



Dartmouth Hitchcock
Medical Center

Post Acute COVID Syndrome: “Long Haulers”

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Objectives

At the conclusion of this learning activity, participants will be able to:

- ✓ **List at least 2 common post-acute COVID sequelae**
- ✓ **Identify one theory to the cause of Long COVID**

Conflicts of Interest

No conflicts of interest to disclose

Name & Definition

Post COVID-19 condition occurs in individuals with a **history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others (see [Table 3](#) and [Annex 2](#)) which generally have an **impact on everyday functioning.** Symptoms may be **new onset**, following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.

*Lack of return to usual state of health
~8-12 weeks after acute SARS-CoV-2
infection*

Annex 1. Repository of published/available definitions of post COVID-19 condition

Source	Text
Wellcome	Symptoms persisting beyond 4 weeks after symptom onset suggestive of COVID-19 (33).
Lancet	Multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients. They range from cough and shortness of breath, to fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, and affect people of varying ages. At the Lancet–Chinese Academy of Medical Sciences conference on 23 November 2020, Bin Cao presented data (in press at the Lancet) on the long-term consequences of COVID-19 for patients in Wuhan, and warned that dysfunctions and complications could persist in some discharged patients for at least 6 months. So-called long COVID is a burgeoning health concern and action is needed now to address it (34).
NICE	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 (35).
Scientific American	Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown (36).
Royal Society	The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more: severe fatigue, reduced exercise capacity, chest pain or heaviness, fever, palpitations, cognitive impairment, anosmia or ageusia, vertigo and tinnitus, headache, peripheral neuropathy, metallic or bitter taste, skin rash joint pain or swelling (3). * Maximum period between acquisition of the infection (if known) and the onset of symptoms, and the minimum duration of symptoms, should be specified in the definition.
Haute Autorité de santé, France	Three criteria: Having presented with a symptomatic form of COVID-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis (37).
CDC	Long COVID: While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms (38).
Wikipedia	Condition characterized by long-term sequelae – persisting after the typical convalescence period – of coronavirus disease 2019 (COVID-19) (39).
Nature	Post-acute COVID-19 as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms (40).

History of Long COVID

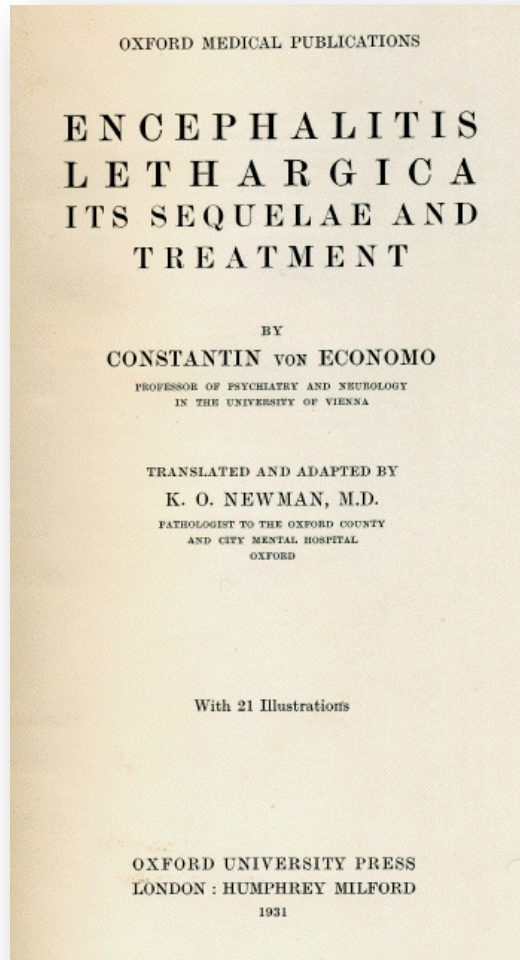


May, 2020

#LongCovid

Post-Ebola Syndrome among Ebola Virus Disease Survivors in Montserrado County, Liberia 2016

Himiede W Wilson¹, Maame Amo-Addae², Ernest Kenu¹, Olayinka Stephen Ilesanmi²,
Donne K Ameme¹, Samuel O Sackey¹



