UNIVERSITÀ DEGLI STUDI DI MILANO

DIPARTIMENTO DI SCIENZE BIOMEDICHE E CLINICHE

La gestione del paziente long COVID

Spinello Antinori

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Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study

Yan Xie, Taeyoung Choi, Ziyad Al-Aly

Lancet Infect Dis 2023

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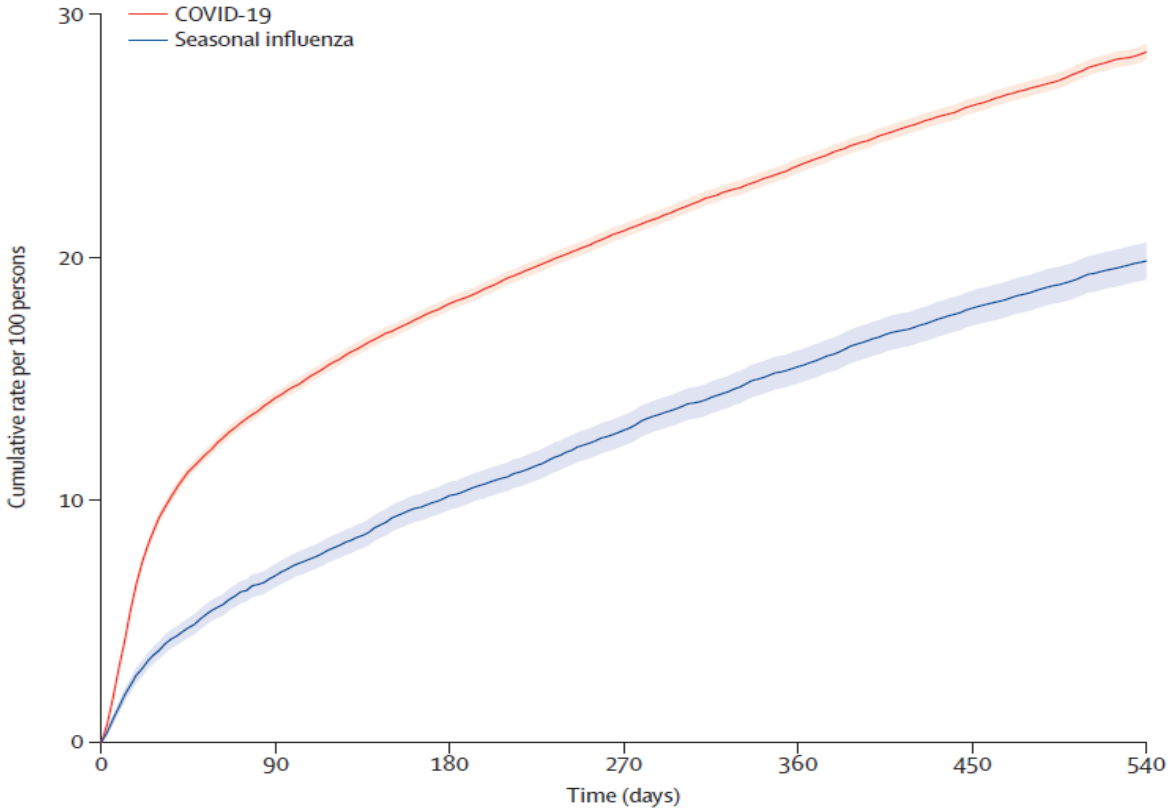
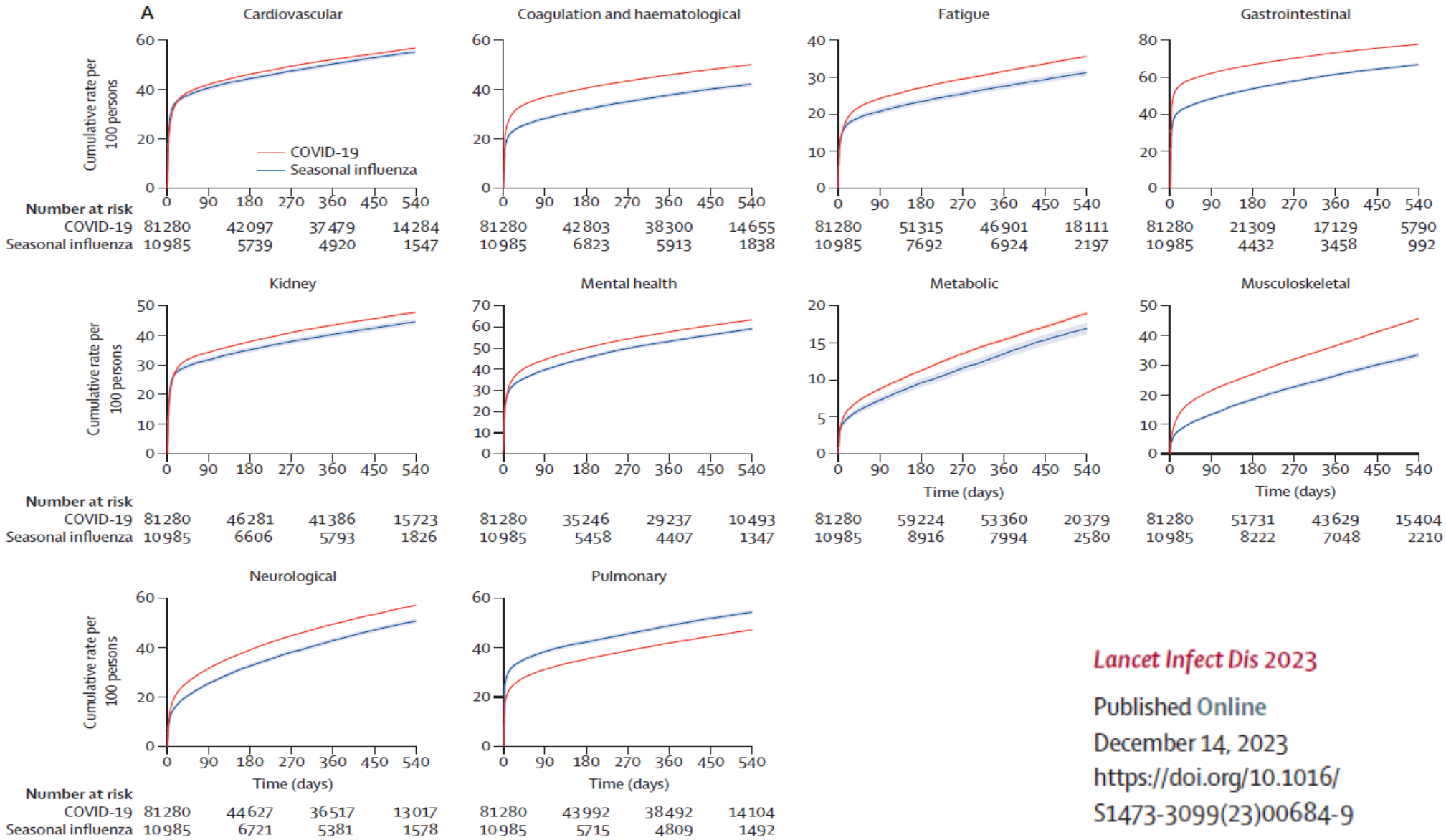


