COVID-19 Immune Dysregulation and Long COVID:
Where Do We Stand?

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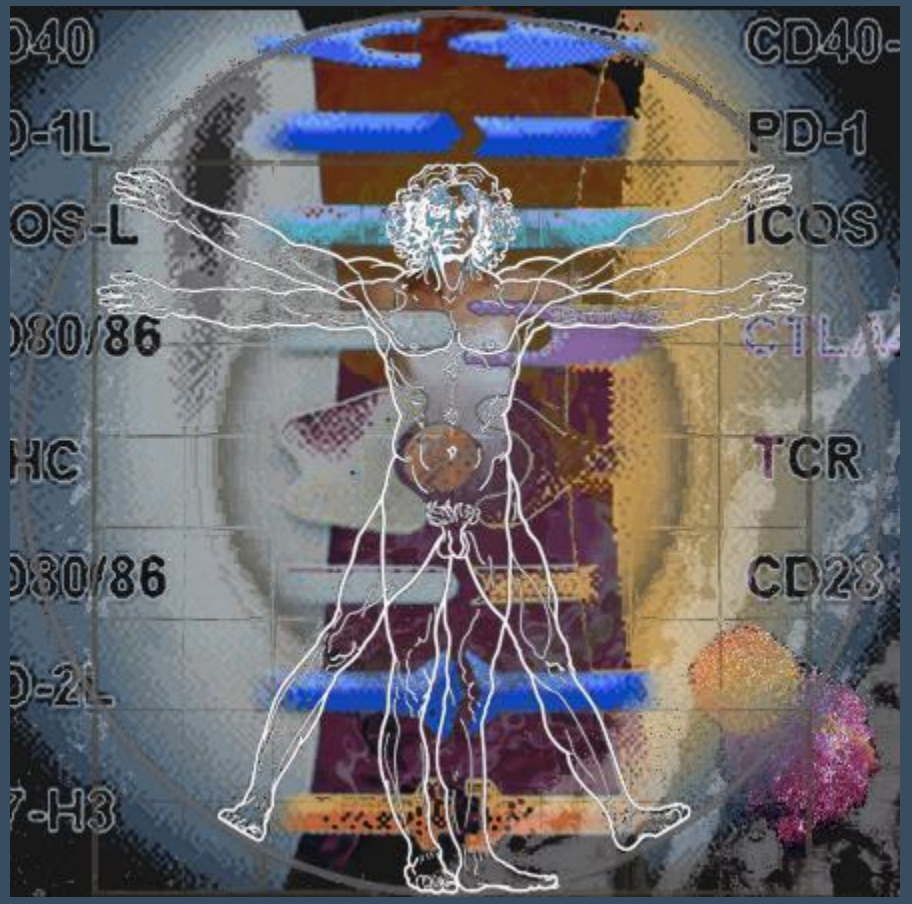

Disclosures

- Consultant / Speaker
  - Genentech, AbbVie, UCB, Janssen, Gilead, Chemocentryx, Sanofi-Regeneron, Novartis, GSK, Galvani

Learning Objectives

- To describe the natural history of COVID 19 and recognize post acute sequelae
- To describe and clinical recognize clinical endotypes of Long COVID including fatigue, pain and neurocognitive dysfunction
- To relate current data on immune dysfunction to target organ and syndromic domains and recognize current standard of care

August 19, 2020 | 2 min read SAVE

COVID-19 presents clinicians with an 'immunology boot camp'

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#rheumtwitter
#MedTwitter

The Epidemic Long COVID-19: -Questions and Implications for Rheumatology

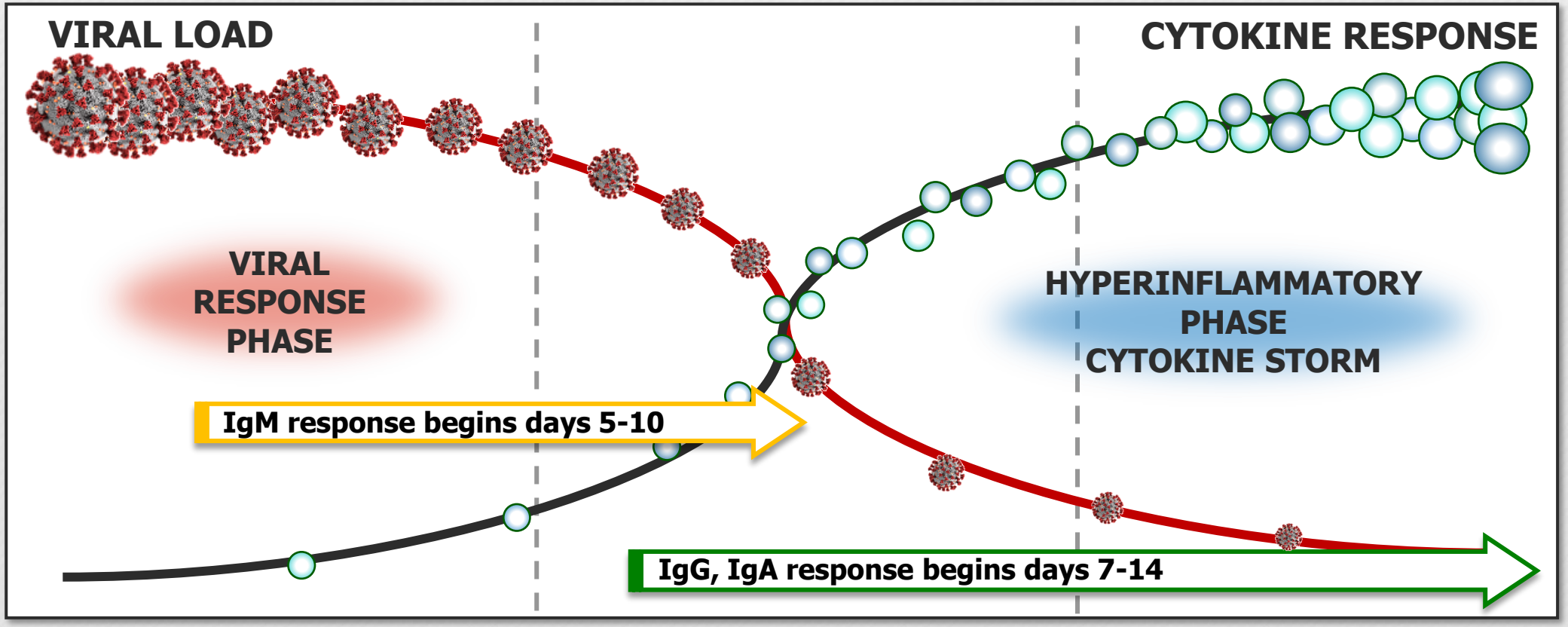
- What is Long COVID?
- What is the epidemiology?
- Long Covid Endotypes?
- What is the immunopathogenesis?
- What is known regarding therapy?

Course of COVID-19 Infection – A Paradigm for Therapy

Asymptomatic
Innate immune activation
STAGE 1

Nonsevere symptomatic
Adaptive immune activation
STAGE 2

Severe respiratory/inflammatory
Cytokine release syndrome
STAGE 3



Disease Course

- Self limiting in 80%
- Severe in 15%-20%
- Fatal in 1%-2%

Risk Factors for Stage 3 Disease

- Age
- Immunosuppressed states
- Diabetes
- ASHD
- Renal disease
- Hypertension
- Male sex
- Other

ASHD = arteriosclerotic heart disease; Ig = immunoglobulin.
Adapted from Calabrese LH. *Cleve Clin J Med*. 2020;87(7):389-393.

COVID-19 Epidemiology: Focus on age, obesity, and co-morbidities

- Risk factors for severe illness from COVID-19 include:
  - **Age DEATH doubles per 5 yrs of age**
  - **Obesity (all age groups)**
  - **Physical inactivity**
  - **Smoking**
  - **Underlying medical conditions (all age groups)**

Medical personnel in an overcrowded intensive care unit battle SARS-CoV-2 in critically ill patients.

IMMUNOLOGY

Why do people die from COVID-19?

Autoantibodies that neutralize type I interferons increase with age

By **Paul Bastard**[1,2,3]

The past 2 years have witnessed the infection of millions of people with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The course of infection is highly variable. Some young patients have died, while several centenarians, having already lived through the 1918 influenza pandemic, have survived SARS-CoV-2 infection—without experiencing severe respiratory symptoms.

These anecdotal observations belie a key risk factor that emerged early on: The risk of death doubles for every 5 years of age (*1*, *2*). Comorbid conditions have also been shown to affect outcome, but with a lower relative risk (*3*). Risk factors are not causal explanations, and the question remains: Why is SARS-CoV-2 infection fatal in more than 10% of people over 80 years old but in fewer than 0.001% of individuals below 18 years old?

Since the onset of the pandemic, the COVID Human Genetic Effort (CHGE) has recruited patients infected with SARS-CoV-2 who exhibit either mild infection or severe and/or critical COVID-19 pneumonia (i.e., requiring oxygen supplementation) (*4*). We sequenced these patients' exomes to test our hypothesis that some individuals with life-threatening COVID-19 have underlying inborn errors of immunity (IEI) (*5*).

Mutations in interferon regulatory factor 7 (IRF7) are already known to underlie severe viral infections such as fulminant influenza pneumonia (*6*). In patients with life-threatening COVID-19 pneumonia, including previously healthy adults, we found IEI that affect Toll-like receptor 3 (TLR3)– and IRF7-dependent type I interferon (IFN) immunity with complete or autosomal-recessive IRF7 or IFN-α/β receptor subunit 1 (IFNAR1) deficiency. A parallel unbiased genome-wide approach found loss-of-function variants of X-linked gene *TLR7* in more than 1% of men with life-threatening COVID-19, leading to deficient type I IFN production (*7*). On this genetic basis, could other types of type I IFN pathway deficiencies account for life-threatening COVID-19 in other patients (*8*)?