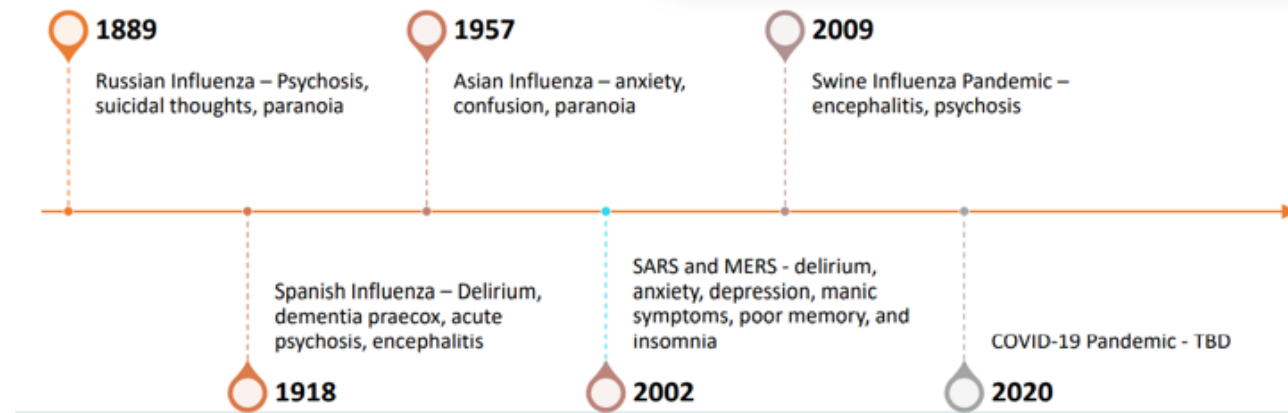
THE LANCET

Access provided by Dartmouth College

Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers

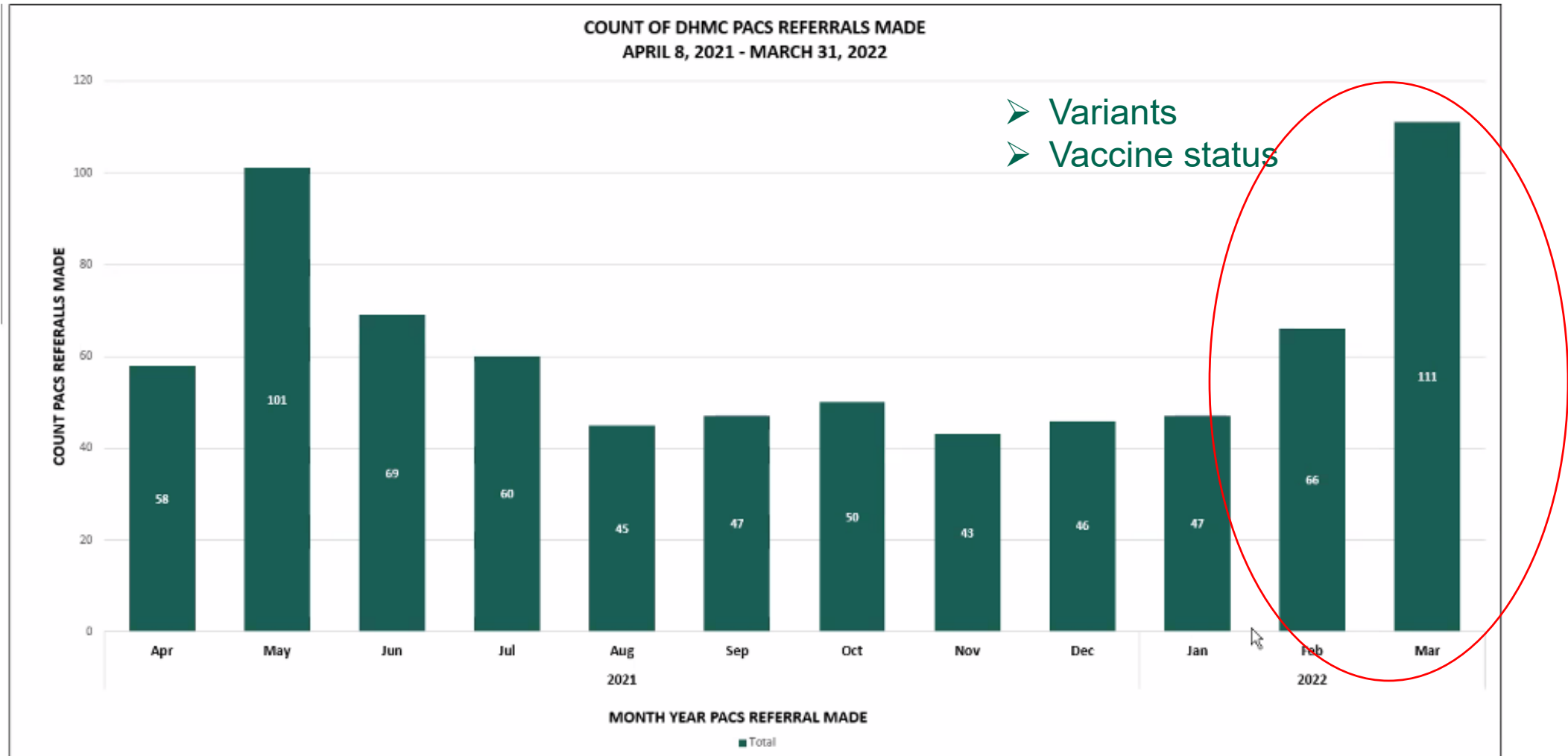
Mark Honigsbaum ✉ • Lakshmi Krishnan

Published: October 12, 2020 • DOI: [https://doi.org/10.1016/S0140-6736\(20\)32134-6](https://doi.org/10.1016/S0140-6736(20)32134-6) • [Check for updates](#)



