Long COVID:
quale entità, quale gestione

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Convegno

COVID-19: DA EPIDEMIA A ENDEMIA.
VECCHIE E NUOVE SFIDE.

Milano, 25 Gennaio 2023

ASST Santi Paolo e Carlo

Outline

- Definizione
- Prevalenza
- Presentazione clinica
- Fattori di rischio
- Durata e outcome
- Possibili cause
- Management e trattamento
- Dati coorte ospedale San Paolo, ambulatorio post COVID

Definition

> CDC uses the term “post-COVID conditions” (PCC) as an umbrella term for the wide range of health consequences that can be present four or more weeks after infection with SARS-CoV-2, the virus that causes COVID-19.

Post-COVID conditions are associated with a spectrum of physical, social, and psychological consequences, as well as functional limitations that can present substantial challenges to patient wellness and quality of life.

Post-COVID conditions are referred to by a wide range of names, including:

- Long COVID
- Post-acute COVID-19
- Long-term effects of COVID
- Post-acute COVID syndrome
- Chronic COVID
- Long-haul COVID
- Late sequelae
- Post-acute sequelae of SARS-COV-2 infection (PASC)

Although standardized case definitions are still being developed, in the broadest sense, post-COVID conditions can be considered a lack of return to a usual state of health following acute COVID-19 illness. Post-COVID conditions might also include development of new or recurrent symptoms or unmasking of a pre-existing condition that occurs after the symptoms of acute COVID-19 illness have resolved.

Post COVID-19 condition, 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.

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

6 October 2021

World Health Organization

Prevalenza

CDC is using multiple approaches to estimate how many people experience post-COVID conditions. Each approach can provide a piece of the puzzle to give us a better picture of who is experiencing post-COVID conditions. For example, some studies look for the presence of post-COVID conditions based on self-reported symptoms, while others collect symptoms and conditions recorded in medical records. Some studies focus only on people who have been hospitalized, while others include people who were not hospitalized. The estimates for how many people experience post-COVID conditions can be quite different depending on who was included in the study, as well as how and when the study collected information. **Estimates of the proportion of people who had COVID-19 that go on to experience post-COVID conditions can vary**:

- 13.3% at one month or longer after infection
- 2.5% at three months or longer, based on self-reporting
- More than 30% at 6 months among patients who were hospitalized

Almeno nel 10% dei pazienti
1-2 milioni di persone con almeno un sintomo persistente ad un anno dalla fase acuta

cluster symptoms they experience as "feeling old". The prevalence of PACS has been reported very differently according to diverse age groups, socioeconomic tiers, ethnicities, and geographical areas, varying from 10% of the people with previously documented infection (Wissler Gerdes et al., 2022) to as high as 50–80% among survivors after hospital discharge (Carfì et al., 2020; Garrigues et al., 2020; Carvalho-Schneider et al., 2021; Arnold et al., 2020; Nehme et al., 2021; Mandal et al., 2021; Tenforde et al., 2020; Stavem et al., 2020).

Presentazione clinica: cluster di sintomi/fenotipi

People with post-COVID conditions (or long COVID) may experience many symptoms.

People with post-COVID conditions can have a wide range of symptoms that can last more than four weeks or even months after infection. Sometimes the symptoms can even go away or come back again.

Post-COVID conditions may not affect everyone the same way. People with post-COVID conditions may experience health problems from different types and combinations of symptoms happening over different lengths of time. Most patients' symptoms slowly improve with time. However, for some people, post-COVID conditions can last weeks, months, or longer after COVID-19 illness and can sometimes result in disability.

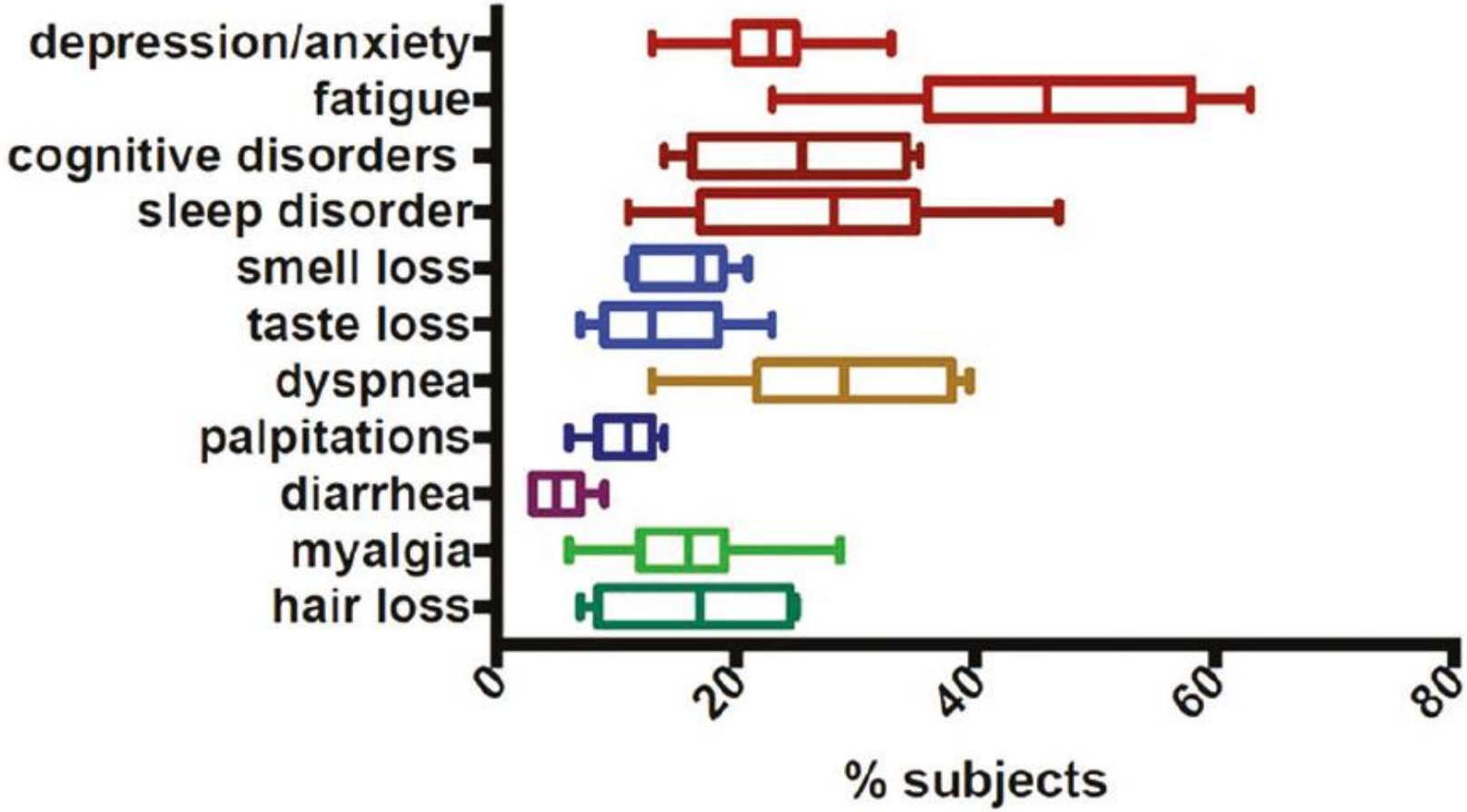

Fig. 1 The frequency of the most common symptoms four week or more after the acute Covid-19 infection. Data presented in meta-analyses, selected on the basis of homogeneous reporting criteria [10–20].

Alkodaymi MS et al. Clin Microbiol Infect. 2022;28:657–66.

General symptoms

- Tiredness or fatigue that interferes with daily life
- Symptoms that get worse after physical or mental effort (also known as “post-exertional malaise”)
- Fever

Respiratory and heart symptoms

- Difficulty breathing or shortness of breath
- Cough
- Chest pain
- Fast-beating or pounding heart (also known as heart palpitations)

* Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks.

Neurological symptoms

- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Headache
- Sleep problems
- Dizziness when you stand up (lightheadedness)
- Pins-and-needles feelings
- Change in smell or taste
- Depression or anxiety

Musculoskeletal symptoms

- Joint pain
- Muscle pain

Digestive symptoms

- Diarrhea
- Stomach pain

Ear, nose and throat symptoms

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

Other symptoms

- Joint or muscle pain
- Rash
- Changes in menstrual cycles

Dermatologiche	▪ Eritema pernio ▪ Eruzioni papulo-squamose ▪ Rash morbilliformi ▪ Eruzioni orticaroidi ▪ Alopecia
Ematologiche	▪ Tromboembolismo
Renali	▪ Ematuria e proteinuria (nefropatia)
Endocrine	▪ Diabete mellito di nuova insorgenza e tiroidite subacuta

Disordini autoimmunitari

Individuals with PASC can be stratified into several subsets.

Males

Those recovering from severe COVID-19 may have lung or other organ damage as a result of pneumonia or acute respiratory distress syndrome, or they may have lingering symptoms consistent with post-ICU syndrome.[2] Prolonged or incomplete recovery has been described for this group of individuals, and seems to be more common among older adults, particularly men[194].

Females

Another prominent subset of patients with PASC includes those who experience a syndrome characterized by unexplained exertion intolerance, debilitating fatigue, cognitive and sensory disturbances, headaches, myalgia, and recurrent flu-like symptoms. The core features of this syndrome share remarkable similarities with other PAISs discussed in this review, as well as with myalgic encephalomyelitis/chronic fatigue syndrome[195,196]. This syndrome is not linked to the severity of acute COVID-19 and frequently appears after mild or moderate initial illness, or even after asymptomatic infection — and has predominantly been identified in females[197].

Danno d’organo: Polmone

- 20% dei pazienti presenta persistenza di dispnea da sforzo, tosse
- Danno in fase acuta per endoteliopatia, manifestazioni trombotiche e infiammazione per tempesta citochinica
- Soprattutto nei pazienti con malattia severa in fase acuta e necessità di ventilazione meccanica
- Alterazione della capacità di diffusione del CO (DLCO <80%) che può persistere per mesi e in alcuni casi evolvere in fibrosi (deposizione di collagene e danno tissutale infiammatorio); possibilità di alterazioni radiologiche alla TAC per mesi con possibili esiti

Alberto Mantovani et al, Cell Death & Differentiation (2022) 29:1891–1900

Danno d'organo: SNC

- Problemi cognitivi (memoria nel 56% dei pazienti a 4/7 mesi; attenzione, funzioni esecutive)
- Studi con 18F-FDG PET hanno evidenziato ipometabolismo in alcune aree cerebrali; modifiche della sostanza bianca e grigia (insulto cerebrale durante la fase acuta?)
- Fattore di rischio per sviluppare deficit cognitivi?

Alberto Mantovani et al, Cell Death & Differentiation (2022) 29:1891–1900

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, long-term illness that affects many body systems. People with ME/CFS are often not able to do their usual activities. At times, ME/CFS may confine them to bed. People with ME/CFS have severe fatigue and sleep problems. ME/CFS may get worse after people with the illness try to do as much as they want or need to do. This symptom is called post-exertional malaise (PEM). Other symptoms can include problems with thinking and concentrating, pain, and dizziness.

According to an Institute of Medicine (IOM) report , an estimated 836,000 to 2.5 million Americans suffer from ME/CFS. However, most of them have not been diagnosed.

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).

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

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

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.

Anyone can get ME/CFS. While most common in people between 40 and 60 years old, the illness affects children, adolescents, and adults of all ages. Among adults, women are affected more often than men. Whites are diagnosed more than other races and ethnicities. But many people with ME/CFS have not been diagnosed, especially among minorities.

As noted in the IOM report:

- An estimated 836,000 to 2.5 million Americans suffer from ME/CFS.
- About 90 percent of people with ME/CFS have not been diagnosed.
- ME/CFS costs the U.S. economy about $17 to $24 billion annually in medical bills and lost incomes.

Some of the reasons that people with ME/CFS have not been diagnosed include limited access to healthcare and a lack of education about ME/CFS among healthcare providers.

- Most medical schools in the United States do not have ME/CFS as part of their physician training.
- The illness is often misunderstood and might not be taken seriously by some healthcare providers.
- More education for doctors and nurses is urgently needed so they are prepared to provide timely diagnosis and appropriate care for patients.

Researchers have not yet found what causes ME/CFS, and there are no specific laboratory tests to diagnose ME/CFS directly. Therefore, doctors need to consider the diagnosis of ME/CFS based on in-depth evaluation of a person's symptoms and medical history. It is also important that doctors diagnose and treat any other conditions that can cause similar symptoms. Even though there is no cure for ME/CFS, some symptoms can be treated or managed.

nature medicine

REVIEW ARTICLE

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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.

Post Acute Infection Syndromes

- Presente solo in una proporzione di pazienti dopo la fase acuta
- Spesso mancata guarigione clinica completa per persistenza di sintomi aspecifici
- Non vi sono marcatori oggettivi da utilizzare nella diagnostica
- Raramente il patogeno risulta ancora presente

- Comunque creano disabilità con impatto sul sistema sanitario

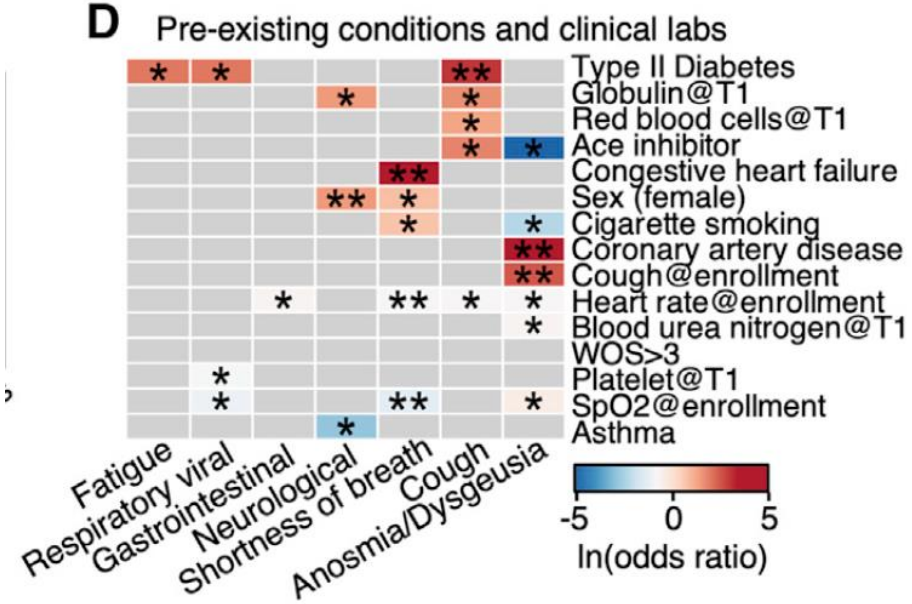
Possibili cause di Post Acute Infection Syndrome : batteri, virus, parassiti

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

Incremento dell'incidenza di diabete mellito

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.



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

Lancet Diabetes Endocrinol 2022; 10: 311–21

Yan Xie, Ziyad Al-Aly

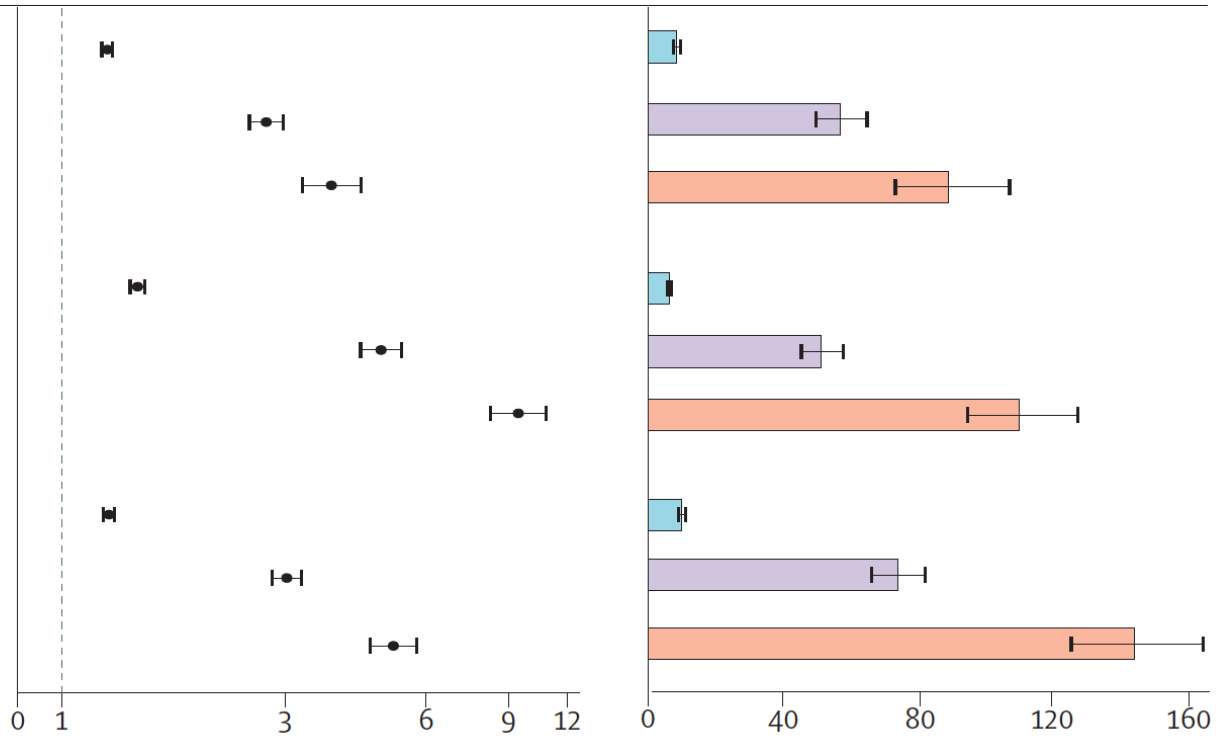
- A cohort of more than 180,000 participants who had a positive COVID-19 test were followed up for about 1 year.
- Compared to a non-infected contemporary and a historical control group (both > 4M subjects) cohort members were observed to have an increased risk of incident diabetes.
- The risk was found to **increase according to the severity of disease** during the acute phase of the infection.
- Comparing three groups of patients (nonhospitalized, hospitalized, and admitted to intensive care), the risk was found to be related to disease severity but also present in the non-hospitalized group.

