Recovery in Patients with Persistent Symptoms “Long” after COVID-19

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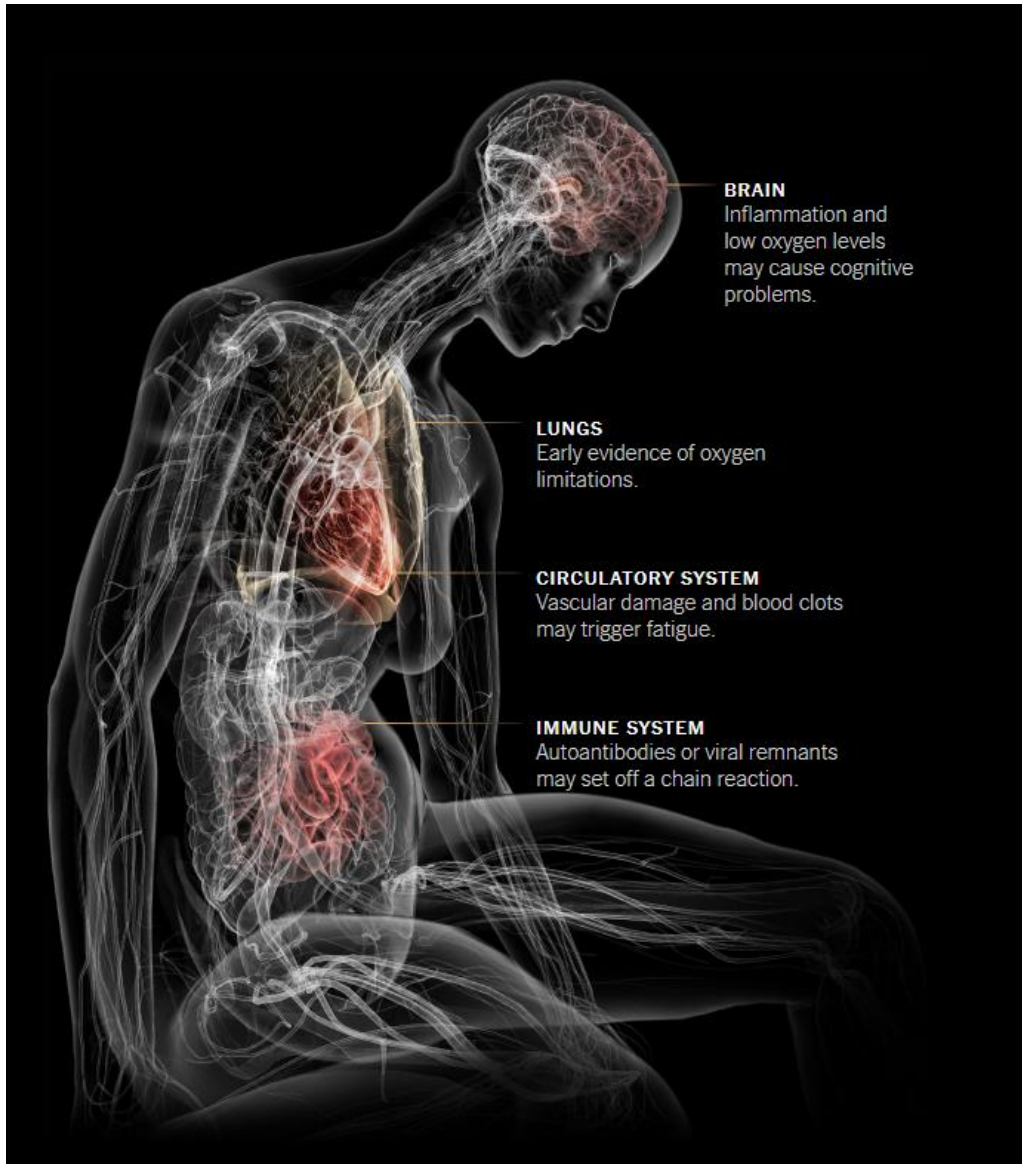
Review of Terminology

Long COVID – Syndrome characterized by varied persistent symptoms and health effects after resolution of the initial infection (lasting for weeks, months, or longer).

Long Hauler – COVID-19 survivor with lingering effects after resolution of infection.

Post-Acute Sequelae of SARS-CoV-2 infection (PASC) – New syndrome name announced by the National Institutes of Health in February 2021.



New York Times, Josh Keller

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Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience **four or more weeks** after first being infected with the virus that causes COVID-19.

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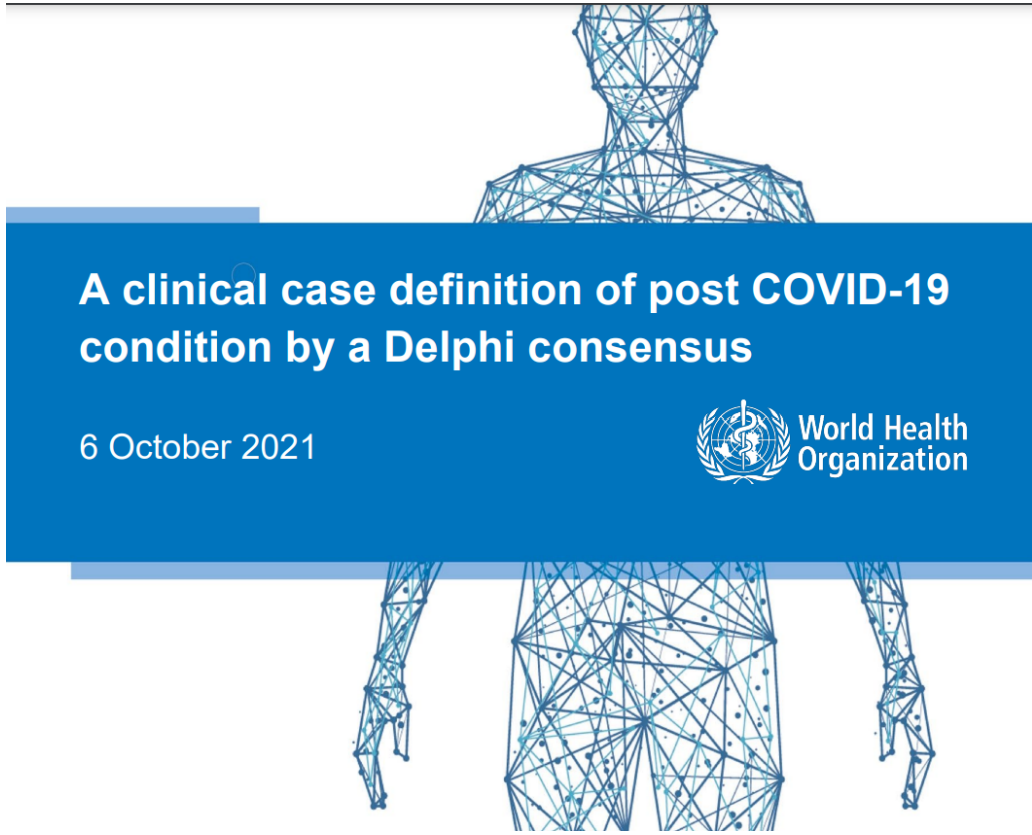
WHO

*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 and 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 and 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.