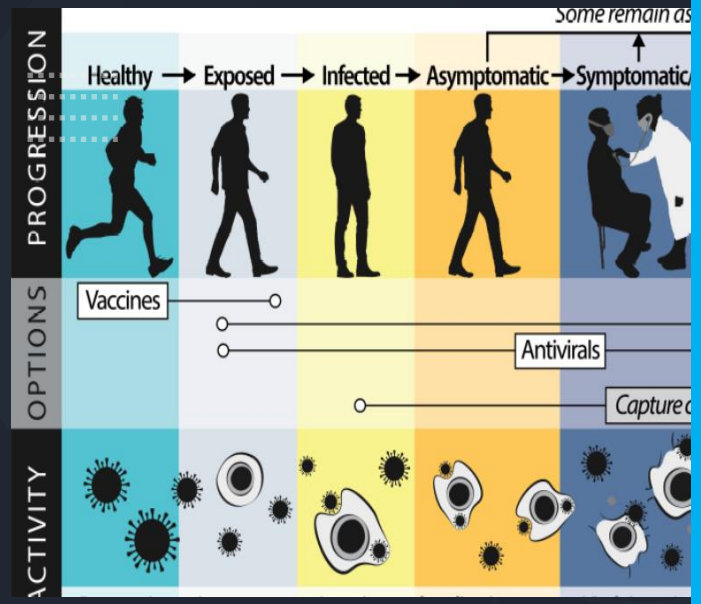
MICHELSON PHILANTHROPIES & Science PRIZE FOR IMMUNOLOGY

[1]Laboratory of Human Genetics of Infectious Diseases, Imagine Institute, University of Paris and INSERM UU163, Paris, France. [2]The Rockefeller University, New York, NY, USA. [3]Department of Pediatrics, Necker Hospital for Sick Children, AP-HP, Paris, France.
Email: paul.bastard@institutimagine.org

PHOTO: ANDREY TESTA/PANOS PICTURES

COVID-19 Clinical Continuum

- Sequela: A condition which is the consequence of a previous disease or injury.



1 Month?
2 Months?
3 Months?
6-12 Months

November 16, 2021

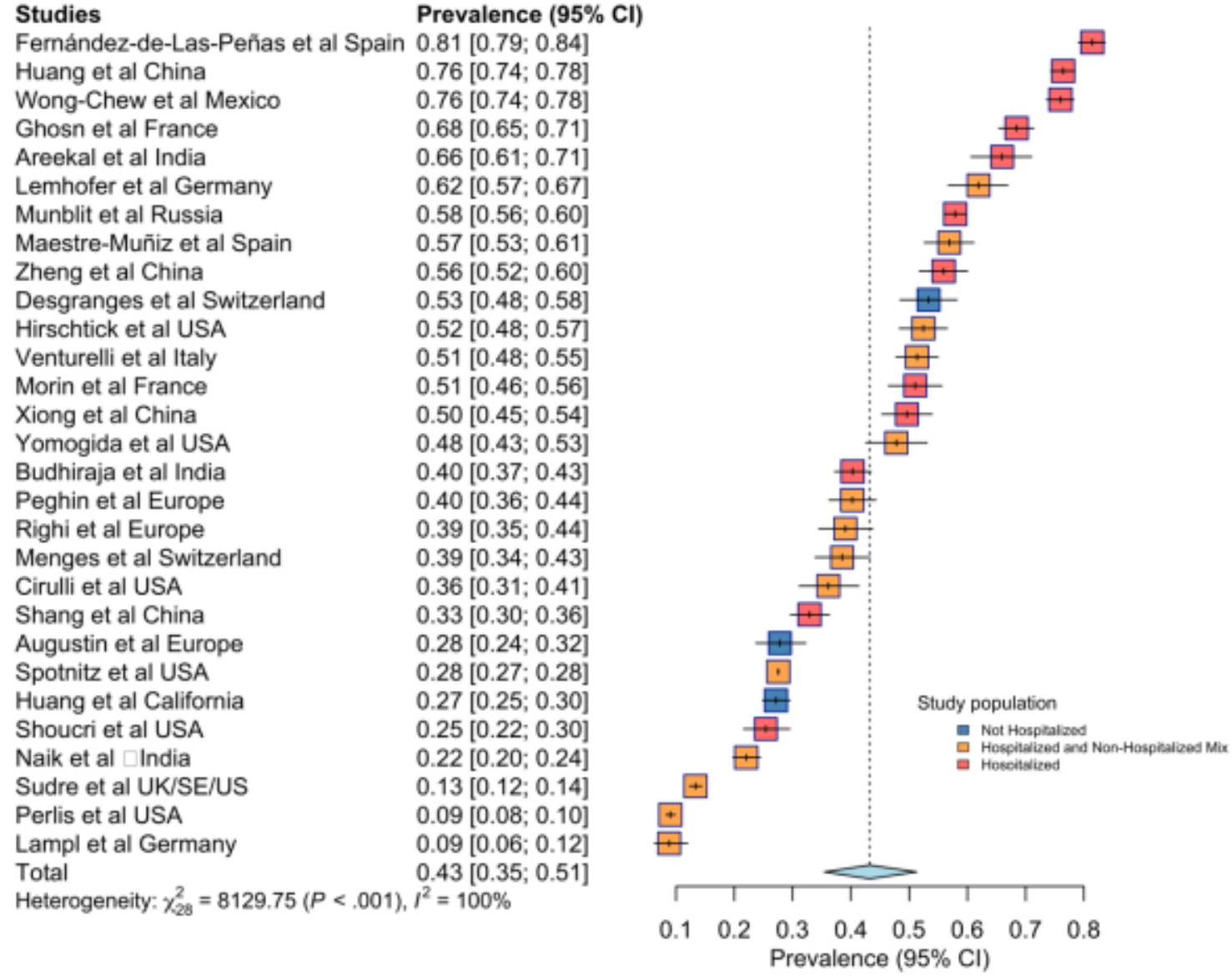
USA 1/3
Global 4/10

Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review

Authors:
Chen Chen, MA[1,*], Spencer R. Haupert, BS[1,*], Lauren Zimmermann, BSc[1,2], Xu Shi, PhD [1], Lars G. Fritsche, PhD[1,3,4], Bhramar Mukherjee, PhD [1,2,3,4,5]

- Objective The primary aim of this study is to examine the prevalence of post-acute sequelae of long COVID, across the world and to assess geographic heterogeneities through a systematic review and meta-analysis.
- A second aim is to provide prevalence estimates for individual symptoms that have been commonly reported as PASC, based on the existing literature.

29 Studies revealed worldwide, PASC comprises a significant fraction (0.43 [95% CI: 0.35, 0.63]) of COVID-19 tested positive cases and more than half of hospitalized COVID-19 cases, based on available literature as of August 12,



nature medicine

REVIEW ARTICLE

https://doi.org/10.1038/s41591-022-01810-6

Check for updates

Unexplained post-acute infection syndromes

Jan Choutka[1]✉, Viraj Jansari[2], Mady Hornig[3] and Akiko Iwasaki[2,4,5,6]✉

May 2022

- While acute infections are commonly thought of as self limiting a sizable number of individuals suffer form post infections syndromes (PAIS) often of unclear nature and complex nosology
- These represent a major burden to the public health
- The ‘tails’ of infections are characterized by an unexplained failure to recover from acute disease
- Have similarities with previously described syndromes such as ME/CFS suggesting common etiopathogenesis

Table 1 | Overview of unexplained PAISs associated with documented infections

Pathogen	Name of PAIS
Viral pathogens	
SARS-CoV-2	Post-acute sequelae of SARS-CoV-2 infection (PASC) Post-acute COVID-19 syndrome (PACS) Long COVID
Ebola	Post-Ebola syndrome (PES) Post-Ebola virus disease syndrome (PEVDS)
Dengue	Post-dengue fatigue syndrome (PDFS)
Polio	Post-polio syndrome (PPS)
SARS	Post-SARS syndrome (PSS)
Chikungunya	Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) Post-chikungunya disease
EBV	No name
West Nile virus	No name
Ross River virus[a]	No name
Coxsackie B[a]	No name
H1N1/09 influenza[a,b]	No name
VZV[a,b]	No name
Non-viral pathogens	
Coxiella burnetii	Q fever fatigue syndrome (QFS)
Borrelia[c]	Post-treatment Lyme disease syndrome (PTLDS)
Giardia lamblia[a,d]	No name

[a]Limited or very limited evidence base. [b]Association with increased use of ME/CFS diagnosis in health registry. [c]Contradicting or unclear evidence base. [d]Supporting evidence derives from a single outbreak in Norway.

Some PAIS are pathogen specific

- Anosmia- SARS CoV-2
- Arthritis – Chikungunya
- Corneal disease – Ebola
- Bowel disease Coxackie B

Others are shared

ME/CFS phenotype – post exertional fatigue; non restorative sleep; neurocognitive dysfunction etc “Long COVID” EBV, SARS,

Confronting Our Next National Health Disaster — Long-Haul Covid

Steven Phillips, M.D., M.P.H., and Michelle A. Williams, Sc.D.

N Engl J Med. 2021 Aug 12;385(7):577-579

What is Long COVID?

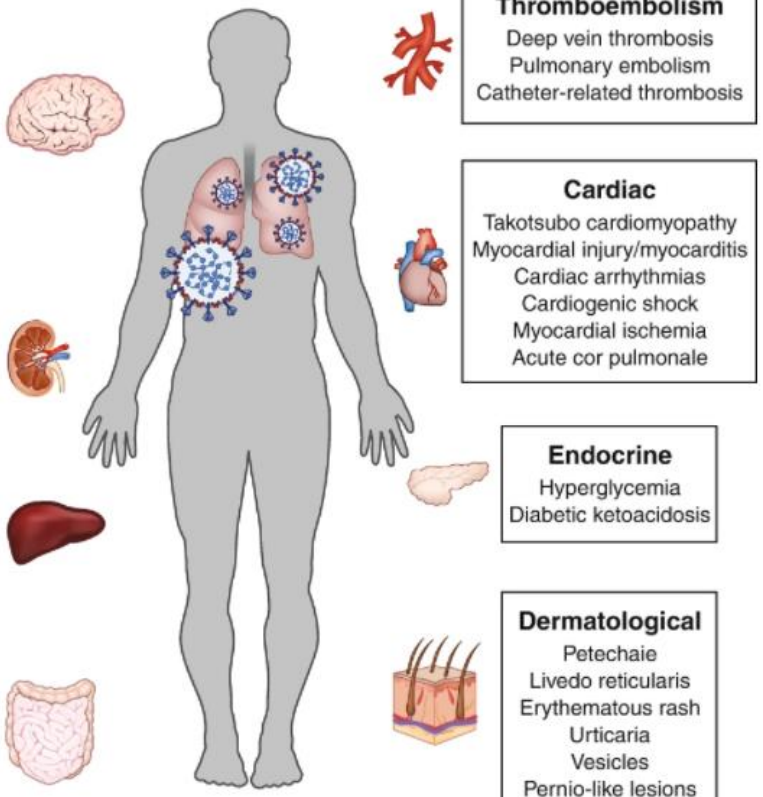
Documented post COVID Pathologic Entities

Persistent symptoms secondary to defined pathology

Defined pathology **without** associated symptoms

Fig. 2: Extrapulmonary manifestations of COVID-19.