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

Lancet Diabetes Endocrinol
2022; 10: 311–21

Yan Xie, Ziyad Al-Aly

	Care setting	Burden per 1000 people at 12 months (95% CI)	
		COVID-19	Contemporary control
Diabetes	Non-hospitalised	42·70 (41·39–44·05)	
	Hospitalised	91·35 (83·80–99·54)	34·42 (34·24–34·61)
	Intensive care	123·48 (107·31–141·89)	
Antihyperglycaemic use	Non-hospitalised	20·10 (19·25–20·98)	
	Hospitalised	65·10 (58·82–72·02)	13·93 (13·82–14·05)
	Intensive care	123·93 (108·32–141·61)	
Composite outcome	Non-hospitalised	48·63 (47·27–50·01)	
	Hospitalised	112·63 (104·61–121·22)	38·84 (38·65–39·03)
	Intensive care	182·92 (163·92–203·84)	



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

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- The excess burden of diabetes among non-hospitalized individuals (**8.3 per 1000 people at 12 months**) points to the magnitude of the problems that health systems might face, considering the hundreds of millions of people infected globally.
- Given the importance of this major risk of Long Covid, it will be important to support the conclusion of these reports with prospective epidemiological studies.
- An immediate implication of the studies is **the necessity of screening for hyperglycemia not only during the acute phase of Covid-19 but also during the follow-up**.

Fattori di rischio

People More Likely to Develop Long COVID

Some people may be more at risk for developing post-COVID conditions (or long COVID).

Researchers are working to understand which people or groups of people are more likely to have post-COVID conditions, and why. Studies have shown that some groups of people may be affected more by post-COVID conditions. These are examples and not a comprehensive list of people or groups who might be more at risk than other groups for developing post-COVID conditions:

- People who have experienced more severe COVID-19 illness, especially those who were hospitalized or needed intensive care.
- People who had underlying health conditions prior to COVID-19.
- People who did not get a COVID-19 vaccine.
- People who experience multisystem inflammatory syndrome (MIS) during or after COVID-19 illness.

Prevalence of long COVID symptoms in studies investigating patients regardless of disease severity and in studies in hospitalized patients [23,25,28,47,55,74,122–140]

	Symptom	All patients (%)	Hospitalized (%)	Outpatients (%)
General	Fever/feverish	0.05–6.8	10.4	1.41
	Fatigue	4–73.2	17.5–54.5	24.6
	Headache	0.05–47.4	24.6	8.8
	Chest pain/tightness	3.1–31.7	0.4–17.9	14.6
Musculoskeletal	Joint pain/arthralgia	9–37.3	5.9–28.6	9.3
	Myalgia	2–44.9	37.4–47.8	10.8
Respiratory	Dyspnoea	21.8–39	5.5–59.7	13.7
	Exertional dyspnoea	39–54.8	14.6–57.1	
	Cough	3.2–23.4	2.5–35.1	6
	Sleep apnoea	24–35.7	30.8–35.1	—
	Throat pain	4–19		4.4
Gustatory	Ageusia/dysgeusia	7–16.1	9–21.6	16.8
	Anosmia	11–45	4.6–26.1	22.2
	Loss of appetite	8–10.2	—	—
Neuropsychological	Confusion/brain fog	3–63.3	—	15.6
	Depression	11–15.7	—	—
	Sleep disorder	24–35.7	—	—
	Posttraumatic stress disorder	—	5.8–10.4	7
Cardiovascular	Palpitations	3.9–40	—	7.3
Skin	Rash	3–35.7	—	1.6

Research paper

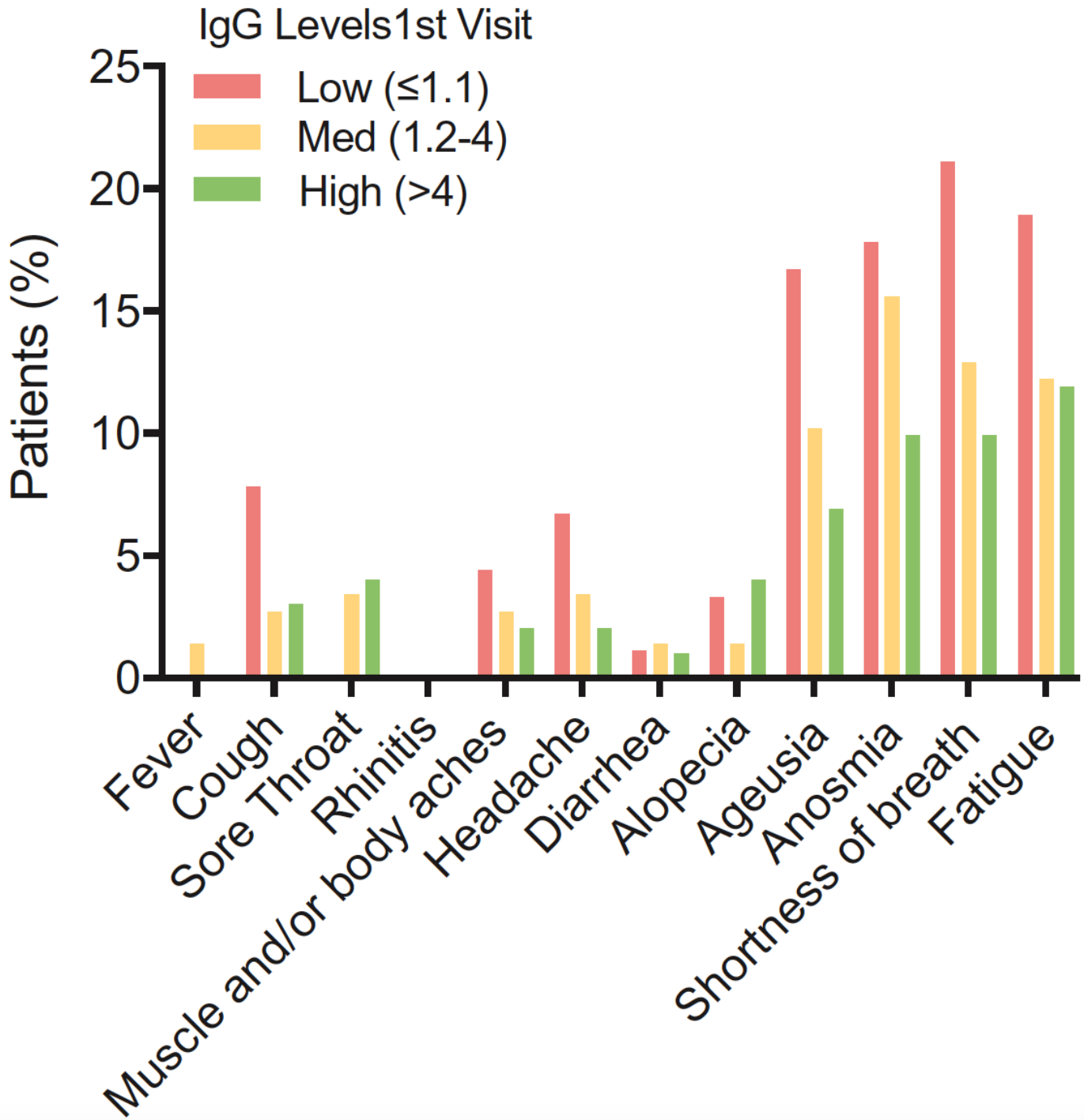
The Lancet Regional Health - Europe

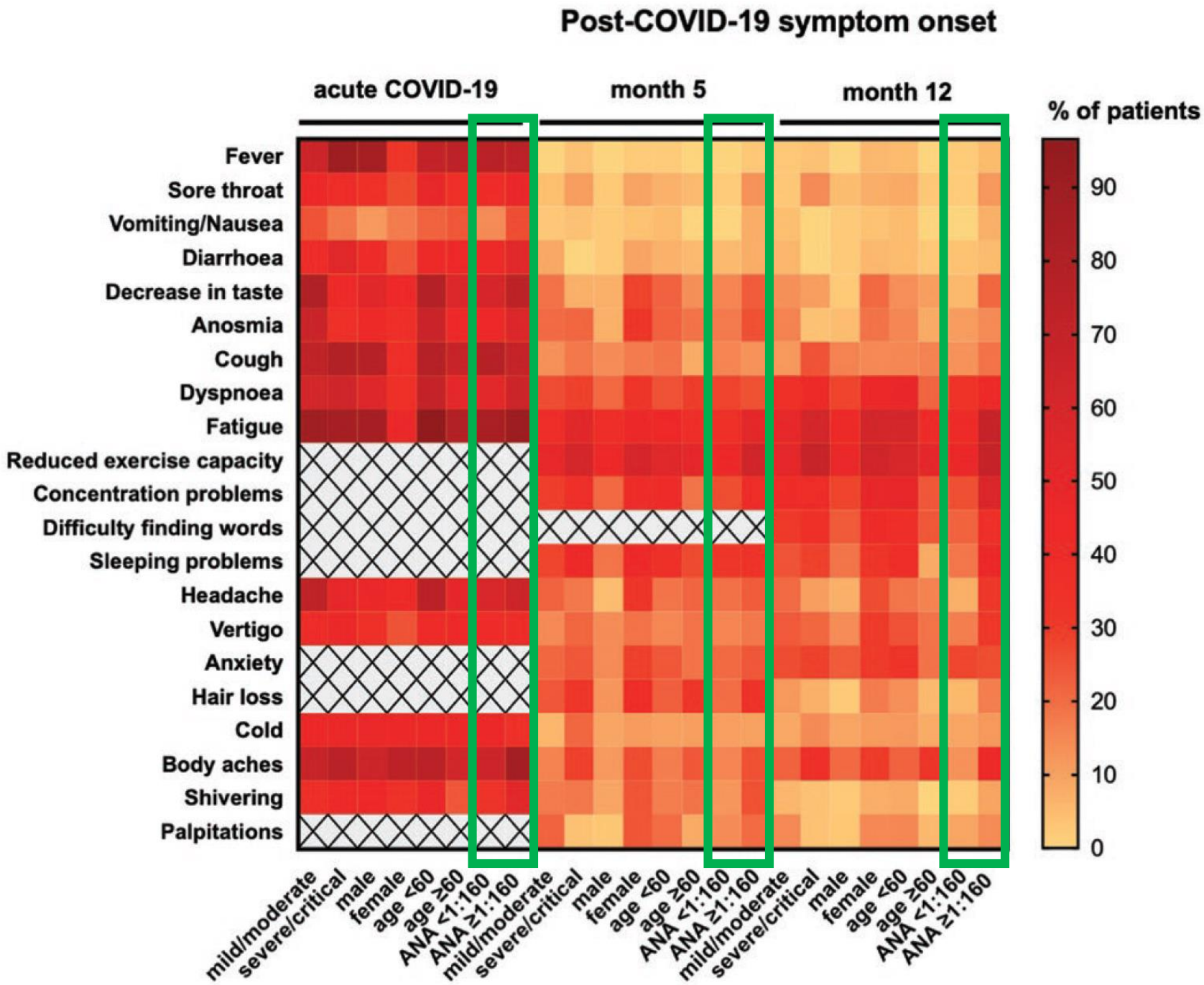
Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study

Max Augustin, MD[a,b,c,1], Philipp Schommers, M.D. PhD.[a,c,d,1], Melanie Stecher, Ph.D.[a,c,1],

Table 2
Predictors of post-COVID syndrome (PCS) based on an uni- and multivariable logistic regression model.

		Post-COVID-19 syndrome		Univariate regression		Multivariable regression	
		No (n = 230)	Yes (n = 123)	OR (95% CI)*	p-value	aOR (95% CI)*	p-value
	Male	112 (48•7%)	39 (31•7%)	0•49 (0•31–0•77)	**•002**	0•59 (0•36–0•98)	**•040**
	Female	118 (51•3%)	84 (68•3%)	ref•			
	Median Age (IQR)	49 (35–56)	47 (33–56)	0•99 (0•97–1•01)	•435		
	Preconditions	63 (28•8%)	31 (26•3%)	0•88 (0•53–1•46)	•626		
	Hospitalisation	8 (3•6%)	0	n•a•			
Symptoms during acute phase	Median duration (days; IQR)	13 (8–16)	14 (11–21)	1•04 (0•91–1•07)	•201		
	Number of symptoms (median; IQR)	4 (2–5)	5 (3–6)	1•28 (1•13–1•46)	<**0•001**	1•29 (1•08–1•55)	**•005**
	Fever	104 (45•2%)	48 (39•0%)	0•78 (0•50–1•21)	•263		
	Cough	147 (63•9%)	87 (70•7%)	1•37 (0•85–2•19)	•179	0•94 (0•53–1•67)	•824
	Sore Throat	72 (31•2%)	45 (36•6%)	1•27 (0•81–2•00)	•316		
	Rhinitis	75 (32•6%)	44 (35•8%)	1•15 (0•73–1•82)	•549		
	Muscle and/or body aches	122 (53•0%)	71 (57•7%)	1•21 (0•78–1•88)	•400		
	Headache	112 (48•7%)	71 (57•7%)	1•44 (0•93–2•23)	•106	0•84 (0•48–1•47)	•537
	Diarrhoea	25 (10•9%)	26 (21•1%)	2•19 (1•21–4•00)	**•010**	1•50 (0•78–2•91)	•277
	Anosmia	117 (57•0%)	85 (42•1%)				
	Ageusia	94 (51•4%)	89 (48•6%)				
IgG Level	**IgG categories**						
	IgG ≤ 1•1	28 (12•8)	21 (17•6)	1•92 (0•99–3•72)	•054	2•05 (0•99–4•22)	•051
	IgG 1•2 - 4	76 (34•7)	53 (44•5)	1•78 (1•09–2•91)	**•021**	1•90 (1•13–3•18)	**•015**
	IgG > 4	115 (52•5)	45 (37•8)	ref•		ref•	
	1st Visit (S/CO-Ratio, median IQR)	4 (2–7)	3 (1–6)				
	2nd Visit (S/CO-Ratio, median IQR)	3 (2–5)	2 (1–4)				
	3rd Visit (S/CO-Ratio, median IQR)	2 (1–4)	2 (1–4)				


IgG Levels1st Visit
Low (≤1.1)
Med (1.2-4)
High (>4)
Patients (%)
25
20
15
10
5
0
Fever
Cough
Sore Throat
Rhinitis
Muscle and/or body aches
Headache
Diarrhea
Alopecia
Ageusia
Anosmia
Shortness of breath
Fatigue