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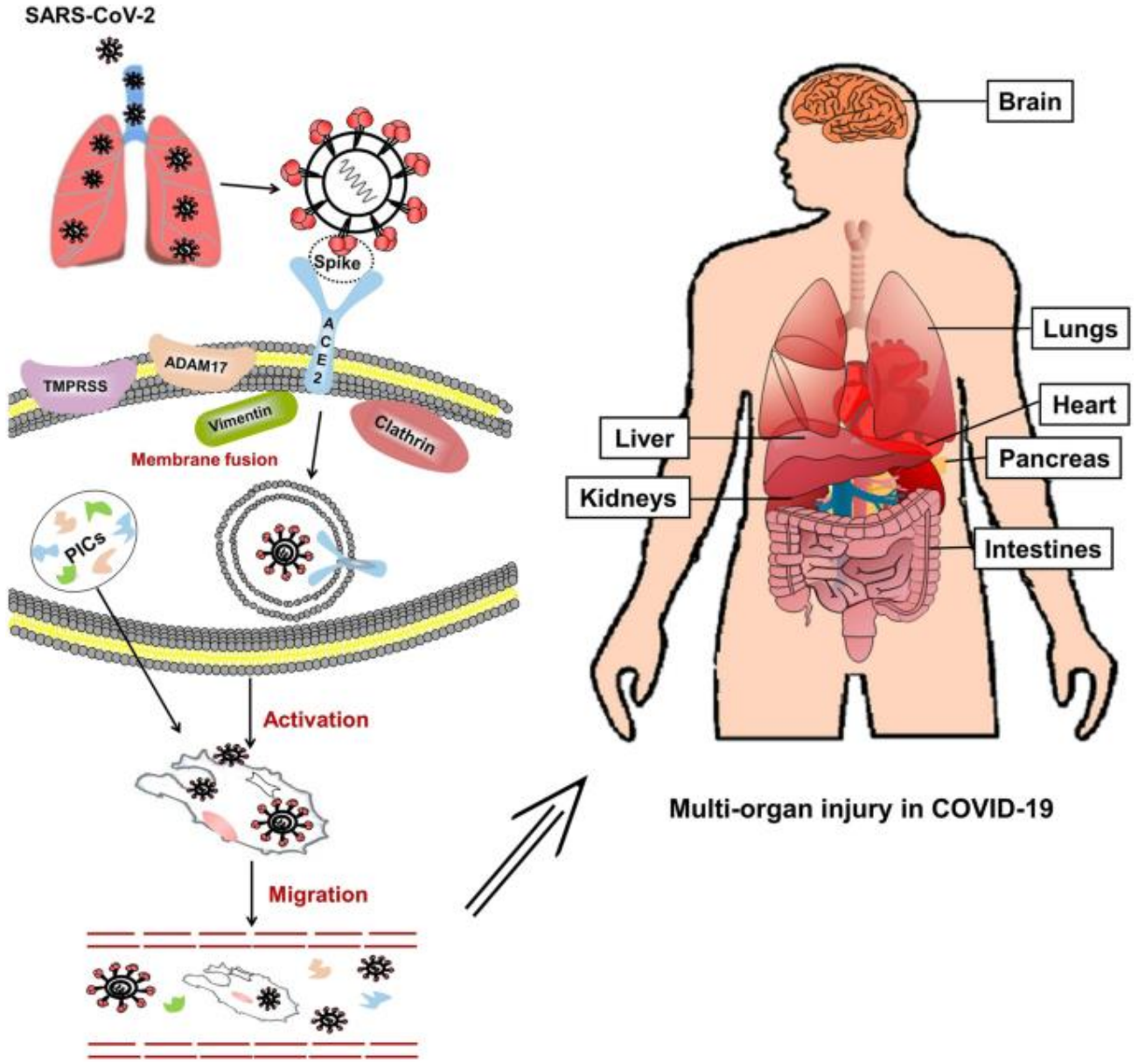
Potential Pathogenesis

- Inflammation
- Post-inflammatory cytokines
- Autoantibodies
- Spike protein & ACE receptor
- Persistent viral presence
- MCAS
- Dysbiosis
- Microclots