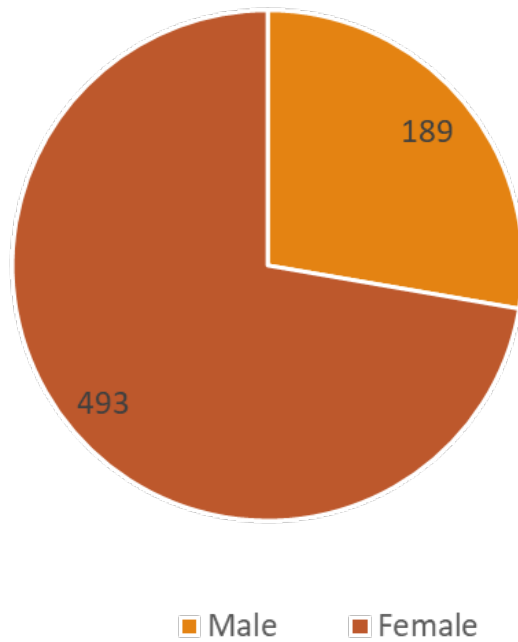
COVID by the numbers

- 515 million people worldwide infected with COVID; 6.2 million deaths (1M US)
- ~ 510 million COVID survivors
- 10 – 30 % go on to develop long COVID
- 125 million long COVID worldwide (23M US)
- 1 million Americans are out of work due to symptoms of long COVID
- Women are less likely to develop severe acute COVID but more likely to develop long COVID than men.
- More than a third of patients with COVID-19 experience more than one persistent symptom