Period	0–30	0–180	0–360	0–540
Number at risk				
COVID-19	81280	67077	63647	25528
Seasonal influenza	10985	9858	9260	3125
Hazard ratio (95% CI)	2·51 (2·28–2·78)	1·86 (1·75–1·98)	1·61 (1·54–1·69)	1·51 (1·45–1·58)
Rate per 100 persons (95% CI)				
COVID-19	9·29 (9·09–9·48)	18·08 (17·81–18·34)	23·76 (23·47–24·05)	28·46 (28·14–28·78)
Seasonal influenza	3·80 (3·44–4·16)	10·17 (9·60–10·73)	15·48 (14·81–16·15)	19·84 (19·07–20·59)
Excess rate per 100 persons (95% CI)	5·48 (5·07–5·89)	7·91 (7·29–8·53)	8·28 (7·55–9·01)	8·62 (7·55–9·44)

Figure 1: **Event rates of death in COVID-19 and seasonal influenza**
Event rates per 100 persons are presented for COVID-19 (red) and seasonal influenza (blue). Shaded areas represent 95% CIs. The hazard ratio, rate, and rate difference per 100 persons during the periods of 0–30, 0–180, 0–360 and 0–540 days are also presented.

Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study

Yan Xie, Taeyoung Choi, Ziyad Al-Aly



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Mitigating neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness

Pratik Pandharipande, Shawniqua Williams Roberson, Fiona E Harrison, Jo Ellen Wilson, Julie A Bastarache, E Wesley Ely

	US Centers for Disease Control and Prevention (CDC)[15,16]	World Health Organization (WHO)[17]	UK National Institute for Health and Care Excellence (NICE)[18]
Primary terms used	Long COVID	Post COVID-19 condition	Ongoing symptomatic COVID-19 or post-COVID-19 syndrome
Current definition	Signs, symptoms, and conditions that last 4 weeks or more after acute infection	New-onset or persistent symptoms in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19, that last for at least 2 months and cannot be explained by an alternative diagnosis; no minimum number of symptoms is required for the diagnosis; a different definition might be applicable for children	Ongoing symptomatic COVID-19 defined as signs and symptoms that last 4–12 weeks after the onset of acute symptoms; post-COVID-19 syndrome defined as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 3 months, and cannot be explained by an alternative diagnosis
Plans to review and revise	Ongoing research initiatives (eg, the NIH RECOVER Initiative) are designed to clarify the clinical spectrum, phenotypes, and duration of long COVID; the CDC National Health Interview Survey 2022 and 2023 contains questions on ME/CFS, a closely related syndrome, and will examine the connections among ME/CFS, long COVID, and other chronic conditions; NASEM has an active committee that is examining the working definitions of long COVID	The definition is expected to change as new evidence emerges and knowledge of the sequelae of COVID-19 continues to evolve	Recommendations for future research include a focus on the clinical course of post-COVID-19 syndrome and the presentation of post-COVID-19 syndrome in children, young people, pregnant women, and older people

ME/CFS=myalgic encephalomyelitis/chronic fatigue syndrome. NASEM=National Academies of Sciences, Engineering, and Medicine. NIH=National Institutes of Health. RECOVER=Researching COVID to Enhance Recovery.

Table 1: Definitions of long COVID

Long COVID: a new word for naming fibromyalgia?

Xavier Mariette

Box 1 The different names of fibromyalgia though medicine history

⇒ Neurasthenia.
⇒ Fibrositis.
⇒ Myalgic encephalomyelitis.
⇒ Chronic fatigue syndrome.
⇒ Idiopathic diffuse polyalgic syndrome.
⇒ Gulf War syndrome.
⇒ Macrophages myofasciitis.
⇒ Postviral syndrome.
⇒ Sicca asthenia polyalgia syndrome.
⇒ Chronic Lyme disease.
⇒ Chronic chikungunya disease.
⇒ Ehlers-Danlos spectrum.
⇒ Long COVID.

In conclusion, 'to name is to soothe' as said by Roland Barthes a famous French philosopher and it is important to put a name on the symptoms present in around 5 to 10% of people more than 3 months after a benign COVID-19 infection. But 'naming things wrongly adds to the world's unhappiness' was saying Albert Camus. Thus, the term of long COVID, which suggests viral persistence of impaired immune response to the virus, is certainly unappropriated and should be replaced by fibromyalgia-like post-COVID-19 syndrome that better reflects the reality and will allow the patients to use all the non-pharmacological therapeutic arsenal used in fibromyalgia for being cured. Indeed, in this specific form of fibromyalgia where the stressing event is clearly identified, the prognosis is better than common fibromyalgia after using these therapeutics.[18] Research on the mecha-

The immunology of long COVID

Daniel M. Altmann[1], Emily M. Whettlock[2], Siyi Liu[1,2], Deepa J. Arachchillage[4,5] & Rosemary J. Boyton[2,3]

Box 1

Defining long COVID

WHO Delphi Consensus definition of long COVID:
Post-COVID-19 condition that 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 and others, 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 to children.

UK National Institute for Health and Care Excellence (NICE) definition:
Long COVID is a multisystem condition with a range of debilitating symptoms — signs and symptoms continue or develop after acute COVID-19, continue for more than 4 weeks, and are not explained by an alternative diagnosis. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Long COVID may consist of a number of distinct syndromes, which can include post-intensive care unit syndrome, post-viral fatigue syndrome, long-term COVID syndrome and permanent organ damage.