Post-COVID-19 symptom onset
acute COVID-19
month 5
month 12
% of patients
90
80
70
60
50
40
30
20
10
0
Fever
Sore throat
Vomiting/Nausea
Diarrhoea
Decrease in taste
Anosmia
Cough
Dyspnoea
Fatigue
Reduced exercise capacity
Concentration problems
Difficulty finding words
Sleeping problems
Headache
Vertigo
Anxiety
Hair loss
Cold
Body aches
Shivering
Palpitations
mild/moderate
severe/critical
male
female
age <60
age ≥60
ANA <1:160
ANA ≥1:160
mild/moderate
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ANA <1:160
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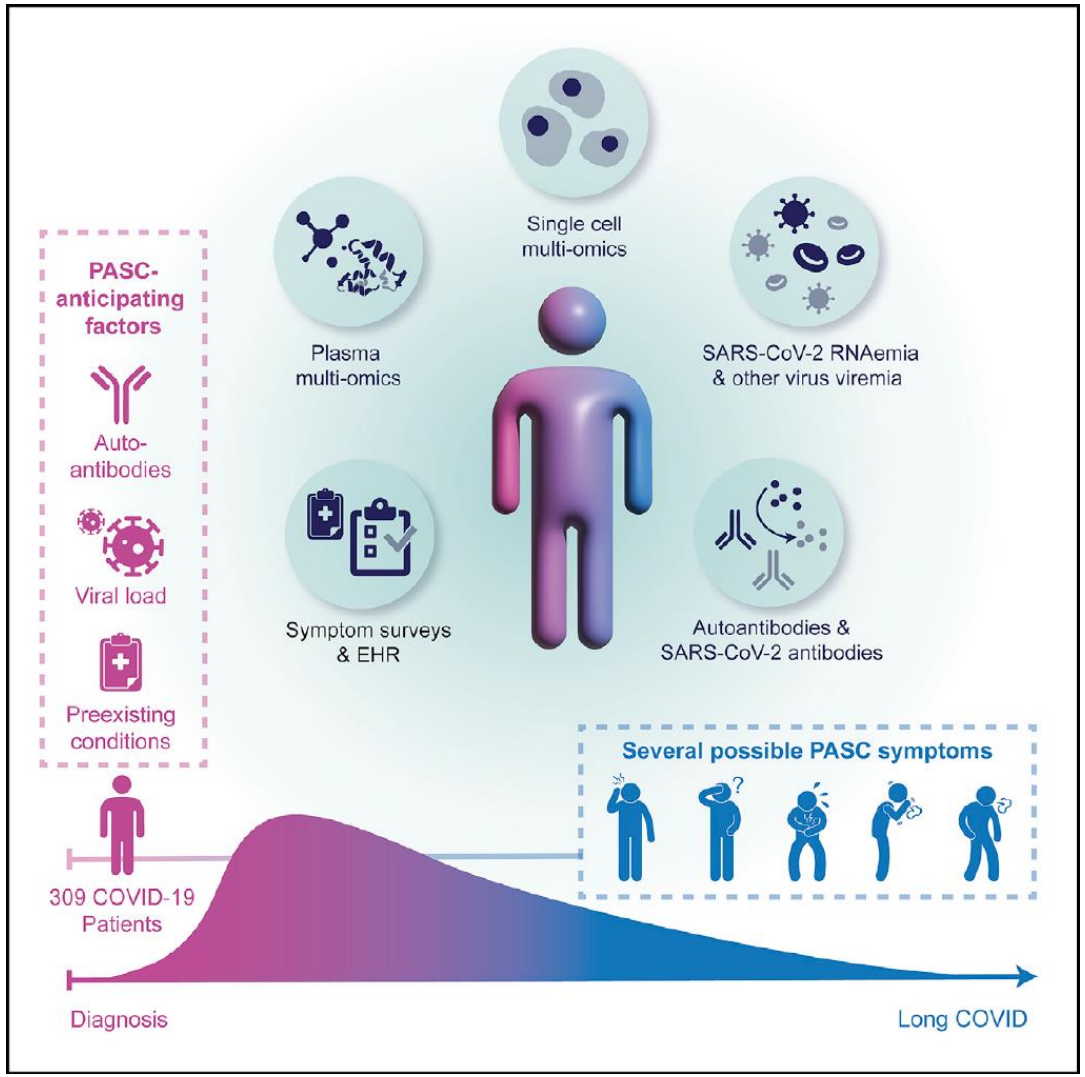
Cell

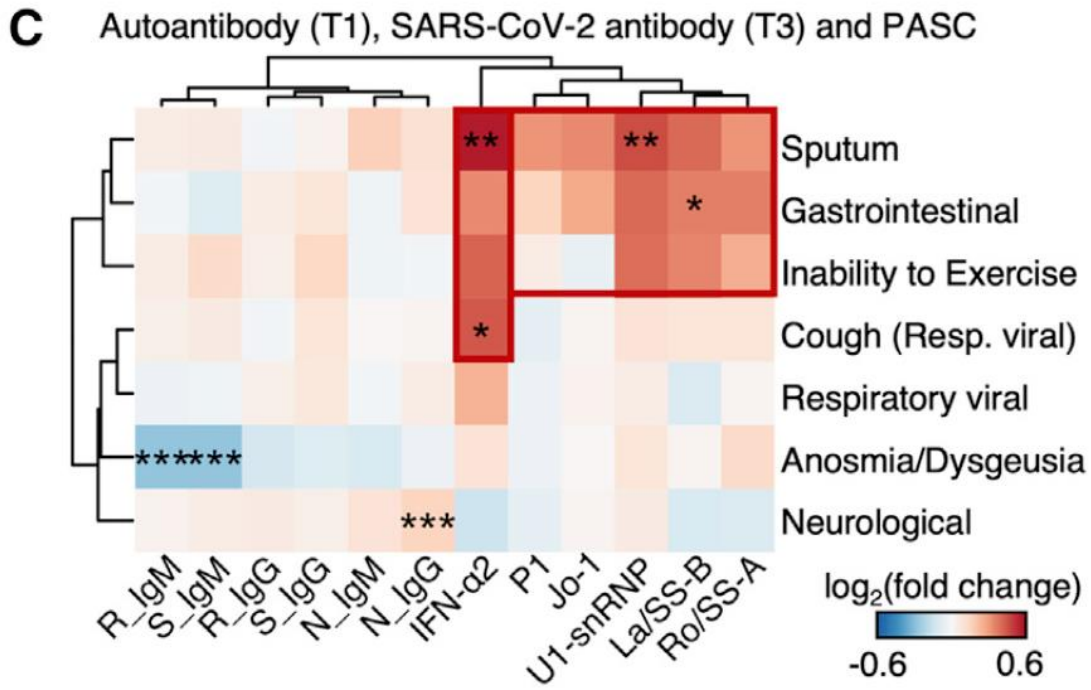
Multiple early factors anticipate post-acute COVID-19 sequelae



Highlights

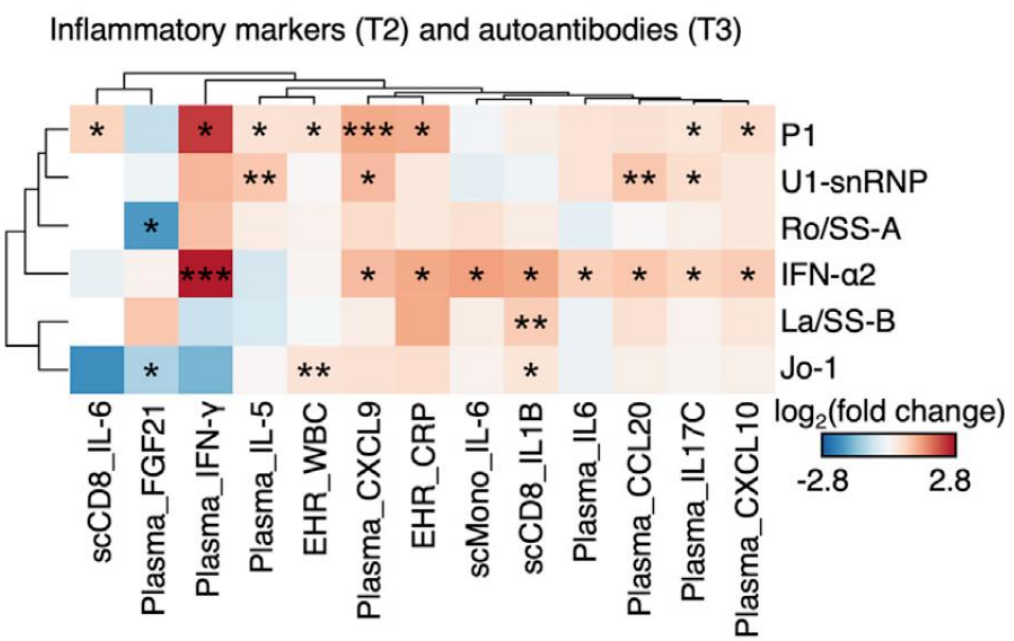
- Longitudinal multi-omics associate PASC with auto-antibodies, viremia, and comorbidities
- Reactivation of latent viruses during initial infection may contribute to PASC
- Subclinical auto-antibodies negatively correlate with anti-SARS-CoV-2 antibodies
- Gastrointestinal PASC uniquely present with post-acute expansion of cytotoxic T cells

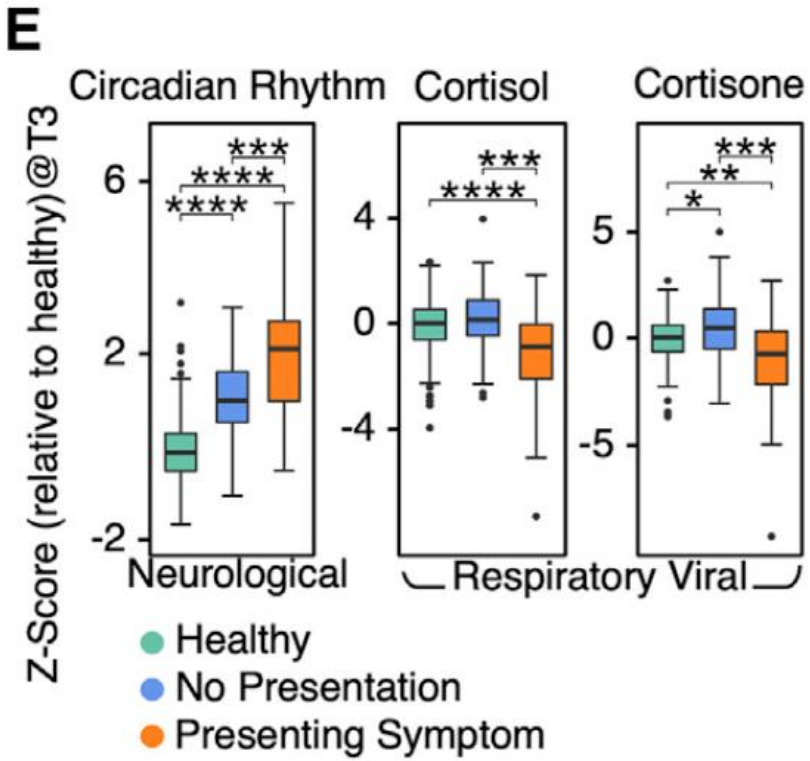
SARS CoV-2 viremia
EBV DNA
Autoanticorpi (che neutralizzano INFs e ANA)
Diabete mellito tipo 2

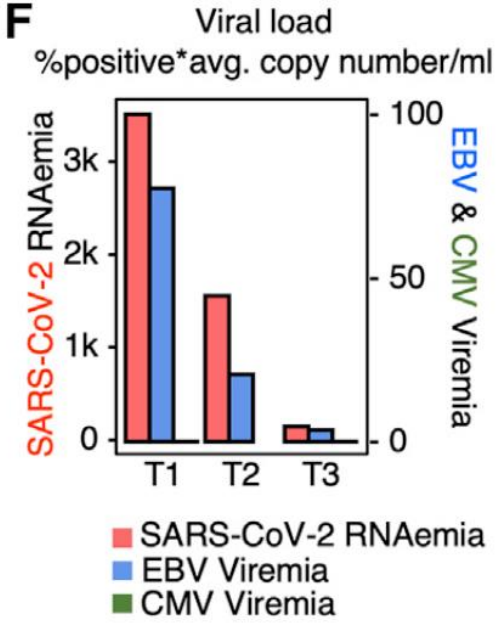


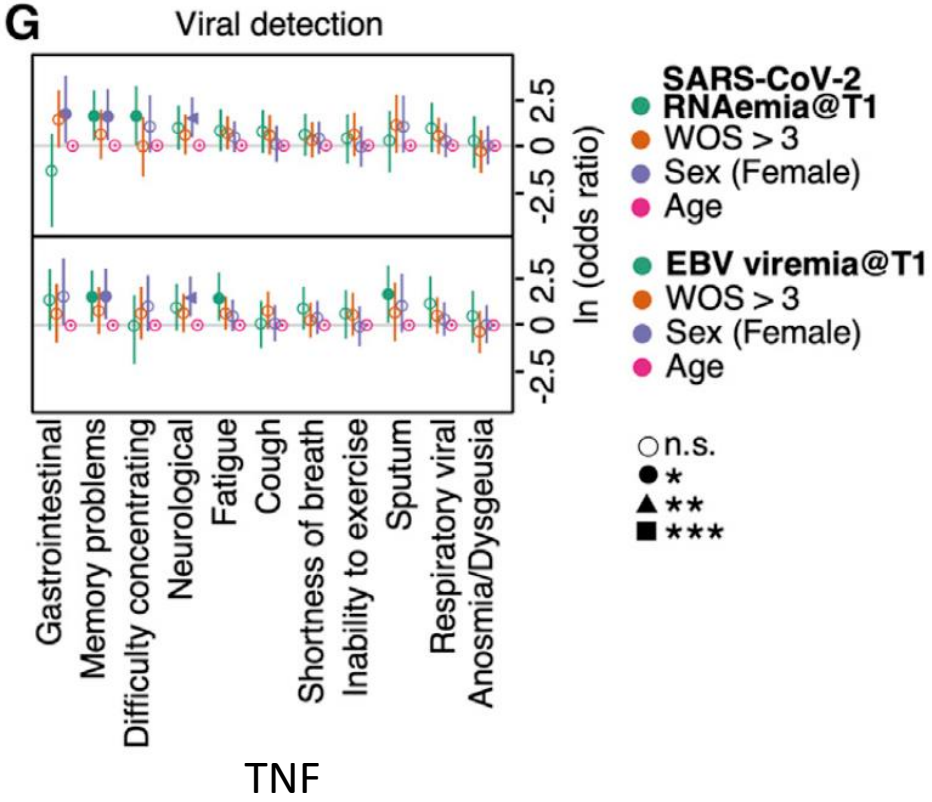
A third major finding was that anti-SARS-CoV-2 Abs and specific autoAbs were associated with different PASC. For example, patients with neurological PASC exhibited slightly higher levels of anti-SARS-CoV-2 nucleocapsid protein IgG, whereas GI-related PASC and sputum production were associated with elevated levels of multiple autoAbs at T3 (Figure S2D; Table S2.4) and even T1 (Figures 2C and S2E; Table S2.4). IFN-α2 autoAbs uniquely associated with respiratory-viral PASC, even after correcting for age, sex, and disease severity (Figures 2C, S2B, and S2F; Table S2.4). These observations suggest that T1 autoAb levels may be anticipating biomarkers of certain PASC (Figures 2C and S2F).