From: Extrapulmonary manifestations of COVID-19



PERSISTENT SYMPTOMS WITHOUT DEFINED PATHOLOGY

www.nature.com/scientificreports

scientific reports

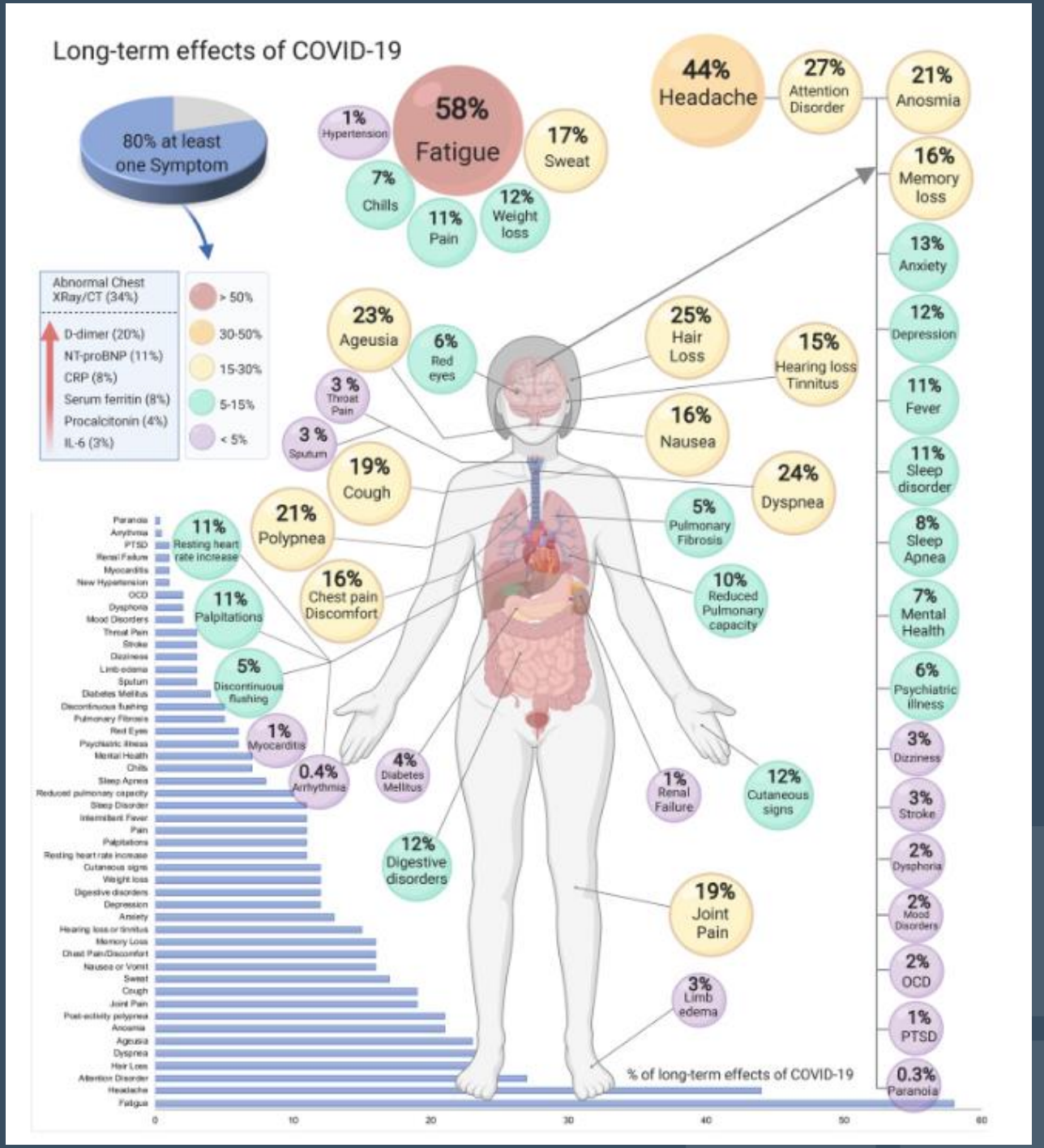
Check for updates

OPEN

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

Sandra Lopez-Leon[1], Talia Wegman-Ostrosky[2], Carol Perelman[3], Rosalinda Sepulveda[4], Paulina A. Rebolledo[5,6], Angelica Cuapio[7] & Sonia Villapol[8,9]

A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included. The follow-up time ranged from 14to 110 days post-viral infection. The age of the study participants ranged between 17 and 87 years. It was estimated that **80% (95% CI 65-92) of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms**. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). All meta-analyses showed medium (n=2) to high heterogeneity (n=13) 11:2021



Are there Risk Factors?
And
Endotypes?

Polling Question

- These ‘risk’ factors have been reproducibly associated with risk of developing Long COVID
    A. Female sex
    B. Advancing age
    C. Severity of COVID-19 acute illness
    D. A and C
    E. A,B, C

What is the Epidemiology of Long COVID?

- **Challenges:** No uniform definition; no specific criteria; Reporting bias; No diagnostic biomarkers*(no treatment)

What we do have: Only questions- Steve Deeks

Risk Factors for Long COVID

*Observational study in a primary care population using data from Platform C19**

- Long COVID was present in 310/3,151 (9.8%) patients with self-diagnosed, clinician-diagnosed, or test-confirmed COVID-19 (34% test confirmed)
- Only 106/310 (34.2%) long COVID patients had test-confirmed COVID-19

Risk Predictors of Long COVID (Adjusted Odds Ratio)

- Age ≥40 years (1.49 [1.05–2.17])
- Female sex (1.37 [1.02–1.85])
- Frailty (2.39 [1.29–4.27])
- Emergency department visit (4.28 [2.31–7.78])
- Hospital admission for COVID-19 symptoms (3.22 [1.77–5.79])

Protective Mitigating factors

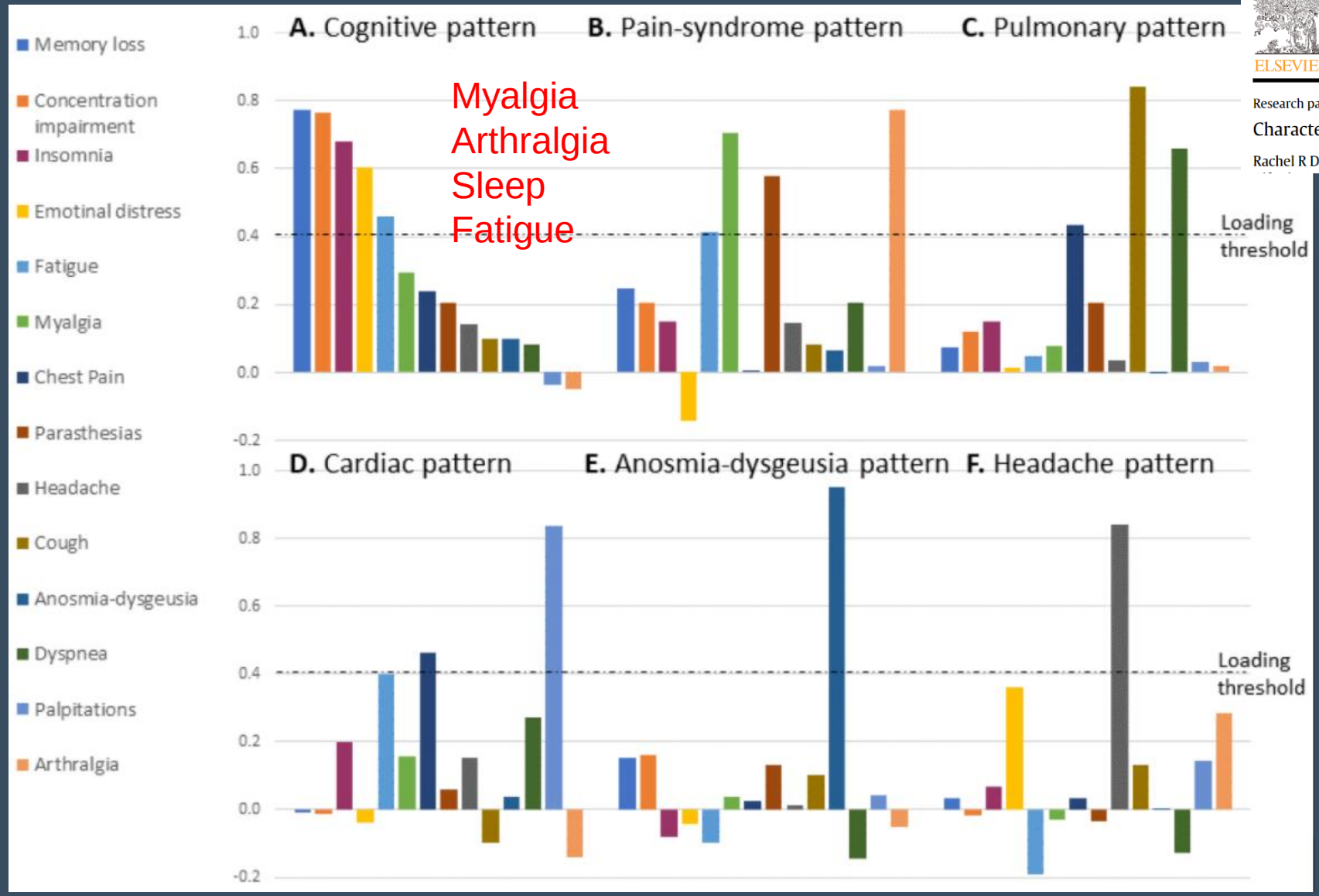
- Younger age
- Milder acute COVID-19 illness
- Previous infection ?
- Vaccination decreases but variable effect (15-50%) depending on study

*A quality improvement program-derived research database linking primary electronic health record data with patient-reported questionnaire information.