Box 3

Lessons from and for ME/CFS and the case of 'long SARS'

It is hard to discuss or present data on long COVID without being challenged about the relationship of findings to mechanisms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), not least by patient groups who understandably feel that their condition has endured decades of neglect in terms of biomedical research prioritization. In light of clear overlaps with long COVID, there now exists an opportunity for cross-hybridization, with much to be learnt from the long, past experience and investigations in ME/CFS, and from the new momentum of long COVID investigations over the past few years. The symptom overlap is self-evident, encompassing the key features of post-exertional fatigue, neurocognitive symptoms, dysautonomia and postural orthostatic tachycardic syndrome. A systematic review found that 25 of 29 CFS symptoms were reported by at least one long COVID study[18], whereas another study compared genes common between the two conditions in a number of ways, including pathway and network analysis[148]. This study found common hub proteins, such as IL-6 and IL-1β, between the two conditions. Another review focused on their similarities through the link of TGFβ signalling and circadian rhythms[148]. There is resonance in the post-acute viral infection symptomology across the two conditions[19]. ME/CFS has commonly been described as a post-viral condition that may ensue following a range of infections, including pandemic H1N1 influenza[149], Varicella zoster virus[150], enteroviruses and SARS-CoV-1[17]. Overlap in the immunopathological analyses is particularly interesting. It is noteworthy that raised CCL11, which has credentials as a long COVID serum biomarker functionally linked to neurocognitive symptoms, is also a biomarker of ME/CFS[151]. Revisiting the ME/CFS data also raises the possibility of investigating some of the implicated biomarkers, such as CXCL10 and leptin, in more detail in long COVID[152]. Furthermore, the ME/CFS data set may offer a reference framework to consider a role for Epstein–Barr virus reactivation in long COVID, noting that CFS can ensue from infectious mononucleosis associated with an enhanced imprint of T cell activation[153].

Long SARS, caused by SARS-CoV-1 infection, is a forerunner of long COVID and thus more helpfully considered as a variant of long COVID rather than a category of ME/CFS. A study from Canada and another from Hong Kong reported findings very similar to long COVID, with many people reporting chronic fatigue and psychiatric illnesses[17,154]. The comparative experience and lessons were recently reviewed and summarized[155]. Reviewing the Toronto University HCW cohort from 2003 to 2004, and with the caveat that it may be hard to extrapolate to long COVID generally as this was a group with severe disease and who were hospitalized, it was concluded that many of the changes were permanent and irreversible, with most patients unable to return to their former occupations.

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Clinical Infectious Diseases
VIEWPOINTS

Long COVID: Alice Evans, Brucellosis, and Reflections on Infectious Causes of Chronic Disease

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LONG COVID

A limitation of long COVID understanding is the very frustration Evans expressed 90 years ago [22] and reiterated in later publications [1, 31]: a lack of definitive diagnostic testing. Though some biomarker testing is in development, and diagnostic testing for some aspects of illness exist (such as tilt table tests for postural orthostatic tachycardia syndrome and magnetic resonance imaging for cardiovascular issues, reviewed in [12]), a lack of universal case definition [32] and definitive testing to confirm long COVID is detrimental to aspects of treatment, diagnosis, and a better understanding of the overall epidemiology of the condition. Though there are now more than 400 long COVID clinics and research sites in the US [33], many have long waitlists, and long COVID clinics in rural areas are sparse. The NIH is sponsoring the RECOVER (Researching COVID to Enhance Recovery) initiative, but of 53 current sites, most are also urban; 6 are in Boston alone.

Lacking such clear objective diagnostics clearly harms patients. As Evans experienced in her time, many long COVID patients today report "medical gaslighting" [34], with physicians suggesting that their symptoms are "psychosomatic" or merely due to "anxiety," reflections of Evans' battle with the diagnosis of "neurasthenia" almost a century ago.

COVID. While Evans had to counter influence from a dairy industry assuring the public that raw milk was perfectly safe, today's scientists have to counter individuals who have profited by pushing COVID-19 misinformation [36], as well as politicians who have staked out a reputation by minimizing COVID-19. This has put individuals at risk by demonizing vaccination (which lowers the risk of developing long COVID [37]) and even suggesting that SARS-CoV-2 does not exist, implying that long COVID patients are suffering from an imaginary illness and increasing stigma for this population.

As such, many long COVID patients are left to navigate the information ecosystem on their own, with social media replacing written letters to experts such as Evans. Thousands participate in Facebook groups such as "COVID-19 Long Haulers Support" and "Long COVID Support group," seeking advice and understanding from others who are experiencing similar symptoms and the isolation and stigma that sometimes accompanies them.

Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review

Chen Chen,[1,a] Spencer R. Haupert,[1,a] Lauren Zimmermann,[1,2] Xu Shi,[1] Lars G. Fritsche,[1,3,4] and Bhramar Mukherjee[1,2,3,4,5]

