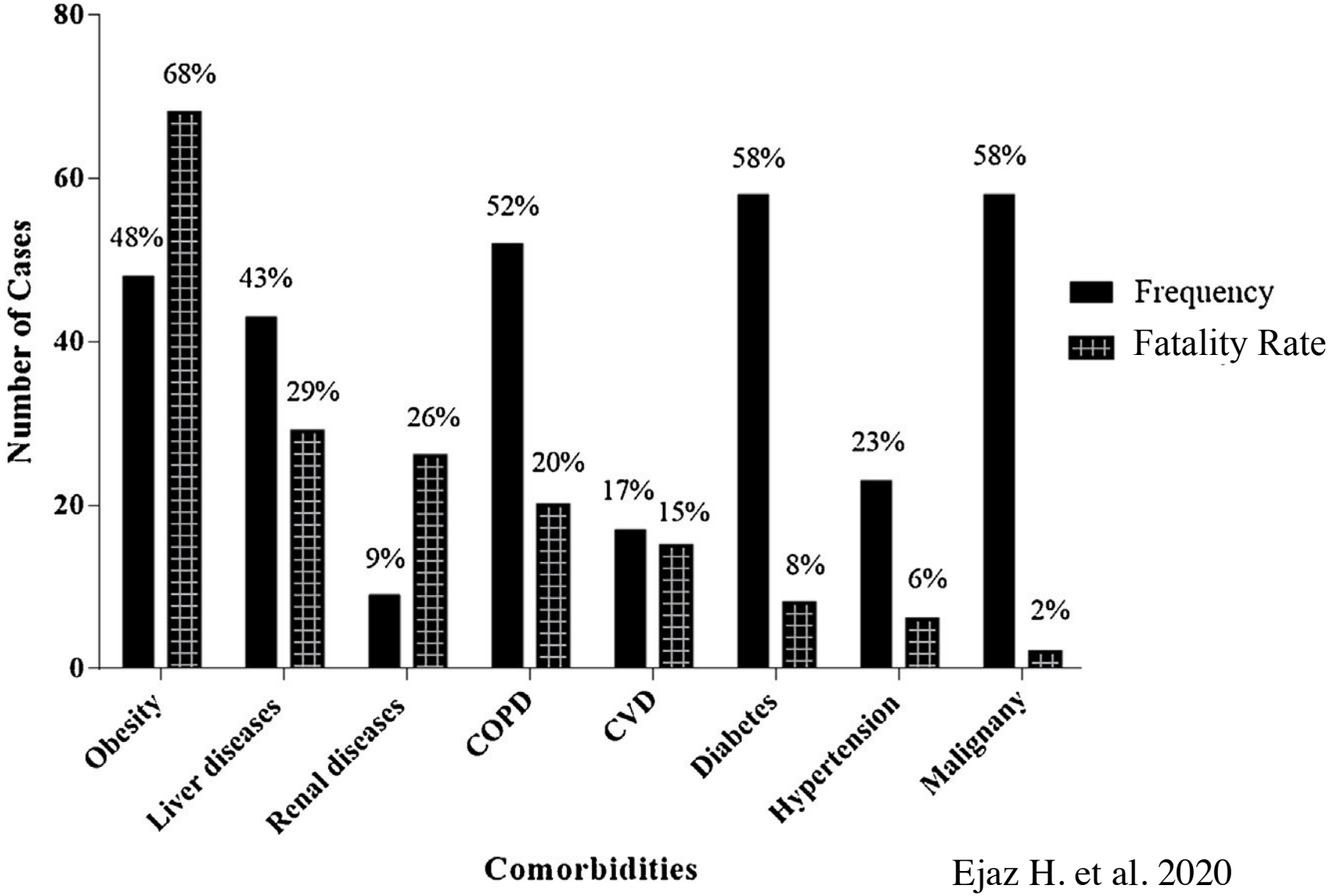
Long term sequalae of covid-19: fatigue



A range of central, peripheral, and psychological factors may cause chronic fatigue in long covid. Chronic inflammation in the brain, as well as at the neuromuscular junctions, may result in long term fatigue. In skeletal muscle, sarcolemma damage and fiber atrophy and damage may play a role in fatigue, as might a number of psychological and social factors

