NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

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UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Long COVID: how to identify, how to manage

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Outline

- ✓Definizione di long COVID
- ✓Prevalenza e fattori associati
- ✓Vaccinazione, breakthrough infections e reinfezioni
- ✓Possibili meccanismi patogenetici di long COVID
- ✓Possibili trattamenti e trials in corso
- ✓Dati preliminari ASST Santi Paolo e Carlo - EUCARE

Post COVID-19 condition-PCC, WHO (Ottobre 2021)

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.

Lancet Infect Dis 2022;
22: e102–07

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021

World Health Organization

Post COVID-19 condition: need of a new definition?

related quality of life, earnings, and health care costs.[7,8] Most existing PASC studies have focused on individual symptom frequency and have generated widely divergent estimates of prevalence due to their retrospective design and lack of an uninfected comparison group. Moreover, defining PASC precisely is difficult because it is heterogeneous, composed of conditions with variable and potentially overlapping etiologies (eg, organ injury, viral persistence, immune dysregulation, autoimmunity, and gut dysbiosis).[9,10]

JAMA. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823
Published online May 25, 2023.

Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

[a] Least absolute shrinkage and selection operator was used to identify which symptoms defined PASC. A symptom score was assigned by dividing the estimated log odds ratio by 0.10 and rounding to the nearest integer. For each person, the total score was defined as the sum of the scores for each symptom a person reported.

Clinical phenotypes of mild acute disease and their association to long-term sequelae: the COVID HOME study (*A. TAMI* \

Aims

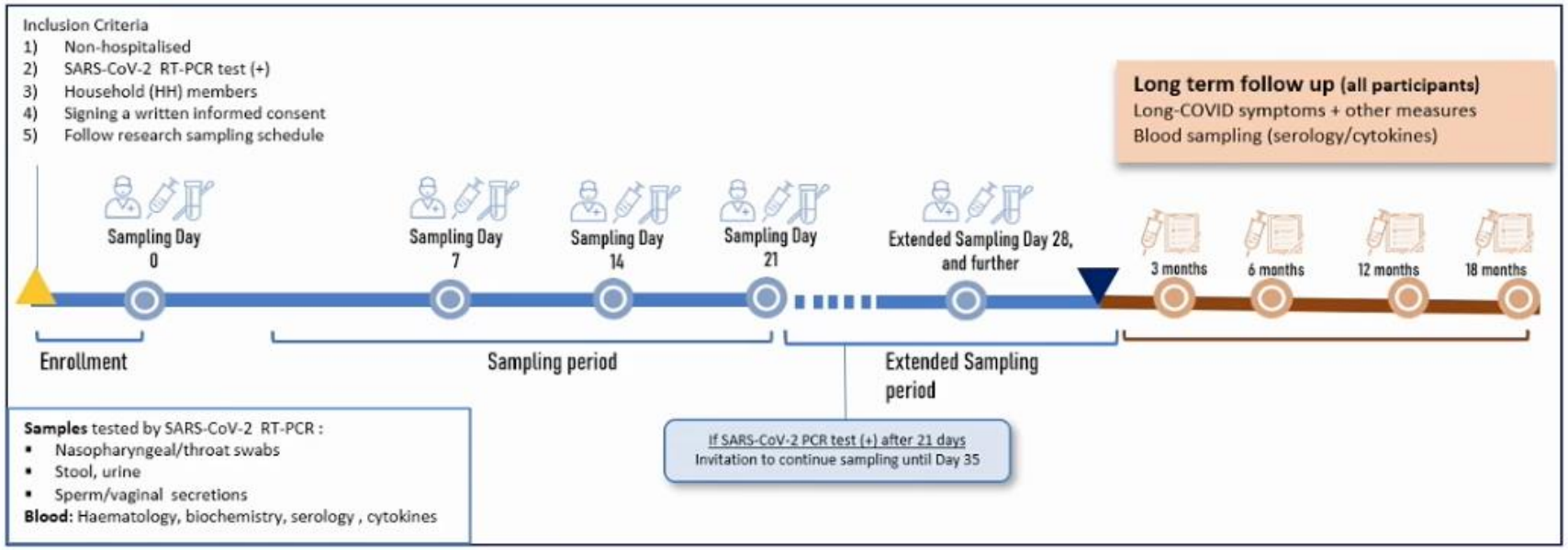
To identify **clinical phenotypes** of COVID-19 mild acute disease presentation

To determine **associations** between phenotypes and the development of **long-term sequelae (Long COVID)**

Methods

In March 2020, a prospective longitudinal study of non-hospitalised COVID-19 individuals and household (HH) members was initiated in the four northern provinces of the Netherlands

We used principal component analysis (PCA) and k-means clustering to identify clinical phenotypes and performed binomial logistic regression to explore associations between phenotypes and Long-COVID

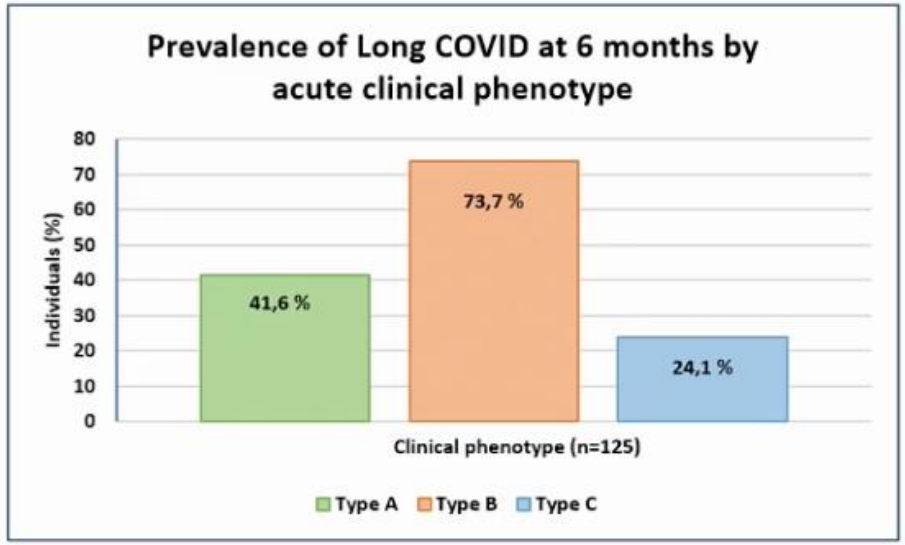


(Tami *et al.* 2022. doi: 10.1371/journal.pone.0273599)

Phenotypes and associations with long-term sequelae

Overall prevalence of Long COVID*
At 6 months post-infection

53 out of 125 individuals = **42.4%**



Phenotyped individuals at 6 months follow up (n = 125)	Complaints at 6 months post-infection			
	n (%)	Crude OR	CI95	P-value
Phenotype A (n = 77)	32 (41.6%) [a]	-	-	-
Phenotype B (n = 19)	14 (73.7%) [b]	3.94	1.29 - 12.03	**0.016**
Phenotype C (n = 29)	7 (24.1%) [a]	0.45	0.17 - 1.17	0.102

(*Long COVID or Post-COVID syndrome as per WHO definition (WHO 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)

Conclusions

- **Three clinical phenotypes** identified for symptomatic mild acute COVID-19 in home-convalescing patients
- Phenotypes differed significantly for age, gender, laboratory test results, number and prevalence of reported symptoms:

Phenotype A

Mildest form

- Youngest median age
- Fewer comorbidities
- 7-10 symptoms
- High prevalence of flu-like symptoms
- Bloodwork within reference range

Phenotype B

Most severe form

- Oldest group (highest median age)
- Higher % females
- Multimorbidity more likely
- Higher number (16-25) & frequency of symptoms
- Mostly general and neurological symptoms
- Tendency for abnormal haematological and biochemical values

Phenotype C

Mixed phenotype

- Similar median age to Phenotype B
- More likely male
- Highest prevalence of 1 comorbidity
- Mainly 0-15 symptoms
- Distribution of symptoms similar to Phenotype A
- Higher tendency for abnormal bloodwork

Long-term sequelae:

- **>40%** of participants report still having complaints at 6 months post-infection
- **Phenotype B** significantly associated with having complaints at 6 months post-infection

University Medical Center Groningen

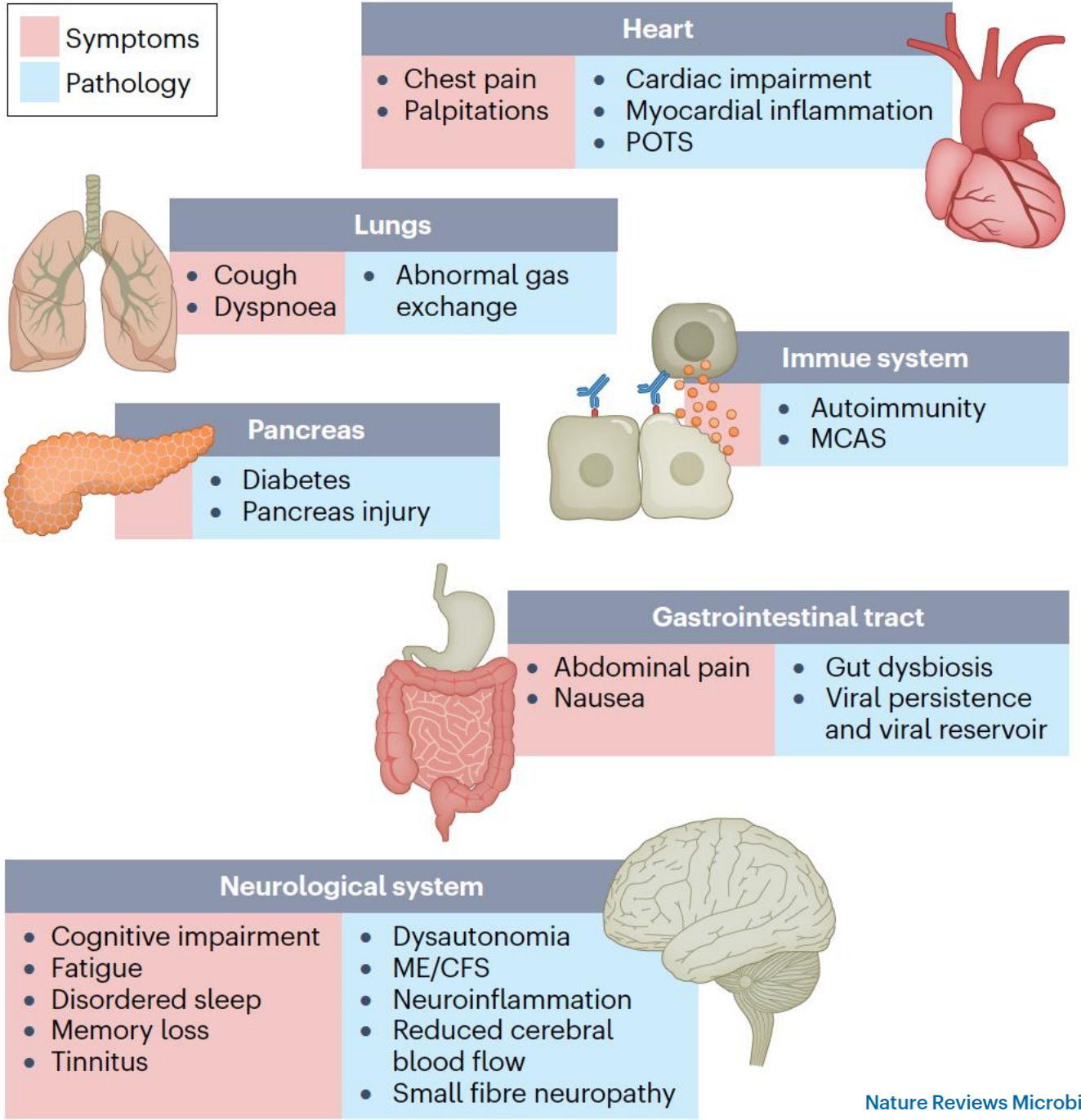
Prevalence of PCC

Long COVID is an often debilitating illness that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. More than 200 symptoms have been identified with impacts on multiple organ systems. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily. Biomedical

cases. The incidence is estimated at 10–30% of non-hospitalized cases, 50–70% of hospitalized cases[2,3] and 10–12% of vaccinated cases[4,5]. Long COVID is associated with all ages and acute phase disease severities, with the highest percentage of diagnoses between the ages of 36 and 50 years, and most long COVID cases are in non-hospitalized patients with a mild acute illness[6], as this population represents the majority of overall COVID-19 cases. There are many research challenges, as out-

Nature Reviews Microbiology | Volume 21 | March 2023 | 133–146

PCC: clinical manifestations



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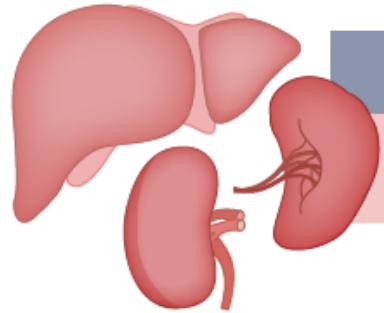


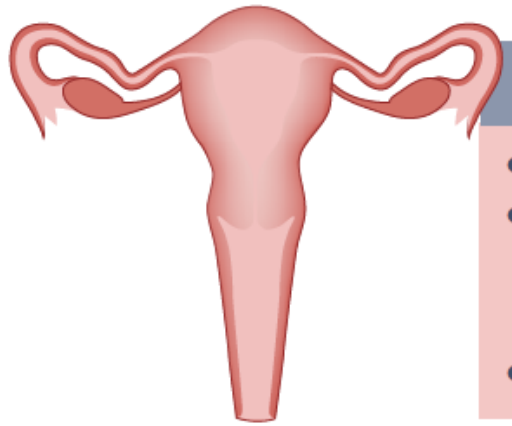
Kidneys, spleen and liver

- Organ injury

Blood vessels

- Fatigue

- Coagulopathy
- Deep vein thrombosis
- Endothelial dysfunction
- Microangiopathy
- Microclots
- Pulmonary embolism
- Stroke



Reproductive system

- Erectile dysfunction
- Increased severity and number of premenstrual symptoms
- Irregular menstruation

- Reduced sperm count

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]✉

SARS-CoV-2 is not unique in its ability to cause post-acute sequelae; certain acute infections have long been associated with an unexplained chronic disability in a minority of patients. These post-acute infection syndromes (PAISs) represent a substantial healthcare burden, but there is a lack of understanding of the underlying mechanisms, representing a significant blind spot in the field of medicine. The relatively similar symptom profiles of individual PAISs, irrespective of the infectious agent, as well as the overlap of clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), suggest the potential involvement of a common etiopathogenesis. In this Review, we summarize what is known about unexplained PAISs, provide context for post-acute sequelae of SARS-CoV-2 infection (PASC), and delineate the need for basic biomedical research into the underlying mechanisms behind this group of enigmatic chronic illnesses.