notable connection between autoAbs, T2 hyperinflammation and T3 PASC



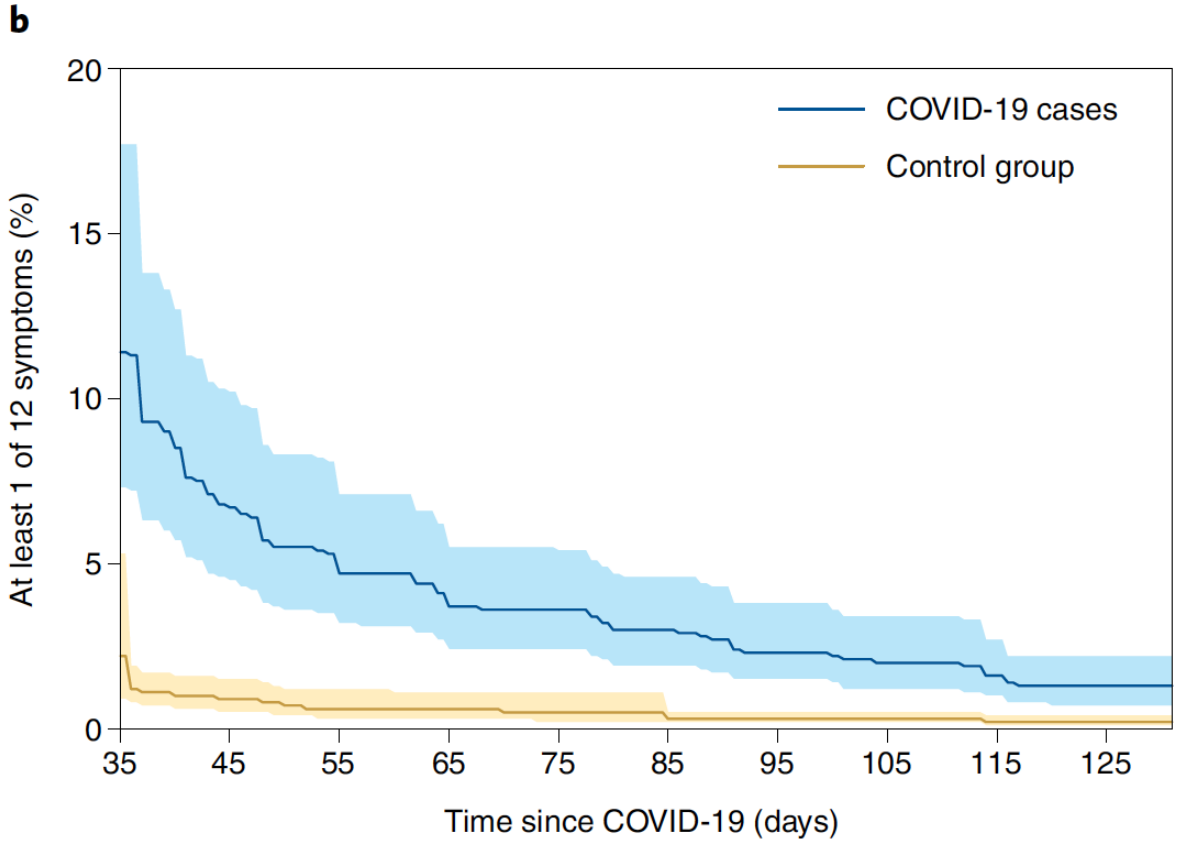


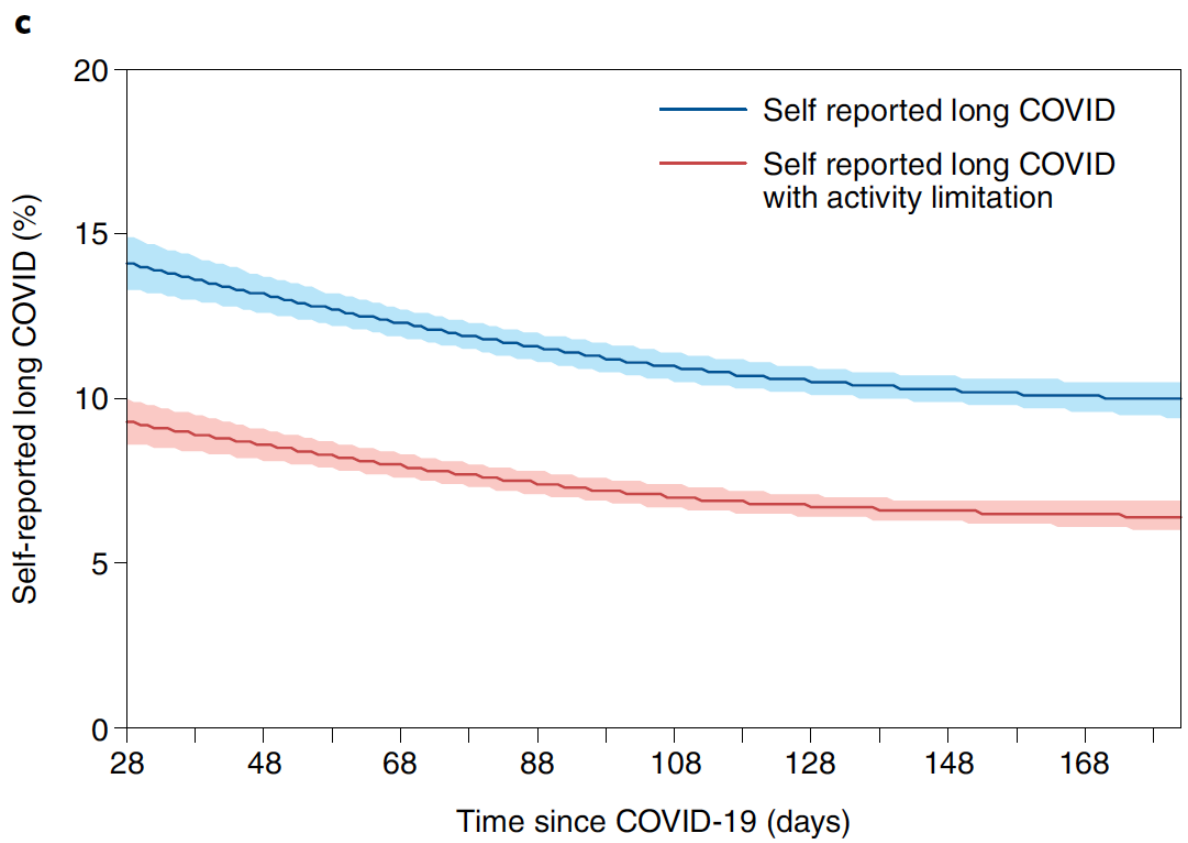




TNF

reactivation of latent EBV and SARS CoV-2 RNAemia at T1 are factors that anticipate, to varying degrees, PASC at T3.


b
20
15
10
5
0
At least 1 of 12 symptoms (%)
COVID-19 cases
Control group
35
45
55
65
75
85
95
105
115
125
Time since COVID-19 (days)


c
20
15
10
5
0
Self-reported long COVID (%)
Self reported long COVID
Self reported long COVID
with activity limitation
28
48
68
88
108
128
148
168
Time since COVID-19 (days)

Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2

Among omicron cases, 2501 (4·5%) of 56 003 people experienced long COVID and, among delta cases, 4469 (10·8%) of 41 361 people experienced long COVID. Omicron cases were less likely to experience long COVID for all vaccine timings, with an odds ratio ranging from 0·24 (0·20–0·32) to 0·50 (0·43–0·59). These results were also confirmed when the analysis was stratified by age group (figure).

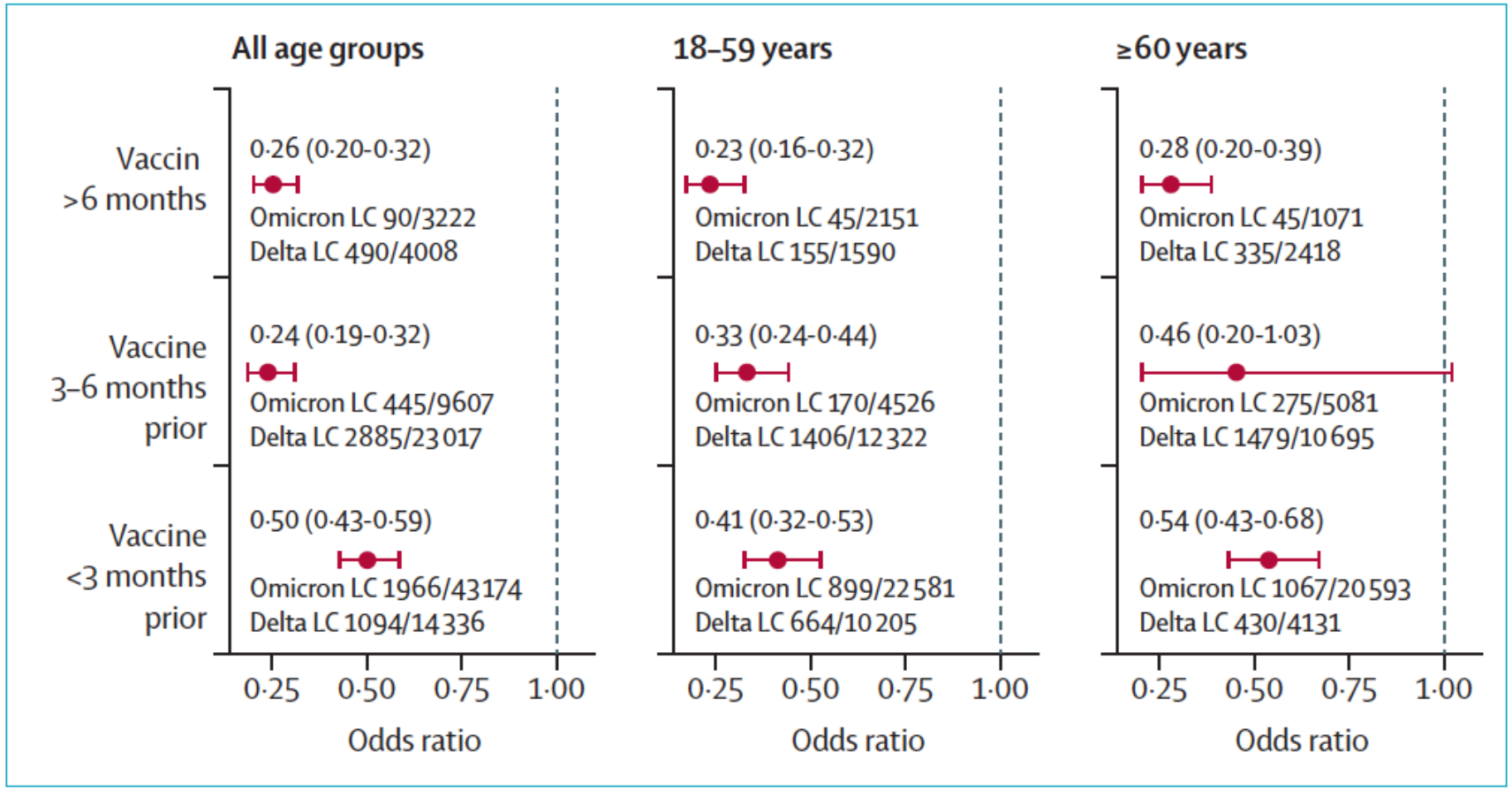
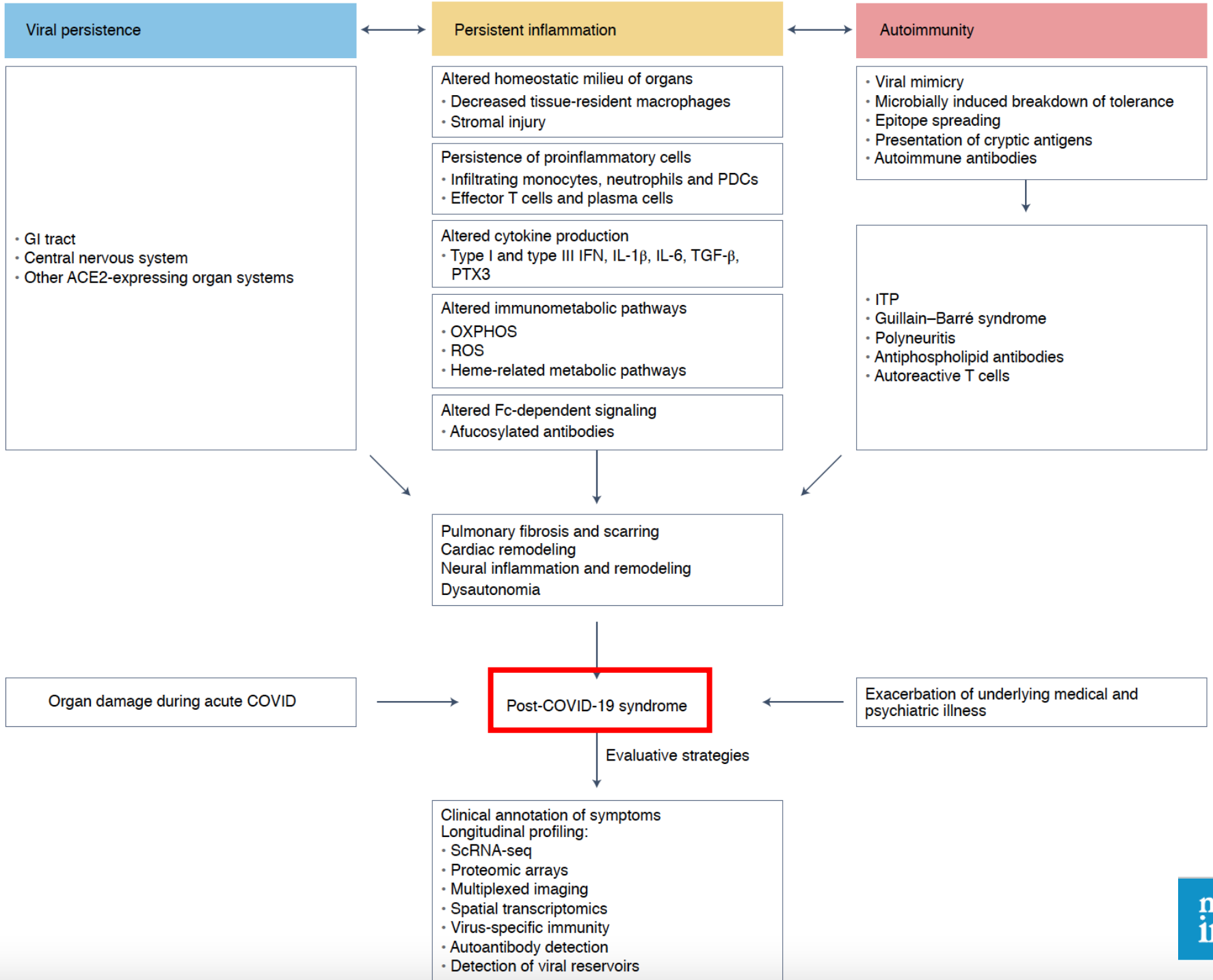
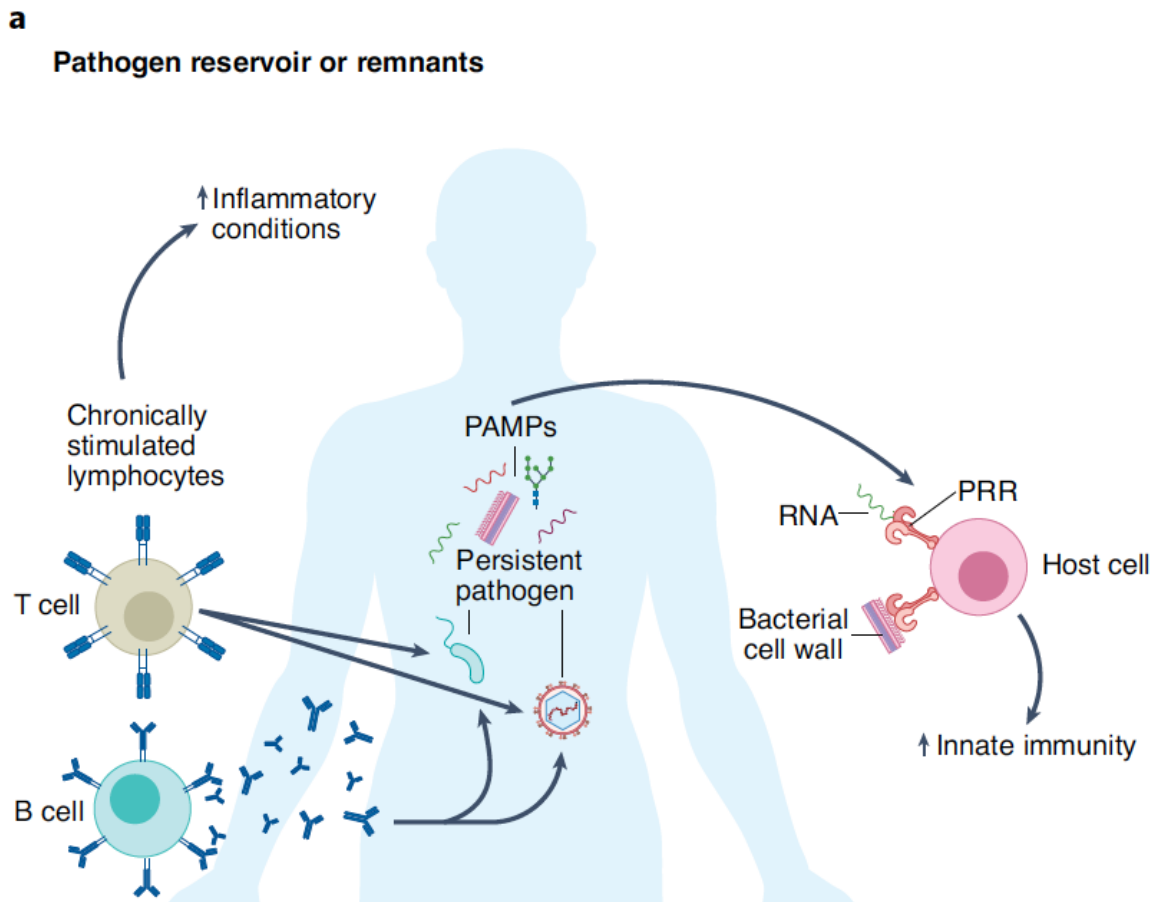


***Figure*: Odds ratio of long COVID (LC) adjusted by age, sex, body-mass index, Index of Multiple Deprivation, presence of comorbidities, and vaccination status**

Omicron long COVID and delta long COVID indicate, for each stratum, the number of users with long COVID over the total number of users of that stratum.