The Journal of Infectious Diseases

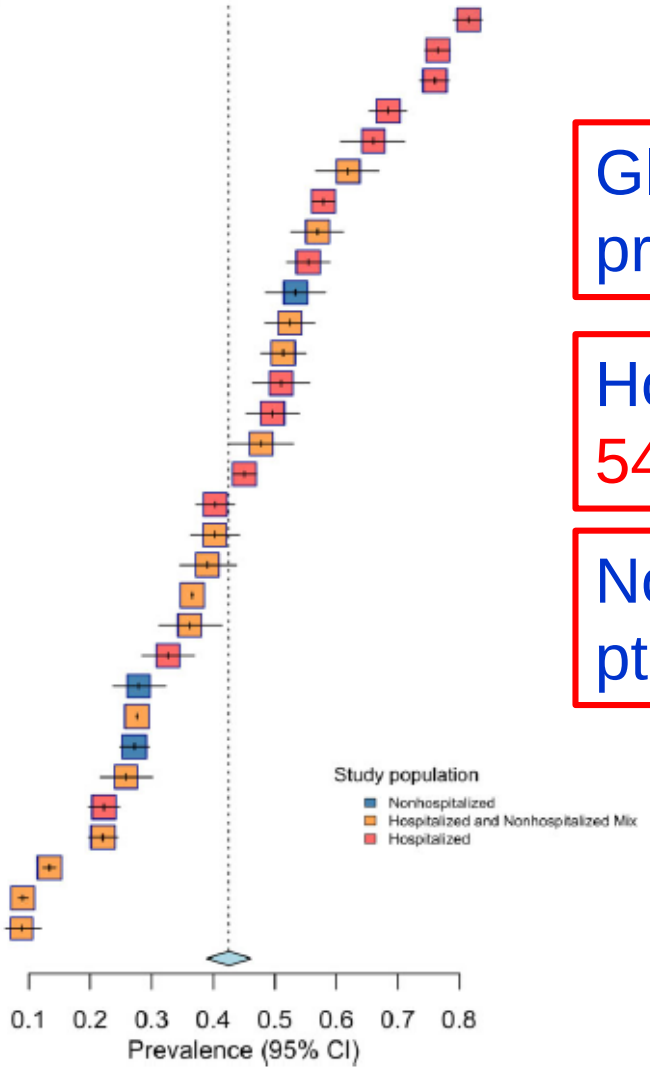
MAJOR ARTICLE

Asia 51%
Europe 44%
USA 31%

Female *vs* male 49% *vs* 37%

Studies	Prevalence (95% CI)
Fernández-de-Las-Peñas et al Spain	0.81 [0.79; 0.84]
Huang et al China	0.76 [0.74; 0.78]
Wong-Chew et al Mexico	0.76 [0.74; 0.78]
Ghosn et al France	0.68 [0.65; 0.71]
Areekal et al India	0.66 [0.61; 0.71]
Lemhofer et al Germany	0.62 [0.57; 0.67]
Munblit et al Russia	0.58 [0.56; 0.60]
Maestre-Muñiz et al Spain	0.57 [0.53; 0.61]
Shang et al China	0.55 [0.52; 0.59]
Desgranges et al Switzerland	0.53 [0.48; 0.58]
Hirschtick et al USA	0.52 [0.48; 0.57]
Venturelli et al Italy	0.51 [0.48; 0.55]
Morin et al France	0.51 [0.46; 0.56]
Xiong et al China	0.50 [0.45; 0.54]
Yomogida et al USA	0.48 [0.43; 0.53]
Zhang et al China	0.45 [0.43; 0.47]
Budhiraja et al India	0.40 [0.37; 0.43]
Peghin et al Europe	0.40 [0.36; 0.44]
Righi et al Europe	0.39 [0.35; 0.44]
Taquet et al USA+others	0.37 [0.36; 0.37]
Cirulli et al USA	0.36 [0.31; 0.41]
Chopra et al USA	0.33 [0.28; 0.37]
Augustin et al Europe	0.28 [0.24; 0.32]
Spotnitz et al USA	0.28 [0.27; 0.28]
Huang et al California	0.27 [0.25; 0.30]
Menges et al Switzerland	0.26 [0.22; 0.30]
Evans et al UK	0.22 [0.20; 0.25]
Naik et al India	0.22 [0.20; 0.24]
Sudre et al UK/SE/US	0.13 [0.12; 0.14]
Perlis et al USA	0.09 [0.08; 0.10]
Lampl et al Germany	0.09 [0.06; 0.12]
Total	0.43 [0.39; 0.46]

Heterogeneity: χ^2_{30} = 13875.94 (P < .001), I^2 = 100%



Global pooled prevalence 43%

Hospitalized pts 54%

Non hospitalized pts 34%

Prevalence and risk factors for long COVID and post-COVID-19 condition in Africa: a systematic review

Sophie Alice Müller, Lynda Isaaka, Rebekka Mumm, Christa Scheidt-Nave, Katharina Heldt, Angela Schuster, Mohammed Abdulaziz, Charbel El Bcheraoui, Johanna Hanefeld, Ambrose Agweyu

The included studies were conducted across eight African countries (table 1; appendix p 7): 13 papers from Egypt (n=3219),[26–31,35,36,40,42–45] four from South Africa (n=3491),[33,39,41,48] two from Tunisia (n=168),[37,46] and one from each of Ethiopia (n=79),[47] Ghana (n=2334),[32] Morocco (n=118 cases),[34] Uganda (n=1),[38] and Zambia (n=302).[49] All studies were conducted between March, 2020, and November, 2021, during the first three waves of the pandemic in Africa (appendix p 8), driven by the ancestral strain (first wave), the alpha variant (B.1.1.7) and beta variant (B.1.351; second wave), and the delta variant (B.1.617.2; third wave).[50] This time window corresponds to a period when less than 0·1% of the African population was vaccinated.[51]