Box 2 | Symptoms and signs of post-acute infection syndromes

Main categories of symptoms and signs:

- Exertion intolerance, fatigue
- Flu-like and 'sickness behavior' symptoms: fever, feverishness, muscle pain, feeling sick, malaise, sweating, irritability
- Neurological/neurocognitive symptoms: brain fog, impaired concentration or memory, trouble finding words
- Rheumatologic symptoms: chronic or recurrent joint pain
- Trigger-specific symptoms: for example, eye problems post-Ebola, IBS post-*Giardia*, anosmia and ageusia post-COVID-19, motor disturbances post-polio and post-West Nile virus

Could You Have ME/CFS?
(Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)

ME/CFS is a complex illness and symptoms of ME/CFS may seem similar to many other illnesses. ME/CFS requires **three** symptoms:

1 **Not being able to participate in routine activities that were possible before becoming ill**, such as work, school, social life, and/or personal life, that:

- **Lasts** for more than **6 months**
- Is accompanied by **fatigue** that is:
  - Often serious
  - Just started (not lifelong)
  - Not the result of ongoing activities
  - Not from more than usual effort
  - Not made better by rest

2 **Post-exertional malaise (PEM).** Worsening of symptoms after physical, mental, or emotional effort that would not have caused a problem before the illness. This is sometimes referred to as "crashing" by people with ME/CFS.

3 **Unrefreshing sleep.** People with ME/CFS may not feel better even after a full night of sleep (e.g., feeling just as tired upon waking up as before going to bed).

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

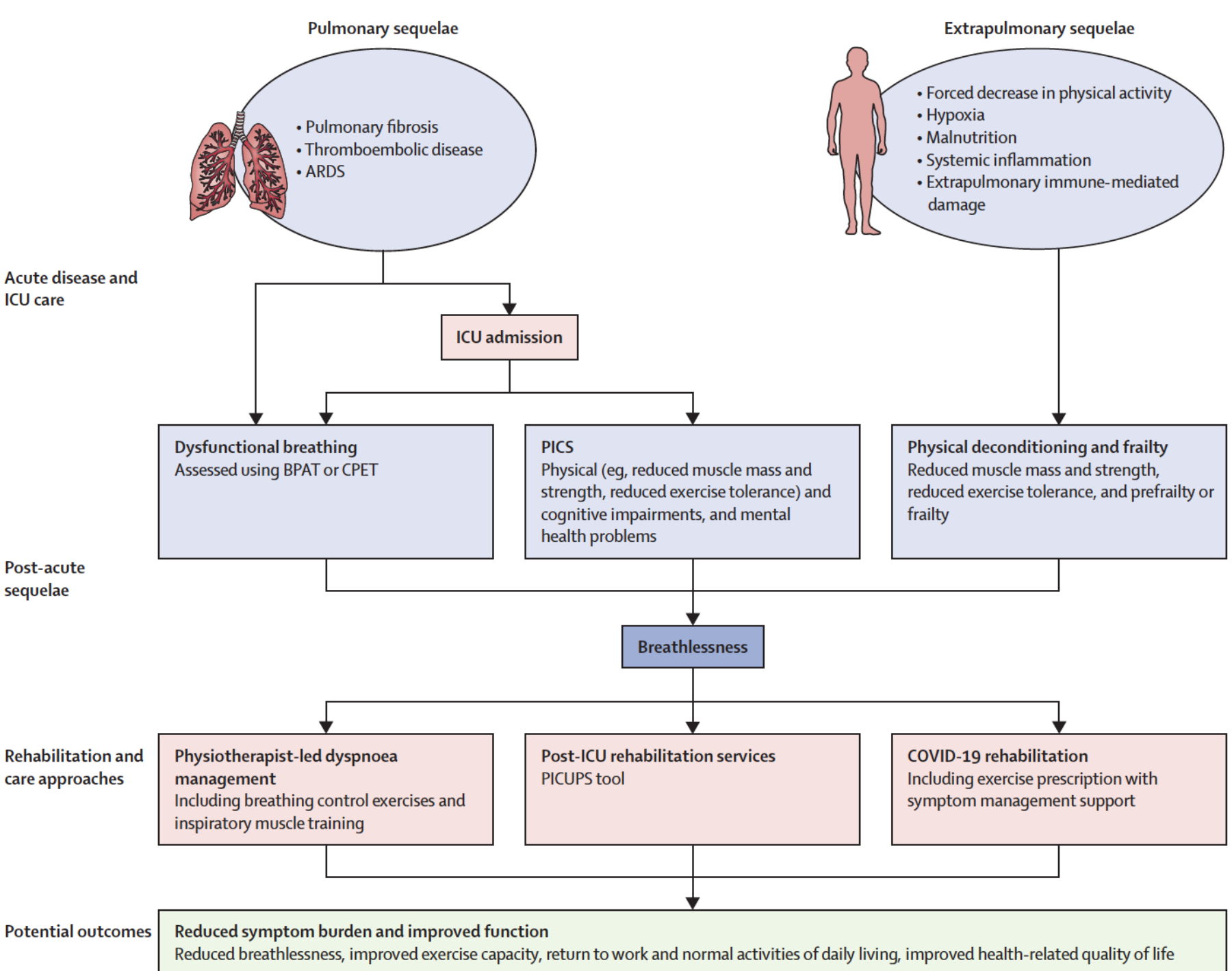
In addition, **at least one** of the following symptoms is also required:

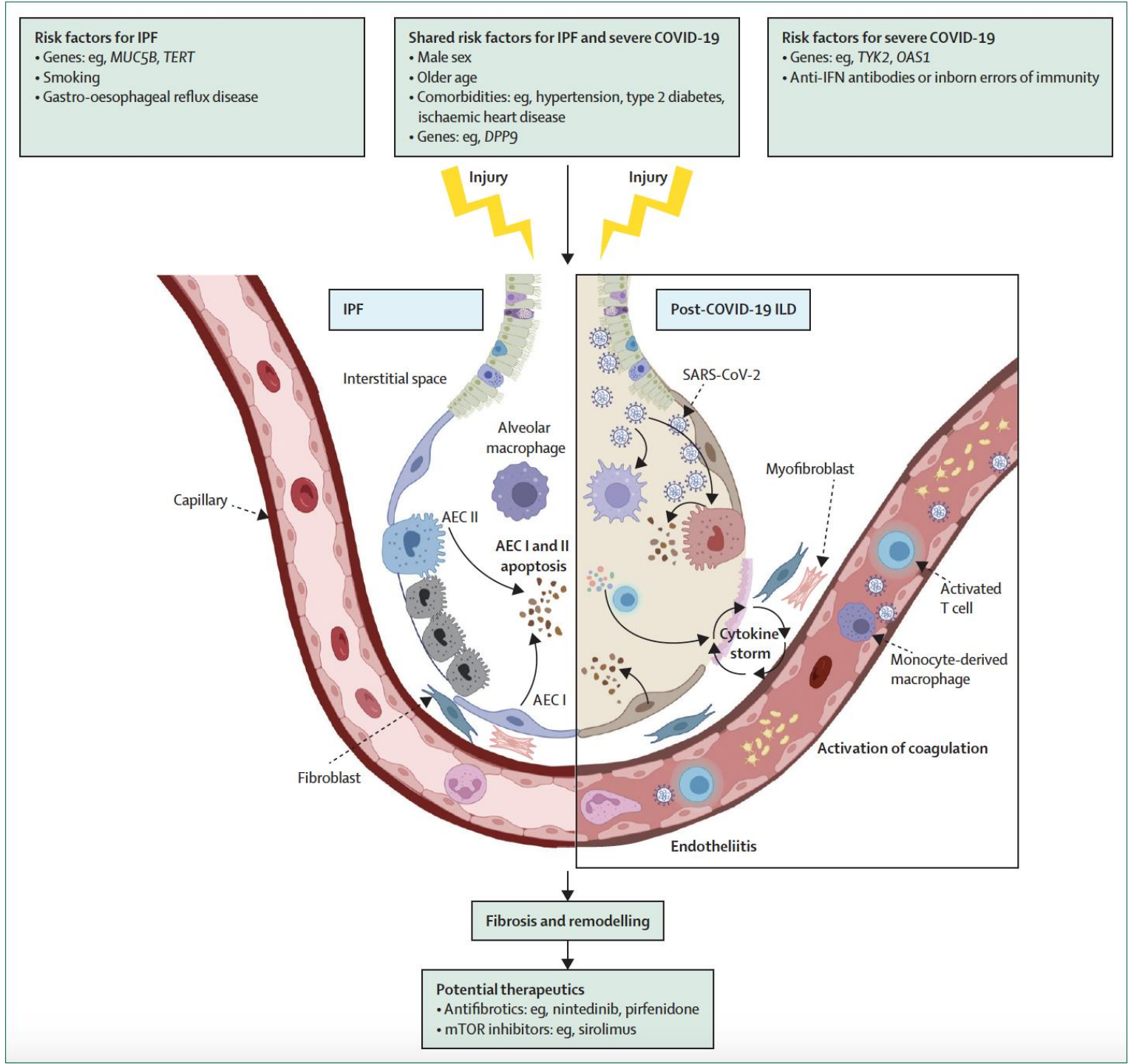
Impaired memory or ability to concentrate. People with ME/CFS may have trouble remembering, learning new things, concentrating, or making decisions.

Orthostatic intolerance (symptoms that occur when standing upright). People with ME/CFS may feel lightheaded or dizzy when standing upright and may even faint.

The list of key symptoms is drawn from an Institute of Medicine (IOM) report by an expert committee of the National Academies of Sciences, Engineering, and Medicine and published in 2015: *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. You may experience some additional symptoms.

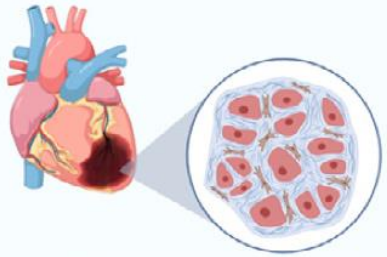
Only a healthcare provider can diagnose ME/CFS. A healthcare provider will ask about how often your symptoms occur and how much they affect you. Sometimes you may need to make more than one visit to a healthcare provider before being diagnosed. While not all healthcare providers are familiar with diagnosing ME/CFS, resources are available to help them make a diagnosis.


Pulmonary sequelae
• Pulmonary fibrosis
• Thromboembolic disease
• ARDS
Extrapulmonary sequelae
• Forced decrease in physical activity
• Hypoxia
• Malnutrition
• Systemic inflammation
• Extrapulmonary immune-mediated damage
Acute disease and ICU care
ICU admission
Post-acute sequelae
Dysfunctional breathing
Assessed using BPAT or CPET
PICS
Physical (eg, reduced muscle mass and strength, reduced exercise tolerance) and cognitive impairments, and mental health problems
Physical deconditioning and frailty
Reduced muscle mass and strength, reduced exercise tolerance, and prefrailty or frailty
Breathlessness
Rehabilitation and care approaches
Physiotherapist-led dyspnoea management
Including breathing control exercises and inspiratory muscle training
Post-ICU rehabilitation services
PICUPS tool
COVID-19 rehabilitation
Including exercise prescription with symptom management support
Potential outcomes
Reduced symptom burden and improved function
Reduced breathlessness, improved exercise capacity, return to work and normal activities of daily living, improved health-related quality of life

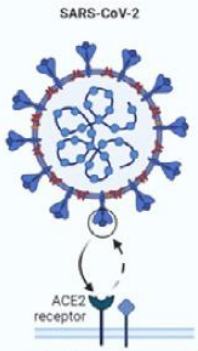

Risk factors for IPF
• Genes: eg, MUC5B, TERT
• Smoking
• Gastro-oesophageal reflux disease
Shared risk factors for IPF and severe COVID-19
• Male sex
• Older age
• Comorbidities: eg, hypertension, type 2 diabetes, ischaemic heart disease
• Genes: eg, DPP9
Risk factors for severe COVID-19
• Genes: eg, TYK2, OAS1
• Anti-IFN antibodies or inborn errors of immunity
Injury
Injury
IPF
Post-COVID-19 ILD
Interstitial space
SARS-CoV-2
Alveolar macrophage
Myofibroblast
Capillary
AEC II
AEC I and II apoptosis
Activated T cell
Cytokine storm
Monocyte-derived macrophage
AEC I
Activation of coagulation
Fibroblast
Endotheliitis
Fibrosis and remodelling
Potential therapeutics
• Antifibrotics: eg, nintedinib, pirfenidone
• mTOR inhibitors: eg, sirolimus

Cardiovascular implications of Long COVID syndrome

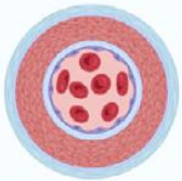
CAUSES OF MYOCARDIAL INJURY



Direct myocardial injury



ACE2 mediated viral infiltration

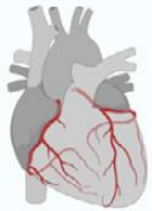


Microvascular thrombosis

Cytokine storm & systemic inflammation

Anti-viral therapies

Acute coronary syndrome



Supply demand mismatch

Screening strategies

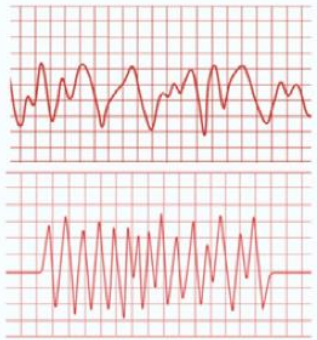
- Cardiac biomarkers (BNP, Troponin)
- Echocardiography
- Cardiac MRI

CARDIAC INJURY —Risk factors→ **PERSISTENT CARDIAC INJURY**

Possible preventive therapies

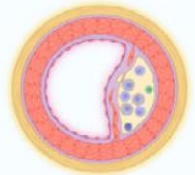
- RAAS inhibition
- Statins
- Anti-platelets
- Anti-coagulants
- Anti-inflammatory agents

LONG-TERM COMPLICATIONS

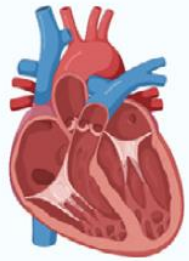


Arrhythmias

Ventricular fibrillation
Ventricular tachycardia
Atrial fibrillation
Atrial tachycardia