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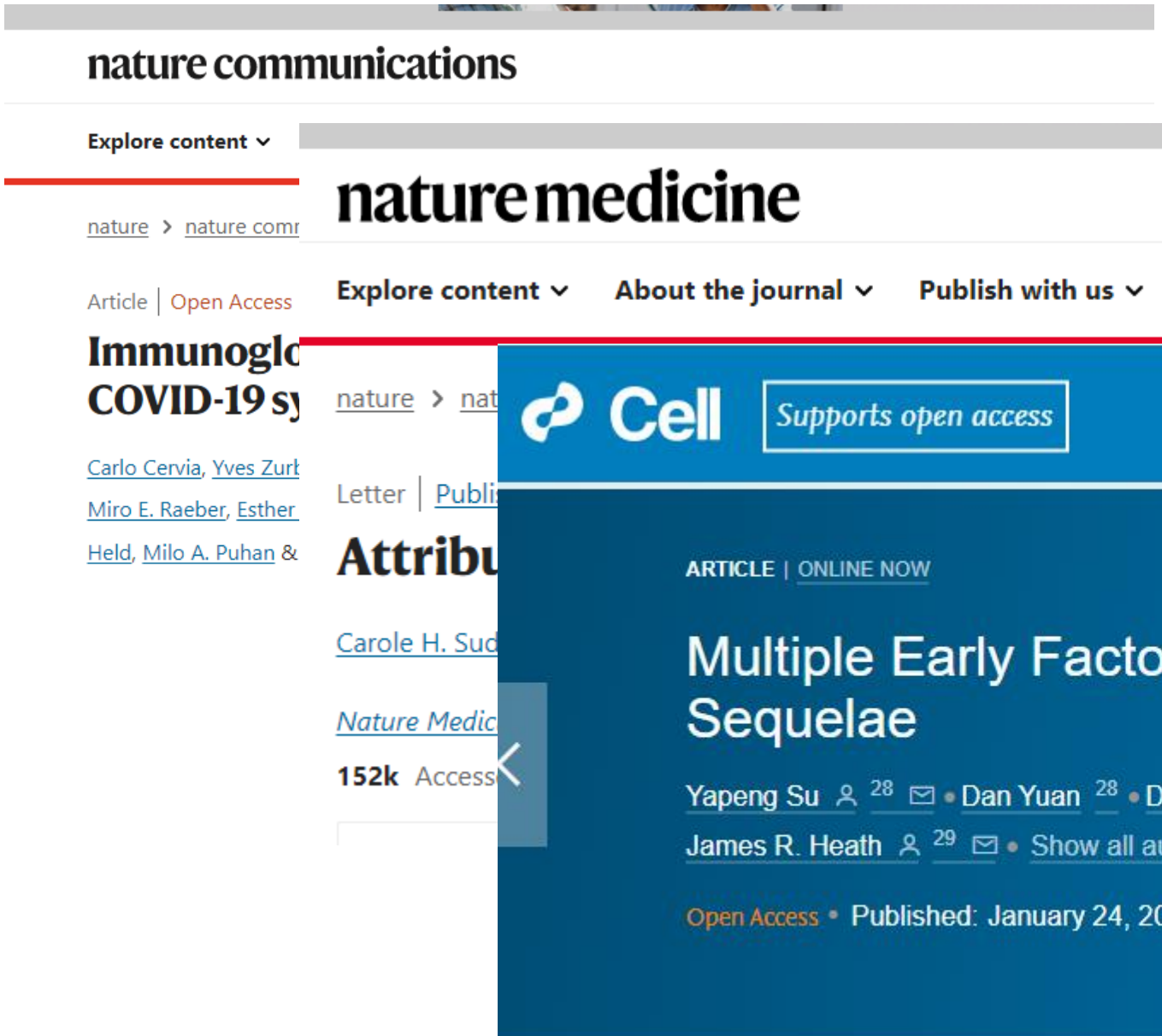
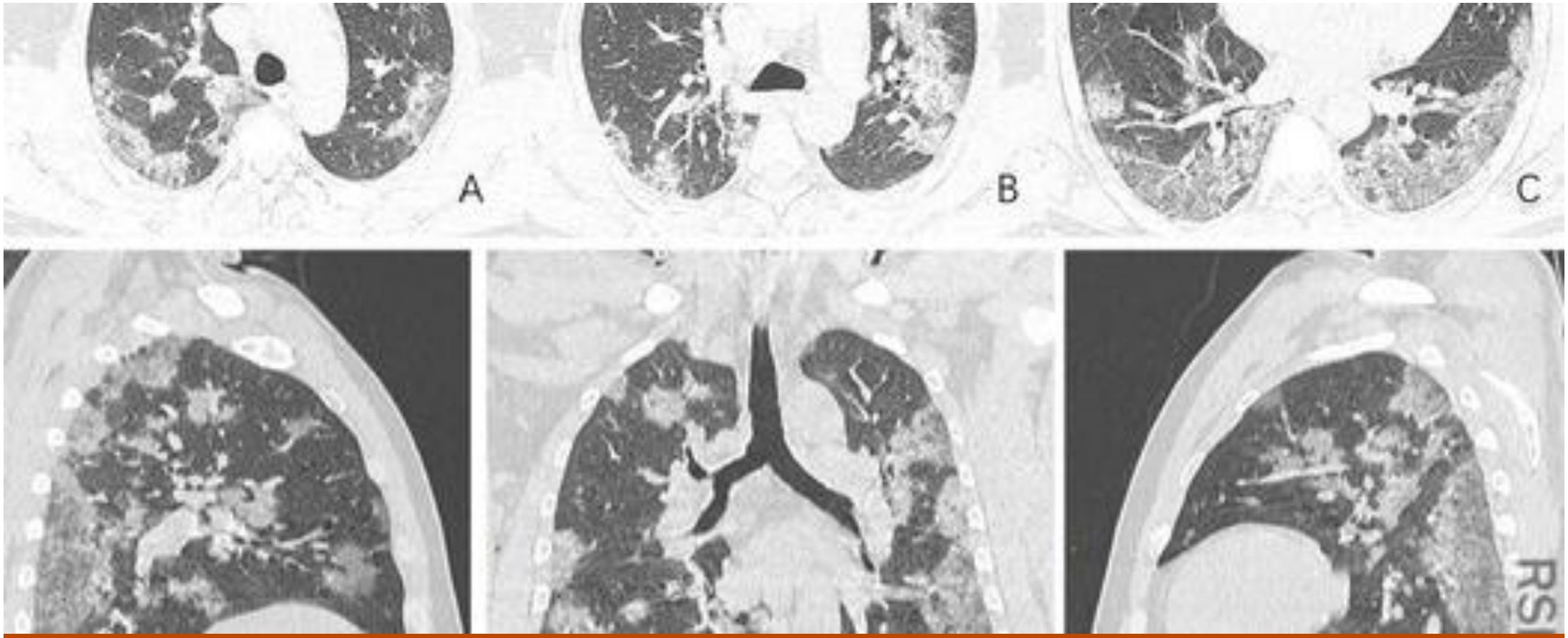
Who gets Long COVID?





What does recovery look like?

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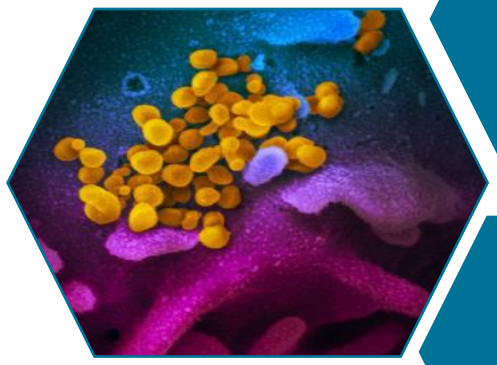
COVID-19 Outcomes

Mild
Mod



Silent

Severe

Death
17%

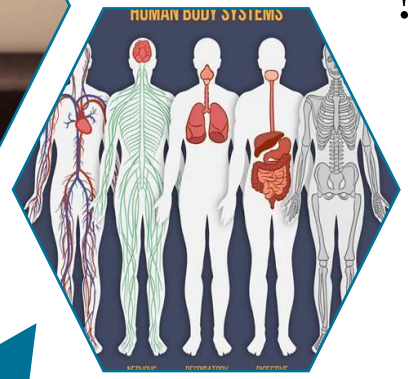
End organ damage

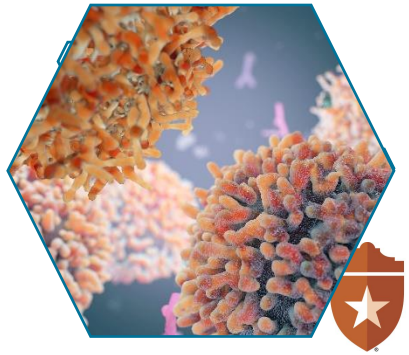
Recover

Long-COVID
10% - 50%

More Sx

?