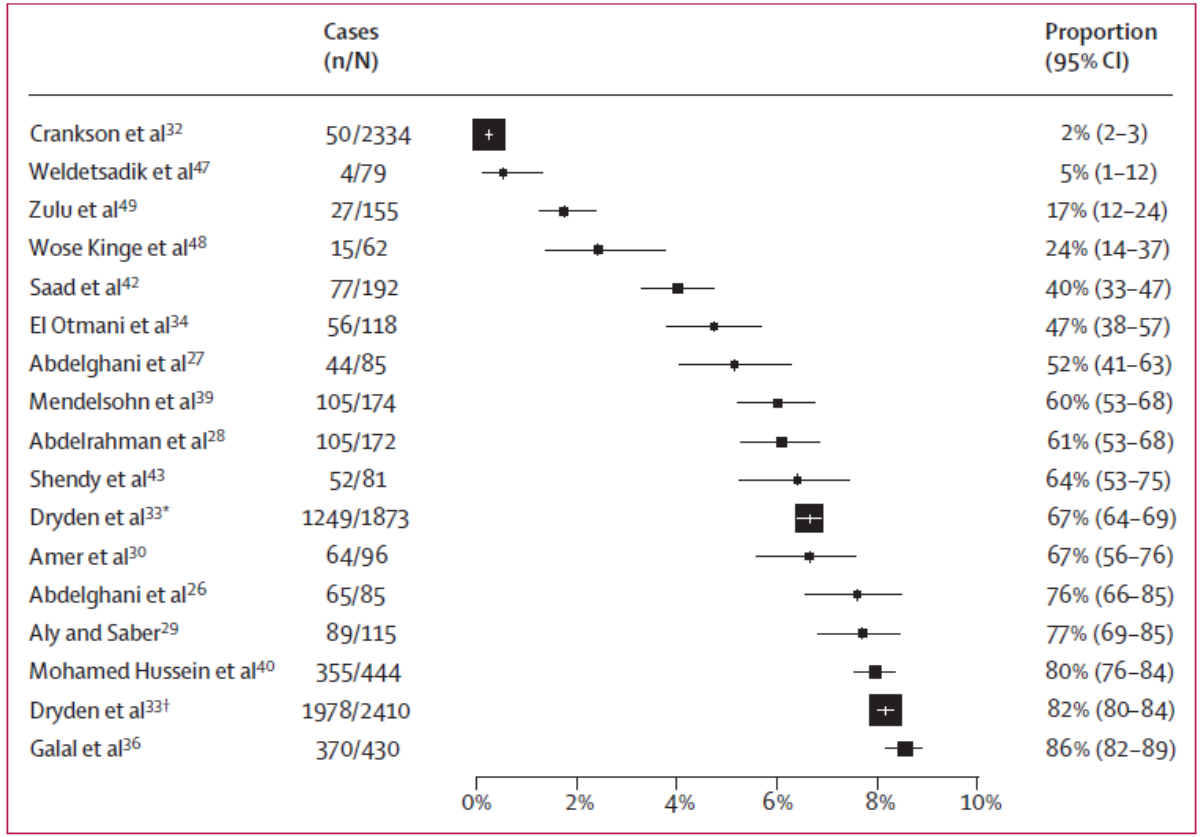
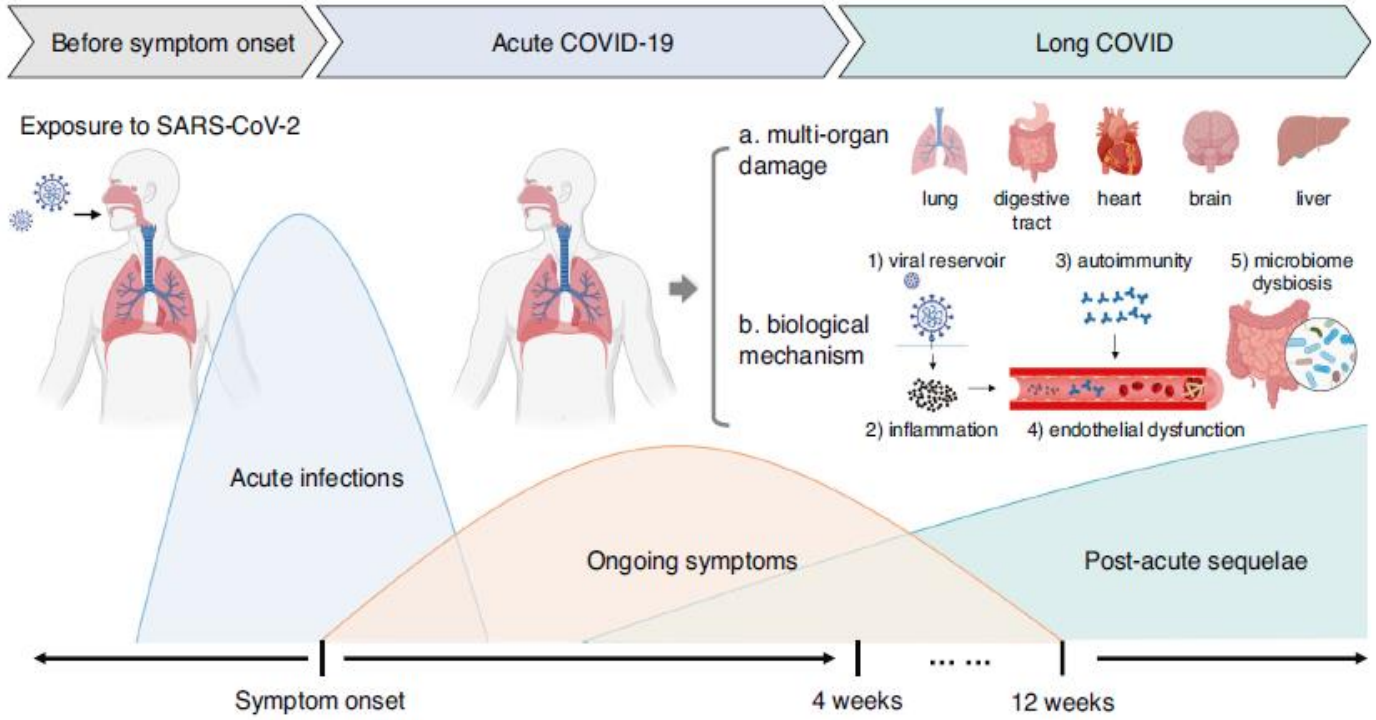
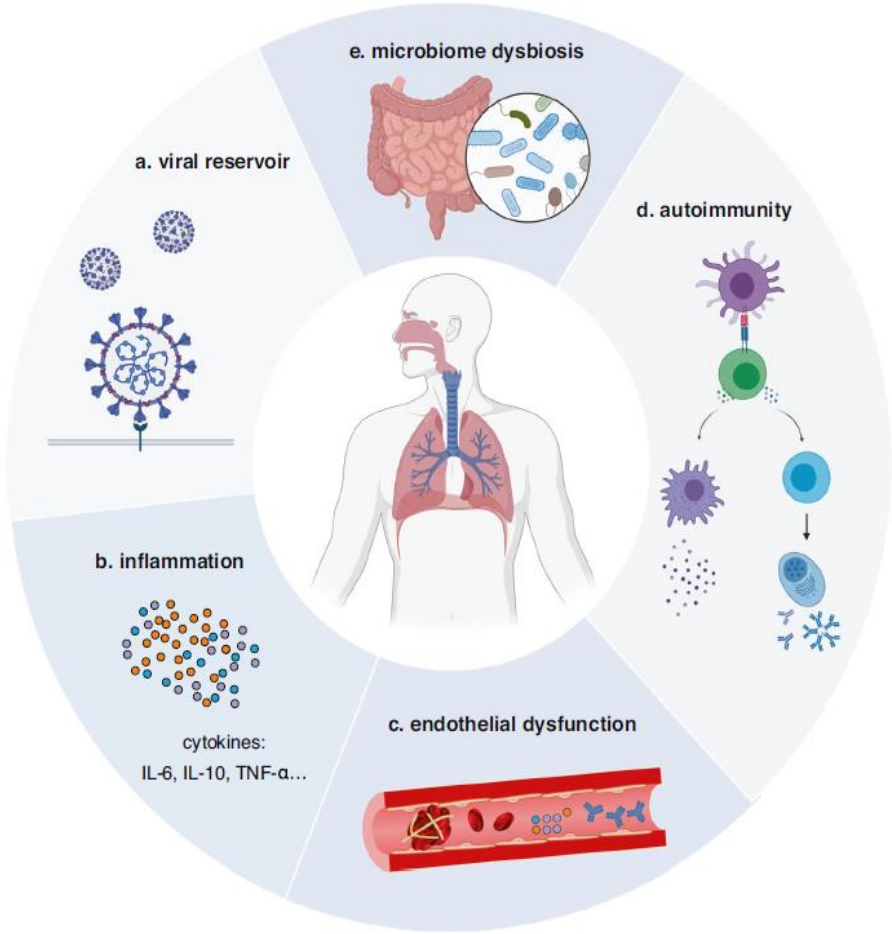


Figure 2: **Forest plot on prevalence of long COVID in included studies**
*After 3 months. †After 1 month.