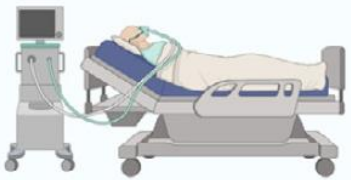


Atherosclerotic cardiovascular disease



Heart failure

Cardiovascular death



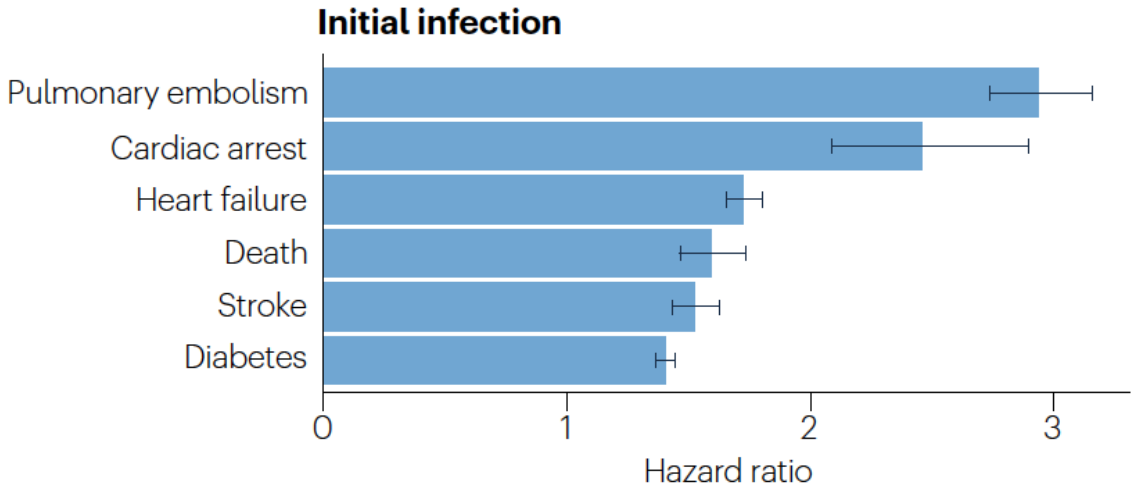
Neurological PCC

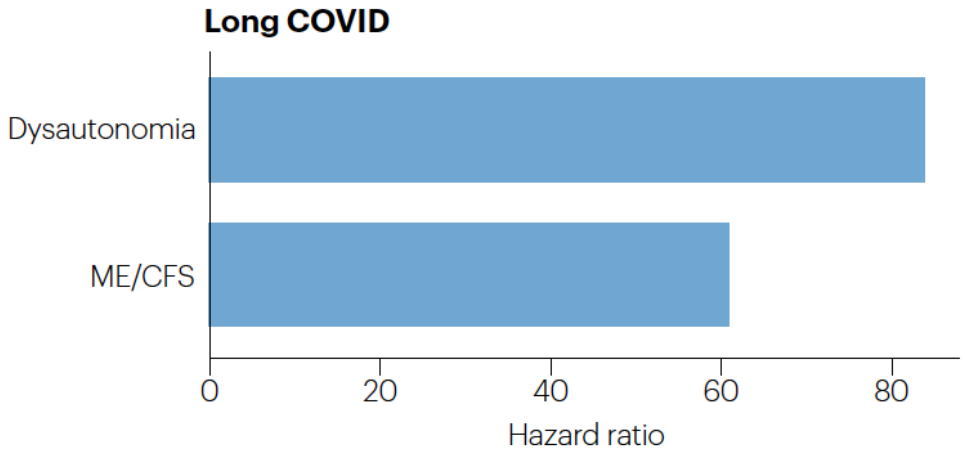
Neurological and cognitive symptoms are a major feature of long COVID, including sensorimotor symptoms, memory loss, cognitive impairment, paresthesia, dizziness and balance issues, sensitivity to light and noise, loss of (or phantom) smell or taste, and autonomic dysfunction, often impacting activities of daily living[7,32]. Audiovestibular manifestations of long COVID include tinnitus, hearing loss and vertigo[7,72].

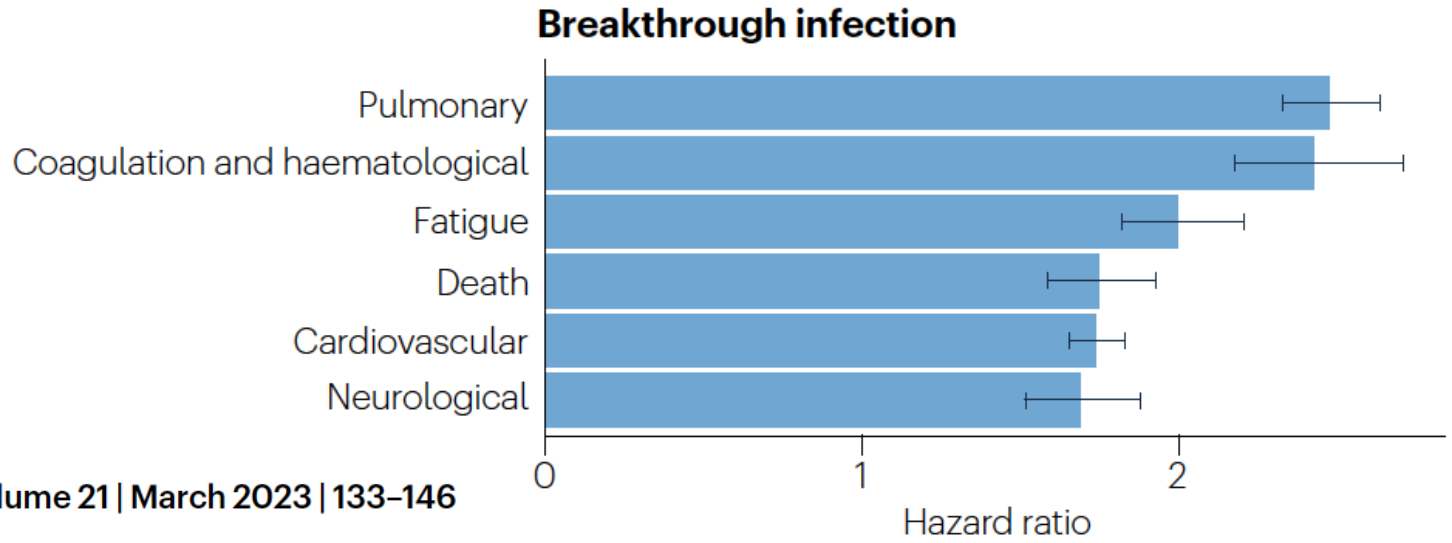
In a meta-analysis, fatigue was found in 32% and cognitive impairment was found in 22% of patients with COVID-19 at 12 weeks after

Possible mechanisms for these neuropathologies include neuroinflammation, damage to blood vessels by coagulopathy and endothelial dysfunction, and injury to neurons[32]. Studies have found Alzheimer

New clinical conditions after SARS COV-2







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Risks and burdens of incident diabetes in long COVID: a cohort study

Yan Xie, Ziyad Al-Aly

Methods In this cohort study, we used the national databases of the US Department of Veterans Affairs to build a cohort of 181 280 participants who had a positive COVID-19 test between March 1, 2020, and Sept 30, 2021, and survived the first 30 days of COVID-19; a contemporary control (n=4 118 441) that enrolled participants between March 1, 2020, and Sept 30, 2021; and a historical control (n=4 286 911) that enrolled participants between March 1, 2018, and Sept 30, 2019. Both control groups had no evidence of SARS-CoV-2 infection. Participants in all three comparison groups were free of diabetes before cohort entry and were followed up for a median of 352 days (IQR 245–406). We used inverse probability weighted survival analyses, including predefined and algorithmically selected high dimensional variables, to estimate post-acute COVID-19 risks of incident diabetes, antihyperglycaemic use, and a composite of the two outcomes. We reported two measures of risk: hazard ratio (HR) and burden per 1000 people at 12 months.

Lancet Diabetes Endocrinol
2022; 10: 311–21

Risks and burdens of incident diabetes in long COVID: a cohort study

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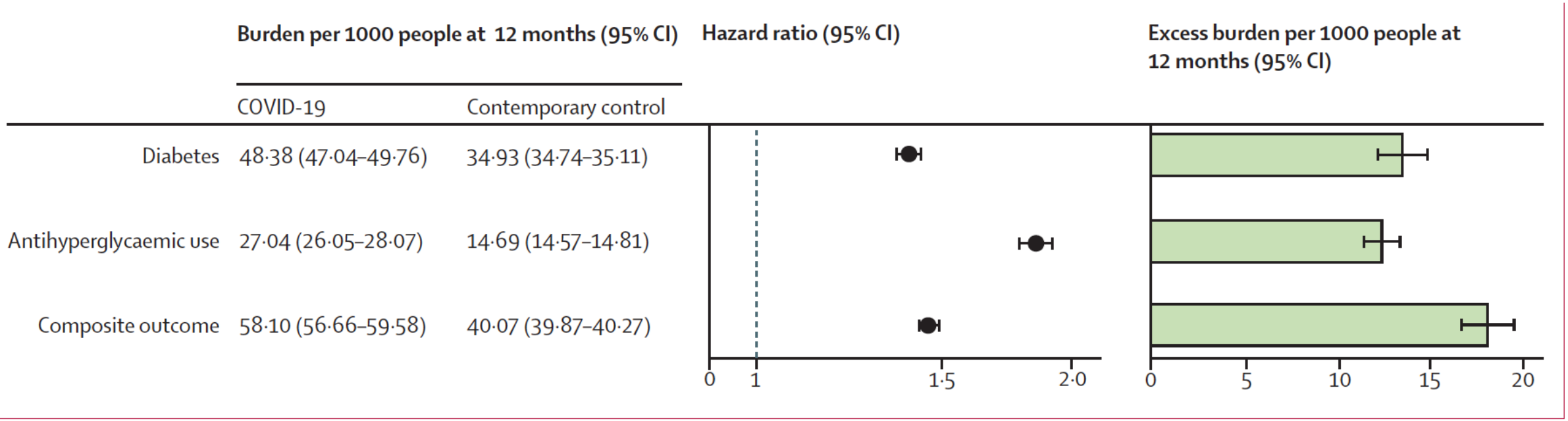
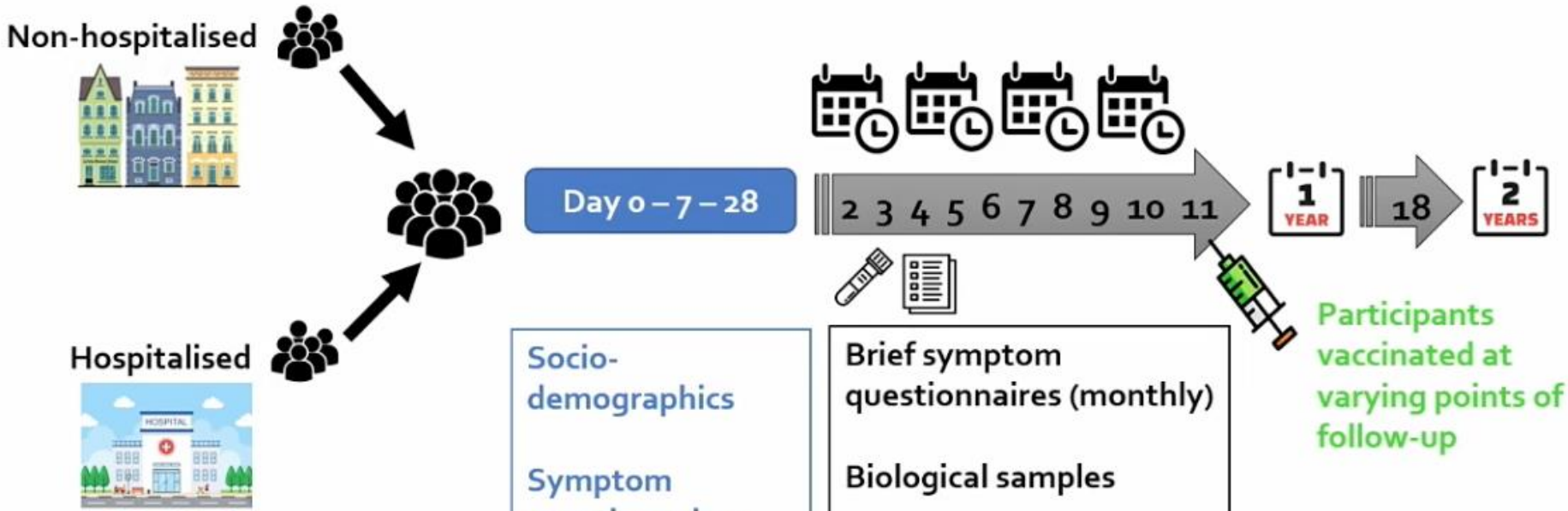


Lancet Diabetes Endocrinol
2022; 10: 311–21

Higher incidence of diabetes post COVID-19?