Jones R et al. *Pragmat Obs Res*. 2021;12:93-104. Al-Aly, Z et al Nature Med 2022 Antonelli M Lancet Infect Dis 22:43-55,2022

Clinical Endotypes

- Chronic Fatigue
- Brain Fog
- Autonomic Dysfunction (POTS, dysrhythmias)
- Pain Fibromyalgia
- Neuropsychiatric



EBioMedicine 74 (2021) 103722

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

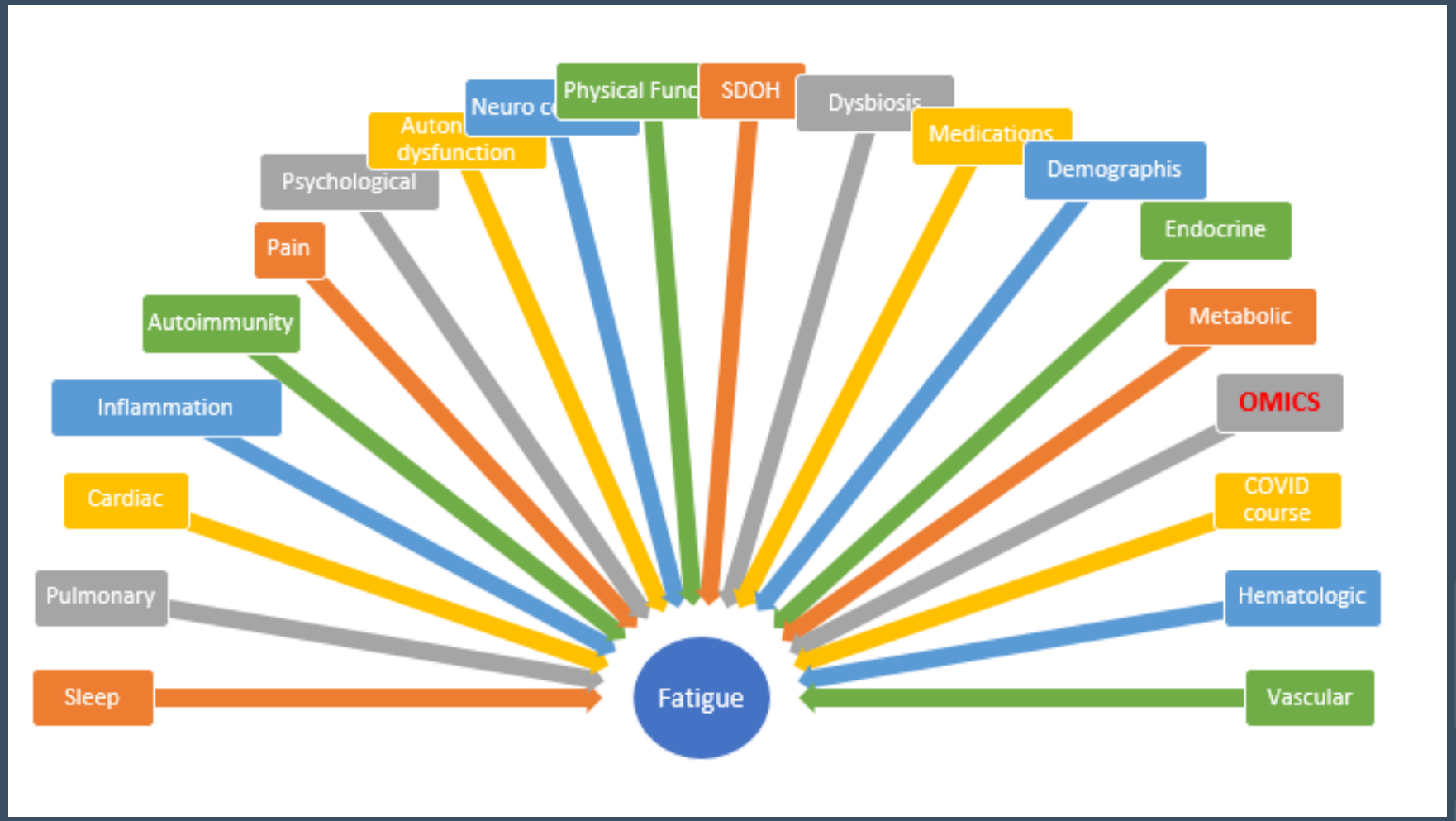
Research paper

Characterizing Long COVID: Deep Phenotype of a Complex Condition

Rachel R Deer[1,*], Madeline A Rock[1], Nicole Vasilevsky[2,3], Leigh Carmody[3,4], Halie Rando[2,5],

. The pain-syndrome pattern was associated with the severity of the acute disease (0.22 (0.98) vs. −0.08 (1.00), p < 0.001) and was higher in women (0.11 (1.08) vs. −0.13 (0.88), p < 0.001).

Fatigue post COVID-19 Matrix



frontiers in Microbiology

REVIEW
published: 23 June 2021
doi: 10.3389/fmicb.2021.698169

Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms

Amy D. Proal[1] *and Michael B. VanElzakker*[1,2]*

[1] PolyBio Research Foundation, Kenmore, WA, United States, [2] Division of Neurotherapeutics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Symptoms after 7 months
N= 996

Institute of Medicine Criteria (IOM-2015)

- Severe fatigue, > 6 months
- Unrefreshing sleep
- Post Exertional Malaise (PEM-Crashes)
- Brain fog or dysautonomia

52% Prevalence of ME/CFS in PASC-Total 96 Pts Stanford PASC Clinic – Hector Bonilla MD

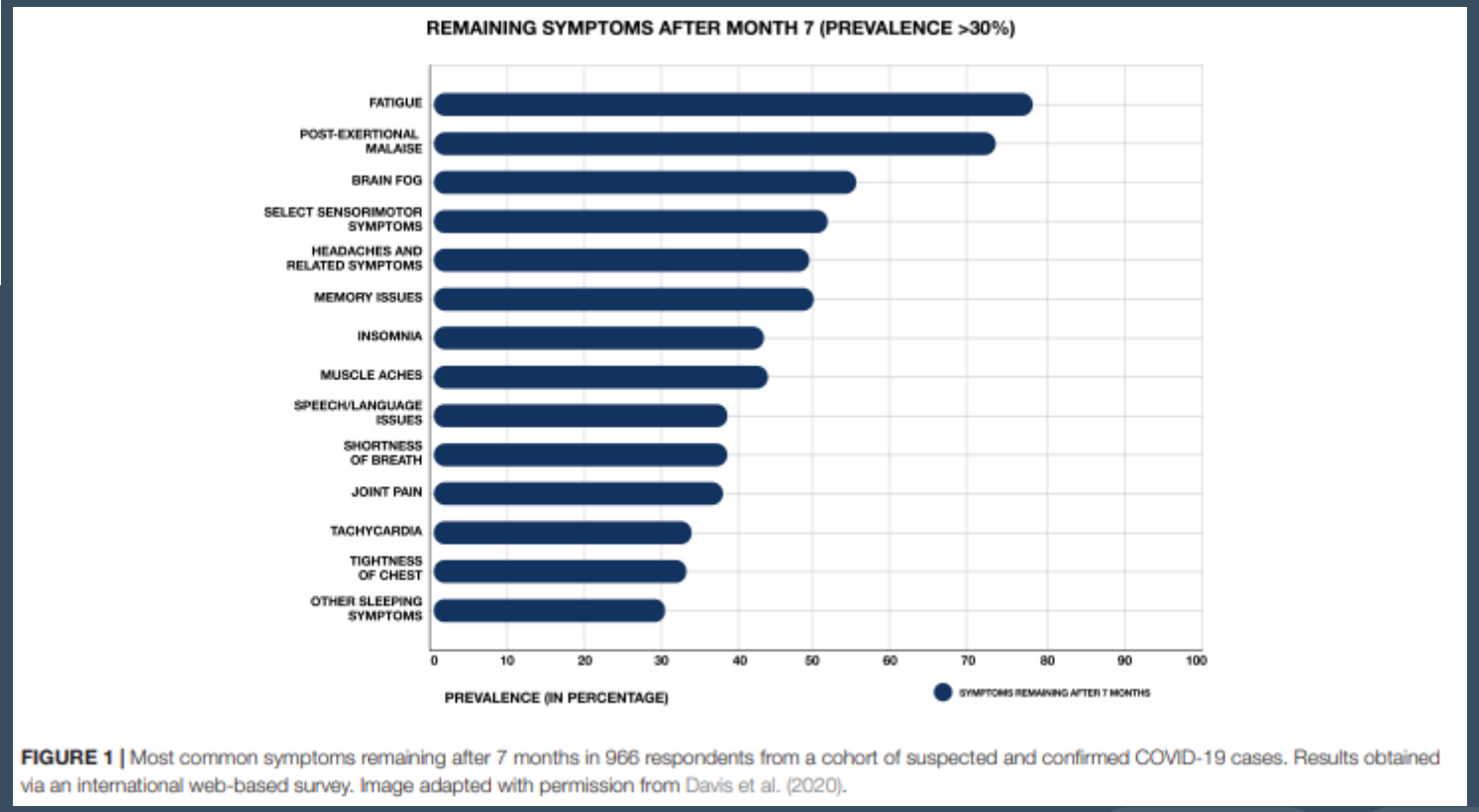


FIGURE 1 | Most common symptoms remaining after 7 months in 966 respondents from a cohort of suspected and confirmed COVID-19 cases. Results obtained via an international web-based survey. Image adapted with permission from Davis et al. (2020).

REVIEW
published: 23 June 2021
doi: 10.3389/fmicb.2021.698169

ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers"

Edith L. Graham, Jeffrey R. Clark, Zachary S. Orban, Patrick H. Lim, April L. Szymanski, Carolyn Taylor, Rebecca M. DiBiase, Dan Tong Jia, Roumen Balabanov, Sam U. Ho, Ayush Batra, Eric M. Liotta & Igor J. Koralnik

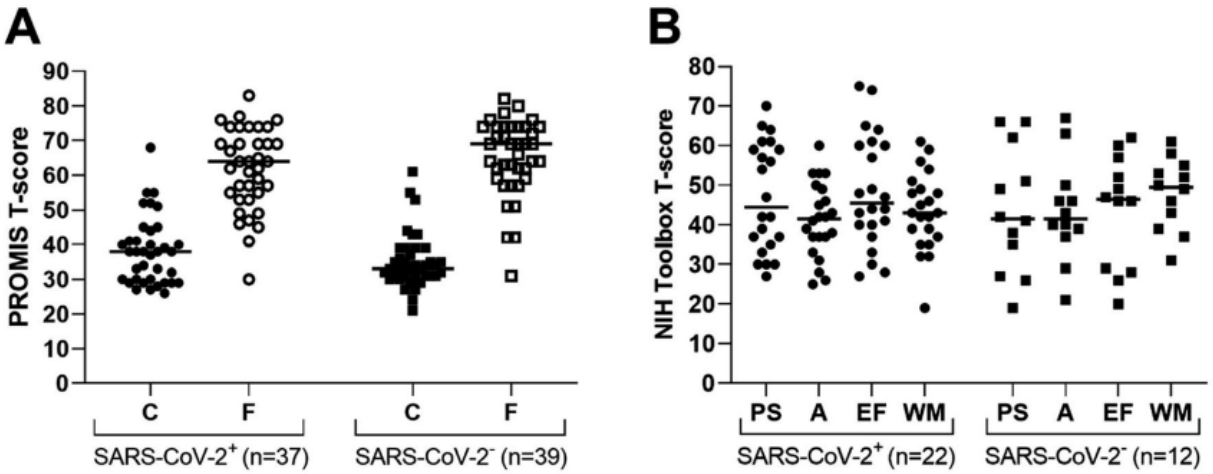
Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Annals of Clinical and Translational Neurology 2021; 8(5): 1073–1085

100 consecutive patients attending Neuro-cognitive clinic

50 PCR confirmed
50 –suspected but not confirmed

Both groups exhibited impaired quality of life in cognitive and fatigue domains. SARS-CoV-2+ patients performed worse in attention and working memory cognitive tasks compared to a demographic-matched US population (T-score 41.5 [37, 48.25] and 43 [37.5, 48.75], respectively; both $p < 0.01$).