The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID

Jingwei Li[1], Yun Zhou[1], Jiechao Ma[2], Qin Zhang[1,3], Jun Shao[1], Shufan Liang[1], Yizhou Yu[4]✉, Weimin Li[1]✉ and Chengdi Wang[1]✉





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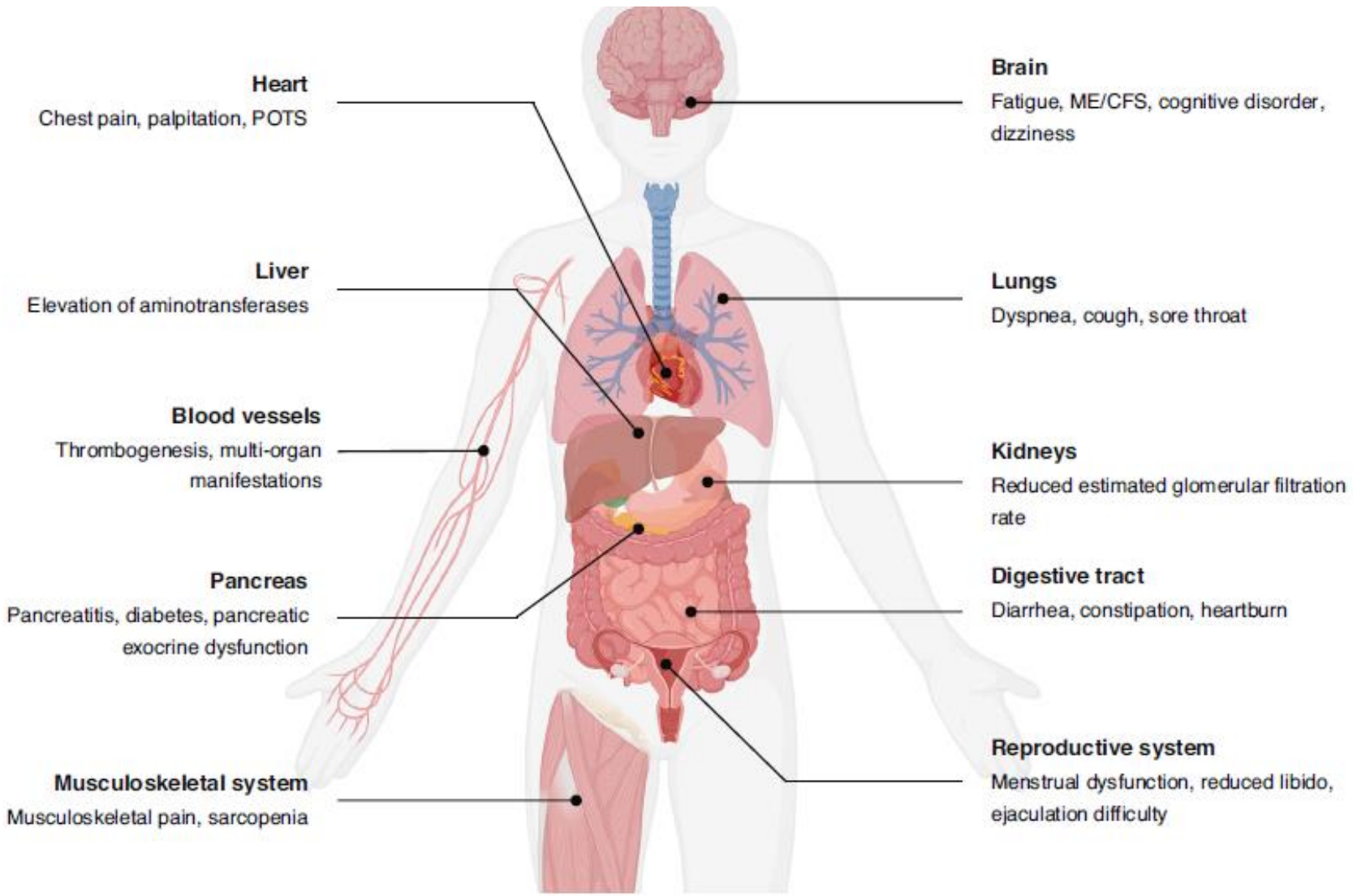

Signal Transduction and Targeted Therapy (2023)8:416

Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: A systematic review and meta-analysis

Cesar Fernandez-de-las-Peñas [a,*], Kin Israel Notarte [b], Raymart Macasaet [c], Jacqueline Veronica Velasco [d], Jesus Alfonso Catahay [e], Abbygail Therese Ver [d], William Chung [b], Juan A. Valera-Calero [f], Marcos Navarro-Santana [f]

Table 3
Pooled demographic and clinical data of the total sample (n = 7912).