?

2020 2nd qtr, 240 pts

Vehar. Cleve Clin J Med. 2021.

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Rehab After Critical Illness

Elsevier Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Ann Phys Rehabil Med. 2020 Apr 18
doi: 10.1016/j.rehab.2020.04.001 [Epub ahead of print]
PMCID: PMC7166018
PMID: 32315802

The role of physical and rehabilitation medicine in the COVID-19 pandemic: The clinician's view

Stefano Carda,[a,1,*] Marco Invernizzi,[b,1] Ganesh Bavikatte,[c] Djamel Bensmaïl,[d] Francesca Bianchi,[e] Thierry Deltombe,[f] Nathalie Draulans,[g] Alberto Esquenazi,[h] Gerard E. Francisco,[i] Raphaël Gross,[j,k] Luis Jorge Jacinto,[l] Susana Moraleda Pérez,[m] Michael W. O'Dell,[n] Rajiv Reebye,[o] Monica Verduzco-Gutierrez,[p] Jörg Wissel,[q] and Franco Molteni[r]

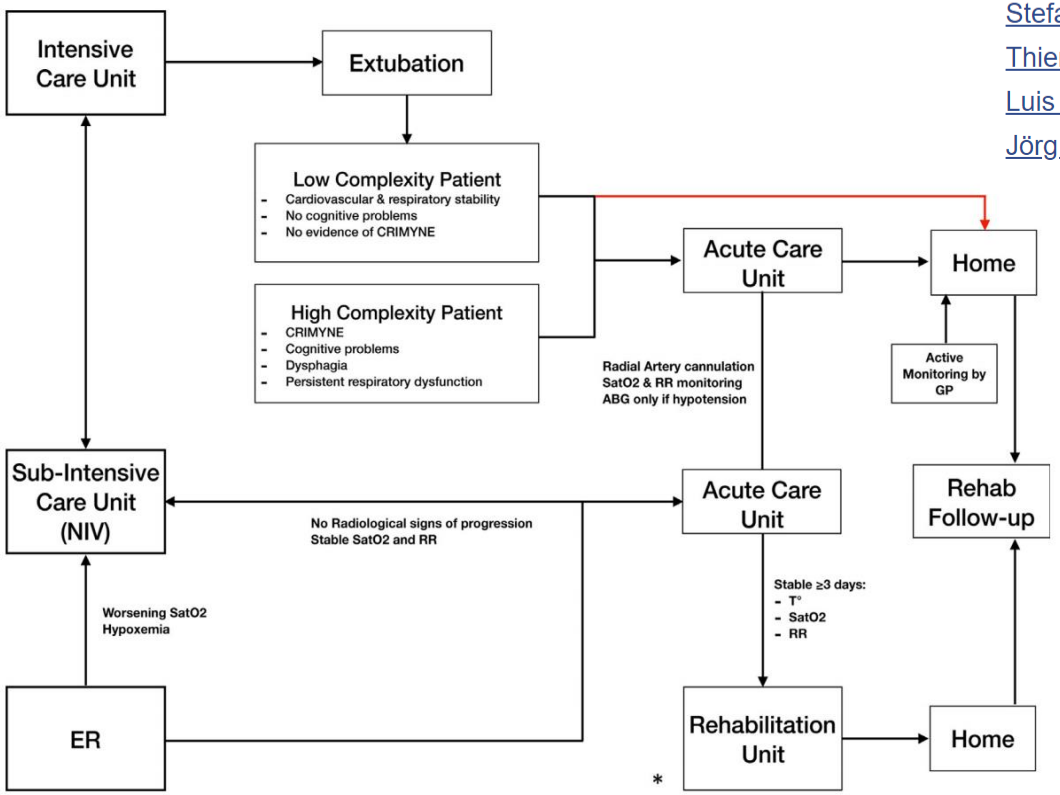

Fig. 1. Flow of COVID-19 patients to rehabilitation. ER: emergency room; NIV: non-invasive ventilation; $SatO_2$: arterial oxygen saturation; RR: respiratory rate; ABG: arterial blood gas; GP: general practitioner; Red line: in case of congestion of acute care unit services.

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Evidence for Early Mobilization

- Results of immobility
- Muscle Wasting
-

Bailey et al, Crit Care Med 2007

Journal of Hospital Medicine

shm Society of Hospital Medicine

ORIGINAL RESEARCH | Free Access

Disparities in the allocation of inpatient physical and occupational therapy services for patients with COVID-19

Sarah Jolley MD, MSc, Amy Nordon-Craft PT, DSc, Melissa P. Wilson MSc, Kyle Ridgeway PT, DPT, Michelle R. Rauzi PT, DPT, ATC, Jacob Capin PT, DPT, PhD, MS, Lauren M. Heery BS ... See all authors

First published: 11 February 2022 | https://doi.org/10.1002/jhm.12785 | Citations: 1

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Taylor & Francis
Taylor & Francis Group

Disability and Rehabilitation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/idre20

Inpatient rehabilitation can improve functional outcomes of post-intensive care unit COVID-19 patients—a prospective study

Margarida Rodrigues, Ana João Costa, Rui Santos, Pedro Diogo, Eugénio Gonçalves, Denise Barroso, Miguel P. Almeida, Inês Machado Vaz & Ana Lima

Inpatient Rehab

Prospective
N = 42
Avg 32 days of inpatient rehab

IMPLICATIONS FOR REHABILITATION

- Post-ICU COVID-19 survivors present multiple sequelae and disabilities.
- An intensive and interdisciplinary inpatient rehabilitation results in significant improvement in limb and respiratory muscle strength, cough effectiveness, fatigue, balance, exercise capacity, and ability to perform activities of daily living.
- Timely referral from the acute care setting to rehabilitation services is crucial to minimize the functional impact of severe multisystemic disease and prolonged hospitalization.

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Long COVID Incidence

- America: 23.2% overall & in 50% hospitalized (of 1.9 million)
- Spain: 44.2% of 1142 hospitalized
- Russia: 47.1% of 2649 hospitalized

FAIR Health White Paper. 2021. (based off of insurance claims)
Fernández-de-Las-Peñas et al. J Infect. 2021.
Munblit et al. medRxiv. 2021.