Assessment Domain	SARS-CoV-2+ T-score	*p*, against normative population median T-score of 50	SARS-CoV-2- T-score	*p*, against normative population median T-score of 50	*p*, between SARS-CoV-2 groups
PROMIS Quality of Life (median (IQR))					
Cognition	38 (30, 41)	<0.001	33 (31, 37.5)	<0.001	0.24
Fatigue	64 (55, 69)	<0.001	69 (61.25, 74)	<0.001	0.15
NIH Toolbox (median (IQR))					
Processing Speed	44.5 (35.5, 59)	0.28	41.5 (33, 53.75)	0.25	0.61
Attention	41.5 (37, 48.25)	<0.001	41.5 (38.5, 47)	0.15	0.64
Executive Function	45.5 (40, 60)	0.71	46.5 (28.75, 53.25)	0.22	0.49
Working Memory	43 (37.5, 48.75)	0.007	49.5 (42, 53.5)	0.53	0.19

Horrifying new map shows no country is safe from coronavirus' deadly tentacles

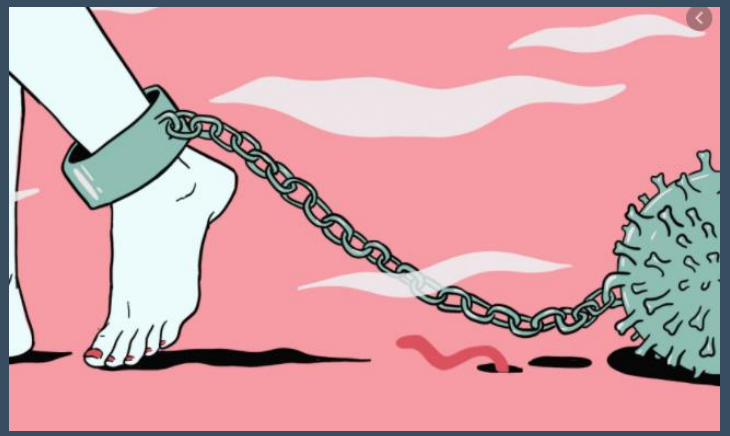
MISLEADING

'Double Mutant' COVID; Waiting to Exhale on Fourth Wave; Teen Vax Trials

Social Learning

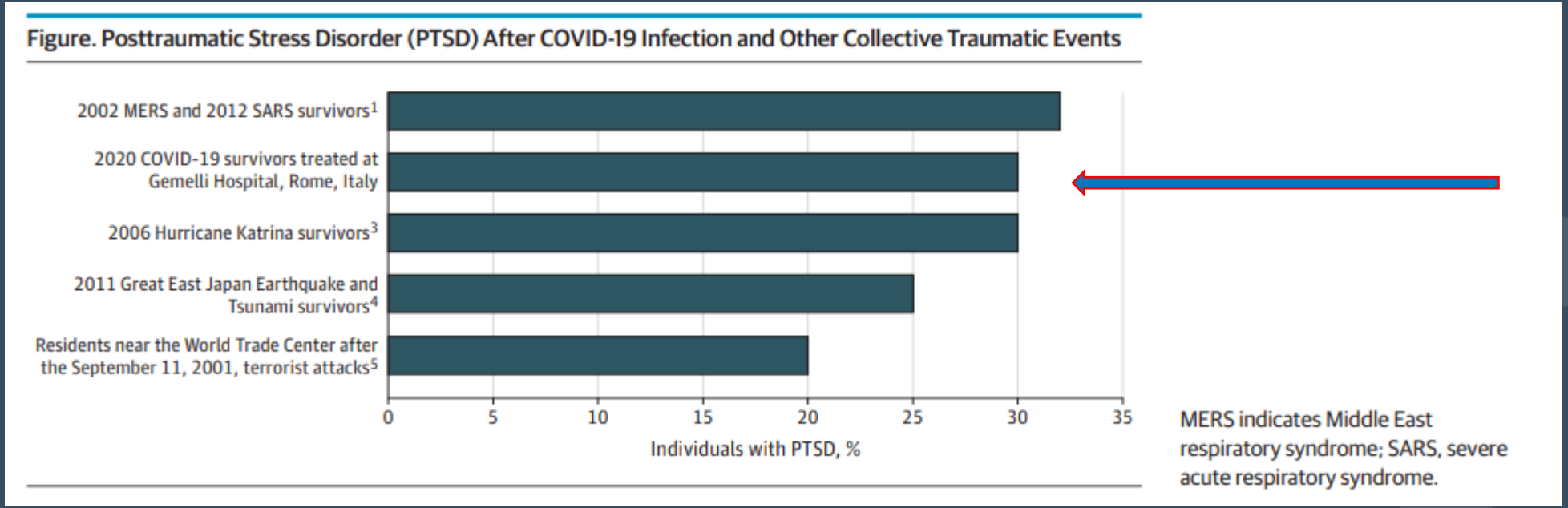
Long haul COVID19 > 83,000, 000 results on GOOGLE

WHERE PEOPLE LEARN TO EXPECT AND FEAR SYMTOMS AFTER COVID-19



Posttraumatic Stress Disorder in Patients After Severe COVID-19 Infection (JAMA Psychiatry May 2021 p567-9)

381 patients presenting with COVID19 to an ER in Italy and recovered
Followed up by questionnaires and structured interviews
Associated characteristics: female sex, history of psychiatric disorders, and delirium or agitation during acute illness. Also correlated with persistent medical symptoms, often reported by patients after recovery from severe COVID-19 (1-3 m latter)- Not associated with ICU admission or ventilation status

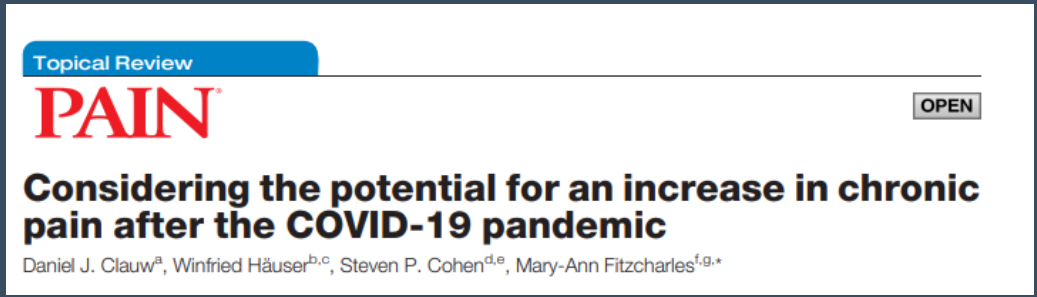


Neurocognitive Profiles in Patients With Persisting Cognitive Symptoms Associated With COVID-19

Kamini Krishnan [1,2], Ashley K Miller [1], Katherine Reiter [1,2], Aaron Bonner-Jackson [1,2]

Arch Clin Neuropsych 2022 Feb 5

- 90% were women and 70% had previous history of anxiety or depression suggesting patients with prior psychiatric history may experience greater levels of cognitive dysfunction.
- Cognitive deficits, when present, appear mild and isolated to domains of attention and processing speed, and executive function
- This finding may be a consequence of other factors developed as a result of COVID-19 (worsening mood, sleep disruption, fatigue, etc.)
- Patients appear receptive to psychoeducation about the impact of factors such as mood, pain, sleep, and fatigue on cognition.



- Infections as a trigger for pain (Ross River, EBV, chikungunya ; part pf ME CFS phenotype
- Chronic pain as a result of COVID-19
  - Well documented in epidemiologic studies confounded by psychologic factors, critical (ICU) related events
- Exacerbation of chronic pain in the absence of actual infection
- New onset pain related to psychologic stressors

J Pain D.J. Clauw et al.·161 (2020) 1694–1697

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Fibromyalgia: a new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey

Francesco Ursini [1,2] Jacopo Ciaffi,[1] Luana Mancarella,[1] Lucia Lisi,[1] Veronica Brusi,[1] Carlotta Cavallari,[1] Martina D'Onghia,[1] Anna Mari,[1] Elena Borlandelli,[3] Jacopo Faranda Cordella,[4] Micaela La Regina,[5] Pasquale Viola,[6] Piero Ruscitti,[7] Marco Miceli,[8] Roberto De Giorgio,[9] Nicola Baldini,[10] Claudio Borghi,[11] Alessandro Gasbarrini,[12] Annamaria Iagnocco,[13] Roberto Giacomelli,[14] Cesare Faldini,[15] Maria Paola Landini,[16] Riccardo Meliconi [1,17]

Methods Data were anonymously collected between 5 and 18 April 2021. The collection form consisted of 28 questions gathering demographic information, features and duration of acute COVID-19, comorbid diseases, and other individual's attributes such as height and weight. The American College of Rheumatology (ACR) Survey Criteria and the Italian version of the Fibromyalgia Impact Questionnaire completed the survey.

RMD Open
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ORIGINAL RESEARCH

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	Overall (n=616)	Weight-adjusted (n*=591)
Age (years)	45±12	45±12
Female gender, n (%)	477 (77.4)	–
Marital status		
Single, n (%)	116 (18.8)	126 (21.3)
Married, n (%)	437 (70.9)	417 (70.6)
Separated, n (%)	51 (8.3)	39 (6.6)
Widowed, n (%)	12 (1.9)	9 (1.6)

	Overall (n=616)	Weight-adjusted (n*=591)
BMI (kg/m^2)	25.3±4.8	25.6±4.7
BMI category		
Underweight, n (%)	19 (3.1)	14 (2.3)
Normal weight, n (%)	335 (54.4)	302 (51.1)
Overweight, n (%)	160 (26.0)	172 (29.1)
Obese, n (%)	102 (16.6)	103 (17.5)
FM (FS score ≥13), n (%)	189 (30.7)	234 (39.5)

Key messages

What is already known about this subject?

- Postacute COVID-19 syndrome (PACS) is emerging as a complex condition with a wide range of clinical manifestations.
- Clinical features of PACS include musculoskeletal pain, fatigue, cognitive impairment and sleep disturbances.

What does this study add?

- Our study suggests that up to 30% of patients with PACS may satisfy criteria for fibromyalgia (FM).
- Obesity and male gender represent the strongest risk factors for post-COVID-19 FM.

How might this impact on clinical practice or further developments?