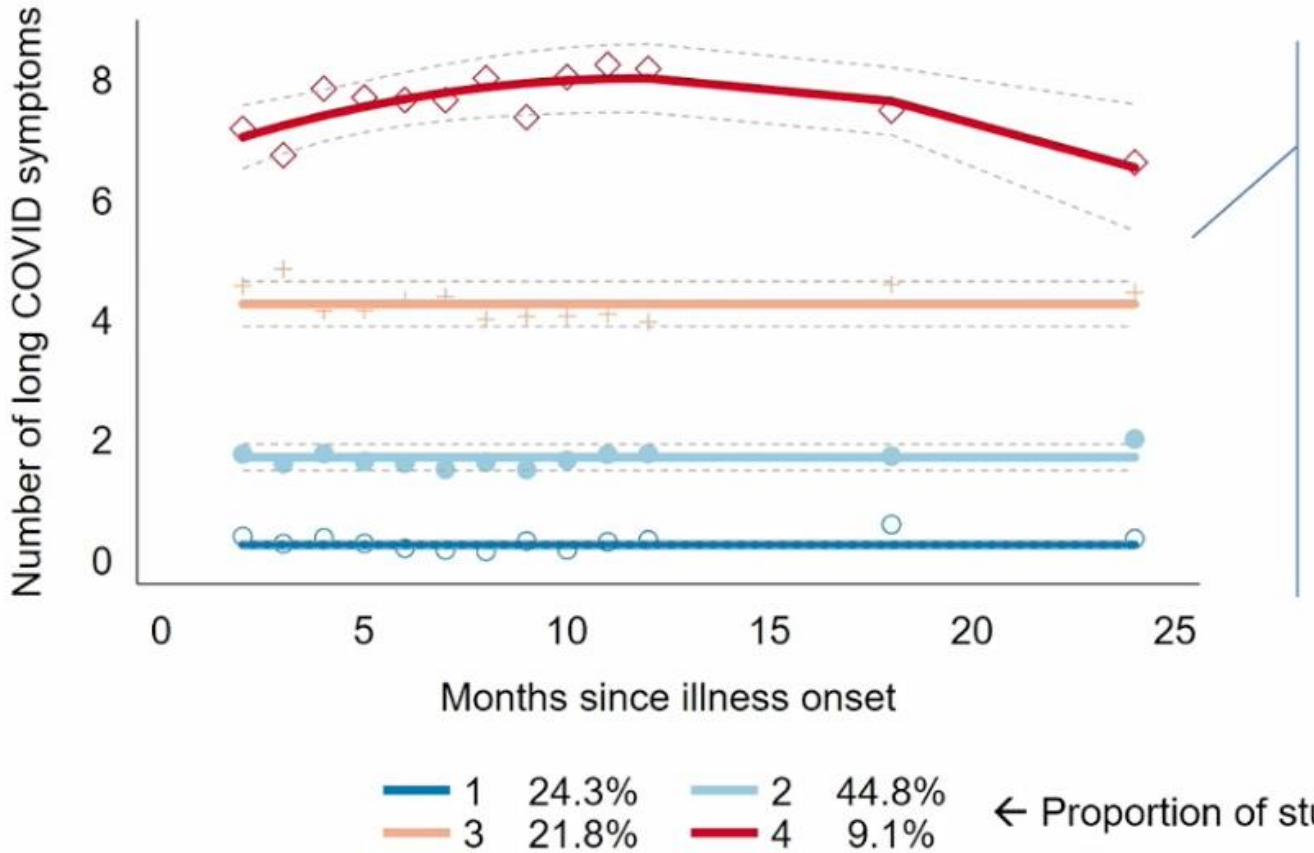
COVID-19. In one study evaluating 734 patients with severe disease 28 days after recovery, an increase in insulin dependency from 18% to 63% was noted, and 1.4% of new-onset diabetes cases were identified [35]. Two additional studies found an increase in new-onset diabetes in the months after recovery from COVID-19 [36,37] This might be a result of surveillance bias in previously unknown diabetics or a real shift from prediabetes to diabetes caused by the acute disease or its treatment, although there is no evidence for the latter.

Data collection throughout the RECoVERED cohort study



B-IPQ Sub-domains: consequences, expected duration, personal control, expected treatment effect, symptom perception and understanding of the condition

Results: Group-based trajectories of mean total number of long COVID symptoms



1 in 10 participants: 6+ symptoms over two year period

1 in 4 participants: no symptoms

Majority have 2-4 symptoms

Little fluctuation over time

33rd ECCMID

Group-based trajectories based on mean total number of long COVID symptoms reported at 2-24 months after illness onset, adjusted for age (years), sex, BMI category and timing of infection (first wave versus subsequent waves)

Risk factors of PCC

to address. Risk factors potentially include female sex, type 2 diabetes, EBV reactivation, the presence of specific autoantibodies[27], connective tissue disorders[33], attention deficit hyperactivity disorder, chronic urticaria and allergic rhinitis[34], although a third of people with long COVID have no identified pre-existing conditions[6]. A higher prevalence of long Covid has been reported in certain ethnicities, including people with Hispanic or Latino heritage[35]. Socio-economic risk factors include lower income and an inability to adequately rest in the early weeks after developing COVID-19 (refs. [36,37]). Before the emergence of SARS-CoV-2,

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Results – Multivariable analysis of risk and preventive factors associated with at least one symptom (WHO definition)

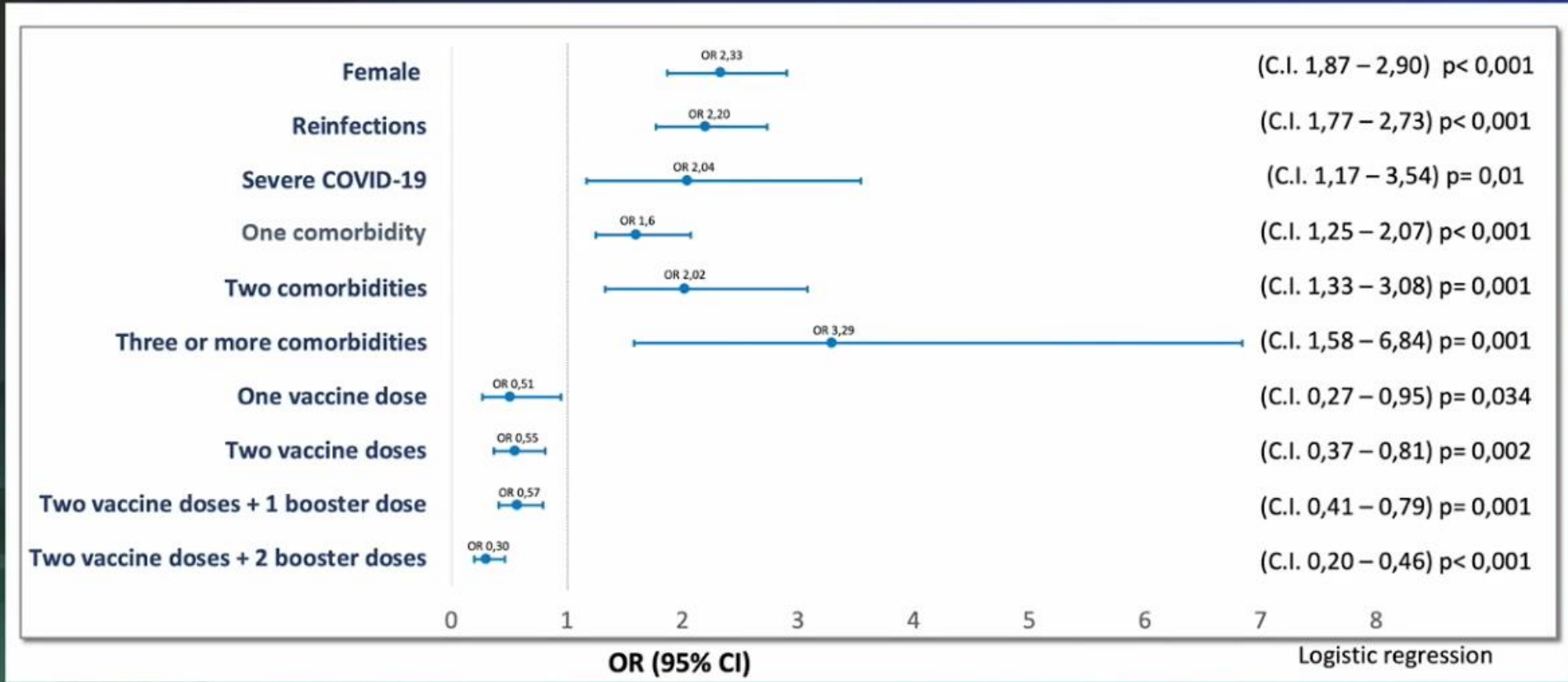
	At least 1 symptom according to WHO definition of post- COVID-19 syndrome			
	OR	95%CI		p-value
		LB	UB	
Female sex	1·811	1·337	2·461	<0·001
Age	1·007	0·996	1·019	0·197
Neurological symptoms[1]	2·163	1·559	3·009	<0·001
Hospital admission[1]	0·616	0·373	1·015	0·058
Monoclonal antibody therapy[1a]	0·191	0·105	0·333	<0·001
Oxygen therapy[1]	1·536	0·961	2·459	0·073

OR: odd ratio; CI: confident interval; LB: lower bound; UB: upper bound; WHO: World Health Organization.[1]during the acute infection; [a]monoclonal antibodies administered during the study period: bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab.

33rd ECCMID

PREDICTORS of long-covid

Multicenter Cohort of individuals from São Paulo and Rio de Janeiro, 2020-2022 (n= 1907)



Reduced probability of long COVID during Omicron

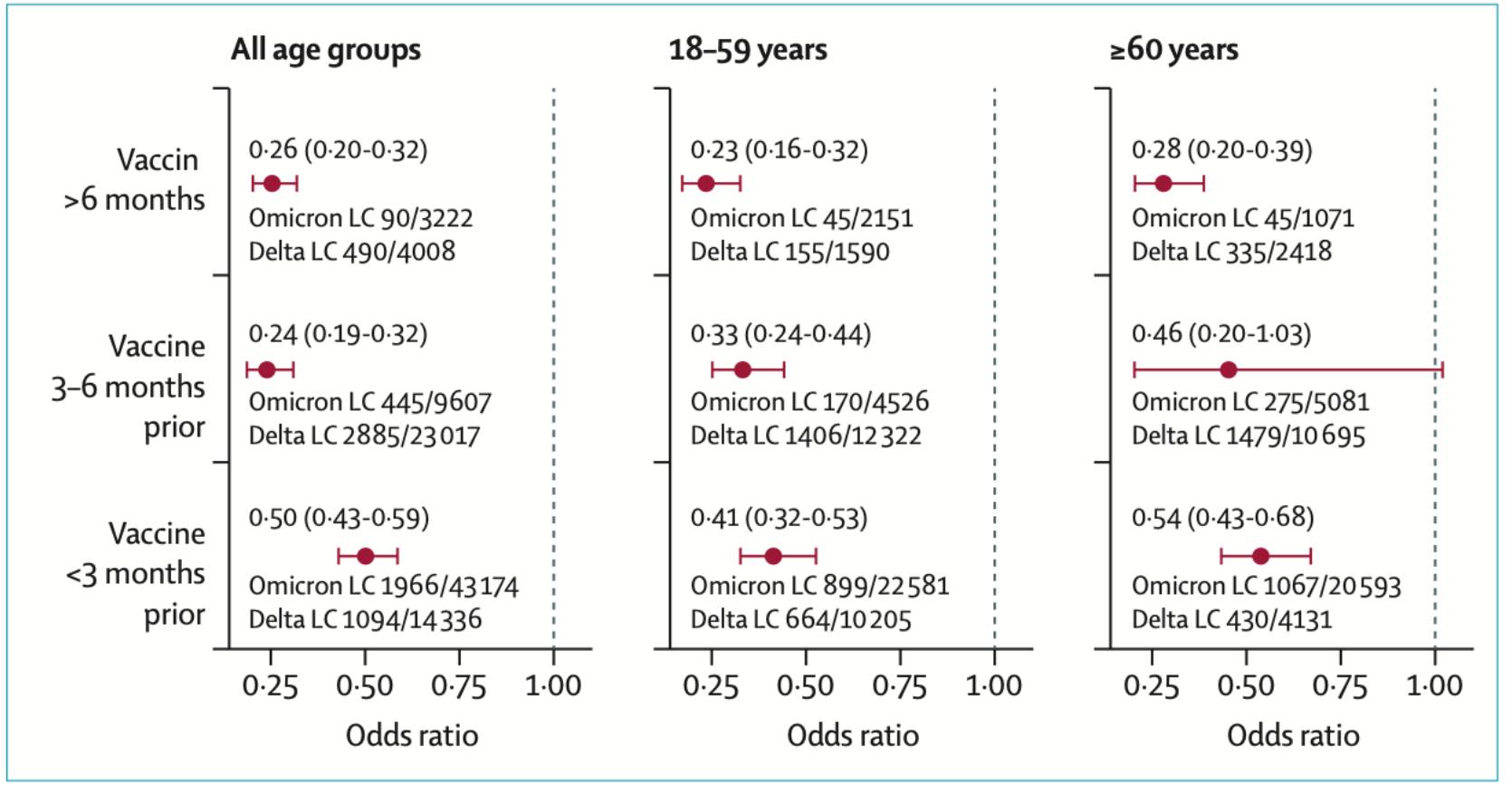


***Figure*: Odds ratio of long COVID (LC) adjusted by age, sex, body-mass index, Index of Multiple Deprivation, presence of comorbidities, and vaccination status**

Antonelli M et al .Lancet. 2022 Jun 18;399(10343):2263-2264;

Vaccination and PCC

Table 3. PASC Frequencies, Overall and Stratified by Subcohort, Infection, Vaccination, and Reinfection

	Total No.	PASC positive, No. (%)
PASC frequencies stratified by study cohort, prevalent SARS-CoV-2 strain, and vaccination (infected participants only)[b]		
Acute Omicron		
Vaccinated	2016	195 (9.7)
Not vaccinated	86	15 (17)
Postacute pre-Omicron		
Vaccinated	491	154 (31)
Not vaccinated	2967	1090 (37)
Postacute Omicron		
Vaccinated	2208	356 (16)
Not vaccinated	232	50 (22)

JAMA. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823
Published online May 25, 2023.