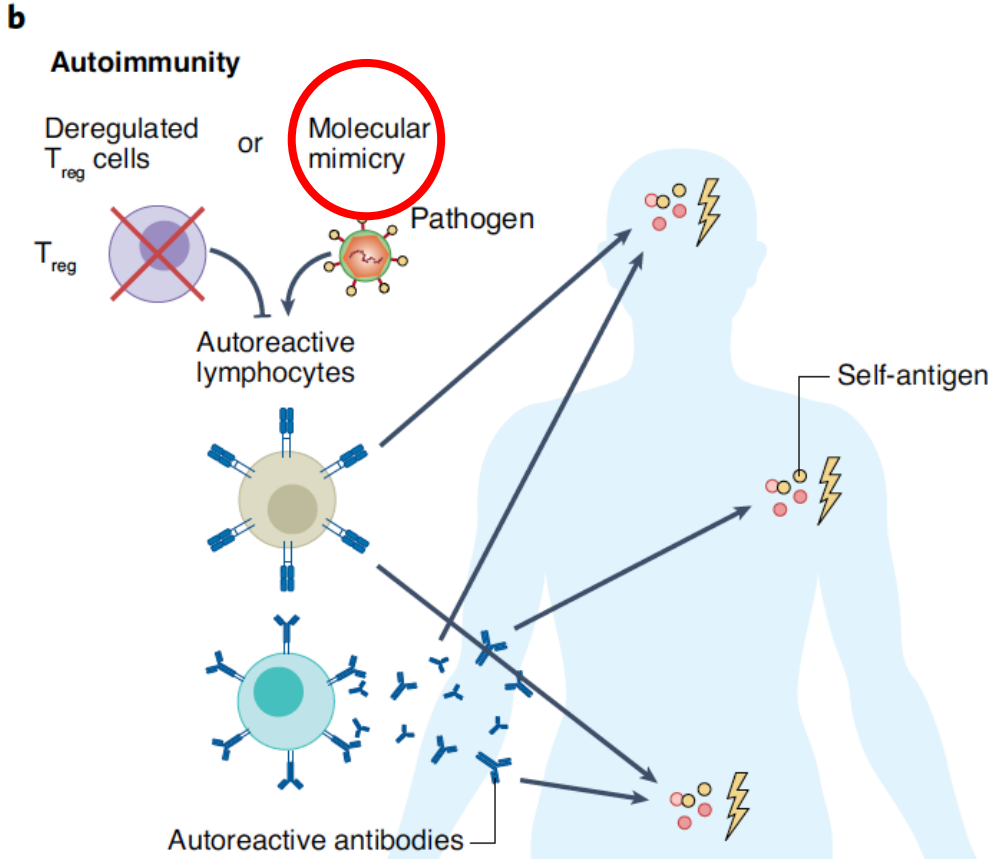

Viral persistence
Persistent inflammation
Autoimmunity
Altered homeostatic milieu of organs
• Decreased tissue-resident macrophages
• Stromal injury
Persistence of proinflammatory cells
• Infiltrating monocytes, neutrophils and PDCs
• Effector T cells and plasma cells
Altered cytokine production
• Type I and type III IFN, IL-1β, IL-6, TGF-β, PTX3
Altered immunometabolic pathways
• OXPHOS
• ROS
• Heme-related metabolic pathways
Altered Fc-dependent signaling
• Afucosylated antibodies
• Viral mimicry
• Microbially induced breakdown of tolerance
• Epitope spreading
• Presentation of cryptic antigens
• Autoimmune antibodies
• GI tract
• Central nervous system
• Other ACE2-expressing organ systems
• ITP
• Guillain–Barré syndrome
• Polyneuritis
• Antiphospholipid antibodies
• Autoreactive T cells
Pulmonary fibrosis and scarring
Cardiac remodeling
Neural inflammation and remodeling
Dysautonomia
Organ damage during acute COVID
Post-COVID-19 syndrome
Exacerbation of underlying medical and psychiatric illness
Evaluative strategies
Clinical annotation of symptoms
Longitudinal profiling:
• ScRNA-seq
• Proteomic arrays
• Multiplexed imaging
• Spatial transcriptomics
• Virus-specific immunity
• Autoantibody detection
• Detection of viral reservoirs

Post Acute Infection Syndromes: cause comuni?



SARS CoV-2 RNA o Ag può persistere in linfonodi, colon, ileo, appendice, colecisti, fegato, SNC, cuore, rene, muscoli per 9/180 giorni dopo la guarigione (TNF negativo)

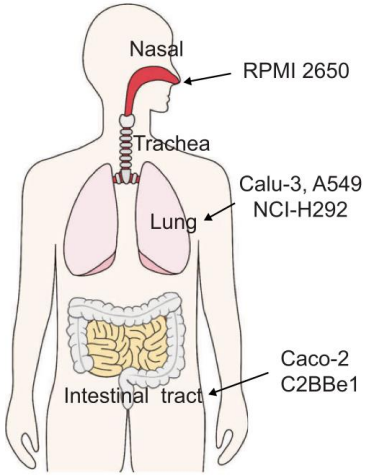
Gaebler, C. et al. Nature 591, 639–644 (2021).
Cheung, C. C. L. et al. Gut 71, 226–229 (2022).



Attivazione autoimmune per trigger da parte del patogeno o per attivazione di linfociti T/B per stimolazione citochinica

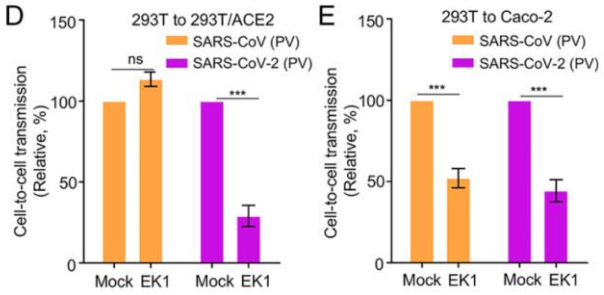
Chang, S. E. et al. Nat. Commun. 12, 1–15 (2021).
Wallukat, G. et al. J. Transl. Autoimmun. 4, 100100 (2021).

Persistenza virale



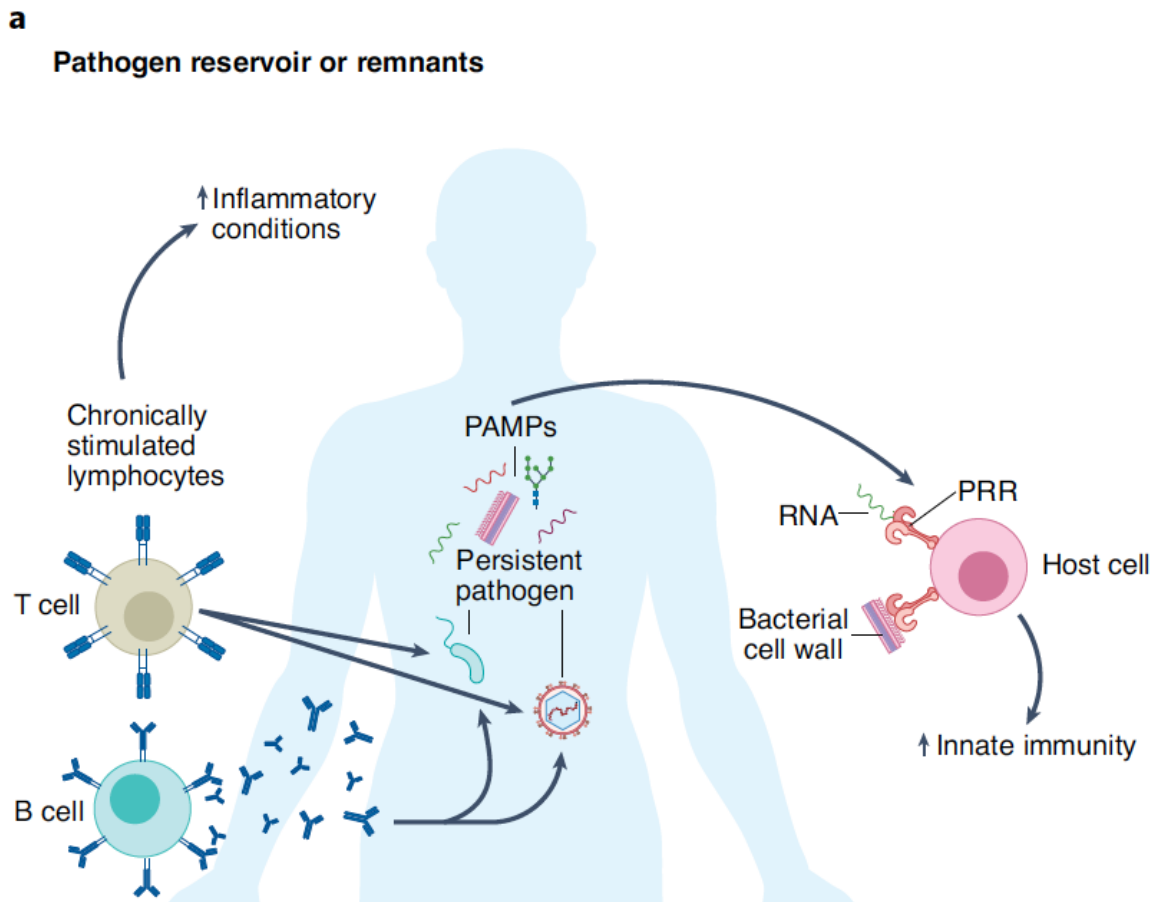
- In the case of SARS-CoV-2, it has been recently shown that the virus can establish a long-term, non-productive persistent infection in different types of cells in vitro

- Due to the high cell–cell fusion activity of its spike protein, the SARS-CoV-2 virion or some of the virus components may spread through cell–cell contact. This insidious strategy, which is adopted by other RNA viruses, including the respiratory syncytial virus, the measles virus and HIV, allows the pathogen to spread in a particle-independent way, promoting immune evasion.
- **Cell-to-cell transmission of SARS-CoV-2** has been recently demonstrated in human cells.



Lee S, et al. Robust and persistent SARS-CoV-2 infection in the human intestinal brush border expressing cells. Emerg Microbes Infect. 2020;9:2169–79.
GamageAM, et al. Human nasal epithelial cells sustain persistent SARS-CoV-2 infection in vitro, despite eliciting a prolonged antiviral response. mBio. 2022;13.
Cong Zeng et al, Proc Natl Acad Sci 2022; 119(1):e2111400119

Post Acute Infection Syndromes: cause comuni?



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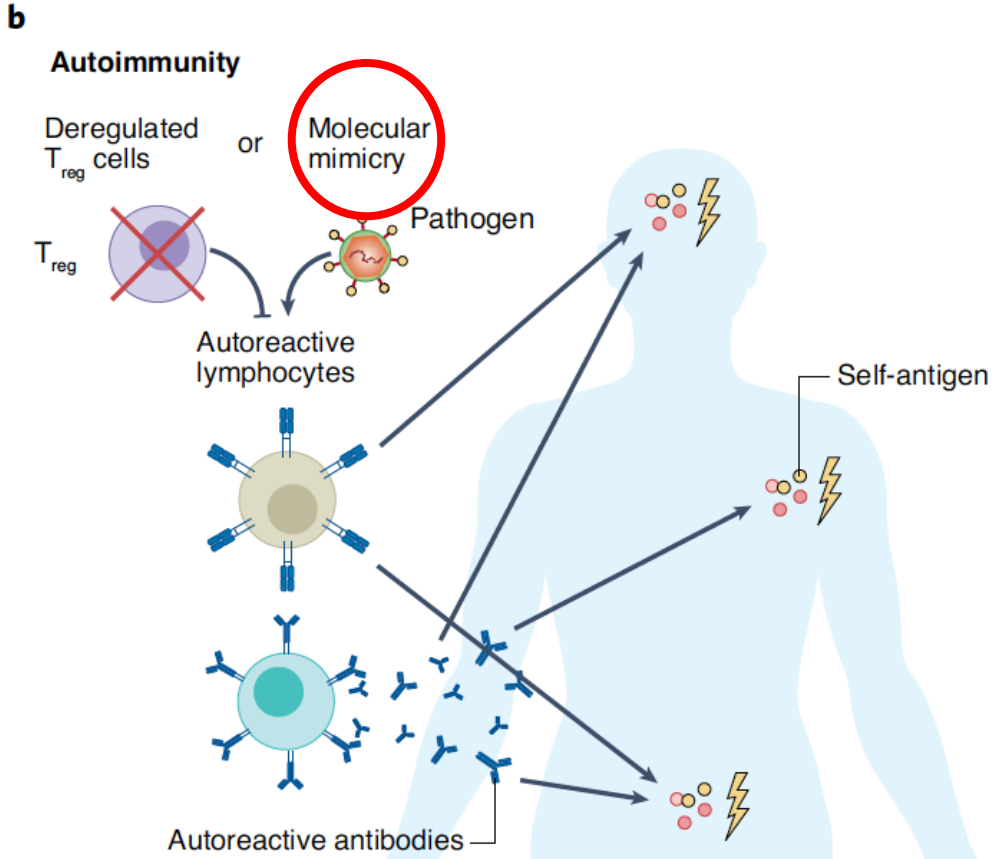

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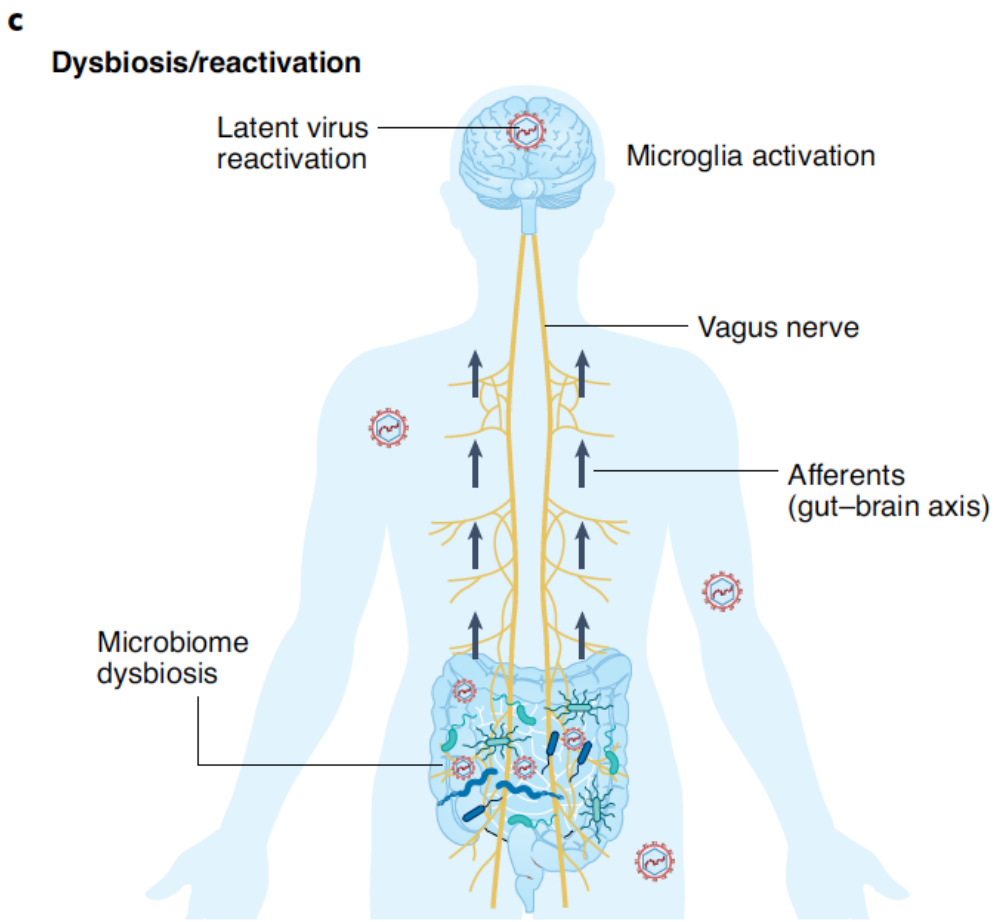
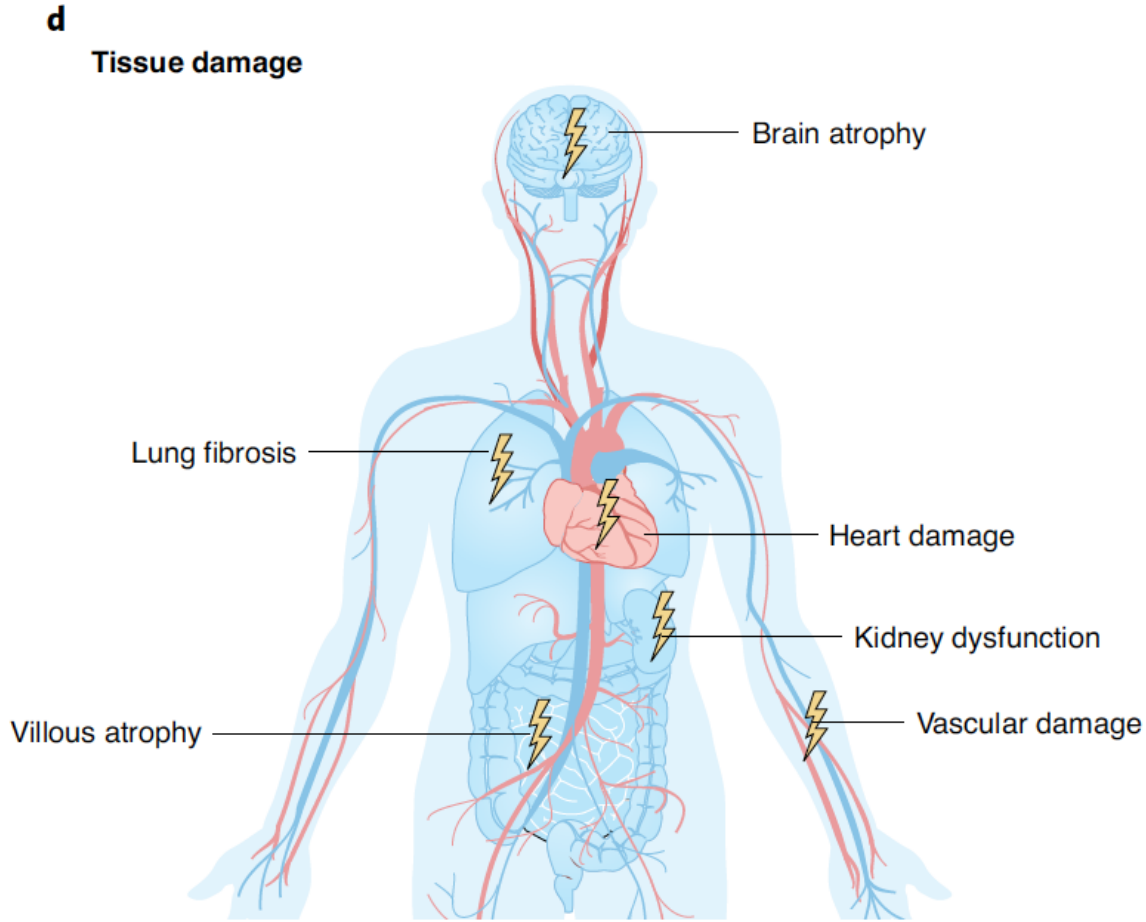
Post Acute Infection Syndromes: cause comuni?