- It is reasonable to expect that rheumatologists will soon face up with a sharp rise of cases of this new entity that we defined 'FibroCOVID'.

Journal of Clinical Medicine

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Open Access Article

Patterns of Long COVID Symptoms: A Multi-Center Cross Sectional Study

by Dana Yelin [1,2,*], Ili Margalit [1,2,3], Mayssam Nehme [4], Jaume Bordas-Martínez [5,6], Francesco Pistelli [7,8], Dafna Yahav [2,3], Idris Guessous [4,9], Xavier Durà-Miralles [9,10], Laura Carrozzi [6], Irit Shapira-Lichter [2,11], Pauline Vetter [12], Dolores Peleato-Catalan [13], Giusy Tiseo [14], Eytan Wirtheim [15], Laurent Kaiser [12], Carlota Gudiol [6,16,17], Marco Falcone [14], Leonard Leibovici [18] and on behalf of the LongCOV Research Group †

- 75 % Moderate COVID
- International
- Mixed methods for clinical assessments
- Principle component analysis

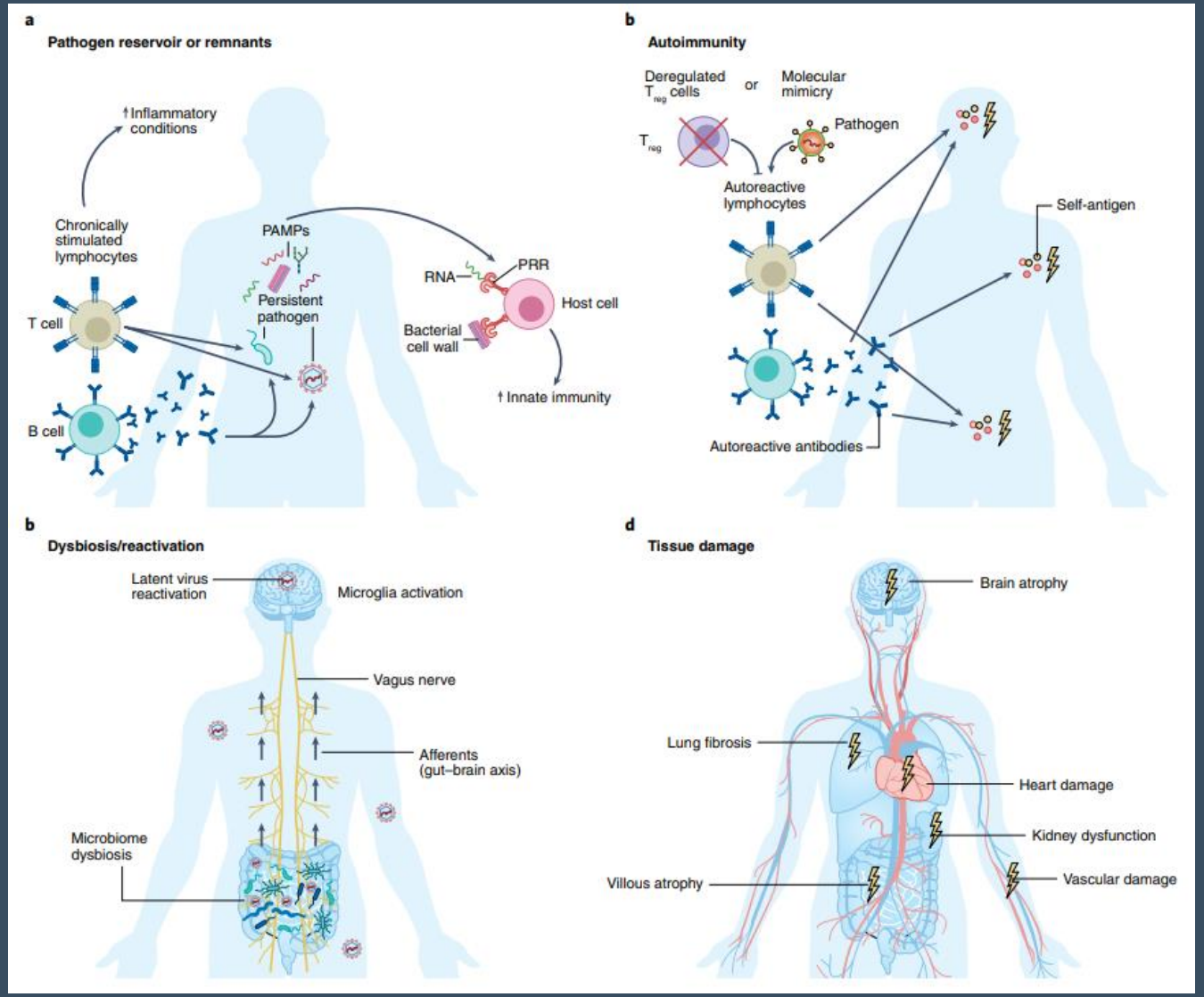
	All	Israel	Switzerland	Spain	Italy
No. of patients, N (%)	1027	544 (53)	256 (24.9)	115 (11.2)	112 (10.9)
Gender–women, N (%)	559 (54.4)	307 (56.4)	144 (56.3)	60 (52.2)	48 (42.9)
Age, mean (SD)	49.2 (16.1)	46.4 (15.5)	45.5 (15.1)	58.4 (12.4)	61.2 (15.5)
BMI, mean (SD)	28 (5.6)	27.6 (5.6)	28.7 (7.7)	29.8 (6.1)	28.2 (4.6)
Obese, N (%)	223 (30.2)	149 (29.0)	3 (15.7)	42 (42.4)	29 (26.1)
* missing 280	N = 738	N = 518	N = 19	N = 99	N = 111
Smoking, N (%) * missing 79	255 (24.8)	132 (24.3)	59 (23.0)	41 (35.7)	23 (20.5)
Diabetes, N (%)	92 (9.0)	45 (8.3)	10 (3.9)	22 (19.1)	15 (13.4)
Hypertension, N (%)	206 (20.1)	89 (16.4)	27 (10.5)	50 (43.5)	40 (35.7)
IHD, N (%)	52 (5.1)	25 (4.6)	17 (6.6)	1 (0.9)	9 (8.0)
Prior lung disease, N (%)	79 (7.7)	35 (6.4)	19 (7.4)	16 (13.9)	9 (8.0)
Hospitalization, N (%) * Missing 78	337 (32.8)	122 (22.4)	26 (10.2)	79 (68.7)	112 (100)
Severe disease [a], N (%)	264 (25.7)	86 (15.8)	26 (10.2)	72 (62.6)	80 (71.4)
Time to clinic visit (days), median (IQR) * Missing 26	123 (80–204)	97 (66–130)	217 (203–233)	115 (87–224)	146 (127–185)
Fatigue [b], N (%)	691 (67.2)	411 (75.6)	129 (50.4)	90 (78.3)	61 (54.5)
Dyspnea [b], N (%)	480 (46.7)	277 (50.9)	62 (24.2)	85 (73.9)	56 (50.0)
Cough [b], N (%)	187 (18.2)	108 (19.9)	21 (8.2)	35 (30.4)	23 (20.5)
Chest pain [b], N (%)	204 (19.9)	166 (30.5)	14 (5.5)	24 (20.9)	0 (0)
Palpitations [b], N (%)	104 (10.1)	67 (12.3)	18 (7.0)	19 (16.5)	0 (0)
Myalgia [b], N (%)	332 (32.3)	204 (37.5)	37 (14.5)	46 (40.0)	45 (40.2)
Arthralgia [b], N (%)	157 (15.3)	51 (9.4)	23 (9.0)	33 (28.7)	50 (44.6)
Parasthesias [b], N (%)	193 (18.8)	109 (20.0)	13 (5.1)	32 (27.8)	39 (34.8)
Insomnia [b], N (%)	259 (25.2)	204 (37.5)	27 (10.5)	28 (24.3)	0 (0)
Headache[b], N (%)	153 (14.9)	69 (12.7)	44 (17.2)	24 (20.9)	16 (14.3)
Memory loss [b], N (%)	315 (30.7)	201 (36.9)	35 (13.7)	33 (28.7)	46 (41.1)
Concentration impairment [b], N (%)	312 (30.4)	212 (39.0)	31 (12.1)	26 (22.6)	43 (38.4)
Anosmia/dysguesia [b], N (%)	289 (28.2)	160 (29.4)	70 (27.3)	24 (20.9)	30 (26.8)
Worse physical activity status [c], N (%) * missing 42	326 (31.7)	142 (26.1)	134 (52.3)	43 (37.4)	7 (6.3)

Myalgia 14-40%
Arthralgia 9-44%
HA 12-20%
Chest pain 5-30%

Commonly suggested biomedical hypotheses explaining PAISs

PERSISTENT PATHOGEN

DYSBIOSIS Neuro-Immune axis



AUTOIMMUNE / AUTOINFLAMMATORY

PATHOLOGIC TISSUE DAMAGE

SCIENCE ADVANCES | RESEARCH ARTICLE

IMMUNOLOGY

Islet expression of type I interferon response sensors is associated with immune infiltration and viral infection in type 1 diabetes

Paola S. Apaolaza[1], Diana Balcacean[1], Jose Zapardiel-Gonzalo[1], Gra
Nataliya Lenchik[2], Pouria Akhbari[3], Ivan Gerling[2], Sarah J. Richards
Teresa Rodriguez-Calvo[1]*, nPOD-Virus Group

Previous results indicate the presence of an interferon (IFN) signature in type
chronic inflammation and compromising β cell function. Here, we determine

VIRUS-INDUCED DIABETES MELLITUS

Isolation of a Virus from the Pancreas of a Child with Diabetic Ketoacidosis

Ji-Won Yoon, Ph.D., Marshall Austin, M.D., Ph.D., Takashi Onodera, PhD., and Abner Louis Notkins, M.D.

death. Neutralization data showed that the
s related to a diabetogenic variant derivec
xsackievirus B4. Inoculation of mice wit
man isolate produced hyperglycemia, inflam

PNAS

Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy

Guo Luo[a], Aditya Ambati[a,1], Ling Lin[a,1], Mélodie Bonvalet[a], Markku Partinen[b,c], Xuhuai Ji[d], Holden Terry Maecker[d], and Emmanuel Jean-Marie Mignot[a,2]

[a]Center for Sleep Sciences and Medicine, Stanford University School of Medicine, Palo Alto, CA 94304; [b]Helsinki Sleep Clinic, Vitalmed Research Centre