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JAMA Network | Open

Original Investigation | Public Health

**Prevalence of Select New Symptoms and Conditions Among Pe
Younger Than 20 Years and 20 Years or Older at 31 to 150 Days A
Positive or Negative for SARS-CoV-2**

Alfonso C. Hernandez-Romieu, MD, MPH; Thomas W. Carton, PhD, MS; Sharon Saydah, PhD; Eduardo Azziz-Baumgartner, MD; Teg
Nedra Y. Garret, MS; L. Charles Bailey, MD, PhD; Lindsay G. Cowell, MS, PhD; Christine Draper, BS; Kenneth H. Mayer, MD; Kshema
Sonja A. Rasmussen, MD, MS; William E. Trick, MD; Valentine Wanga, PhD; Jennifer R. Chevinsky, MD, MPH; Brendan R. Jackson, MD
Jennifer R. Cope, MD, MPH; Adi V. Gundlapalli, MD, PhD; Jason P. Block, MD, MPH

40 systems' EHR data

Cohort study of:

338,024 persons younger than 20 years

1,790,886 persons 20 years or older who were tested for SARS-CoV-2 Mar-Dec 2020.

Looked at prevalence of new symptoms & conditions for those with med encounters between 31 and 150 days after testing.

168,701 (+) aged 20+

26,665 (+) aged <20

Monica Verduzco-Gutierrez, MD
@MVGutierrezMD

4/ Some take home points 👉
The study says ≤11% prevalence of #PASC in nonventilated was "infrequent." (by the way, it was much higher in those hospitalized)

I still think 11% is high!
🦠 #COVID19 has impacted 75 million Americans.

#LongCOVID is real. More research needed!

Hov

>2C

In hospitalized: T2DM, Anxiety & depression, Ataxia or trouble walking.

<20: Change in bowel habits, fatigue, SOB. Most prevalent new diagnosis was anxiety & depression.

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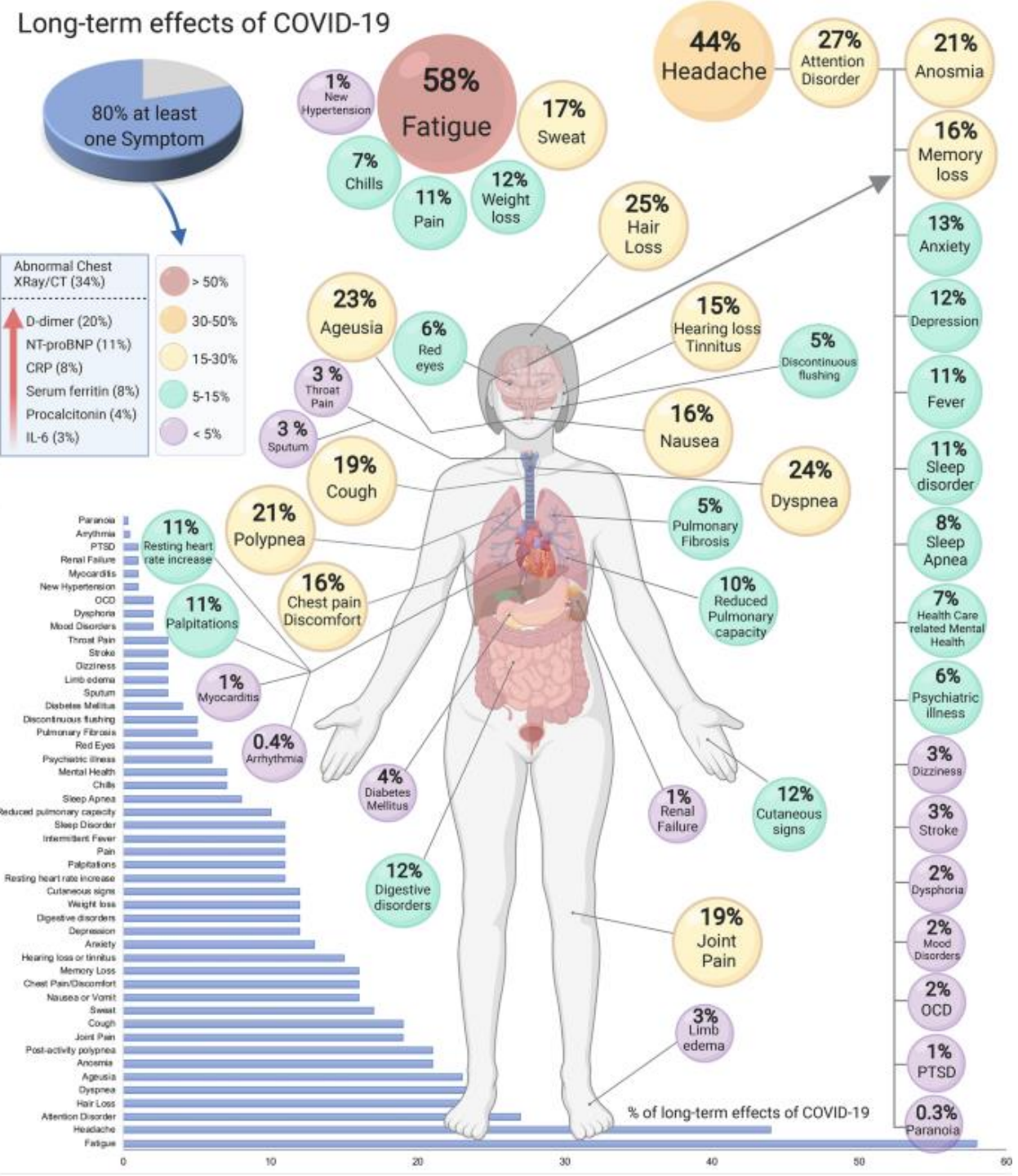

More than 50 long-term effects of COVID-19: a systematic review and meta-analysis

The prevalence of 55 long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included (age 17–87 years).

The five most common symptoms were:

- Fatigue (58%)
- Headache (44%)
- Attention disorder (27%)
- Hair loss (25%)
- Dyspnea (24%)

Lopez-Leon Scientific Reports 2021

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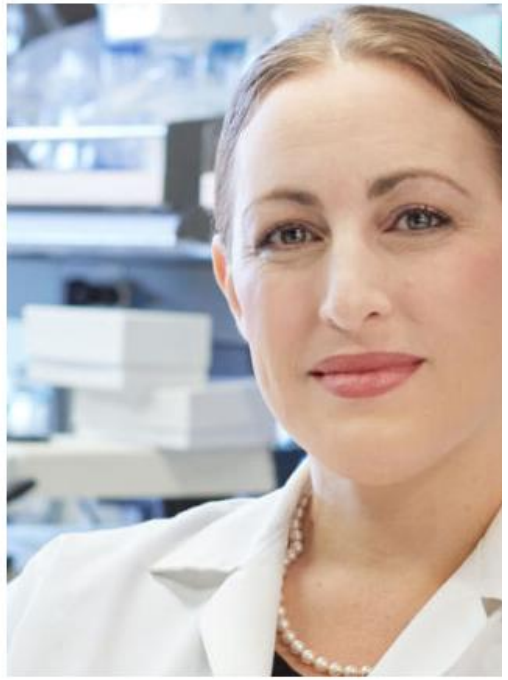
What's happening in the brain?