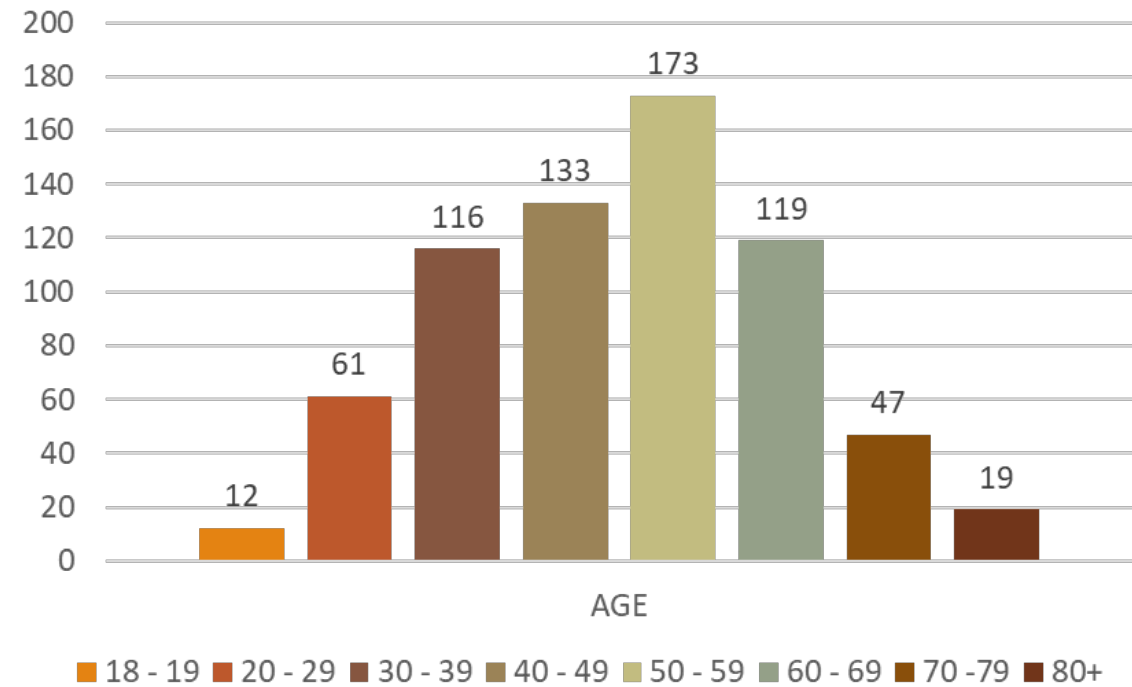


Dartmouth PACS clinic

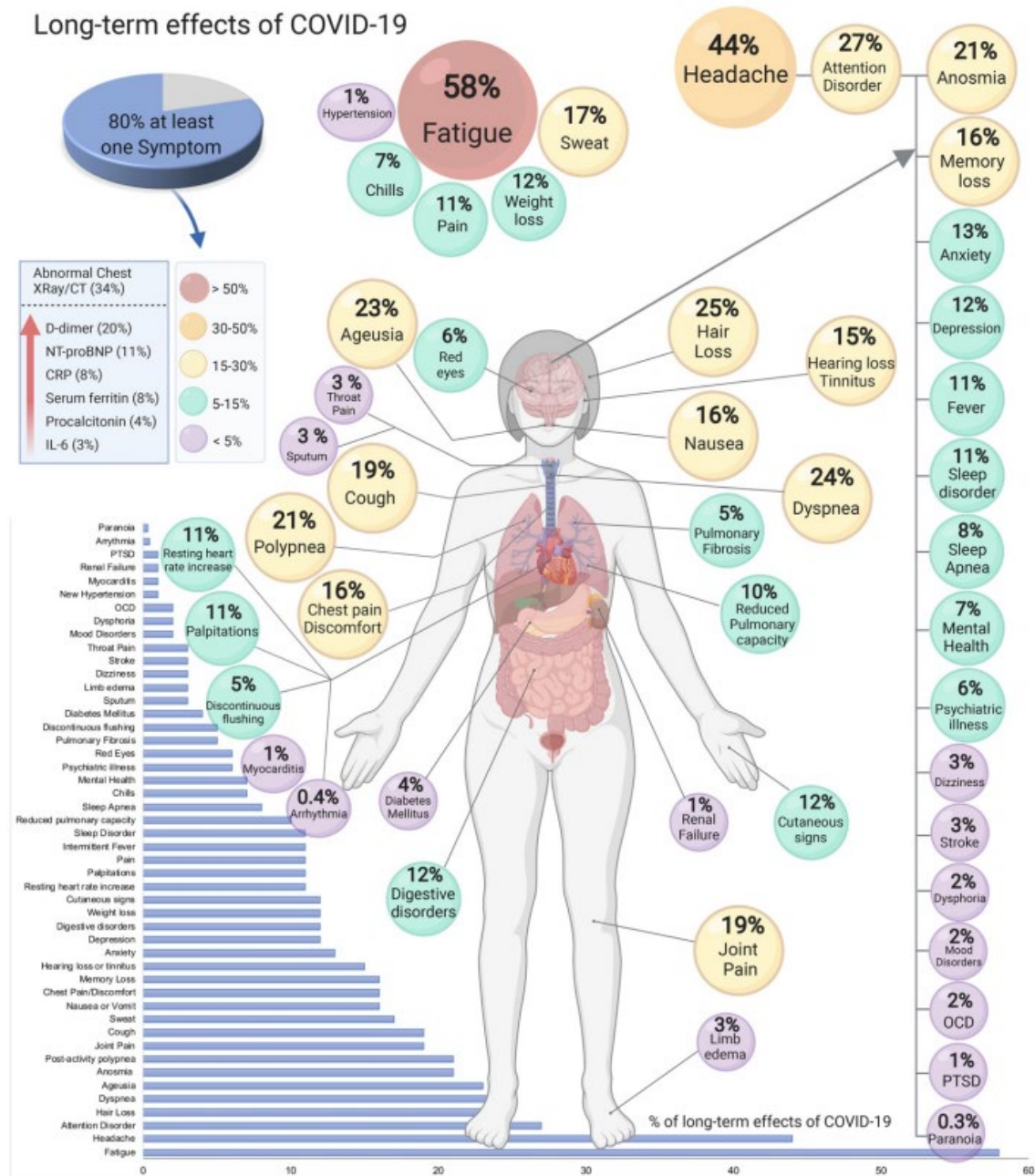
D-H PACS Referrals



D-H PACS Referrals by Age



Long-term effects of COVID-19



Long COVID Sequelae

More than a third of patients with COVID-19 experience more than one persistent symptom.

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES



BMJ Yale

More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis

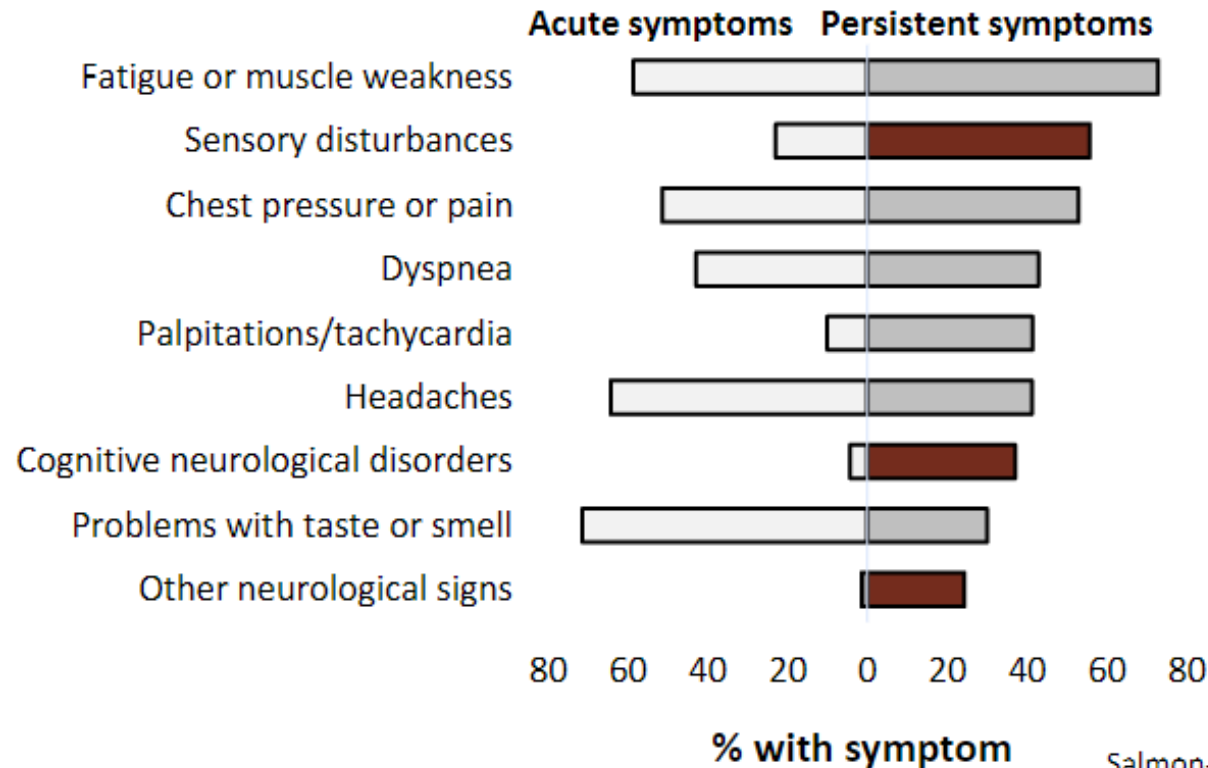
Sandra Lopez-Leon,
 Talia Wegman-Ostrosky,
 Carol Perelman,
 Rosalinda Sepulveda,
 Paulina A Rebolledo,
 Angelica Cuapio,
 Sonia Villapol