Crook H.. et al. 2021

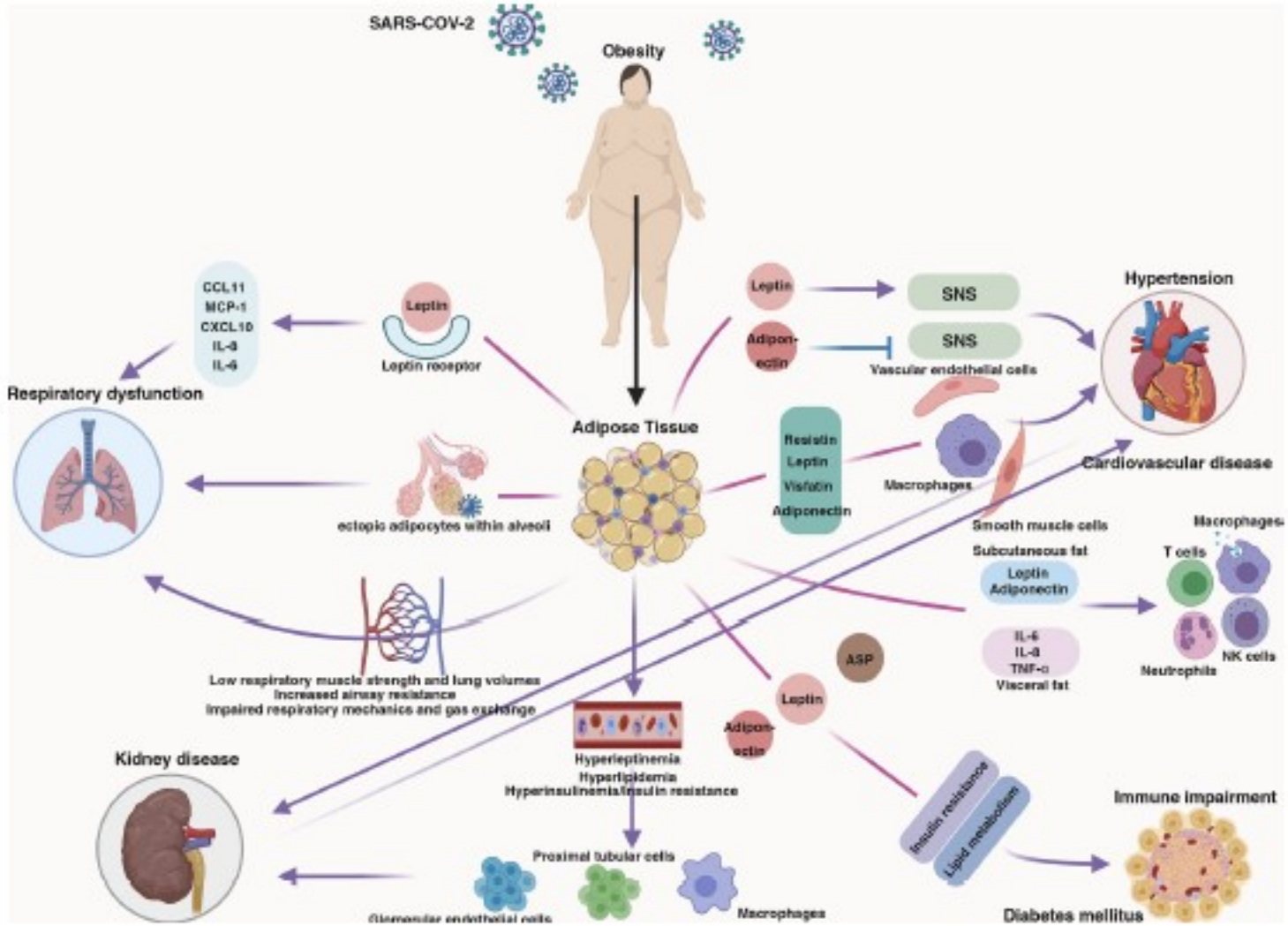
The frequency of comorbidity and its fatality in COVID-19 infections



Ejaz H. et al. 2020

The centrality of obesity in the course of severe COVID-19.

Schematic demonstrating the interaction between obesity and multiple body systems, contributing to severe COVID-19.



Liu D. et al. 2021

Journal List › Elsevier Public Health Emergency Collection › PMC8379817

Elsevier Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Am J Med. 2021 Aug 21

doi: 10.1016/j.amjmed.2021.07.037 [Epub ahead of print]

PMCID: PMC8379817

PMID: 34428463

The Long-COVID Conundrum

Adam W Gaffney, MD MPH[1,2,*]

Indeed, although there are no FDA-approved therapies for Long COVID, various non-evidence-based therapies are now being prescribed, ranging from ivermectin to antivirals directed against Herpesviridae, as described in media reports. Tenuous connections between COVID and such entities as mast cell activation syndrome (MCAS) and postural orthostatic tachycardia syndrome (POTS) are also being widely asserted.

Ironically, one treatment with clear efficacy for patients with chronic lung disease—physical rehabilitation—is now among the most controversial in Long COVID.
This controversy stems from a longstanding dispute about the use of exercise therapy for patients with Chronic Fatigue Syndrome that culminated in its removal from Centers for Disease Control recommendations and NICE clinical draft guidelines.