	Total (n = 7912)
Age, mean (SD), years	59.5 (16.3) n = 7054 - 12 studies
Gender, female/male, n (%)	2823 (50.7%)/2741 (49.3%) 8 studies
Medical co-morbidities	
1 or more comorbidities	54.0% (30.65; 76.45) n = 1767/4747 I^2 = 99.3% - 5 studies
Hypertension	33.95% (25.95; 41.2) n = 1248/3669 I^2 = 94.1% - 6 studies
Obesity	22.35% (10.65; 36.8) n = 209/1173 I^2 = 96.9% - 5 studies
Diabetes	9.4% (5.4; 14.3) n = 744/6032 I^2 = 96.9% - 9 studies
Heart Disease	6.6% (4.4; 9.2) n = 613/6865 I^2 = 91.4% - 10 studies
COPD	3.5% (1.6; 5.9) n = 197/6501 I^2 = 95.1% - 8 studies
Cancer	3.0% (1.85; 4.4) n = 172/5738 I^2 = 86.2% - 6 studies
Kidney disease	2.2% (0.93; 3.93) n = 135/5615 I^2 = 87.6% - 6 studies
Stay at the hospital, mean (SD), days	14.5 (8.8) n = 4975 - 7 studies
ICU admission	
Yes/No, n (%)	235/7208 (3.2%) n = 8 studies
Stay at ICU, mean (SD), days	21.2 (19.4) n = 125 - 3 studies
Follow up, mean (SD), days	722.9 (51.5) n = 7912 - 12 studies

COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; SD: Standard Deviation.

study was excluded because the data cannot be extracted.[19] Thus, 12 studies were finally included (Fig. 1).[20–31] Seven studies were conducted in European countries such as France,[26] Sweden,[25] Spain,[23] Switzerland,[21] Faroe Islands,[29] Italy,[30] and Germany.[31] Four studies were conducted in China[20,22,24,28] and one was conducted in the United States of America.[27]

Prevalence of post-COVID symptoms two-years after

Overall, the most prevalent post-COVID symptoms two-years after an acute SARS-CoV-2 infection were fatigue (28.0%, 95% CI 12.0 to 47.0, 11 studies, Fig. 2A), cognitive problems (27.6%, 95%CI 12.6 to 45.8, 6 studies, Fig. 2B), and pain symptoms (8.4%, 95%CI 4.9 to 12.8, 11 studies, Fig. 3). In addition, psychological problems such as anxiety (13.4%, 95%CI 6.3 to 22.5, 7 studies) and depressive (18.0%, 95%CI 4.8 to 36.7, 4 studies) levels as well as sleep problems (20.9%, 95%CI 5.25 to 43.25, 4 studies) also exhibited higher pooled prevalence rates (Fig. 4). All pooled data showed high heterogeneity ($I^2 \geq 75\%$).

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Journal of Infection xxx (xxxx) xxx–xxx

Pooled mean (95% confidence interval) pooled prevalence of post-COVID sympto
two-years after an acute SARS-CoV-2 infection.

Respiratory and General Symptoms	
Fatigue	**28.0% (12.0; 47.0)**
I^2	99.0%
Event/Total	1318/6432
Studies	11
Dyspnea	**9.4% (4.25; 16.35)**
I^2	96.4%
Event/Total	314/5452
Studies	11
Runny Nose	**8.2% (0.0; 31.5)**
I^2	98.2%
Event/Total	73/553
Studies	3
Sore Throat	**5.9% (1.2; 13.65)**
I^2	97.7%
Event/Total	186/3833
Studies	6
Cough	**4.0% (1.0; 8.6)**
I^2	94.8%
Event/Total	144/4544
Studies	8
Expectoration	**1.5% (1.0; 2.0)**
I^2	17.1%
Event/Total	51/3246
Studies	3
Neurological and Cognitive Symptoms	
Cognitive Alterations	**27.6% (12.6; 45.8%)**
I^2	98.7%
Event/Total	589/2837
Studies	6
Ageusia	**4.85% (1.1; 10.8)**
I^2	95.79%
Event/Total	110 /3823
Studies	8
Anosmia	**5.25% (1.25; 11.55)**
I^2	97.1%
Event/Total	160/3623
Studies	6
Dizziness or Vertigo	**6.7% (1.7; 14.5)**
I^2	98.4%
Event/Total	267/5484
Studies	8
Gastrointestinal Symptoms	
Pooled Gastrointestinal Problems	**4.5% (1.85; 8.2)**
I^2	96.9%
Event/Total	305/8958
Studies	9
Diarrhea	**2.65% (0.01; 8.75)**
I^2	NA
Event/Total	55/2433
Studies	5
Nausea or Vomiting	**1.35% (0.2; 3.3)**
I^2	92.4%
Event/Total	49/4167
Studies	6
Stomach Pain	**6.35% (0.00; 21.95)**
I^2	95.2%
Event/Total	31/383
Studies	2
Pain Symptoms	
Pooled Pain Symptoms	**8.4% (4.9; 12.8)**
I^2	98.1%
Event/Total	1292/18,199
Studies	11
Chest/Thoracic Pain	**4.25% (2.0; 7.1)**
I^2	91.5%
Event/Total	234/5764
Studies	10
Joint Pain	**5.2% (1.3; 11.4%)**
I^2	96.2%
Event/Total	135/1875
Studies	3
Headache	**8.9% (2.3; 19.0)**
I^2	98.3%
Event/Total	286 /4020
Studies	9
Myalgia	**8.1% (0.99; 20.9%)**
I^2	98.3%
Event/Total	273/5271
Studies	7
Dermatological symptoms	
Hair Loss	**7.35% (3.2; 13.05)**
I^2	95.6%
Event/Total	247/2813
Studies	5
Skin Rashes	**2.45% (0.90; 4.65)**
I^2	82.9%
Event/Total	78/2926
Studies	6
Other type of post-COVID symptom	
Ocular problems	**7.7% (3.0; 14.2)**
I^2	95.8%
Event/Total	151/2198
Studies	7
Palpitations or Tachycardia	**4.15% (0.5; 10.93)**
I^2	98.6%
Event/Total	231/5832
Studies	7
Psychological Symptoms	
Sleep problems	**20.9% (5.25; 43.25)**
I^2	99.1%
Event/Total	443/2018
Studies	4
Anxiety	**13.4% (6.3; 22.5)**
I^2	96.2%
Event/Total	392/4856
Studies	7
Depression Symptoms	**18.0% (4.8; 36.7)**
I^2	98.1%
Event/Total	211/1738
Studies	4