doi: <https://doi.org/10.1101/2021.01.27.21250617>

Now published in *Scientific Reports* doi: [10.1038/s41598-021-95565-8](https://doi.org/10.1038/s41598-021-95565-8)

More than one quarter of patients developed new neurological symptoms after their acute COVID-19 illness.

COVID-19 symptoms among 70 non-hospitalized patients, France

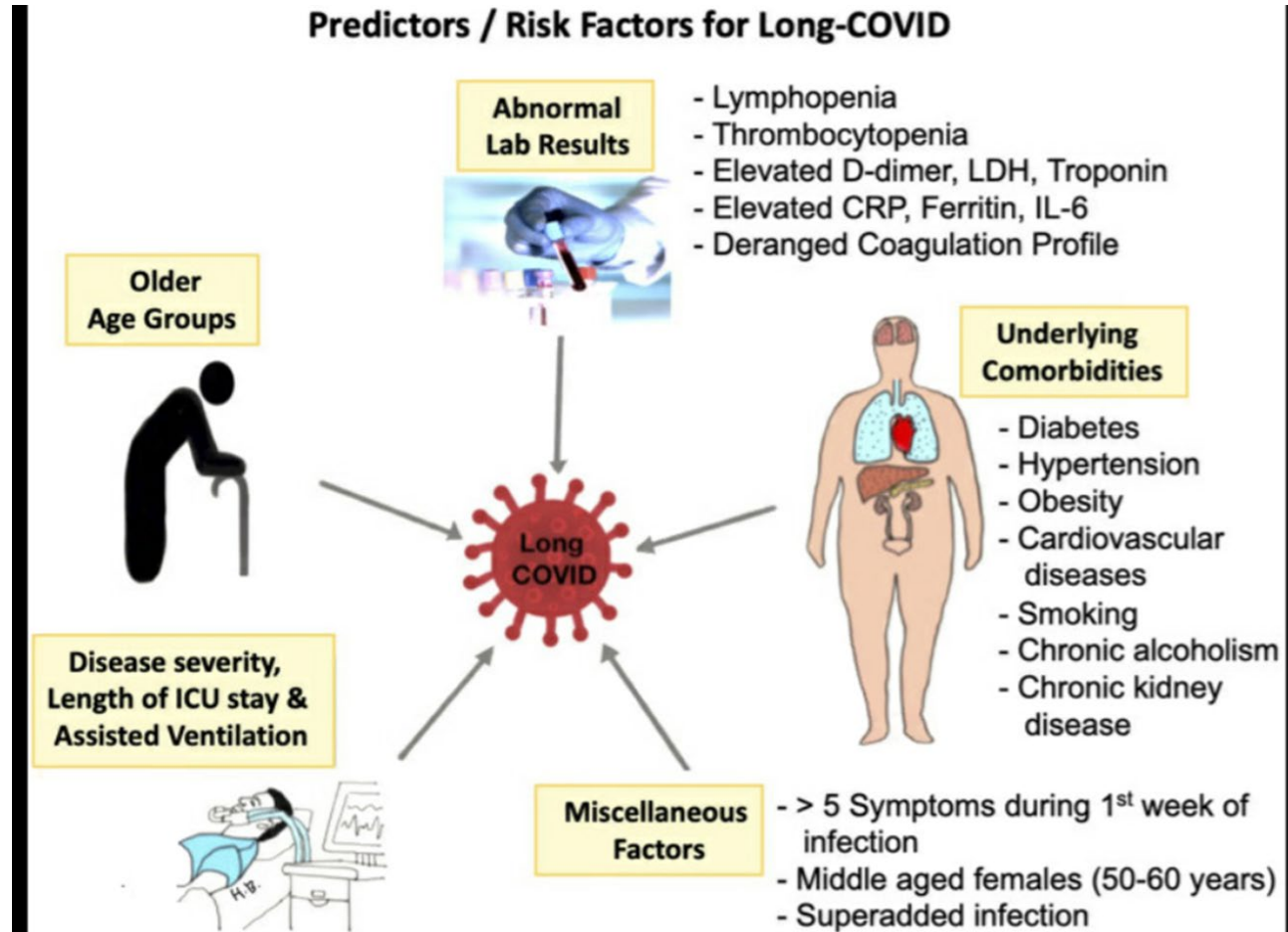


Salmon-Ceron et al., J Infect. 2020

Causes of Long COVID?