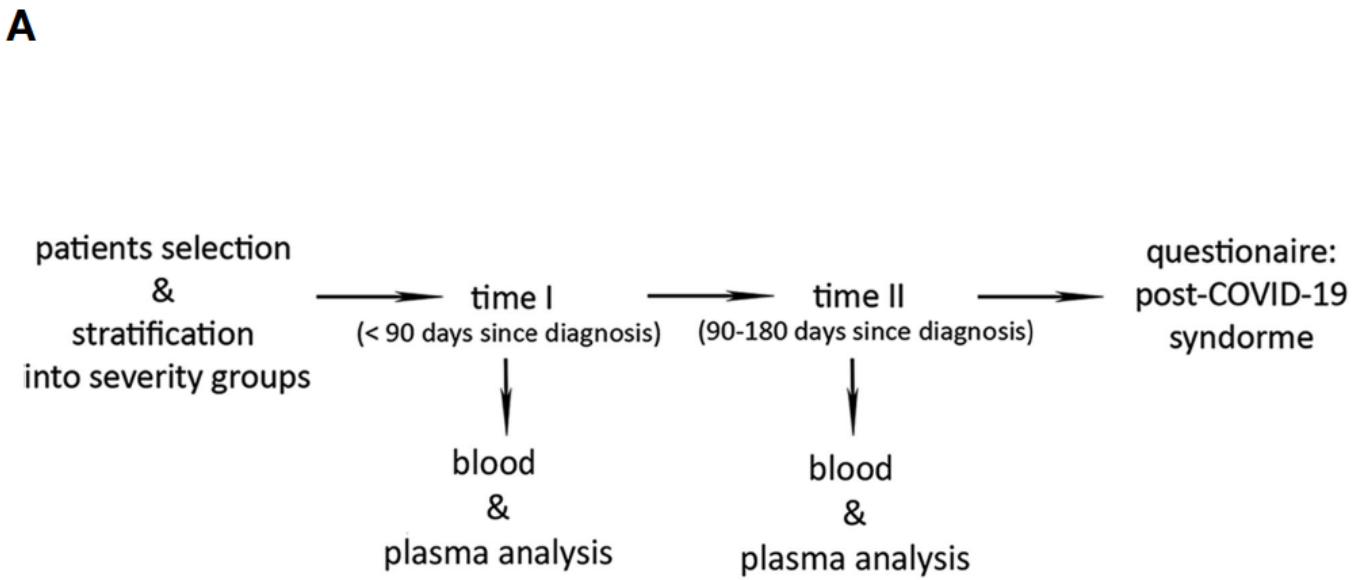
Disregolazione del microbioma, viroma o micobioma indotto dall'infezione acuta o dalla risposta immunitaria
Possibile riattivazione EBV/CMV/HSV

Su, Y. et al. Cell 185, 881–895 (2022).

Incapacità a riparare il danno tissutale per effetto del patogeno o della risposta immunitaria (fibrosi)

Matthay, M. A. et al. Nat. Rev. Dis. Prim. 5, 18 (2018).

Remodeling of T Cell Dynamics During Long COVID Is Dependent on Severity of SARS-CoV-2 Infection



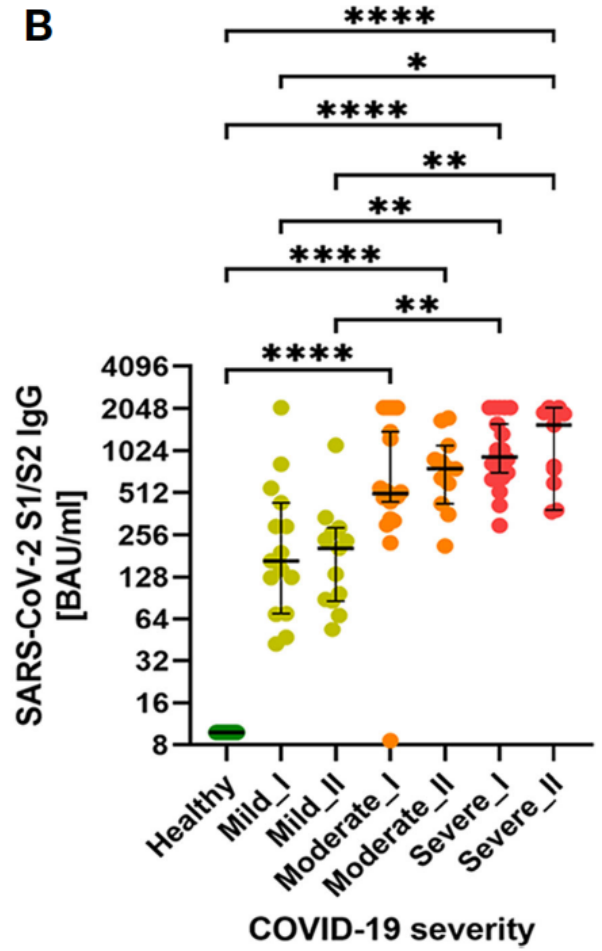
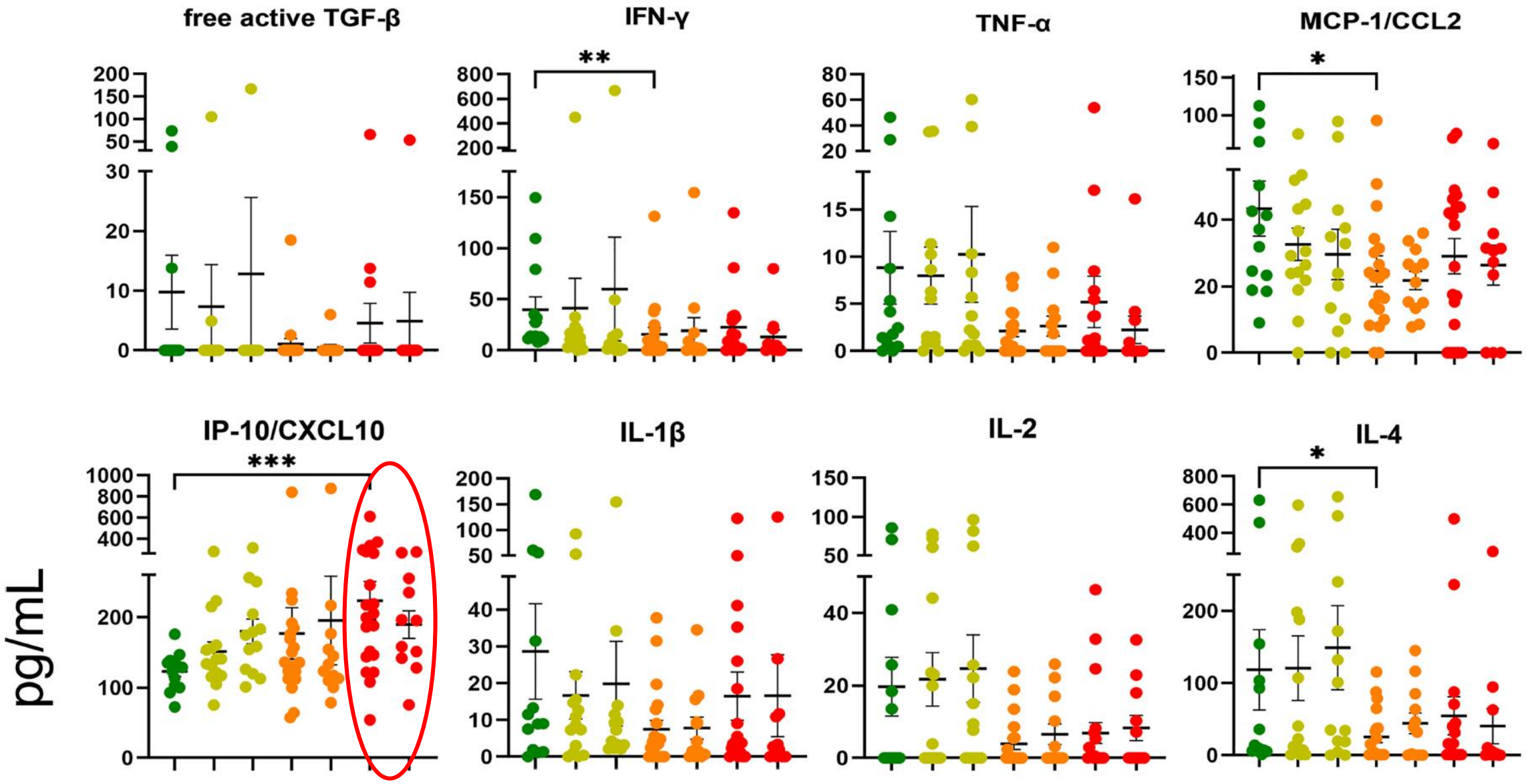


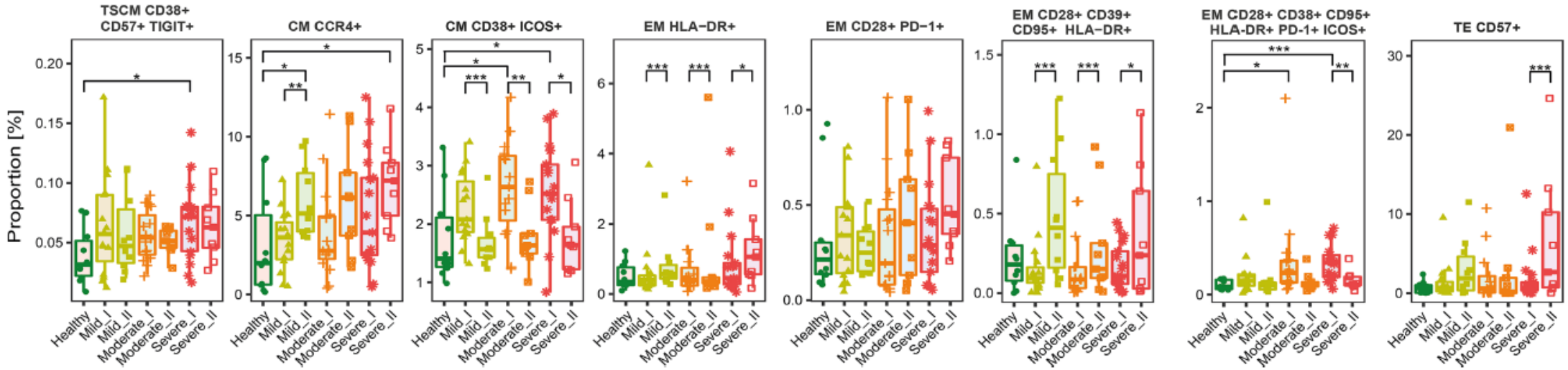
TABLE 3 | Appearance of post- acute COVID-19 syndrome (PACS, signs and symptoms beyond 12 weeks) in post-COVID-19 patients from all severity groups.

COVID-19 severity group	Cognitive dysfunction	Fatigue	Dyspnea
MILD (n=13)	30,7% (4/13)	38,4% (5/13)	15% (2/13)
MODERATE (n=17)	70,5% (12/17)	47,1% (8/17)	17,6% (3/17)
SEVERE (n=16)	43,7% (7/16)	50,5% (8/16)	50,0% (8/16)

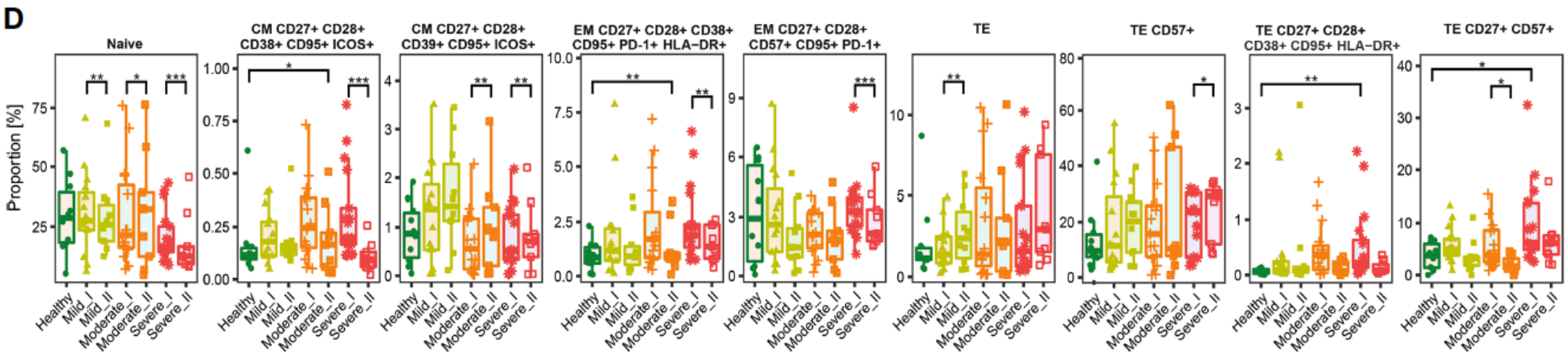
Data have been collected during an interview made by a clinician.


free active TGF-β
IFN-γ
TNF-α
MCP-1/CCL2
IP-10/CXCL10
IL-1β
IL-2
IL-4
pg/mL
**
*
***
*

CD4 T cells



CD8 T cells



At the immunological level, aging is often described as the interplay between changes in the native immune system, mainly depicted by the construct of inflammaging (Franceschi et al., 2000), and those occurring in the adaptive immune system, represented by senescence of T-cells (Goronzy et al., 2015). In the context of COVID-19 disease in older persons, it is argued that the pre-existing reduction of the total number of naive T cells and increase of memory T cells may explain a higher risk of severe clinical presentation and worse outcomes (Fulop et al., 2018). The older person who survived the acute phase may experience an alteration of the immune-inflammatory homeostasis (Yanes et al., 2017). Persistent immune activation may be associated with ongoing symptoms following COVID-19 (Gibellini et al., 2022).

In a US study, persons who developed PACS presented higher levels of cytokine biomarkers, including tumor necrosis factor alfa and interferon-gamma-induced protein 10. There was also a trend toward more elevated interleukin-6 levels during the recovery (Peluso et al., 2021). It is noteworthy that the SARS CoV-2 infection may negatively impact several, although strongly interacting, hallmarks of aging (e.g., oxidative stress, metabolic derangement, mitochondria dysfunction, DNA damage) (Barzilai et al., 2020).

The virus-induced activation of innate and adaptive immune systems may represent an overwhelming challenge to this crucial defense mechanism, directly contributing to immunosenescence (Bektas et al., 2020; Borella et al., 2022; Gibellini et al., 2020). COVID-19 may predispose individuals to inflammaging through innate immunological response. Leukocytes can remain persistently infected by COVID-19,

Inflammaging and immunosenescence

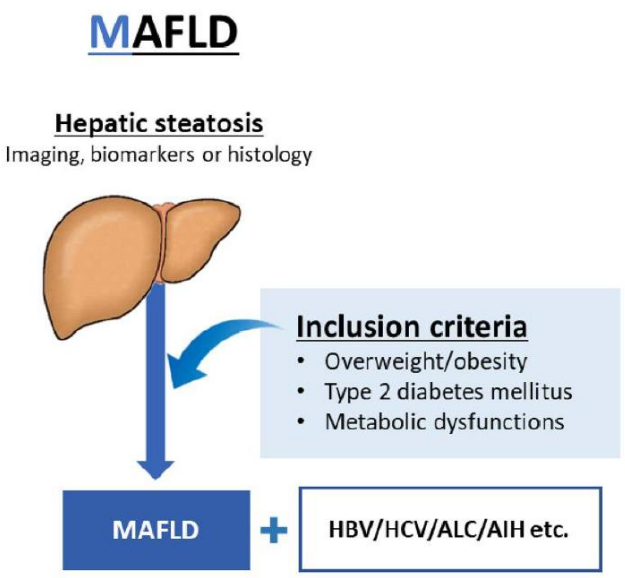
The interplay between inflammaging and immunosenescence (Calabrese et al., 2015) may represent the basis of the immunopathogenesis of PACS, through the accumulation of senescent cells which acquire a senescence-associated secretory phenotype (SASP) (Fulop et al., 2018). It is hypothesized that this phenotypic change results from cellular stress secondary to SARS CoV-2 impairment cellular homeostatic mechanisms. The SASP can release cytokines, chemokines, proteases, reactive metabolites, growth factors, noncoding nucleotides (Coppé et al., 2008; Zhu et al., 2014; Iske et al., 2020). Even after the acute condition is over, the residual burden of senescent cells may cause chronic inflammation through the continuous production of SASP proteins. SASP can cause dysfunction and contribute to cognitive, metabolic, physical, and vascular dysfunction, tissue fibrosis, disease susceptibility and severity, and mortality (Khosla et al., 2020; Xu et al., 2015, 2018; Roos et al., 2016; Schafer et al., 2017; Tchkonia and Kirkland, 2018; Wang et al., 2020).