Study	Odds ratio	Lower limit	Upper limit	p-Value
Antonelli 2021	0.510	0.319	0.816	0.005
Arjun 2022	2.320	1.173	4.590	0.016
Ayoubkhani 2022	0.589	0.502	0.692	0.000
Herman 2022	0.310	0.102	0.942	0.039
Senjam 2021	0.550	0.363	0.834	0.005
Simon 2021	0.220	0.197	0.246	0.000
	0.539	0.295	0.987	0.045

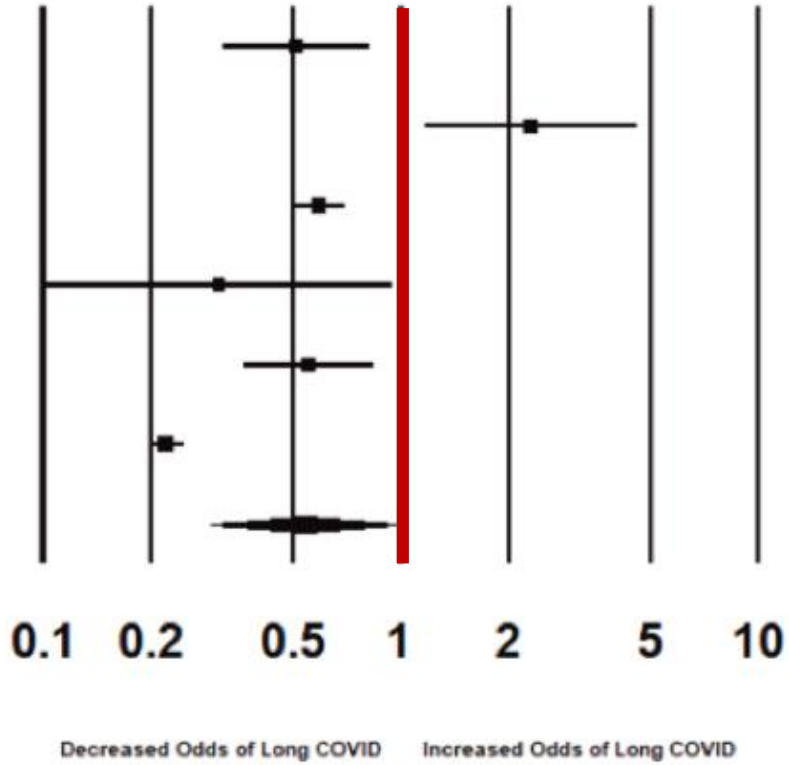
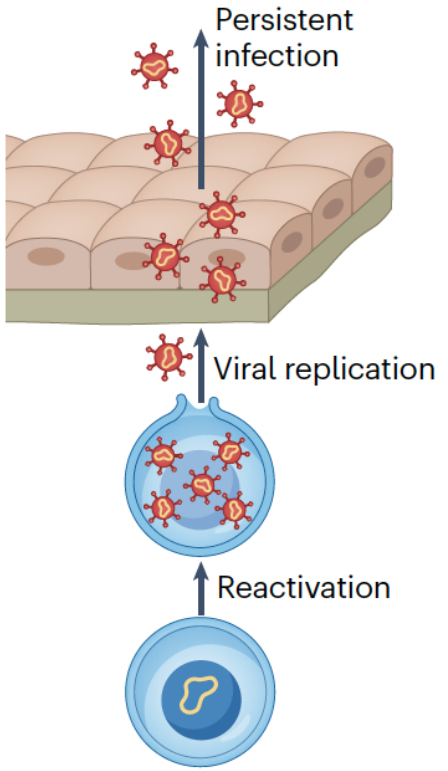


Fig. 2a. Pooled odds ratio for developing long COVID in individuals receiving at least one COVID-19 vaccine dose compared to those who did not receive a COVID-19 vaccine (i.e., 'prevention meta-analysis').

Brain, Behavior, and Immunity 111 (2023) 211–229

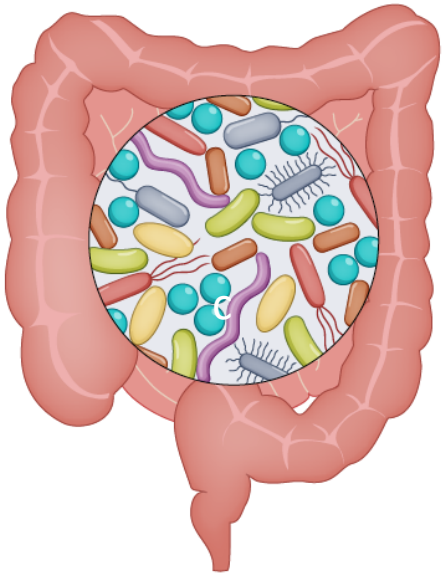
Possible causes of PCC

Immune dysregulation



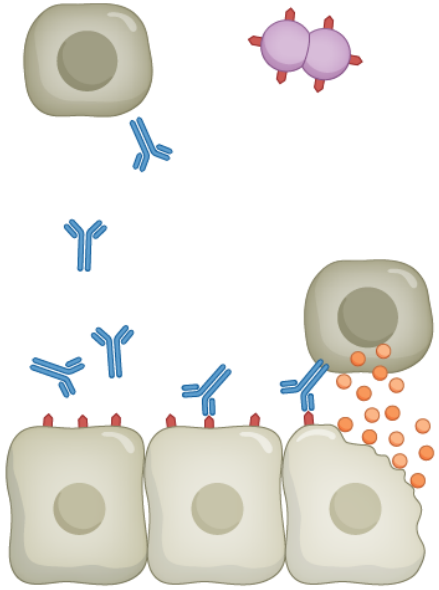
Immune dysregulation, with or without reactivation of underlying pathogens, including herpesviruses such as EBV and HHV-6

Microbiota dysbiosis



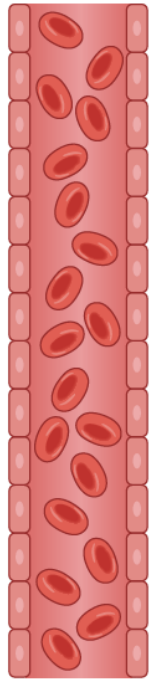
Impacts of SARS-CoV-2 on the microbiota and virome (including SARS-CoV-2 persistence)

Autoimmunity and immune priming



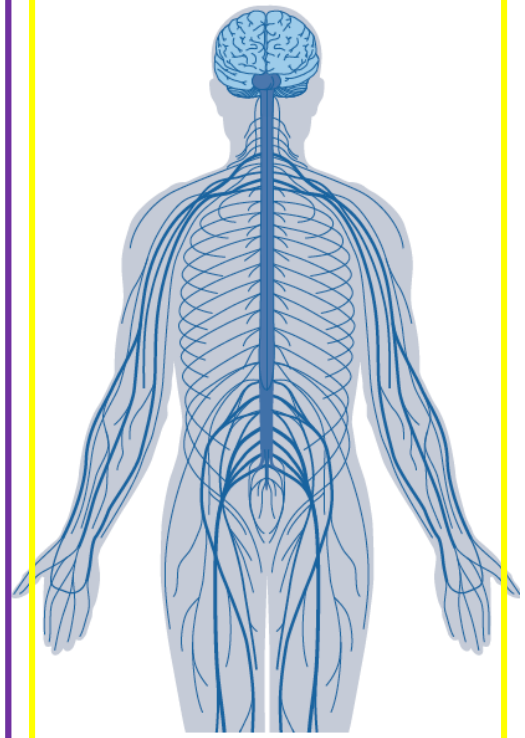
Autoimmunity and primed immune cells from molecular mimicry

Blood clotting and endothelial abnormalities



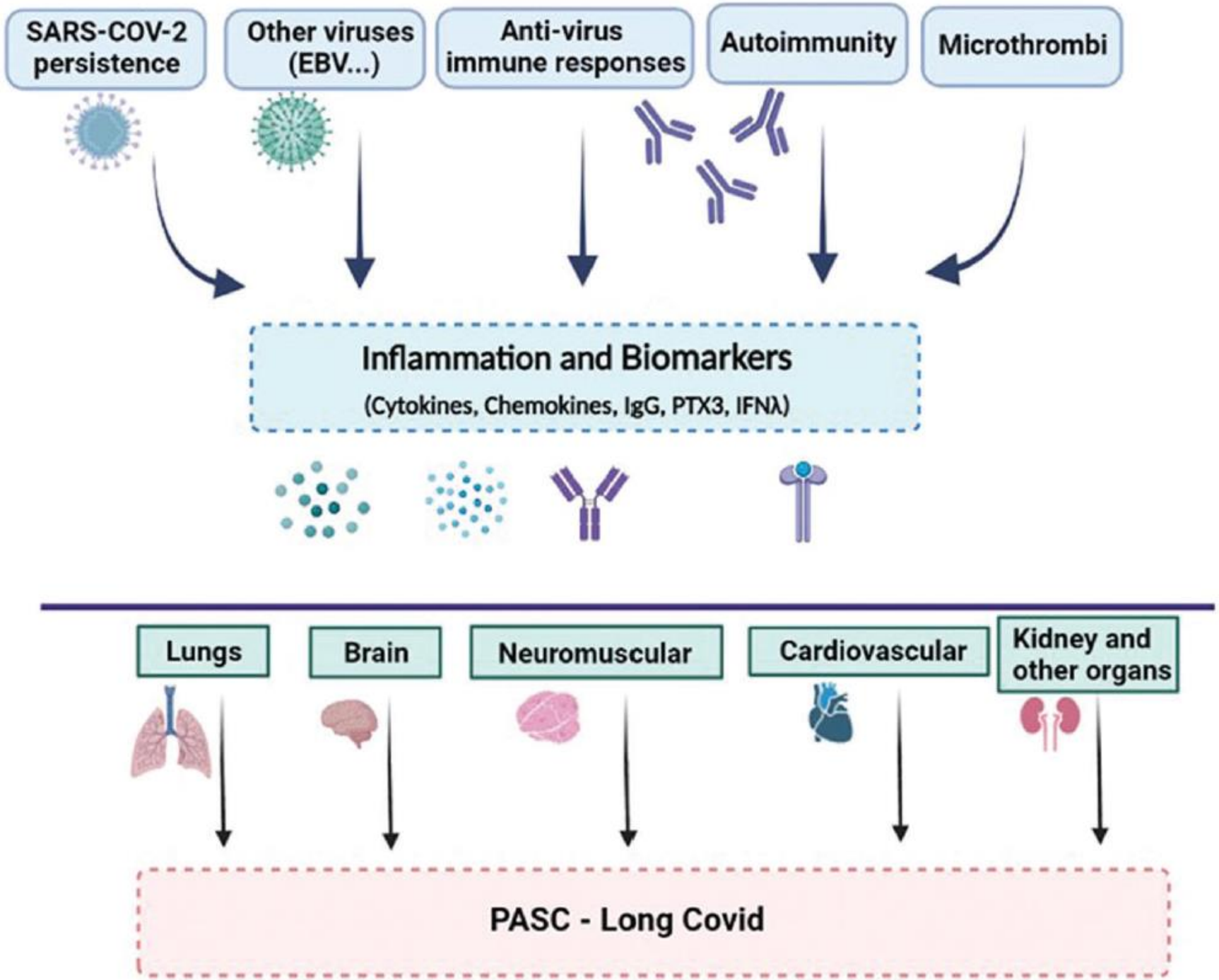
Microvascular blood clotting with endothelial dysfunction

Dysfunctional neurological signalling



Dysfunctional signalling in the brainstem and/or vagus nerve

Nature Reviews Microbiology | Volume 21 | March 2023 | 133–146


SARS-COV-2 persistence
Other viruses (EBV...)
Anti-virus immune responses
Autoimmunity
Microthrombi
Inflammation and Biomarkers
(Cytokines, Chemokines, IgG, PTX3, IFNλ)
Lungs
Brain
Neuromuscular
Cardiovascular
Kidney and other organs
PASC - Long Covid

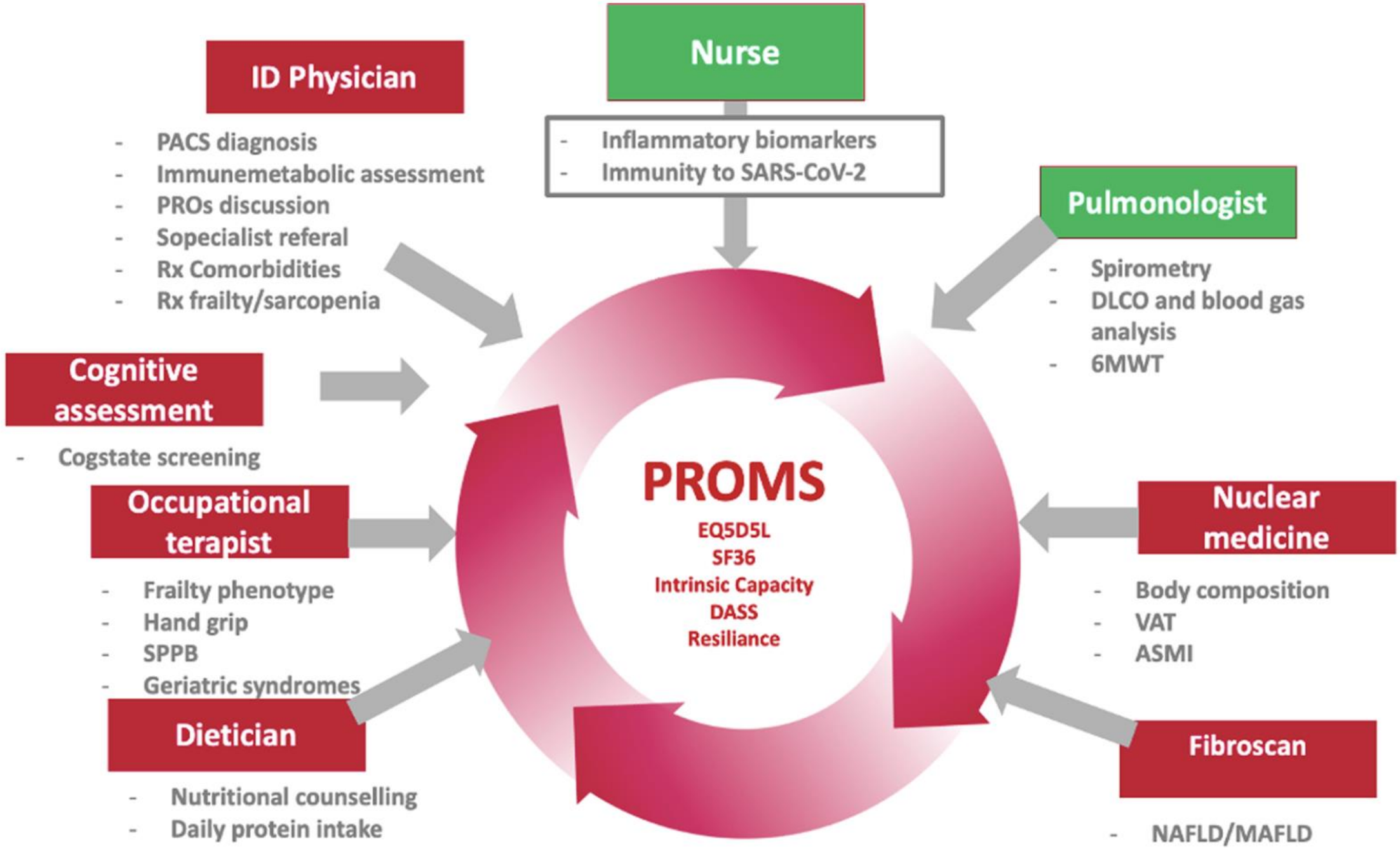

ID Physician
- PACS diagnosis
- Immunemetabolic assessment
- PROs discussion
- Sopecialist referal
- Rx Comorbidities
- Rx frailty/sarcopenia
Nurse
- Inflammatory biomarkers
- Immunity to SARS-CoV-2
Pulmonologist
- Spirometry
- DLCO and blood gas analysis
- 6MWT
Cognitive assessment
- Cogstate screening
Occupational terapist
- Frailty phenotype
- Hand grip
- SPPB
- Geriatric syndromes
PROMS
EQ5D5L
SF36
Intrinsic Capacity
DASS
Resiliance
Nuclear medicine
- Body composition
- VAT
- ASMI
Dietician
- Nutritional counselling
- Daily protein intake
Fibroscan
- NAFLD/MAFLD