- ❖ **Sequelae of serious illness? (e.g. post-ICU syndrome, end organ damage?)**
- ❖ Persistent virus reservoirs/viral remnants in tissues?
- ❖ Re-activation of other pathogens under immune dysregulation (e.g. EBV)?
- ❖ Immune dysregulation, Autoimmunity/Autoantibodies?
- ❖ Stimulation of hyper-inflammatory/cytokine pathways?
- ❖ Endothelial damage and microvascular injury? Hypercoagulation?
- ❖ Autonomic dysregulation/Disrupted brainstem/vagus nerve signaling?

Risk factors



Health disparities for COVID-19 likely to persist with long COVID

Risk Factors

January, 2022

Cell

 CellPress
OPEN ACCESS

Article

Multiple early factors anticipate post-acute COVID-19 sequelae

Yapeng Su,^{1,2,3,28,*} Dan Yuan,^{1,4,28} Daniel G. Chen,^{1,5,28} Rachel H. Ng,^{1,4} Kai Wang,¹ Jongchan Choi,¹ Sarah Li,¹ Sunga Hong,¹ Rongyu Zhang,^{1,4} Jingyi Xie,^{1,6} Sergey A. Kornilov,¹ Kelsey Scherler,¹ Ana Jimena Pavlovitch-Bedzyk,⁷ Shen Dong,⁸ Christopher Lausted,¹ Inyoul Lee,¹ Shannon Fallen,¹ Chengzhen L. Dai,¹ Priyanka Baloni,¹ Brett Smith,¹ Venkata R. Duvvuri,¹ Kristin G. Anderson,^{3,9} Jing Li,⁷ Fan Yang,¹⁰ Caroline J. Duncombe,¹¹ Denise J. McCulloch,¹² Clifford Rostomily,¹ Pamela Troisch,¹ Jing Zhou,¹³ Sean Mackay,¹³ Quinn DeGottardi,¹⁴ Damon H. May,¹⁴ Ruth Taniguchi,¹⁴ Rachel M. Gittelman,¹⁴ Mark Klinger,¹⁴ Thomas M. Snyder,¹⁴ Ryan Roper,¹ Gladys Wojciechowska,^{1,15}

For key risk factors associated with developing long COVID:

- Type 2 Diabetes
- Genetic material of SARS-CoV-2 virus in the blood
- Evidence of Epstein-Barr Virus in the blood
- Presence of auto-antibodies (molecules that attack the body's own tissues)

Post-COVID Fatigue

Post-COVID Fatigue

- Lack of energy; tiredness, muscle weakness, poor endurance.
- Physical, cognitive, emotional
- Persistent or fluctuating; mild to severe
- May be profound, preclude return to any semblance of normal activity.
- Patients report “crashing” if they do too much, can last for days.
- Exacerbated by stress, exercise, physical or mental activity thus complicating rehabilitation and return to work.

Fatigue - management

- Avoid “push and crash” cycles
- Energy conservation strategies
- Heart rate monitoring
- Physical therapy/Occupational therapy*
- Promote healthy lifestyle



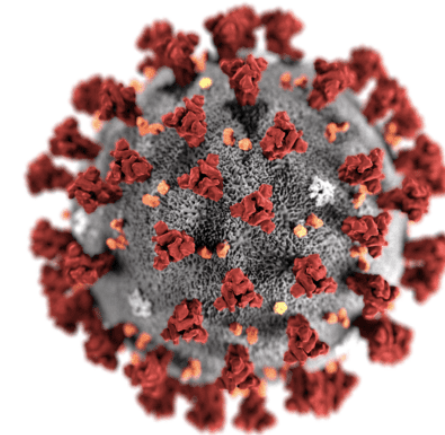


Neurological Manifestations of Long Haul-Covid

Neurological Manifestations of Long Haul Covid

- **Definitions**
- **Common features**
- **Epidemiology**
- **Anatomy and Pathophysiology**
- **Presentation**
- **Exam and Diagnostics**
- **Treatment and Management**
- **Prevention**

COVID-19: Neurologic Manifestations



Definitions

- **Also known as: Post Acute Covid Syndrome, Post Acute Sequelae of Covid, Long-Haul Covid, etc.**
- **Several differing definitions with diverse timelines and symptomology - historically anywhere from 4 weeks to 18 weeks with more than 55 symptoms ranging from fatigue, cognitive deficits, sensory changes, myalgia and cardiopulmonary dysfunction**