Metaflammation: metabolic inflammation

Metaflammation conceptualizes the inflammation which accompanies metabolic diseases associated with nutrient excess. Metaflammation might precede and contribute to inflammaging and metabolic age-related diseases could be considered manifestations of the acceleration of ageing. Inflammaging and metaflammation largely share the same molecular mechanisms, which have been highly preserved in the evolutionary process.

The gut microbiota has a central role in metaflammation and inflammaging, mediated by tryptophan metabolism. In detail, kynurenine (Kyn) metabolism can be described as a homeostatic process balancing kynurenine to tryptophan and quinolinic-to-kynurenic acid ratios. The former has been associated with obesity and the latter with inflammatory states in the general population; interestingly, both appear to be increased in PACS.

MAFLD



- Requirement of metabolic dysfunction
- Combination with other liver diseases
- Independent from alcoholic intake
- No requirement for liver biopsy

At a clinical level, metaflammation in people with PACS can be captured by Non-alcoholic fatty liver disease (NAFLD) (Byrne and Targher, 2015; Chitturi and Farrell, 2007) which carries a high risk of cardiovascular complications and mortality. More recently, Eslam and colleagues suggested a name change from NAFLD to MAFLD that stands for Metabolic (dysfunction)-associated fatty liver disease. This new construct focuses on "positive" criteria that strength the association with metabolic risk factors rather than exclusionary criteria (absence of significant alcohol intake (Eslam et al., 2020). Recent studies have proposed that MAFLD is a hepatic manifestation of a multisystem disorder, which is heterogeneous in its underlying causes, presentation, course, and outcomes (Lonardo et al., 2021; Lonardo, 2021).

In a recent study comprising 235 patients assessed for PACS, the prevalence of MAFLD was 55.3% at the time of PACS diagnosis and 37.3% on hospital admission ($p < 0.001$). MAFLD was independently associated with insulin resistance, body mass index, and metabolic syndrome. Given the high prevalence of MAFLD, the authors argued that it may represent a specific PACS-cluster phenotype, with potential long-term metabolic and cardiovascular health implications (Milic et al., 2022).

ISS

Indicazioni *ad interim* sui principi di gestione del Long-COVID

Versione del 1° luglio 2021

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CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Guidelines

ESCMID rapid guidelines for assessment and management of long COVID

Dana Yelin [1, 2], Charalampos D. Moschopoulos [3], Ili Margalit [1, 2, 4], Effrossyni Gkrania-Klotsas [5], Francesco Landi [6], Jean-Paul Stahl [7], Dafna Yahav [3, 4, *]

PC-COS

Summary results of the Post COVID-19 Condition (Long COVID) Core Outcome Set study's 'how to measure' consensus process

Core Outcome Set (COS) for Long COVID/Post COVID-19 condition

(1) As a reminder, here is 'what' we agreed should be measured:

Outcome domain	Plain language definition
Survival	How long does someone live.
Cardiovascular functioning, symptoms, and conditions	New onset or worsening of problems affecting the heart (e.g. pounding or racing heart) and the blood vessels (e.g., veins or arteries), light-headedness/fainting (including on standing).
Fatigue or exhaustion	New onset or worsening in severity or duration of feeling exhausted, having too little energy, or needing more rest.
Pain	New onset or worsening of problems related to uncomfortable feelings in the body that can include sharp or burning pain, dull ache, or stinging or throbbing feeling, pain that comes and goes.
Nervous system functioning, symptoms, and conditions	New onset or worsening of dizziness, fainting, headache, tremors/shaking, seizures/fits, tingling feelings, decreased sensation, stroke, inability to move part of the body, lack of coordination/balance, or speech difficulty.
Cognitive functioning, symptoms, and conditions	New onset or worsening problems with memory, communication, concentration, or understanding instructions.
Mental functioning, symptoms, and conditions	New onset or worsening problems with emotions and mood, including anxiety/worrying, avoidance, catastrophizing, panic attacks, depression, suicidal thoughts, or post-traumatic stress disorder.
Respiratory functioning, symptoms, and conditions	New onset or worsening problems with lungs or breathing (e.g., shortness of breath, chest tightness. or coughing).
Post-exertion symptoms	Worsening of symptoms following physical or mental exertion that can last for a prolonged duration.
Physical functioning, symptoms, and conditions	New onset or worsening problems with physical abilities, such as walking, dressing, or eating.
Work/occupational changes and study	New onset or worsening problems with being able to resume work, study or activities/hobbies.
Recovery	How long it takes to recover, i.e., feel better, no longer having symptoms.

DLCO, Chest CT scan, Spirometry

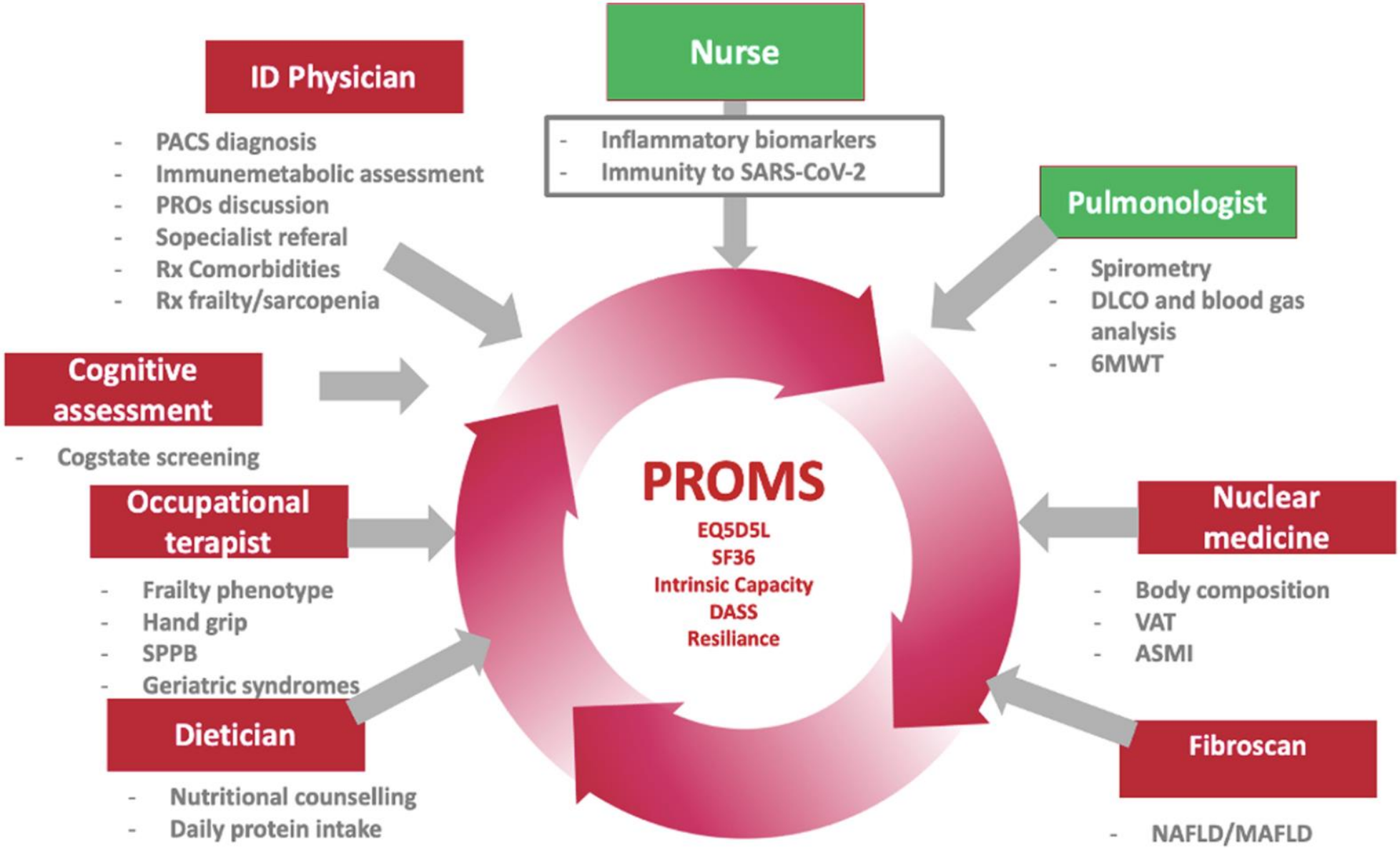
- Evidence is insufficient to provide a recommendation for or against chest imaging or spirometry.
- Chest CT should be considered at 3 to 6 months in patients with dyspnoea or abnormal PFTs, regardless of symptoms, to rule out other causes and identify fibrotic changes.

Cardiac MRI studies have shown common abnormalities ranging from 19% to 71% in recovering patients at 1 to 4 months [63,68–71]. These findings usually did not correlate with symptoms and were temporary, as suggested by Joy *at el.*, and demonstrated resolution of findings at 6 months after diagnosis [72]. In data from systematic reviews, including variable severity of an acute COVID-19 population at a follow-up of 14 to 180 days, cardiac MRI abnormalities were reported with wide variability, and in up to 60% of 73% of tested patients. In four studies reporting formal diagnoses using cardiac MRI, myocarditis was reported in 0% to 37%, myopericarditis in 0% to 11%, pericarditis in 0% to 3%, and myocardial infarction in 0% to 2% of patients [40,73].

Recommendation. Evidence is insufficient to provide recommendations for or against any of the aforementioned cardiac tests. Considering TTE is noninvasive, it may be offered for patients presenting with persistent symptoms suggestive of perimyocardial injury (chest pain, palpitations, signs and symptoms of heart failure). It is reasonable that for patients who had cardiac abnormalities during acute disease (myocarditis, pericarditis, heart failure), a repeat TTE would be performed at 2 to 3 months. Further investigation for cardiac abnormalities should be performed according to symptoms in patients presenting with cardiac symptoms. Cardiac MRI should only be performed on a case-by-case basis with a specific clinical question in mind (e.g. athletes returning to physical activity).

Brain imaging. Few small studies have assessed brain imaging in patients with long COVID (Tables 5–7). Guedj et al. [79] conducted positron emission tomography/CT in 35 patients at a mean of 95.5 ± 30 days after acute COVID-19 and compared the findings with age- and sex-matched historical uninfected controls. They found specific areas of hypometabolism that were associated with symptoms of hyposmia/anosmia, memory/cognitive impairment, pain, and insomnia and that were significantly distinguished from the control group [79]. These findings were also demonstrated in smaller studies [80]. Raman et al. conducted a prospective study including 58 participants 2 to 3 months after acute moderate-to-severe COVID-19 compared with matched controls. Of the study cohort, 53 underwent brain MRI, with 32 showing abnormalities and higher rates of pathology in the thalamus and sagittal stratum compared with controls. Periventricular white matter hyperintensities in the study group did not correlate with cognitive impairment [63].

Recommendation. Limited evidence does not support the use of brain imaging to investigate long-COVID complaints, other than to rule out other causes or for research purposes.


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

7. Follow-up e monitoraggio

- Concordare con il paziente la frequenza del follow-up e del monitoraggio, oltre ai professionisti sanitari da coinvolgere.
- Condividere le decisioni, offrire al paziente la possibilità di un monitoraggio di persona o da remoto a seconda di disponibilità, preferenze e necessità cliniche.
- Adattare il monitoraggio ai sintomi del paziente e discutere ogni eventuale cambiamento, includendo sintomi nuovi e in peggioramento e il loro effetto sul benessere e sulla vita quotidiana.

Follow-up visits with a healthcare professional might be considered every 2–3 months, with frequency adjusted up or down depending on the patient's condition and illness progression. Continuity of care is important in the management of post-COVID conditions.

Should physical or pulmonary rehabilitation be offered to patients, and when?

A living systematic review evaluated rehabilitation specifically in COVID-19, both acute and post-acute phases, with one of the addressed questions being "what is the evidence for effect of intervention for limitation(s) of functioning?" [91,92]. Only three comparative studies were available for this question, addressing different patients and comparisons (Table 8). One of these studies is the RCT by Liu et al. described earlier [90,93,94]. Additional studies presented in this systematic review included noncomparative studies, all reporting significant improvement in symptoms and respiratory and general function in response to the intervention (Table 8).

Explicit timing of starting rehabilitation was not provided in the literature. The British Society of Rehabilitation Medicine recommends that rehabilitation start on patient admission and be continued throughout hospitalization and then after discharge [95]. Other guidelines for rehabilitation after critical illness in general recommend initiating rehabilitation programs within the first 30 days (at the post-acute phase) [96]. Rehabilitation programs

Dati HSP e progetti in corso

Long COVID: dati preliminari

Female gender is associated with long COVID syndrome: a prospective cohort study

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Methods

- Single-centre prospective cohort study
- Inclusion criteria:
  - adult patients hospitalised for COVID-19 at San Paolo and San Carlo hospitals, Milan, between ***March 1st 2020 and November 1st 2020***

AND

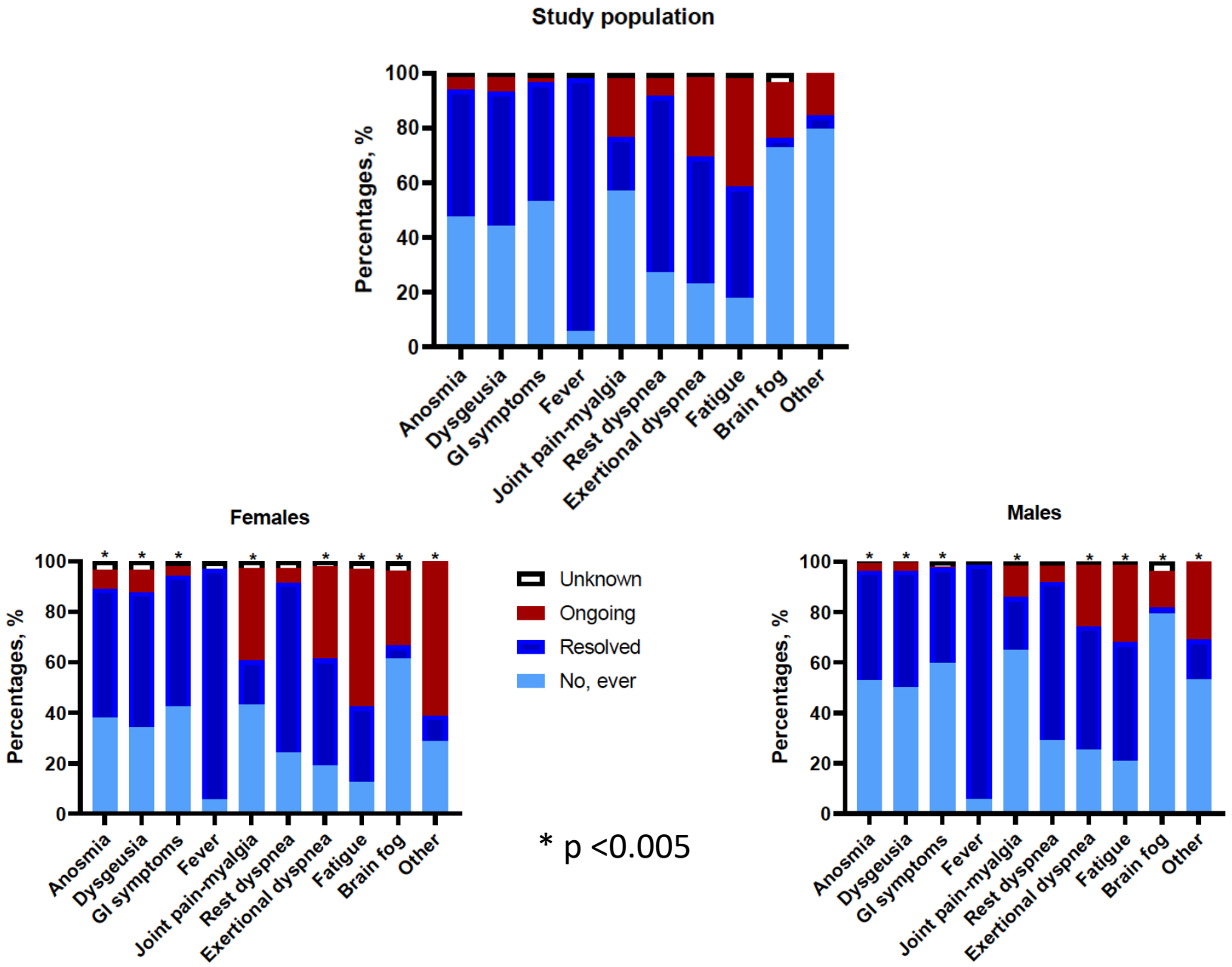
  - evaluated at the **post-COVID ID outpatient clinic between April 15th 2020 and December 15th 2020**