HEALTH

In 'chemo brain,' researchers see clues to unravel long Covid's brain fog

By Elizabeth Cooney Jan. 28, 2022



Stanford neuro-oncologist Michelle Monje is study

Chemo Brain

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

Follow this preprint

Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain

Anthony Fernández-Castañeda, Peiwen Lu, Anna C. Geraghty, Eric Song, Myoung-Hwa Lee, Jamie Wood, Belgin Yalçın, Kathryn R. Taylor, Selena Dutton, Lehi Acosta-Alvarez, Lijun Ni, Daniel Contreras-Esquivel, Jeff R. Gehlhausen, Jon Klein, Carolina Lucas, Tianyang Mao, Julio Silva, Mario A. Peña-Hernández, Alexandra Tabachnikova, Takehiro Takahashi, Laura Tabacof, Jenna Tosto-Mancuso, Erica Breyman, Amy Kontorovich, Dayna McCarthy, Martha Quezado, Marco Hefti, Daniel Perl, Rebecca Folkerth, David Putrino, Avi Nath, Akiko Iwasaki, Michelle Monje

doi: https://doi.org/10.1101/2022.01.07.475453

White matter-selective microglia reactivity

Pro-inflammatory CSF cytokines with persistent elevation of CCL11

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Cognitive Sequelae

PICS

Cognitive impairment can affect:

- 70%-100% of patients at discharge
- 46%-80% still have it one year later
- 20% still have it after 5 years

Memory/ cognitive deficits

- NeuroPsych eval
- Speech therapy
- Memory techniques
- Medications – Donepezil, Memantine, Amantadine, etc

Eur J Nucl Med Mol Imaging. 2021; 48(9): 2823–2833.
Published online 2021 Jan 26. doi: 10.1007/s00259-021-05215-4
PMCID: PMC7
PMID: 33

^{18}F-FDG brain PET hypometabolism in patients with long COVID

E. Guedj,[✉1] J. Y. Campion,[1] P. Dudouet,[2,3] E. Kaphan,[4] F. Bregeon,[2,3,5] H. Tissot-Dupont,[2] S. Guis,[6] F. Barthelemy,[1] P. Habert,[7,8] M. Ceccaldi,[9] M. Million,[2,3] D. Raoult,[2,3] S. Cammilleri,[1] and C. Eldin[2,10]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

ALTERNATE FORMAT RESEARCH ARTICLE | Open Access

Alzheimer's-like signaling in brains of COVID-19 patients

Steve Reiken, Leah Sittenfeld, Haikel Dridi, Yang Liu, Xiaoping Liu, Andrew R. Marks ✉

First published: 03 February 2022 | https://doi.org/10.1002/alz.12558

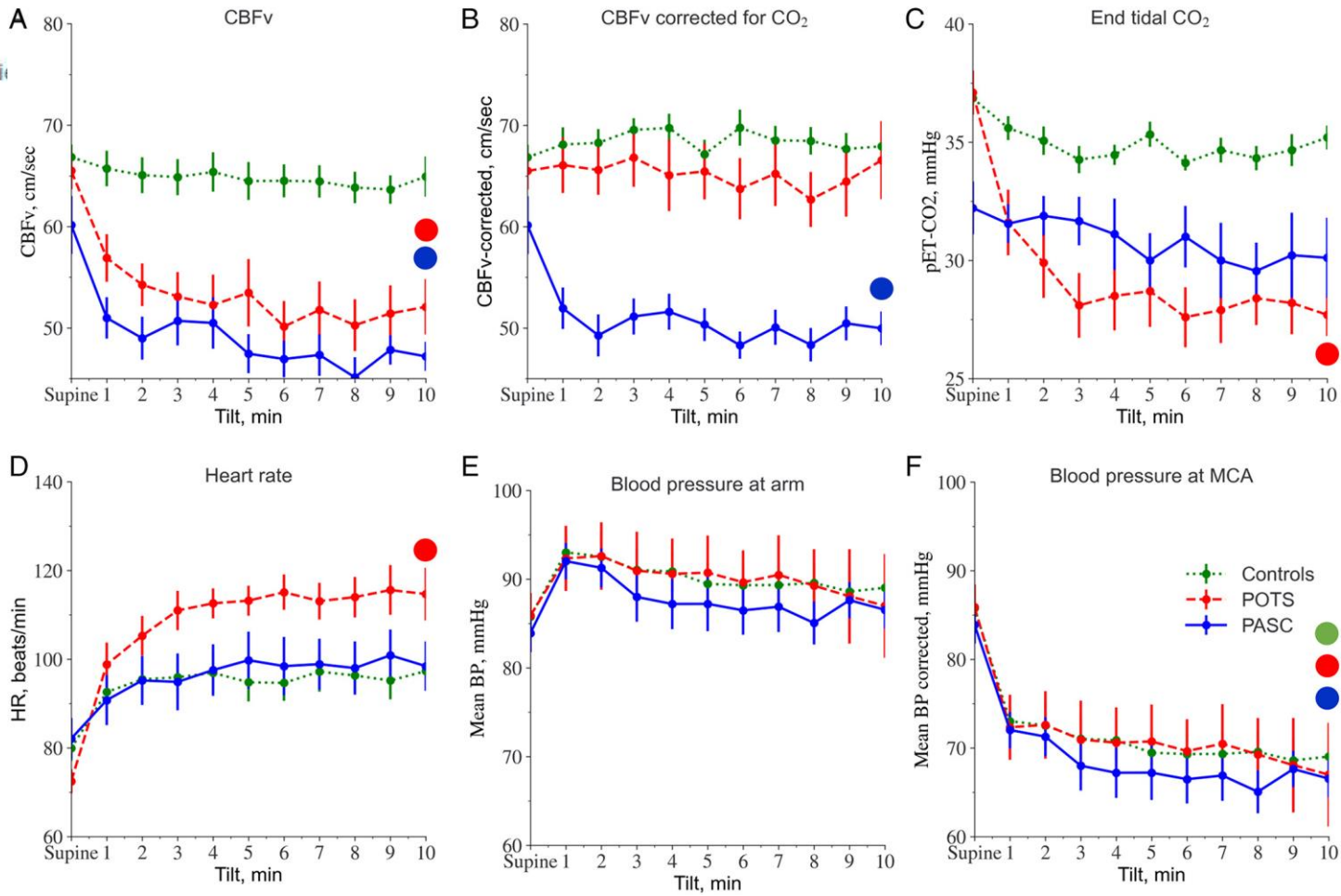
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION

Research Article | Free Access

Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19

Peter Novak MD, PhD, Shibani S. Mukerji MD, PhD, Haitham S. Alabsi DO, David Systrom MD, Sadi
Marciano PA-C, Donna Felsenstein MD, William J. Mullally MD, David M. Pilgrim MD

First published: 24 December 2021 | https://doi.org/10.1002/ana.26286



Mild COVID-19 is associated with **multisystem involvement**:

- Cerebral Blood Flow Dysregulation
- Hypocapnic Hyperventilation
- Small fiber neuropathy
- Dysautonomia
- Pain
- Inflammatory Markers

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Brain, Behavior, and Immunity
Available online 29 December 2021
In Press, Journal Pre-proof

Review Article

Fatigue and Cognitive Impairment in Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis

Felicia Ceban [a, b, c], Susan Ling [a, d], Leanna M.W. Lui [a], Yena Lee [a, b, c], Hartej Gill [a], Kayla M. Teopiz [a], Nelson B. Rodrigues [a, c], Mehala Subramaniapillai [a, b, c], Joshua D. Di Vincenzo [a], Bing Cao [e], Kangguang Lin [f, g], Rodrigo B. Mansur [a, h], Roger C. Ho [i, j], Joshua D. Rosenblat [a, c, d, h], Kamilla W. Miskowiak [k, l], Maj Vinberg [m, n], Vladimir Maletic [o], Roger S. McIntyre [a, b, c, d, h]

Meta-analysis on 81 studies estimating Long COVID prevalence

Key findings:

32% of patients have fatigue at 12 weeks

31% at 6+ months

22% have cognitive impairment at 12 weeks

21% at 6+ months

A significant key finding is that fatigue and cognitive impairment were not statistically significantly different between hospitalized and non-hospitalized patients!

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Long COVID: Psychiatric and Sleep Problems

Spanish multicenter study
7 months after discharge from hospital
n = 1142

50% had anxiety or depressive symptoms and/or poor sleep quality

Anxiety in 16.2%
Depressive in 19.7%
Poor sleep quality in 34.5%

Fernández-de-Las-Peñas et al. J *Infect*. 2021.

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Health Equity IS a problem,

worsened by the COVID-19 pandemic.

US Department of Health and Human Services Office of Minority Health, COVID-19 Health Equity Task Force

CDC's COVID-19 Health Equity Strategy – Principles, Populations, Strategies

AAPM&R, National Call to Action → Equitable Access to Care for Patients

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Am J Phys Med Rehabil. 2020 Aug 13. doi: 10.1097/PHM.0000000000001568. Online ahead of print.

African American Patient Disparities in COVID-19 Outcomes: A Call to Action for Physiatrists to Provide Rehabilitation Care to Black Survivors

Charles A Odonkor [1], Maurice G Sholas [2], Monica Verduzco-Gutierrez [3], Ross D Zafonte [4 5 6], Julie K Silver [4 5 6]

KENS5.com

San Antonio doctor opens South Texas' first coronavirus recovery clinic

SAN ANTONIO — A hospital is probably the last place a ... Which is why Verduzco-Gutierrez has started a new rehab clinic in San Antonio to help ... It's a specialized clinic the Wall Street Journal reports we're seeing a rise in

1 month ago

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UT Health San Antonio Rehab Medicine
Post COVID-19 Recovery Program

Mission

Our mission is to serve our diverse patient population - locally and regionally - who were diagnosed with COVID-19 and suffer from various physical, cognitive, and functional difficulties.

Our vision is to reflect the strength of the community we serve with professional, compassionate, and concierge type of Physical Medicine and Rehabilitation services.

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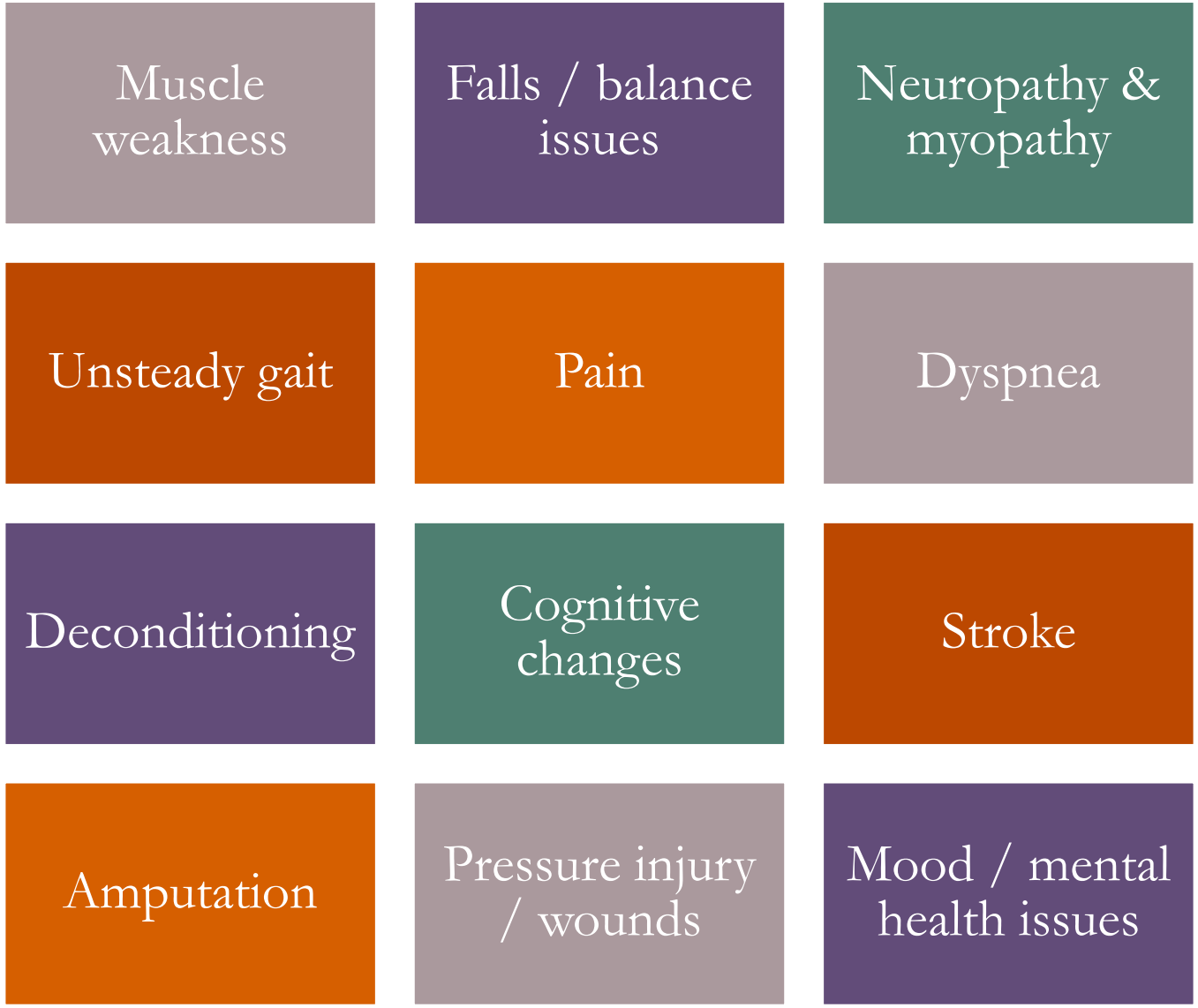
Post COVID-19 Diagnosis Focus