Infections and Autoimmunity

Lars Krogvold,[1] Bjørn Edwin,[2,3] Trond Buanes,[3,4] Gun Frisk,[5] Oskar Skog,[5] Mahesh Anagandula,[5] Olle Korsgren,[5] Dag Undlien,[3,6] Morten C. Eike,[6] Sarah J. Richardson,[7] Pia Leete,[7] Noel G. Morgan,[7] Sami Oikarinen,[8] Maarit Oikarinen,[8] Jutta E. Laiho,[8] Heikki Hyöty,[8,9] Johnny Ludvigsson,[10] Kristian F. Hanssen,[3,11] and Knut Dahl-Jørgensen[1,3]

Detection of a Low-Grade Enteroviral Infection in the Islets of Langerhans of Living Patients Newly Diagnosed With Type 1 Diabetes

Diabetes 2015;64:1682–1687 | DOI: 10.2337/db14-1370

RESEARCH ARTICLE

INFLUENZA

Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2

Syed Sohail Ahmed,[1*†] Wayne Volkmuth,[2] José Duca,[3] Lorenzo Corti,[4] Mic
Alfredo Pezzicoli,[5] Anette Karle,[6] Fabio Rigat,[7] Rino Rappuoli,[8] Vas Narasi
Ilkka Julkunen,[10,11] Arja Vuorela,[10] Outi Vaarala,[10] Hanna Nohynek,[10]
Franco Laghi Pasini,[12,13] Emanuele Montomoli,[14,15] Claudia Trombetta,[14]
Christopher M. Adams,[16] Jonathan Rothbard,[17] Lawrence Steinman[18*]

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

NEUROIMMUNOLOGY

Gut microbiota–specific IgA$^+$ B cells traffic to the CNS in active multiple sclerosis

Anne-Katrin Pröbstel[1,2*], Xiaoyuan Zhou[1], Ryan Baumann[1], Sven Wischnewski[3], Michael Kutza[3], Olga L. Rojas[4], Katrin Sellrie[5], Antje Bischof[1], Kicheol Kim[1], Akshaya Ramesh[1], Ravi Dandekar[1], Ariele L. Greenfield[1], Ryan D. Schubert[1], Jordan E. Bisanz[6,7], Stephanie Vistnes[8], Khashayar Khaleghi[4], James Landefeld[1], Gina Kirkish[1], Friederike Liesche-Starnecker[9], Valeria Ramaglia[3], Sneha Singh[1], Edwina B. Tran[1], Patrick Barba[1], Kelsey Zorn[1], Johanna Oechtering[2], Karin Forsberg[10], Lawrence R. Shiow[8,11†], Roland G. Henry[1],

JCI The Journal of Clinical Investigation

The intersection of COVID-19 and autoimmunity

Jason S. Knight, … , Julia Y. Wang, William J. McCune

J Clin Invest. 2021;131(24):e154886. https://doi.org/10.1172/JCI154886.

Table 1. SARS-CoV-2 shares some characteristic features with other viruses that trigger autoimmunity

Features of other viruses	Evidence for SARS-CoV-2
Precedes autoimmunity	Case reports of patients developing classifiable autoimmune diseases following SARS-CoV-2 infection (56–64)
Induces type I IFNs	SARS-CoV-2 induces robust type I IFN responses in a subset of patients (23–26)
Breaks tolerance	SARS-CoV-2 induces autoantibody production in patients with severe COVID-19 (42, 77)
Superantigen activity	SARS-CoV-2 spike protein contains a superantigen motif and patients with severe COVID-19 exhibit TCR skewing consistent with superantigen activation (109)
Inhibits apoptosis of infected cells	No evidence to date
Interferes with its own destruction	No evidence to date

Autoantibodies in COVID-19 – 2022

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Distinct Autoimmune Antibody Signatures Between Hospitalized Acute COVID-19 Patients, SARS-CoV-2 Convalescent Individuals, and Unexposed Pre-Pandemic Controls

Nahid Bhadelia, Anna C. Belkina, Alex Olson, Thomas Winters, Patricia Urick, Nina Lin, Ian Rifkin, Yachana Kataria, Rachel R. Yuen, Manish Sagar, Jennifer E. Snyder-Cappione

doi: https://doi.org/10.1101/2021.01.21.21249176

Posted January 25, 2021.

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Data/Code

Research Square

Autoantibodies targeting cytokines and connective tissue disease autoantigens are common in acute non-SARS-CoV-2 infections.

Allan Feng

nature
https://doi.org/10.1038/s41586-021-03234-7
Accelerated Article Preview

Global absence and targeting of protective immune states in severe COVID-19

Received: 23 October 2020
Accepted: 12 January 2021
Accelerated Article Preview
Published online 25 January 2021

Alexis J. Combes, Tristan Courau, Nicholas F. Kuhn, Kenneth H. Hu, Arja Ray, William S. Chen, Nayvin W. Chew, Simon J. Cleary, Divyashree Kushnoor, Gabriella C. Reeder, Alan Shen, Jessica Tsui, Kamir J. Hiam-Galvez, Priscila Muñoz-Sandoval, Wandi S. Zhu, David S. Lee, Yang Sun, Ran You, Mélia Magnen, Lauren Rodriguez, K. W. Im, Nina K. Serwas, Aleksandra Leligdowicz, Colin R. Zamecnik, Rita P. Loudermilk, Michael R. Wilson,

Science Translational Medicine
RESEARCH ARTICLES

Cite as: S. Chakraborty *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abm7853 (2022).

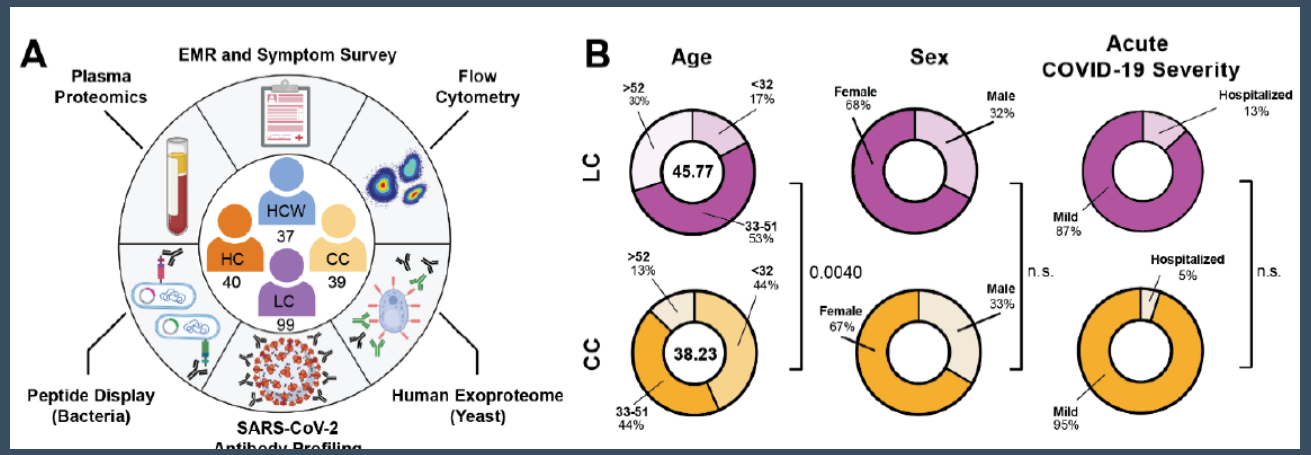
CORONAVIRUS

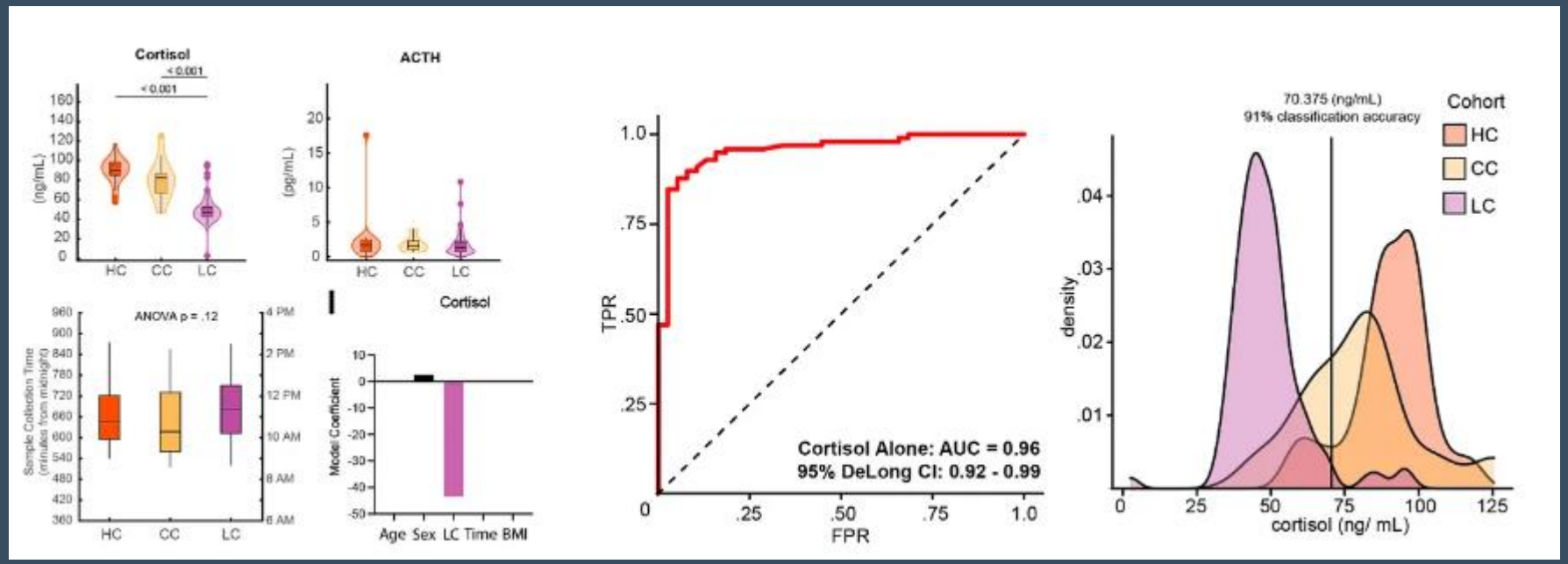
Early non-neutralizing, afucosylated antibody responses are associated with COVID-19 severity