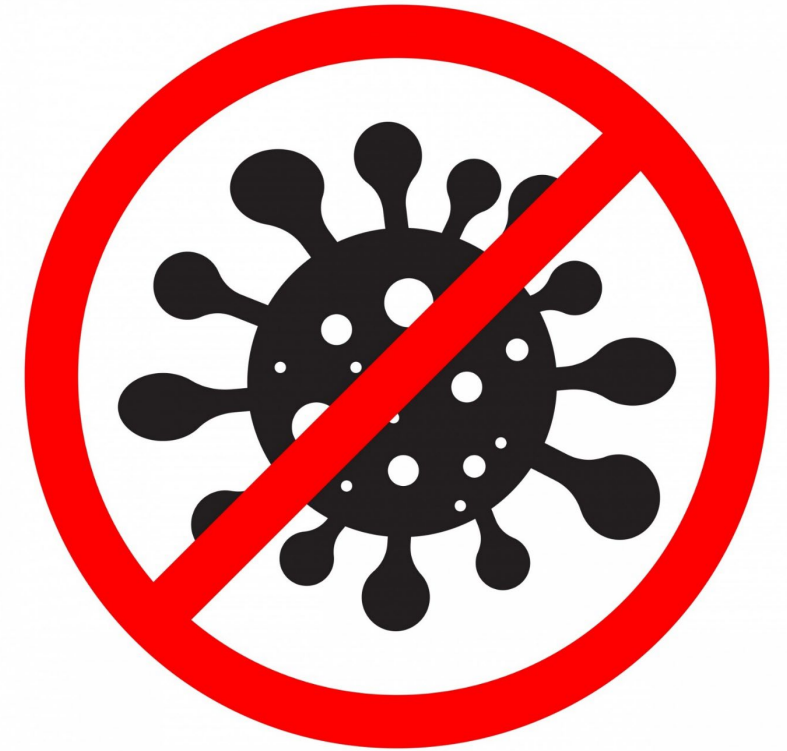
Definitions

General consensus leaning toward 12 week timeline with definition as:

“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 OR ... history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of Covid-19 with symptoms that last for at least 2 months and cannot be explained by and alternative diagnosis.”

Common Features

- Frequent co-morbidities
 - Depression/anxiety – 42%
 - Autoimmune disease – 16%
- Fatigue – 85%
- Brain Fog – 81%
- Headache – 68%
- Paresthesias – 60%
- Dysgeusia – 59%
- Anosmia – 55%



Epidemiology



- Approximately 30% to 50% of patients report symptoms consistent with long-covid when surveyed
- Nearly one-third of these patients will report neurological or psychiatric symptoms between 3-6 months after acute infection.

Anatomy and Pathophysiology – theories for CNS/PNS involvement

1. Viral neuroinvasion

- direct invasion via ACE2 receptor in nasal epithelium and olfactory bulb which extends into frontal cortex

2. Endothelial dysfunction

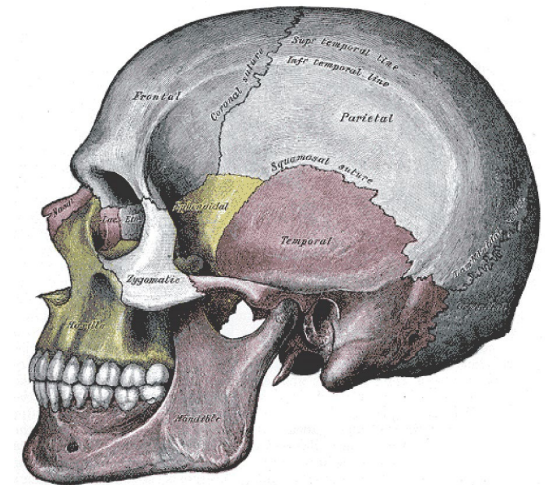
- leaky blood brain barrier due to inflammation

3. Coagulopathies

- Leading to ischemic changes

4. Toxicometabolic/inflammatory changes

- Leading to oxidative stress and cell death



Anatomy and Physiology

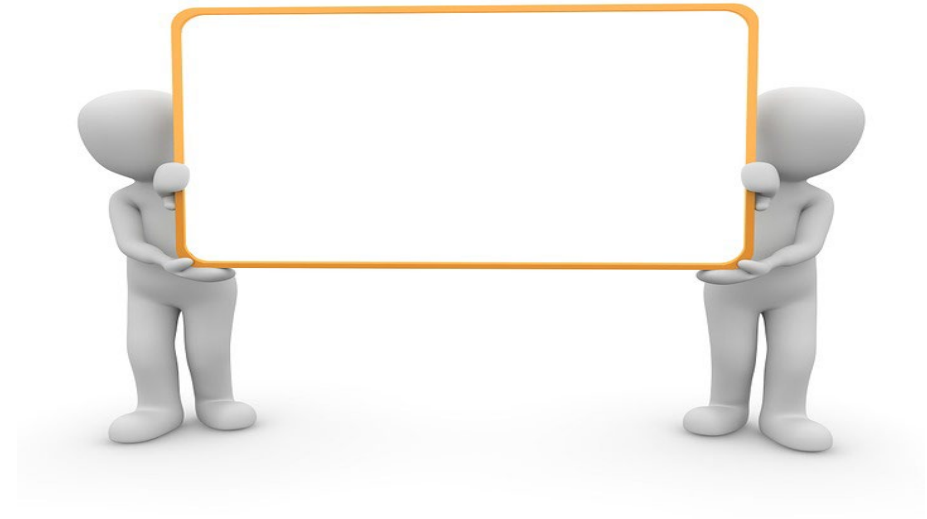
- Theories of Neurological Dysfunction:
 - Neurologic injury secondary to hypoxemia, metabolic dysfunction
 - RAAS – SARS-CoV-2 uses ACE2 protein to enter cells. Normally ACE2 catalyzes the conversion of angiotensin II to angiotensin I-7 acting to down-regulate vasodilation, fibrosis and proliferative properties. Theoretically, SARS-CoV-2 could cause damage by altering functions
 - SARS-CoV-2 utilizes angiotensin converting enzyme 2 (ACE2), a membrane-bound protein, as its point of entry into cells. ACE2 functions to convert angiotensin II into angiotensin-(1-7), which has vasodilator, antiproliferative, and antifibrotic properties [\[22,23\]](#). By binding to ACE2, the SARS-CoV-2 virus may damage vascular endothelial cells by inhibiting mitochondrial function and endothelial nitric oxide synthetase activity resulting in secondary cardio- and cerebrovascular effects