TABLE 1 Published trials on long COVID interventions

Reference/ country	Study design	Population characteristics				Intervention	Comparator	Outcomes
		Sample size (*N*)	Long COVID diagnosis	Acute COVID diagnosis via PCR or antigen testing	Comorbidities			
Charfeddine et al.[25] Tunisia	Quasi-experimental No blinding	290	Diagnosis based on NICE guidelines + endothelial dysfunction	Yes	37% had hypertension; 28% had diabetes mellitus	Sulodexide	None	On Day 21, there was significantly reduced chest pain and endothelial dysfunction in the sulodexide group
Jadhav and Jariwala[26] (Abstract) India	Open label	24	Persistent palpitations 7 days postdischarge	Yes	No known comorbidities	Ivabradine	Carvedilol	Ivabradine more effective in treating palpitations
Dhooria et al.[27] India	Randomized Open label	130	Persistent dyspnea or resting hypoxemia or exertional desaturation; and diffuse lung parenchymal changes 3–7 weeks after acute COVID	Yes	73% had at least one comorbidity (not specified)	High dose prednisolone (starting dose: 40 mg/day)	Low dose prednisolone (starting dose: 10 mg/day)	No differences between high versus low dose prednisolone
Stadio et al.[28] Italy	Randomized Double-blind	158	Persistent olfactory dysfunction 6 months post-COVID	Yes	Excluded subjects with pre-existing olfactory disorders	PEA-LUT + olfactory training	Olfactory training only	PEA-LUT group showed greater improvement in olfactory function
Sabico et al.[29] Saudi Arabia	Randomized Open label	36	Cough and gustatory loss 30 days after acute COVID	Yes	55% of participants had hypertension; 51% had diabetes mellitus	High dose vitamin D3	Low dose vitamin D3	Shorter time to recovery for cough and ageusia among individuals who received high dose vitamin D
Rathi et al.[30] India	Randomized Double-blind	200	Persistent fatigue 4–87 days after acute COVID	Yes	No comorbidities	Systemic and probiotic enzymes	Placebo	Greater improvement in fatigue in the intervention group

JAMA Internal Medicine | Original Investigation

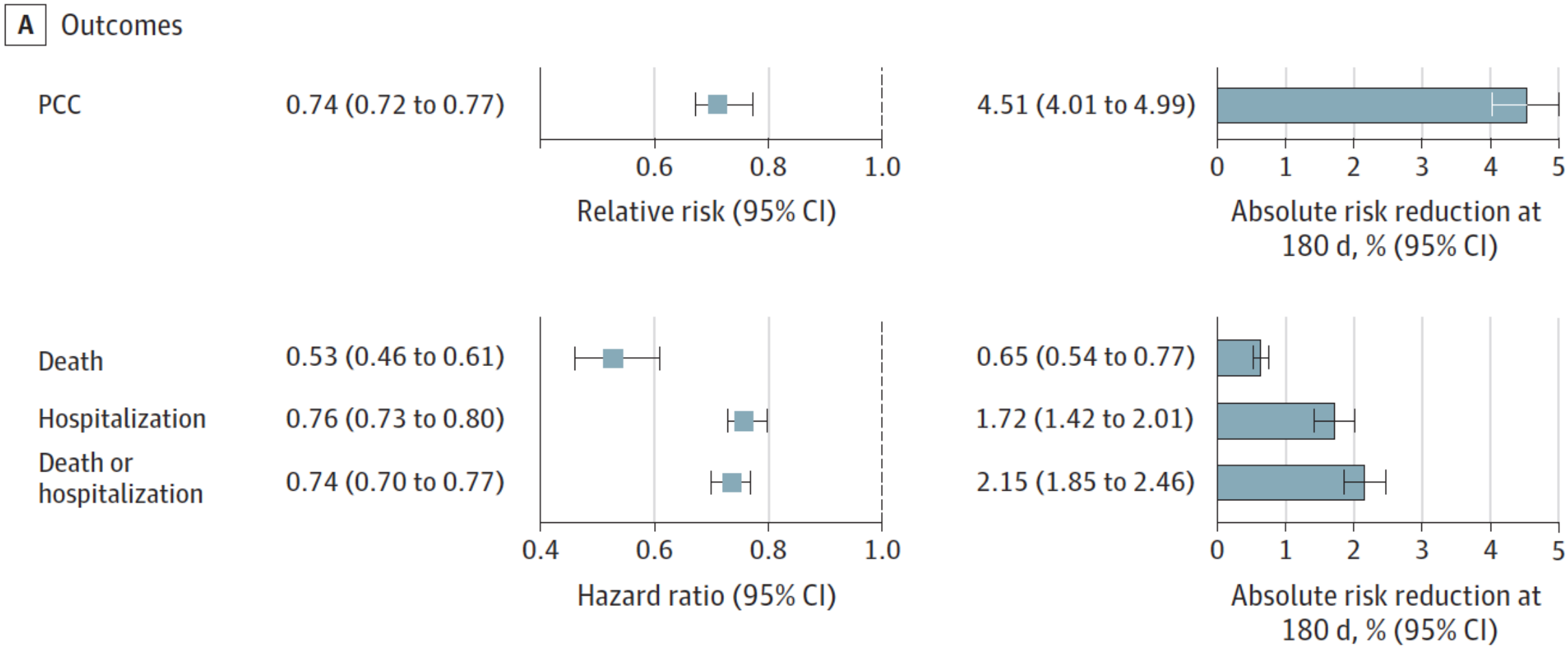
Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition

This cohort study used the health care databases of the US Department of Veterans Affairs (VA) to identify patients who had a SARS-CoV-2 positive test result between January 3, 2022, and December 31, 2022, who were not hospitalized on the day of the positive test result, who had at least 1 risk factor for progression to severe COVID-19 illness, and who had survived the first 30 days after SARS-CoV-2 diagnosis. Those who were treated with oral nirmatrelvir within 5 days after the positive test (n = 35 717) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection (control group, n = 246 076) were identified.

Exposures

Treatment with nirmatrelvir or receipt of no COVID-19 antiviral or antibody treatment based on prescription records.

Figure 1. Relative and Absolute Risk Reduction of Nirmatrelvir Compared With the No-Treatment Control Group



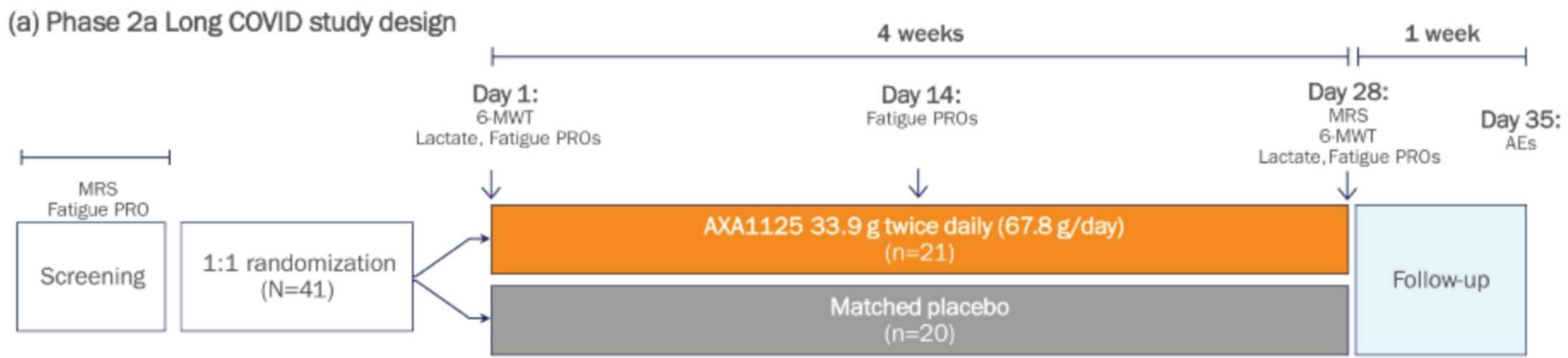
O1122

AXA1125, an endogenous metabolic modulator composition, improves long COVID fatigue, vascular biology and mitochondrial energetics: findings from a Phase 2a placebo-controlled clinical trial

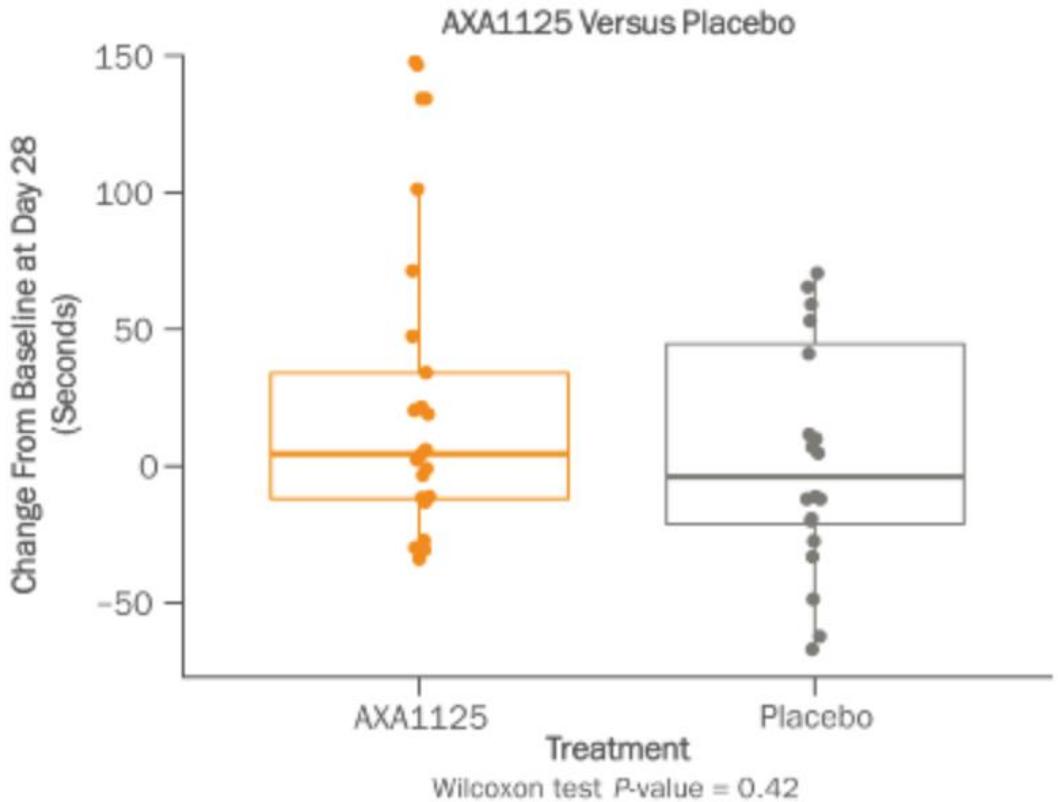
12. COVID-19

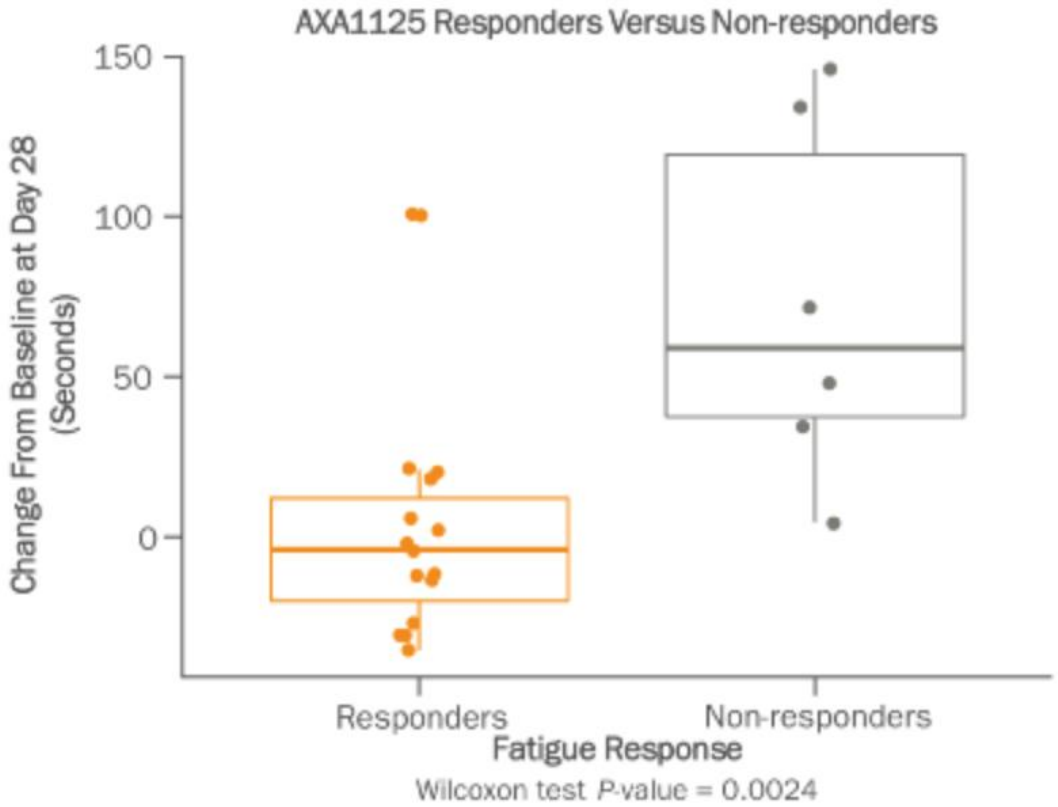
12e. Drug development and treatment modalities (incl. in vitro, animal, clinical trials, resistance)

K. Azer [1], K. Lavery [1], I. Leaf [1], J. Pradines [1], H. Wang [1], M. Koziel [1], H. Montgomery [2], A. Murray [3], L. Finnigan [4], L. Valkovič [4], M.P. Cassar [4], S. Neubauer [5], B. Raman [5].