Demographic and clinical characteristics of patients according to “long COVID”

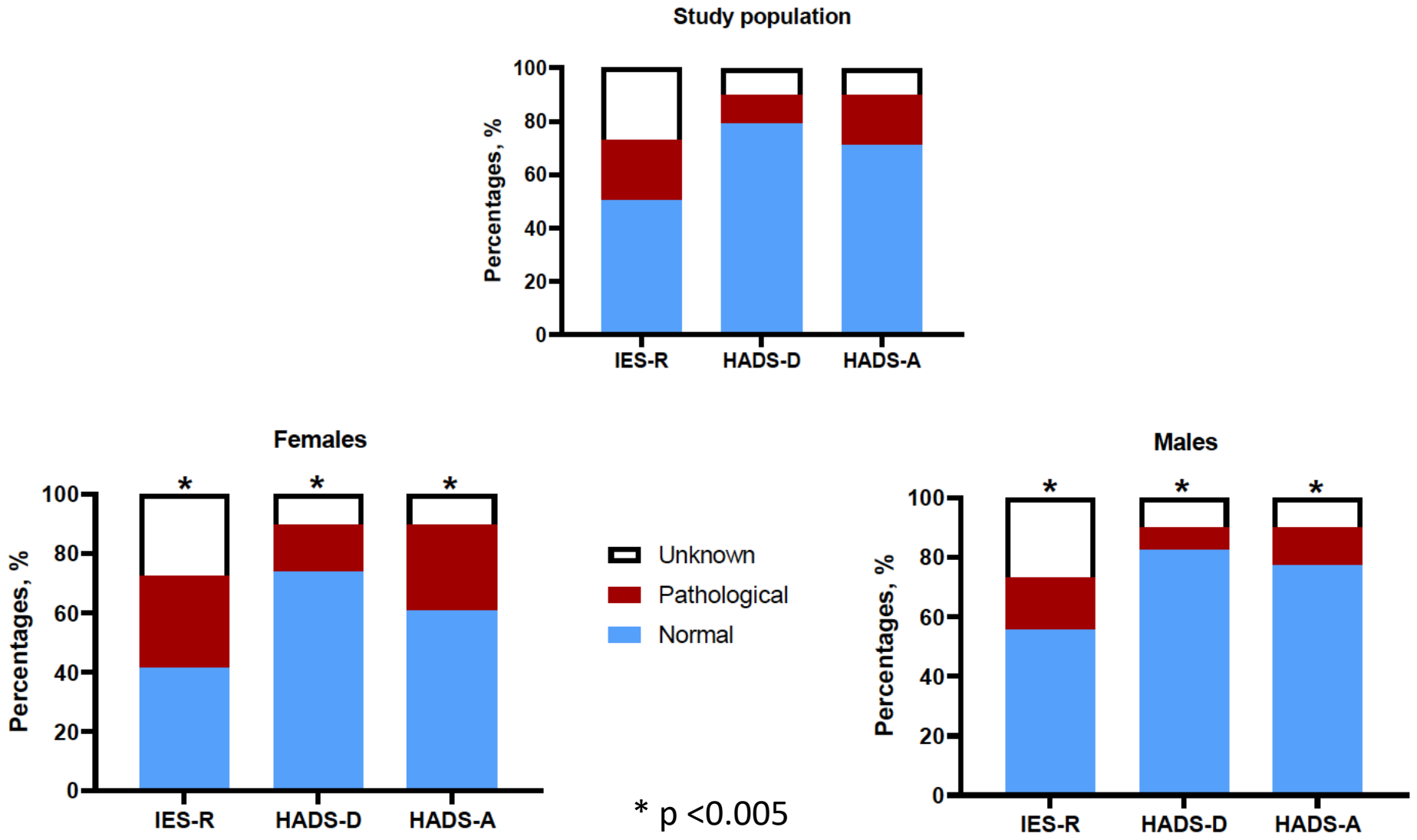
Parameters	Total population (N 377)	No long COVID (N 117)	Long COVID (N 260)	p values
Age, years*	57 (49-68)	56 (42-64)	58 (51-69)	**0,008**
Gender, females°	137 (36,3%)	25 (21,4%)	112 (43,1%)	**<0,0001**
Comorbidities°	164 (43,5%)	45 (38,5%)	119 (45,8%)	0,185
Smoking°:				**0,046**
Never	216 (57,3%)	71 (60,7%)	145 (55,8%)	
Ex smokers	20 (5,3%)	9 (7,7%)	11 (4,2%)	
Active smokers	131 (34,7%)	30 (25,7%)	101 (38,8%)	
Unknown	10 (2,7%)	7 (5,9%)	3 (1,2%)	
Pneumonia:				0,287
Absence of pneumonia	31 (8,2%)	9 (7,7%)	22 (8,5%)	
Pneumonia	346 (91,8%)	108 (92,3%)	238 (91,5%)	
Oxygen therapy°:				0,879
No 02 therapy	35 (9,3%)	13 (11,1%)	22 (8,4%)	
Low/high flows systems	197 (52,2%)	60 (51,3%)	137 (52,7%)	
CPAP, NIV	115 (30,6%)	35 (29,9%)	80 (30,8%)	
OTI	30 (7,9%)	9 (7,7%)	21 (8,1%)	

*median (IQR), Mann Whitney test ° n (%), Chi-square test

Persistent symptoms in «long COVID»



PTSD, anxiety and depression in «long COVID»



Factors associated with “long COVID” in univariable and multivariable logistic regression

PARAMETERS	OR (95%CI)	p values	AOR (95%CI)	p values
Female (*vs* male)	2,78 (1,68-4,62)	<0,0001	3,32 (1,78-6,17)	<0,0001
Age, 10 years older	1,03 (1,01-1,04)	0,001	1,03 (1,01-1,05)	0,01
No 02 therapy low high flows CPAP/NIV/IOT	1 0,67 (0,38-1,19) 0,97 (0,55-1,71)	 0,17 0,91	1 0,39 (0,19-0,82) 0,67 (0,29-1,55)	 0,01 0,34
LOS, Each day more	1,01 (0,99-1,03)	0,28	0,998 (0,97-1,03)	0,92
Comorbidities (*vs* no)	1,35 (0,86-2,11)	0,19	1,05 (0,597-1,84)	0,87
Active smoker Unknown Never smoker Former smoker	1 0,13 (0,03-0,52) 0,61 (0,37-0,997) 0,36 (0,14-0,96)	 0,004 0,05 0,04	1 0,16 (0,04-0,75) 0,56 (0,31-1,01) 0,19 (0,06-0,62)	 0,02 0,05 0,01
BMI ≥30 Unknown BMI <30	1 0,29 (0,096-0,91) 0,55 (2,27-5,06)	 0,03 0,02	1 0,13 (0,30-0,53) 0,55 (0,31-0,98)	 0,004 0,04
Time from symptoms onset to virological clearance, each day more	1,01 (0,99-1,02)	0,64	0,99 (0,98-1,01)	0,47

EUCARE-POSTCOVID Study: Objectives

Primary objective is to assess the prevalence and risk factors of post COVID-19 condition in a cohort of recovered COVID-19 patients.

EUCARE-POSTCOVID Study: study design and centers

Observational multicenter cohort study.

- The coordinator center is the Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo and Carlo, Department of Health Sciences, University of Milan, Milan, Italy.
- The other centers that will participate in the study are:

Vilnius University Hospital, Santaros Klinikos, Vilnius, Lithuania;
University Hospital Heinrich Heine of Dusserldorf, Dusserldorf, Germany;
Infectious Diseases, AIDS and Clinical Immunology Research Center Tbilisi, Georgia;
Policlinico “Tor Vergata”, Università degli Studi di Roma “Tor Vergata”, Rome, Italy;
Regional Hospital Dr. Juan Graham Casasús, Villahermosa, Tabasco, Mexico;
St. Mary Hospital, Imperial College Healthcare NHS Trust, London, England;
Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal;
St. Petersburg Phthisiopulmonology Research Institute, Russia

EUCARE-POSTCOVID Study: patients group

Patients diagnosed with acute COVID-19 disease from 01/03/2020 to 01/02/2025 will be enrolled in the study:

- **Group 1 (hospitalized patients):** patients hospitalized for COVID-19 disease; at hospital discharge patients will be given the appointments for the follow-up post COVID examinations;
- **Group 2 (outpatients):** patients diagnosed with mild COVID-19 disease and thus not hospitalized
- **Group 3 (non COVID, control group):** non-COVID-19 hospitalized patients (hospitalized for other viral/bacterial pneumonia).

EUCARE-POSTCOVID Study: procedures

At each post COVID-19 visit (**at 2-3 months, 6-9 months, 12-15 months**):

- Short version of **WHO CRF** for collection of symptoms, Fatigue Numerical Rating Scale, MRC dyspnea scale
- **Routine blood exams** and collection of blood/serum samples
- **Hr-QoL** (EQ5D-5L)
- **Psychological questionnaires**: HADS-A/D (anxiety/depression), PTSD (Post-Traumatic Stress Disorder)
- **Hospital re-admissions,** COVID vaccination status

If clinical needs: pneumological/cardiological/neurological/other consultant evaluation

Patients with confirmed diagnosis of SARS-CoV-2 infection/COVID-19 hospitalized at San Paolo Hospital (Milan, Italy), from 24 February 2020 to 04 November 2021, and at Policlinico Tor Vergata (Rome, Italy), from 24 February 2020 to 07 January 2022 and discharged alive.
Analysis included a proportion of these who underwent a visit to a post COVID-19 outpatient clinic set-up in each center.

In details, the patients enrolled in the EUCARE-POSTCOVID study cohort were **612 from San Paolo hospital and 160 from Policlinico Tor Vergata**.
During the same period, a total of 2802 patients have been hospitalized because of SARS-CoV-2 infection/COVID-19 in the two centres, but just 787 were enrolled in the post-COVID-19 clinic (27.5%).
PASC cohort consist of **772 patients**.

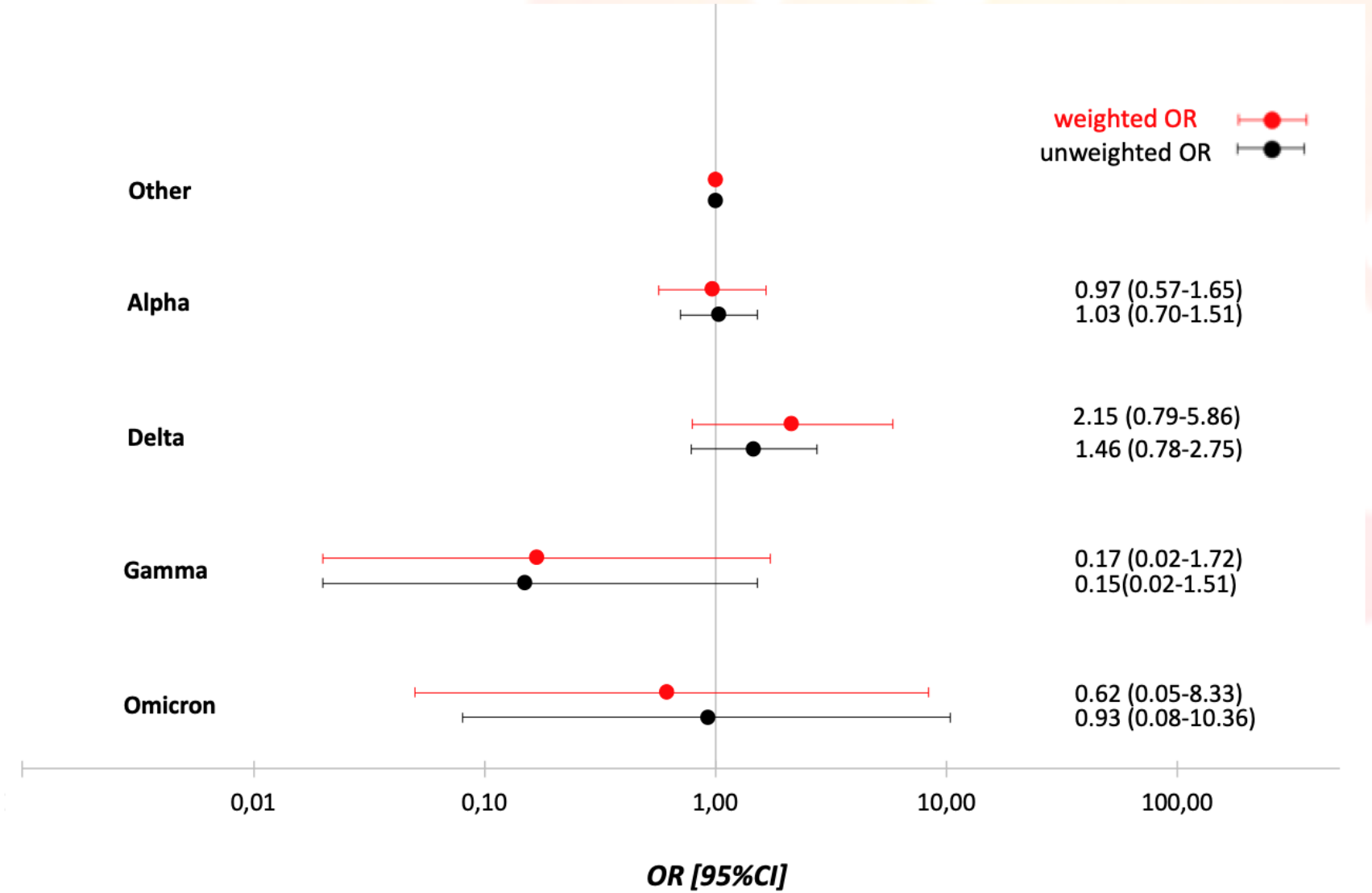
Table 5. PASC cohort description by PASC definitions.

PASC Definitions	Number of patients N=772	% of PASC study cohort
WHO PASC	530	68.7%
Physical PASC	505	65.4%
Psychological PASC	229	29.7%
Only physical symptoms	204	26.0%
Only psychological symptoms	25	0.03%

Table 6. PASC cohort description by clusters of PASC symptoms.

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 Encephalomiyelitis	446	57.8%
Other	7	0.9%

Figure 4. Forest plot OR on the role of the different virial variants in developing WHO PASC.



Key recommendations for research

1 Interventions for post-COVID-19 syndrome

What are the most clinically effective interventions (including social prescribing and structured community support) for managing post-COVID-19 syndrome?

Does effectiveness vary for different population groups (for example, sex, age, socioeconomic group, black, Asian and minority ethnic group communities or people with a learning disability)?

Do any symptoms of post-COVID-19 syndrome predict the need for specialist intervention?

Are there clusters of symptoms that identify response to interventions in post-COVID-19 syndrome?

What is the clinical effectiveness of different service models of multimodality/multidisciplinary post-COVID-19 syndrome rehabilitation in improving patient-reported outcomes (such as quality of life)?

What is the clinical effectiveness of exercise interventions for people with post-COVID-19 syndrome? Does effectiveness vary for different population groups (for example, sex, age, socioeconomic group, black, Asian and minority ethnic group communities or people with a learning disability)?

Does early exercise rehabilitation assist in improving symptoms of post-COVID-19 syndrome?

2 Prevalence of post-COVID-19 syndrome

What is the prevalence and incidence of post-COVID-19 syndrome in people who have received single, double or boosted doses of the approved vaccinations in the UK? Does this vary across different population groups (for example in black, Asian and minority ethnic group communities)? [updated 2021]

Other recommendations for research

Prognostic markers of developing post-COVID-19 syndrome

What is the clinical effectiveness of D-dimer and other blood tests and clinical features as prognostic markers of developing post-COVID-19 syndrome?

Presentation of post-COVID-19 syndrome in children, young people, pregnant women and older people

What symptoms do children, young people, pregnant women and older people with suspected post-COVID-19 syndrome present with?

Clinical course of post-COVID-19 syndrome

What is the natural history of post-COVID-19 syndrome?

What pathophysiological mechanism(s) underlie the most common presentations of post-COVID-19 syndrome? For example, generalised fatigue, breathlessness and 'brain fog'? [new, 2021]

Validated tools for screening for post-COVID-19 syndrome

Develop and validate new and existing screening tools (including physical, psychological and psychiatric aspects) for post-COVID-19 syndrome in a UK population.

What tools are validated for screening for post-COVID-19 syndrome, which are the most accurate at identifying post-COVID-19 syndrome in a UK population and what is their effectiveness in guiding management?