Post Viral Syndromes

- Not uncommon for patients to experience post-viral syndromes
 - EBV, Lyme, Giardia
- In long-term SARS follow-up (15 years)
 - people found that fatigue and psychological problems saw most improvement in 1-2 year range
 - About 40% still experience chronic fatigue two years after SARS diagnosis

Presentation

- In a review of 18 studies comprised of 10,530 patients:
 - 59% female
 - Mean age 52
 - ½ were hospitalized (13% in ICU)
 - Most common:
 - Fatigue 37%
 - Brain fog 32%
 - Sleep disturbance 31%
 - Memory deficit 28%



Exam and Diagnostics



- Because Covid is a multi-system disease and symptoms are extremely heterogeneous, must rule out other contributing causes
 - ECG, CXR, MRI brain, CAT scan chest, TTE, Tilt Table testing, orthostatic testing, autonomic testing, nerve conduction studies, nerve/vascular biopsies, blood count, endocrine function, renal/hepatic function, 6-minute walk testing, multiple assessment scales (depression, fatigue, anxiety, apathy, smell tests, PTSD), MOCA, neuropsychological testing, endothelial testing, PET (restricted to research at this point), spirometry, O2 saturation, autoimmune biomarkers

Treatment and Management



- Largely supportive at this point and based on mimicking conditions such as CFS and ME (myalgic encephalomyelitis)
- Limited research-based evidence at this point. There is anecdotal evidence currently for:
 - Propanolol/betablockers – use in tachycardia syndromes without overt hypotension
 - Duloxetine/Pregabalin/Gabapentin – neuropathies/depression, though can affect cognition
 - Modafinil/stimulants – cognition, sleep wake cycle dysfunction
 - Anti-inflammatories – melatonin, CoQ10, fish oil, Vitamin D, Vitamin E,
 - Immune modulation – singulair

Prevention

- VACCINATION, VACCINATION, VACCINATION
- Healthy lifestyle and exercise
- Socialization



Work / Life Complications

- ADLs, IADLs
- Social/family dynamics
- Loss of employment, enrollment in school
- Loss of income
- Loss of identity
- Disability
- Legal / workman's comp
- Returning to work / Vocational Rehab

Guidance on “Long COVID” as a Disability Under the ADA, Section 504, and Section 1557



U.S. Department of Health
Human Services
Office for Civil Rights

U.S. Department of Justice
Civil Rights Division
Disability Rights Section



Although many people with COVID-19 get better within weeks, some people continue to experience symptoms that can last months after first being infected, or may have new or recurring symptoms at a later time. ¹ This can happen to anyone who has had COVID-19, even if the initial illness was mild. People with this condition are sometimes called “long-haulers.” This condition is known as “long COVID.” ²

In light of the rise of long COVID as a persistent and significant health issue, the Office for Civil Rights of the Department of Health and Human Services and the Civil Rights Division of the Department of Justice have joined together to provide this guidance.

This guidance explains that long COVID can be a disability under Titles II (state and local government) and III (public accommodations) of the Americans with Disabilities Act (ADA), ³ Section 504 of the Rehabilitation Act of 1973 (Section 504), ⁴ and Section 1557 of the Patient Protection and Affordable Care Act (Section 1557). ⁵ Each of these federal laws protects people with disabilities from

Patient experience

PACS clinic at Dartmouth Hitchcock:

Purpose: To address the issues of patients who are experiencing long-term effects of COVID-19.

Referral process

- Age ≥ 18
- Prior COVID-19 infection
- Symptoms with or after onset of COVID, continuing at least 12 weeks
- PCP Referral to “Post-Acute COVID Syndrome Clinic”
- Entered into Patient Registry

Multidisciplinary team

- Infectious Disease PACS – initial consult*
- Neurology
- Neuropsychiatry
- Psychiatry
- Pulmonary Medicine
- Cardiology
- Rehabilitation Medicine

PACS phone: 603-650-9484
PACS e-mail: postCOVID@Hitchcock.org



Take Home Messages

- ✓ DON'T GET COVID!
- ✓ Vaccinate
- ✓ No magic bullet; focus is on symptom management and supportive care
- ✓ There is a lot we still do not understand
- ✓ Empathy toward patients experiencing long COVID is fundamental.
 - ✓ Listen
 - ✓ Validate
- ✓ Not everything is PACS

The Impact of COVID Vaccination on Symptoms of Long COVID. An International Survey of People with Lived Experience of Long COVID

21 Pages • Posted: 17 Jun 2021



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Thank you!

Any questions?

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