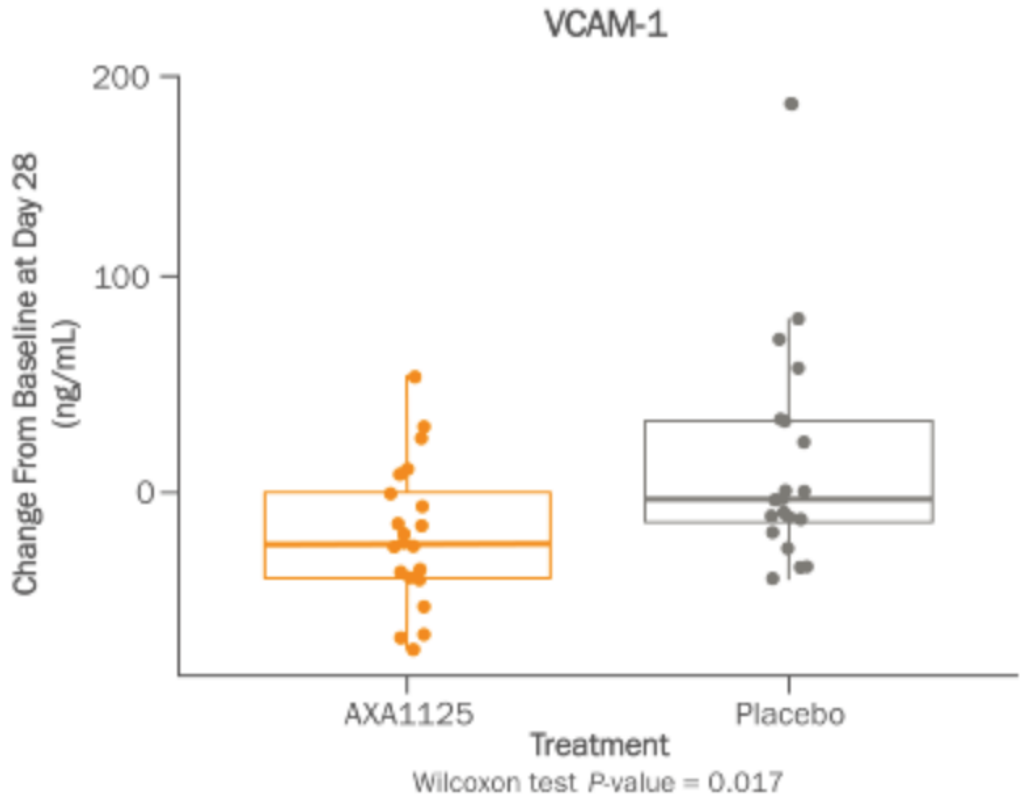


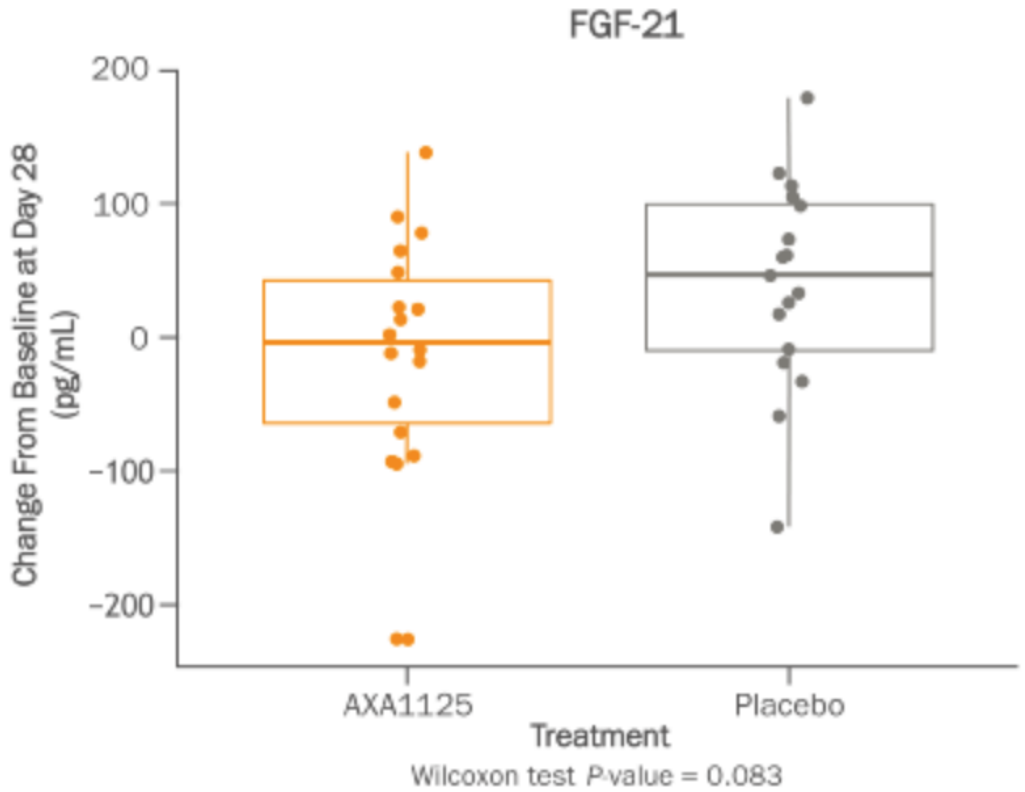
(b) Individual changes in phosphocreatine recovery time constant





(c) Individual changes in plasma biomarker levels





frontiers | Frontiers in Immunology

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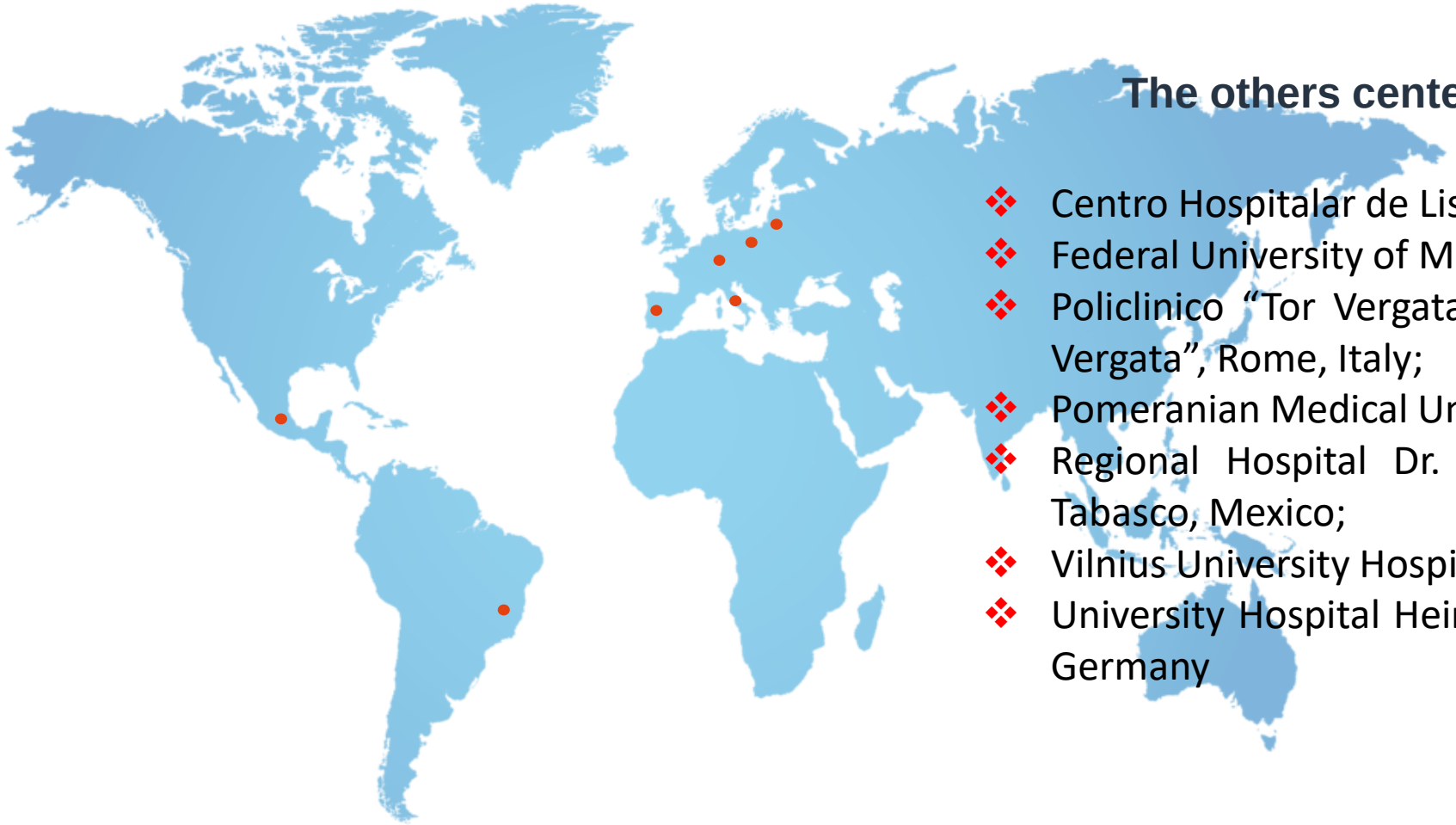
Long-term high-dose immunoglobulin successfully treats Long COVID patients with pulmonary, neurologic, and cardiologic symptoms

John S. Thompson[1]*, Alice C. Thornton[2], Timothy Ainger[3] and Beth A. Garvy[4]

Patient	Age	Sex	Pre-existing conditions	Acute Covid onset date	Symptoms	Immune perturbations	Ig q/2 wks.	Onset to Ig (days)!
# 1	63	male		03/25/2020	encephalitis fatigue digital tingling	high IgG high IgG1 low IgM	0.5g/kg	298
# 2	50	female	hypertension hyperlipidemia	03/04/2020	brain fog* chest pain fatigue dyspnea	low IgG2 low IgG3	0.5g/kg.	547
# 3	38	female	sinusitis	03/11/2020	brain fog* dyspnea nausea/ vomiting tingling left side	low IgG2 low IgG3	0.4g/kg	452
# 4	73	male	Hypertension sinusitis	01/02/2021	brain fog* chest pain dyspnea fatigue	low IgM low CD8 HLA-DR on T cell 15%	0.5g/kg.	258
# 5	34	female	asthma	01/02/2022	brain fog* tingling hands numbness feet	low IgG2 low IgG3	0.5g/kg**	101
# 6	39	male	Wegener's sinusitis	11/08/2021	dyspnea severe hypoxia pneumonia x3 fatigue	low IgG, M and A very low CD4, CD8 and CD19. HLA-DR on T cells CD4 14%, CD8 36%	0.5g/kg.	140

EuCARE-PASC Study: *Centers and study design*

The **coordinator center** is the **Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo and Carlo**, Department of Health Sciences, University of Milan



The others centers that will partecipate are:

- Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal;
- Federal University of Minas Gerais, Minas Gerais, Brasil;
- Policlinico "Tor Vergata", Università degli Studi di Roma "Tor Vergata", Rome, Italy;
- Pomeranian Medical University, Szczecin, Poland;
- Regional Hospital Dr. Juan Graham Casasús, Villahermosa, Tabasco, Mexico;
- Vilnius University Hospital, Santaros Klinikos, Vilnius, Lithuania;
- University Hospital Heinrich Heine of Dusserldorf, Dusserldorf, Germany

Aims

The primary aim was to investigate the prevalence of post COVID-19 condition:

- According to WHO definition (October 2021)
- Clusters of symptoms

The secondary aim was to explore predictors of post COVID-19 condition (*age, gender, comorbidities, **viral variant**, disease severity*)

Materials and methods: study population

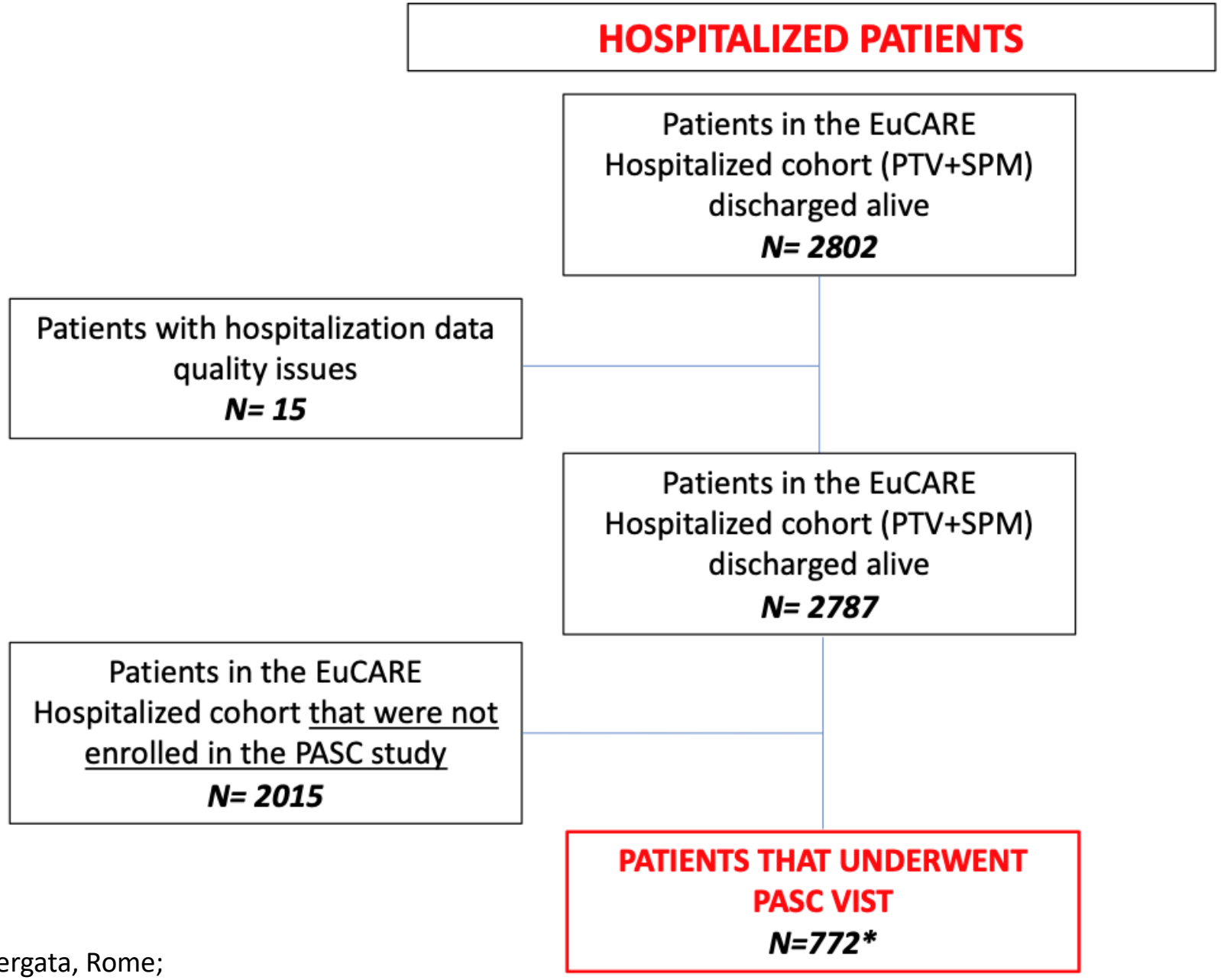
- Patients with confirmed diagnosis of SARS-CoV-2 infection hospitalized at San Paolo Hospital (Milan, Italy) and at Policlinico Tor Vergata (Rome, Italy), from 24 February 2020 to 07 January 2022 and discharged alive (*Hospitalized cohort*).