Saborni Chakraborty[1]†, Joseph C. Gonzalez[1,2]†, Benjamin L. Sievers[3], Vamsee Mallajosyula[4], Srijoni Chakraborty[5], Megha Dubey[6], Usama Ashraf[1], Bowie Yik-Ling Cheng[1], Nimish Kathale[1], Kim Quyen Thi Tran[1], Courtney Scallan[1], Aanika Sinnott[3], Arianna Cassidy[7], Steven T. Chen[8,9,10], Terri Gelbart[3], Fei Gao[4], Yarden Golan[11], Xuhuai Ji[4], Seunghee Kim-Schulze[8], Mary Prahl[12], Stephanie L. Gaw[7], Sacha Gnjatic[8,9,10,13], Thomas U. Marron[8,9], Miriam Merad[8,9,10,13], Prabhu S. Arunachalam[4], Scott D. Boyd[14], Mark M. Davis[4,6,15], Marisa Holubar[1], Chaitan Khosla[16], Holden T. Maecker[4], Yvonne Maldonado[17], Elizabeth D. Mellins[17], Kari C. Nadeau[18], Bali Pulendran[4], Upinder Singh[1,6], Aruna Subramanian[1], Paul J. Utz[19], Robert Sherwood[20], Sheng Zhang[20], Prasanna Jagannathan[1,6], Gene S. Tan[3,21]*, Taia T. Wang[1,6,22]*‡

Distinguishing features of Long COVID identified through immune profiling

Jon Klein[1†], Jamie Wood[2†], Jillian Jaycox[1†], Peiwen Lu[1†], Rahul M. Dhodapkar[3†], Jeff R. Gehlhausen [1,4†], Alexandra Tabachnikova[1†], Laura Tabacof[2], Amyn A. Malik[5], Kathy Kamath[6], Kerrie Greene[1], Valter Silva Monteiro[1], Mario Peña-Hernandez[7], Tianyang Mao[1], Bornali Bhattacharjee[1], Takehiro Takahashi[1], Carolina Lucas[1], Julio Silva[1], Dayna Mccarthy[2], Erica Breyman[2], Jenna Tosto-Mancuso[2], Yile Dai[1], Emily Perotti[1], Koray Akduman[1], Tiffany J. Tzeng[1], Lan Xu[1], Inci Yildirim[5,8,9,10], Harlan M. Krumholz[8,11,12,13], John Shon[6], Ruslan Medzhitov[1,8,14], Saad B. Omer[5,8,10,15], David van Dijk[16,17*], Aaron M. Ring[1*], David Putrino[2,18*], Akiko Iwasaki[1,8,14*]





AUG 2022

Treatment of PASC

- No specific therapies
- Antivirals
- Small pipeline
- Autonomic targeting, immunologic targeting
- PACING
- Psychologic support

nature medicine
REVIEW ARTICLE
https://doi.org/10.1038/s41591-022-01810-6
Check for updates

Unexplained post-acute infection syndromes

Jan Choutka[1], Viraj Jansari[2], Mady Hornig[3] and Akiko Iwasaki[2,4,5,6]

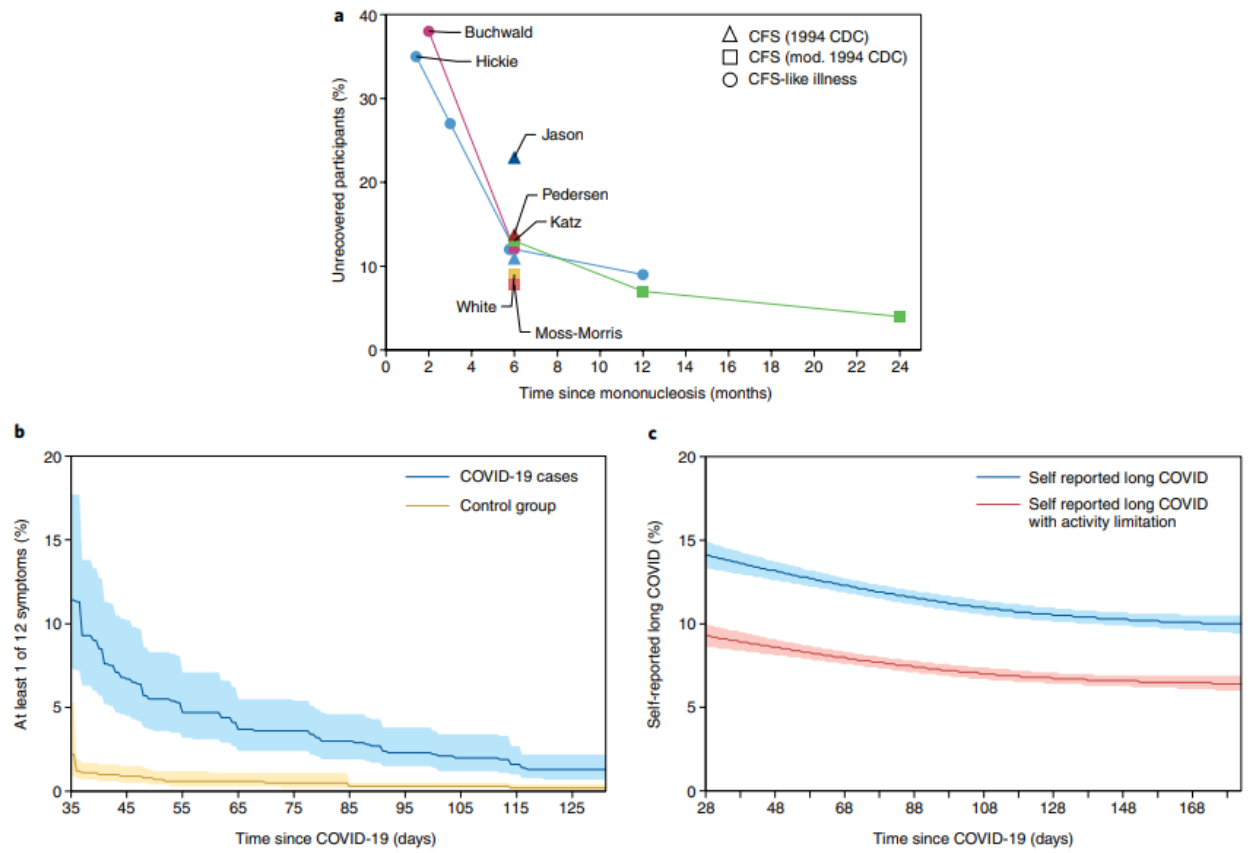


Fig. 1 | Prevalence and prognosis estimates of selected PAISs. a, Comparison of available estimates of persistent symptoms after infectious mononucleosis, based on the 1994 CDC criteria for CFS (Hickie et al.[31,38], Jason et al.[38], Pedersen et al.[39]), its modification (Katz et al.[37,41], White et al.[41], Moss-Morris et al.[68]), or self-reported CFS-like illness (Hickie et al.[31], Buchwald et al.[69]). **b**, Prevalence of at least 1 of 12 selected symptoms following COVID-19 (blue) compared with healthy unexposed controls (orange). **c**, Prevalence of self-reported 'long COVID' of any severity (blue) and with activity limitation (red). Plots in **b** and **c** are adapted from the estimate of Office for National Statistics (ONS)[191]. Lighter-colored bands around plotted lines show 95% confidence intervals. Plots in **b** and **c** contain public sector information licensed under the Open Government License v3.0.

Natural History of PAIS is partially PATHOGEN SPECIFIC

Heavily influenced by ascertainment strategy

Being a person vs. a doctor

A cautionary tale of ‘long haulers”
Leonard Sigal MD “What is causing the ‘long hauler’ phenomenon after COVID-19

- All to often families and clinicians minimize these chronic symptoms and all to often misguided therapies can lead to toxicity, frustration and despair”

Clev Clin J Med 88:273, May 2021

Perspective

Long COVID-19 and the Role of the Patient–Clinician Interaction in Symptom Management

Journal of Patient Experience
Volume 9: 1-3

DOI: 10.1177/23743735221077514
journals.sagepub.com/home/jpx
SAGE

Leonard Calabrese[1] **and Luana Colloca**[2]

Keywords
patient/relationship centered skills, quality of life, communication, COVID-19, imaging

Table 1. Six Recommendations for Leveraging the Patient–Clinician Interaction to Optimize Symptom Management

Treat the symptoms and causes while empathically understanding the patient's experience of sickness
Recognize that the diagnosis itself of Long coronavirus disease (COVID) carries with it a strong personal dimension
Validate the patients' symptoms and expunge them of guilt
Dispel patients' fears surrounding the diagnosis of Long COVID
Establish a genuine working relationship with the patient
Find meaning and compassion to minimize burnout when facing such a complex problem as Long COVID.

Image available at: https://i.imgur.com/G4hJD.jpg.

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SPASTICITY

View Dashboard Assumptions, Methodology, and Sources

BY STATE

FILTERS

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Select Est. PASC %

30%

Select a State

All

Select a County

All

MODEL ASSUMPTIONS AND SOURCES

(see all)

1. Model assumes 30% of COVID-19 surviving cases in the U.S. result in PASC.

2. COVID-19 surviving cases are confirmed cases less deaths.

3. U.S. case data is pulled nightly from JHU CSSE COVID-19 Data. U.S. Census data uses 2019 1-year estimates.

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COVID-19 SURVIVING CASES (TOTAL)

91,067,924

PASC CASES (ESTIMATED)

27,320,377

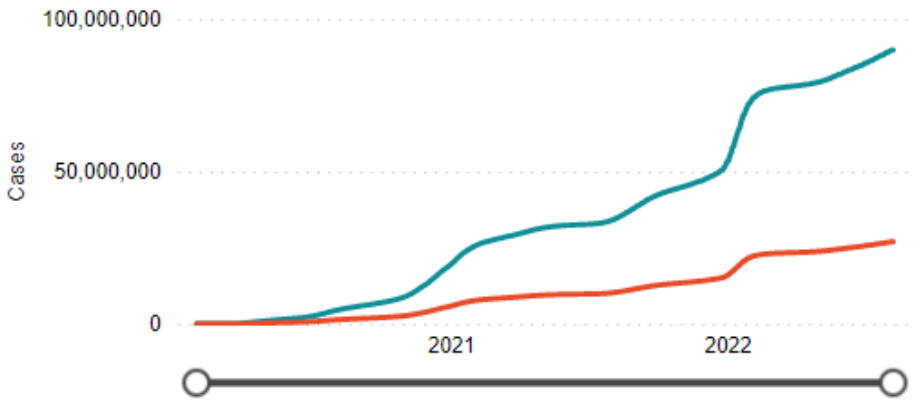
ESTIMATED PASC CASES PER STATE

State	PASC Cases (Estimated)
California	3,213,575
Texas	2,230,353
Florida	2,025,752
New York	1,738,034
Illinois	1,067,968
Pennsylvania	917,724
North Carolina	897,212
Ohio	881,070
Georgia	791,466
Michigan	782,462
New Jersey	773,999
Arizona	654,186
Tennessee	625,467
Virginia	584,250
Indiana	545,855
Massachusetts	534,743
Wisconsin	532,780

CUMULATIVE AND DAILY CASES

Select Display: Cumulative / Daily

COVID-19 Surviving Cases PASC Cases (Estimated)



PASC CASES (ESTIMATED)