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PM&R

Consensus Guidance Statement

Multidisciplinary co
the assessment and
of SARS-CoV-2 infec

Joseph E. Herrera DO, William N
MD, MBA, Talya K. Fleming MD

TABLE 1 PASC fatigue assessment recommendations

#	Statement
1	Patients should be assessed for fatigue patterns throughout their normal day to guide activity recommendations.
1a	Patients should be assessed for their responses to initiating and escalating activity on their fatigue.
1b	Patients should be evaluated for changes in daily functioning and activity levels.
1c	Patients' physical functioning and endurance should be assessed to inform activity and therapy recommendations. (Examples of tests that can be chosen based on an individual's activity tolerance: 30 s sit to stand[55]; 2-min step (seated or standing)[56]; 6 min walk test[57]; 10 m walk test[58]).
2	Clinicians should assess for changes in activities of daily living, independent activities of daily living, school, work, and avocational (ie, hobbies)

TABLE 3 National Aademy of Sciences proposed diagnostic criteria for ME/CFS

Proposed Diagnostic Criteria for ME/CFS
Diagnosis requires that the patient has the following three symptoms: 1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, education, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, 2. Postexertional malaise[a] and 3. Unrefreshing sleep[a]
At least one of the following manifestations is also required: 1. Cognitive impairment[a] or 2. Orthostatic intolerance

w of preexisting conditions should be conducted

for conditions that may exacerbate fatigue symptoms and warrant further testing and potential subspecialty
icular areas include:

pression and PTSD. Note: Patients often report dissatisfaction with their care because of their persistent
to psychological factors. It is important to note that mood disorders may be secondary to persistent medical
ors leading to fatigue.

e conducted to investigate medications that may be contributing to fatigue. Of note, antihistamine,
pressant/anxiolytic medications can contribute to fatigue in patients with PASC.

p should be considered in new patients or those without lab workup in the 3 months before visit including
differential, chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive
mentation rate, and creatinine kinase.
considered based on the results of these tests or if there is specific concern for comorbid conditions as

e of SARS-CoV-2 infection; PTSD, posttraumatic stress disorder.

CLINICAL GUIDANCE

PM&R

Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC)

Jeffrey S. Fine MD, FAAPMR[1] | Anne Felicia Ambrose MD, MS[2] | Nyaz Didehbani PhD[3] | Talya K. Fleming MD[4] | Lissette Glashan MS, CCC-SLP, CBIS[5] | Michele Longo MD, MPH[6] | Alexandra Merlino MS, CCC-SLP[7] | Rowena Ng PhD[8] | Gerald J. Nora MD, PhD[9] | Summer Rolin PsyD[10] | Julie K. Silver MD[11] | Carmen M. Terzic MD, PhD[12] | Monica Verduzco-Gutierrez MD[13]

CLINICAL GUIDANCE

PM&R

Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC)

Jason H. Maley MD[1] | George A. Alba MD[2] | John T. Barry PT, DPT[3] | Matthew N. Bartels MD, MPH[4] | Talya K. Fleming MD[5] | Christina V. Oleson MD[6] | Leslie Rydberg MD[7] | Sarah Sampsel MPH[8] | Julie K. Silver MD[9] | Sabrina Sipes PT, DPT[10] | Monica Verduzco-Gutierrez MD[11] | Jamie Wood PhD[12] | Joseph D. Zibrak MD[1] | Jonathan Whiteson MD[13]

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Treatment with Vaccination

n=44 hosp patients with persistent Sx after 8 mo: fatigue (75%), breathlessness (61%), and insomnia (53%); median 4 Sx/pt

1 mo after Pfizer or AstraZeneca vaccination: specific questions on improvement

Among the 159 symptoms reported before vaccination:

23.2% improved

5.6% worsened

71.1% unchanged

? helpful for persistent viral activity. No control group.

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Support For Disability & Work Accommodations

Likely the 2nd most important thing we can do!

- All patients need to time to recover
- Relapses are common
- Working, stress, pushing themselves too hard is the most common trigger for relapses and PEM
- Facilitating respite and / or reasonable reentry back to work is enormously beneficial for quality-of-life faster recovery

Accommodations & Disability for Fatigue & Brain Fog

Possible Disability Accommodations:

Limited hours

Frequent breaks

Avoid standing

Parking close to entry

Adjust work activities

Limit tasks with divided attention

Optimize range of movements

Limit environments with multiple sensory inputs

Return home if breathing rate is increased for more than a few minutes?

For Disability Applications, Document:

Activity levels pre/post infection

Symptoms that are remitting and relapsing

Specific work activities will result in physical and mental fatigue

Environmental settings that result in sensory overload (markets, etc)

Work-ups that rule out other associated causes including pre-existing conditions

Long COIVD is now a Disability Under the ADA

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 discrimination.[6] This guidance also provides resources for additional information and best practices. This document focuses solely on long COVID, and does not address when COVID-19 may meet the legal definition of disability.

The civil rights protections and responsibilities of these federal laws apply even during emergencies.[7] They cannot be waived.

1. **What is long COVID and what are its symptoms?**

30

This is a game changer!

Health systems will need to rally our resources to support patients accordingly

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Get your patients enrolled in trials

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Post-COVID Rehab

Community-based approach

Early and often

Inpatient Rehab

Home-based Rehab

Respiratory Rehab / Breathing Program

Autonomic Reconditioning

Mobility and Functional Rehab

Education

Mental health services

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THANK YOU

QUESTIONS?

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