- A proportion of these patients underwent a post COVID-19 visit at the post COVID outpatient clinic of each center (*Post COVID cohort*); post COVID-19 evaluations at 2-3, 6-9 and 12-15 months after the acute phase, patients with ≥1 visit have been included.

Statistical analyses: Inverse Probability Weighting

- ***Inverse Probability Weighting*** (IPW) was used to create a pseudo-sample where individuals are weighted according to the inverse of the probability of being sampled for the Post COVID visit.

- The association between age, gender, comorbidities, disease severity and viral variants with post COVID-19 condition has been evaluated using ***weighted logistic regression models***.



772 (27.5%) underwent at least one post COVID visit;

84.6% patients had a post COVID visit at 2-3 months visit

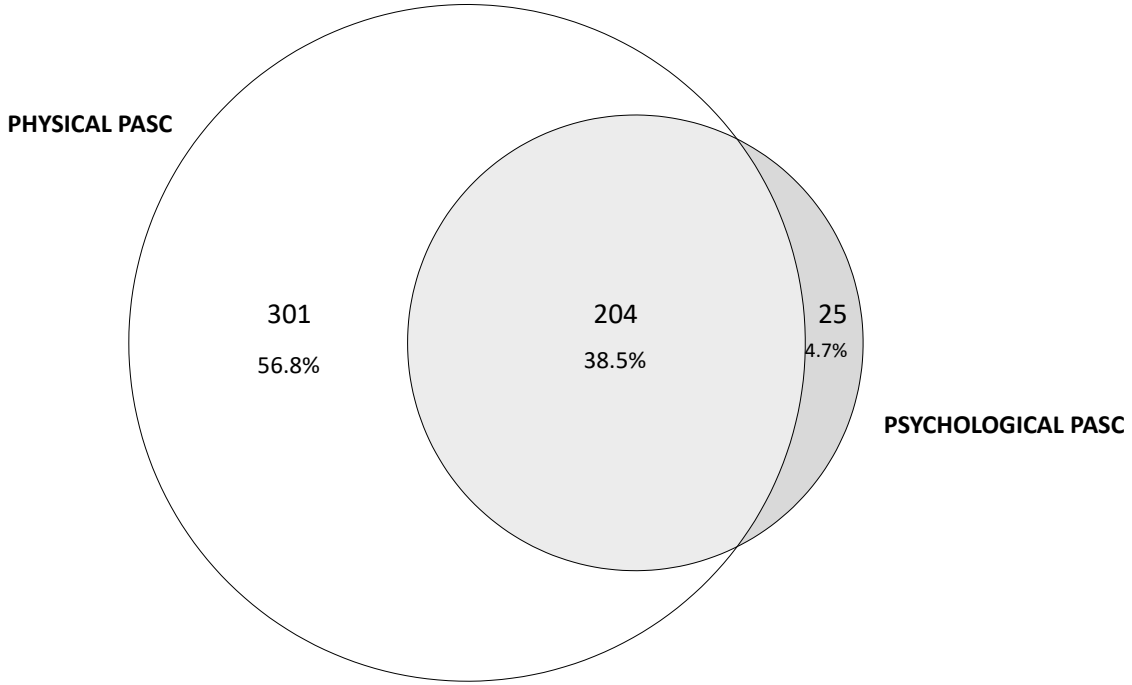
13.6% at 6-9 months

1.8% at 12-15 months

PTV, Policlinico Tor Vergata, Rome;
SPM, San Paolo Hospital, Milan

Prevalence of Post COVID condition

PASC definitions	N of patients: N 772	% of PASC
WHO PASC	**530**	**68.7%**
Physical PASC	505	65.4%
Psychological PASC	229	29.7%



Phenotypes of Post COVID-19 condition

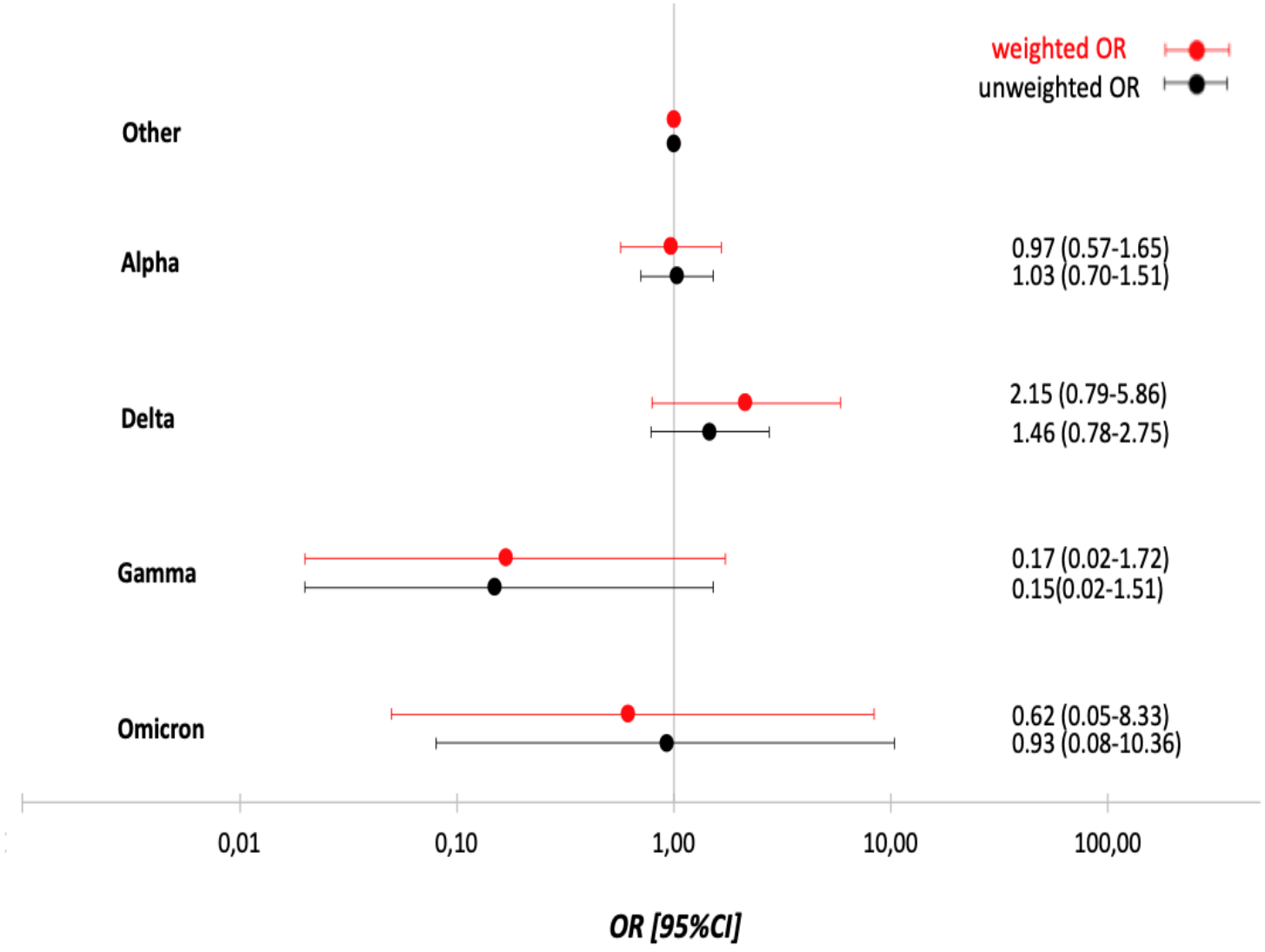
EUCARE

PASC Clusters Definitions	Number of patients N=772	% of PASC study cohort
Brain fog	243	31.5%
Fatigue	318	41.2%
Respiratory symptoms	231	30.0%
Cardiovascular symptoms	26	3.4%
Peripheral Nervous System symptoms (PNS)	23	3.0%
Hormonal Disorders	0	0%
Musculoskeletal symptoms	196	25.4%
Dermatological symptoms	9	1.2%
Gastrointestinal symptoms	27	3.5%
ENT symptoms	75	9.7%
Orthostatic Intolerance	28	3.6%
Myalgic Encephalomyelitis	446	57.8%
Other	7	0.9%

Variables	PASC (N=530)	No PASC (N=242)	p-values
Age, years, median (IQR)	59 (51-69)	57 (49-69)	0.199
Female gender, n (%)	232 (43.8%)	59 (24.4%)	<0.0001
Italian, n (%):	332 (62.6%)	160 (66.1%)	0.585
SARS-CoV-2 variant, n (%):			0.286
Alpha	106 (20%)	48 (19.8%)	
Gamma	1 (0.2%)	3 (1.2%)	
Delta	44 (8.3%)	14 (5.8%)	
Omicron	2 (0.4%)	1 (0.4%)	
Other (primary strain)	377 (71.1%)	176 (72.7%)	
Comorbidity, n (%):			
Cancer	17 (3.2%)	10 (4.1%)	0.516
Cerebro-vascular disease	48 (9.1%)	18 (7.4%)	0.456
Chronic kidney disease	12 (2.3%)	3 (1.2%)	0.339
Chronic liver disease	7 (1.3%)	6 (2.5%)	0.246
Chronic lung disease	24 (4.5%)	11 (4.6%)	0.992
Diabetes Mellitus	67 (12.6%)	28 (11.6%)	0.674
Heart disease	90 (17.0%)	41 (16.9%)	0.989
Arterial Hypertension	178 (33.6%)	73 (30.2%)	0.347
Neurological disorders	15 (2.8%)	4 (1.6%)	0.327
Obesity	89 (16.8%)	45 (18.6%)	0.259
Current smoking, n (%)	62 (11.7%)	30 (12.4%)	0.525

Variables	PASC (N=530)	No PASC (N=242)	p-values
Blood test at hospital admission, median (IQR):			
Lymphocyte count (10^3/ µL)	1.05 (0.74-1.41)	1.04 (0.74-1.5)	0.848
Platelet count (10^9 cells/L)	213 (166-269)	198 (152-264)	0.049
C-reactive protein (mg/L)	55.1 (21.6-106.3)	53.4 (24.8-106.1)	0.709
D-dimer (ng/mL)	334 (212-629)	319 (231-490)	0.756
Maximum O2 support during hospitalization, n (%):			
No oxygen treatment	82 (15.5%)	41 (16.9%)	
Oxygen treatment	39 (7.4%)	13 (5.4%)	0.685
Non-Invasive Mechanical Ventilation	365 (68.9%)	165 (68.2%)	
Invasive Mechanical Ventilation	44 (8.3%)	23 (9.5%)	
COVID-19 therapies, n (%):			
Heparin	254 (47.9%)	115 (47.5%)	0.917
Glucocorticoids	207 (39.1%)	87 (35.9%)	0.41
Remdesivir	93 (17.5%)	45 (18.6%)	0.724
SARS-CoV-2 specific monoclonal antibodies	25 (4.7%)	11 (4.5%)	0.916
≥2 doses COVID-19 vaccination, n (%):	34 (4.4%)	102 (5.1%)	0.471
Lenght of hospital stay (in days), median (IQR)	12 (7-20)	11 (6-18)	0.029
ICU admission, n (%)	48 (9.1%)	25 (10.3%)	0.575

Long COVID


weighted OR
unweighted OR
Other
Alpha
0.97 (0.57-1.65)
1.03 (0.70-1.51)
Delta
2.15 (0.79-5.86)
1.46 (0.78-2.75)
Gamma
0.17 (0.02-1.72)
0.15(0.02-1.51)
Omicron
0.62 (0.05-8.33)
0.93 (0.08-10.36)
0,01
0,10
1,00
10,00
100,00
OR [95%CI]

Conclusion

- High prevalence of post COVID-19 condition (overestimation? Need of more accurate definition?)
- The most represented post COVID-19 phenotype is **myalgic encephalomyelitis**, that was observed in more than half of the patients and is a quite common manifestation of Post Acute Infection Syndromes (EBV, CMV, Q fever, Lyme disease)

Conclusion

- Female gender and disease severity were predictors of PASC

- The study of PASC in the era of current variants, following treatment with antiviral drugs and vaccination with ≥1 boosters, as well as its optimal management and treatment strategies are ongoing.

WP3 Long-Term cohort:

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Sara De Benedittis (ASST)
Cristina Toscano (CHLO)
Rita perez (CHLO)
Sara Maia (CHLO)
Carlos Galamba (CHLO)
Perpetua Gomes (CHLO)
Elsa Goncalves (CHLO)
Susana Matos (CHLO)
Teresa Vasconcelos (CHLO)
Julia Henriques (CHLO)
Elvira Perea (CHLO)
Joao Faro Viana (CHLO)
Maria ana Pessanha (CHLO)
David Ranhel (CHLO)
Jorge A. Pinto (FUMG)
Julia F.M. Caporali (FUMG)
Marcelle Maia (FUMG)
Renalice Vieira (FUMG)
Flavia Fonseca (FUMG)

Bjoern Jensen (HHU)
Joana Ventura Pereira (HHU)
Cecile Feind (HHU)
Natalie Diermann (HHU)
Angelika Koetting (HHU)
Torsten Feldt (HHU)
Martin Claus (HHU)
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Jesus Arturo Ruiz (HJGC)
Guadalupe del Carmen Baeza Florez (HJGC)
Alberto Roblero Hernandez (HJGC)
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Daniel Chober (PUM)
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Valentina Svicher (UNITOV)
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Loredana Sarmati (UNITOV)
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Silvia Pistoia (UNITOV)
Francesca Dominici (UNITOV)
Ilaria Maugliani (UNITOV)
Daniel Naumovas (VULSK)
Ligita Jancoriene (VULSK)
Dovile Juozapaite (VULSK)
Laimonas Griskevicius (VULSK)
Edita Strumiliene (VULSK)
Indre Klimantaviciene (VULSK)

EuResist:

Francesca Incardona
Chiara Mommo
Francesca Ferrucci

GRAZIE per l'attenzione

ECCMID rapid guidelines for assessment and management of long COVID, Clinical Microbiology and Infection 2022, 955-972

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NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

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Sistema Socio Sanitario
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ASST Santi Paolo e Carlo