	Symptoms	Examples of related diagnoses	Possible mechanisms
Impaired memory and cognition	Brain fog, trouble concentrating, word-finding difficulty	Alzheimer's disease, mild cognitive impairment, COVID-19-associated encephalitis	Global brain atrophy[20] and atrophy of structures related to memory and cognition (eg, parahippocampal gyrus); hippocampal hypometabolism;[21] autoimmune encephalitis[22]
Disorders of equilibrium	Dizziness, imbalance	Vertigo, orthostasis	Cerebellar atrophy and hypometabolism;[21] secondary cardiopulmonary insufficiency (eg, due to decreased respiratory efficiency and increased metabolic requirement)
Constitutional disorders	Fatigue, headache	Chronic fatigue syndrome, migraine, tension-type headache	Residual systemic inflammatory state[23] leading to increased tissue energy consumption; impaired tissue oxygenation (eg, due to functional anaemia, small vessel endothelial dysfunction impairing capillary blood flow, or impaired trans-alveolar O_2 transport); inadequate sleep efficiency; impaired CO_2 clearance and mild metabolic acidosis; increased intracranial pressure; subclinical meningeal inflammation; dysregulated pain receptor physiology
Disorders of the peripheral nerves or neuromuscular junction	Limb weakness, paraesthesia, facial palsy, difficulty swallowing	Guillain-Barré syndrome, peripheral neuropathy, dysautonomia, Bell's palsy	Axonal degeneration, multifocal demyelination, or small fibre neuropathy[24]
Seizures	Brief, paroxysmal alterations in behaviour, staring spells with loss of awareness, convulsions	Focal onset epilepsy, multisystem inflammatory syndrome in children, encephalitis	Post-infection inflammatory cascade affecting focal brain areas[25] (eg, mesial temporal regions)
Mental health disorders	Mood changes (depression, anxiety), hallucinations, delusions, catatonia	Major depressive disorder, stress and adjustment disorders, anxiety disorders, psychotic disorders	Modulation of affective information processing via alterations in olfactory cortical firing;[26] structural changes in brain regions responsible for emotional processing (eg, anterior cingulate cortex, orbitofrontal cortex, ventral striatum, amygdala);[20] decreased psychological resilience (premorbid or context-specific)[27]
Sensory disorders	Altered smell and taste, hearing abnormalities, or vision changes	Meniere's disease, anosmia, dysgeusia, tinnitus	Prolonged chemokine induction, microglial activation, and suppression of neuronal transcriptome in olfactory bulb and olfactory epithelium;[28] dysfunctional sensory integration due to loss of function in parietal association cortex;[20] direct viral invasion of inner ear[29]
Extrapyramidal and movement disorders	Abnormal involuntary movements, tremor, bradykinesia, dystonia, myoclonus	Parkinsonism, chorea, dystonia	Inflammatory cytokines, microglial activation or molecular mimicry leading to structural or functional damage to the basal ganglia[30,31]
Cerebrovascular disorders	Sudden-onset weakness, sensory changes, or vision deficits	Ischaemic stroke, transient ischaemic attack, haemorrhagic stroke, cerebral venous thrombosis	Hypercoagulable state;[32] microvascular endothelial dysfunction[33]
Myelopathies	Paraplegia, incontinence, pain	Transverse myelitis, acute disseminated encephalomyelitis, spinal epidural abscess, spinal cord ischaemia	Autoimmune activation due to molecular mimicry;[34] coagulopathy, arterial thrombosis, or abscess formation[35]

Composite outcomes are shown with symptoms, related diagnoses, and possible underlying mechanisms.

Table 2: **Neurological, cognitive, and psychiatric complications and related symptoms after SARS-CoV-2 infection**

Lancet Respir Med 2023; 11: 726–38

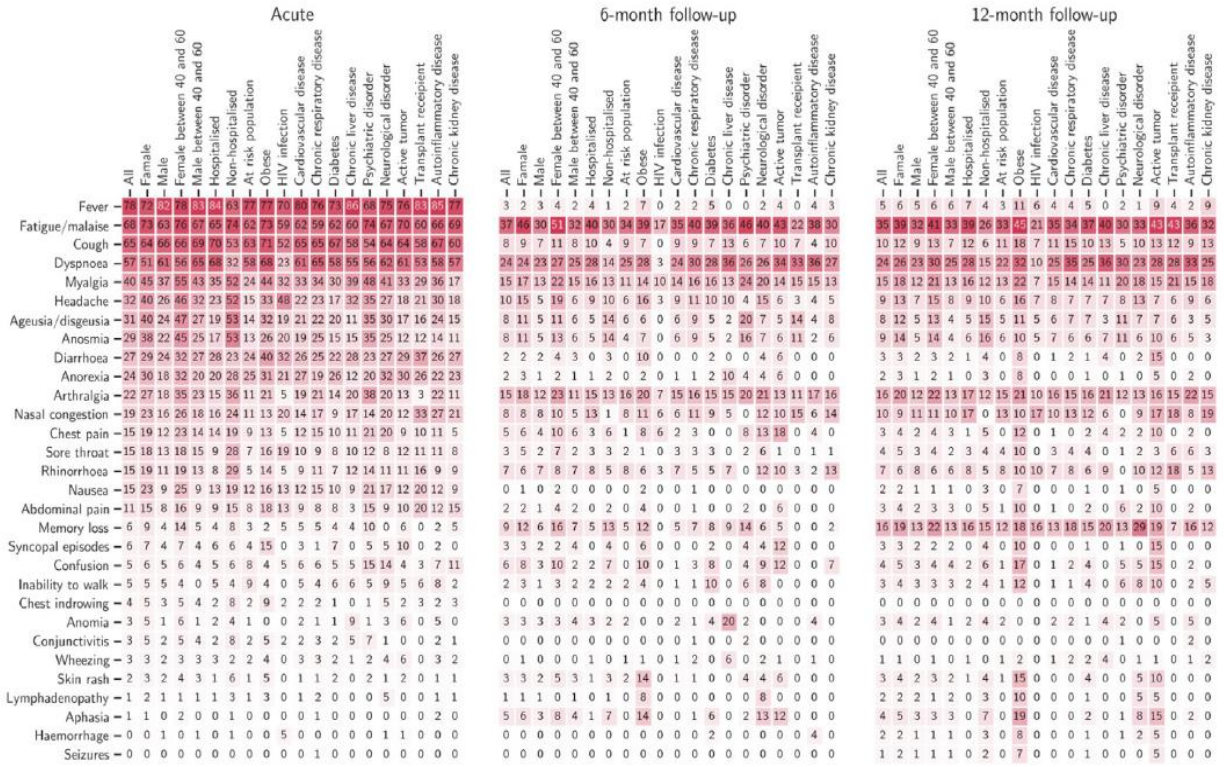
Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort

Elisa Gentilotti,[a,r] Anna Górska,[a,r] Adriana Tami,[b] Roy Gusinow,[c] Massimo Mirandola,[a] Jesús Rodríguez Baño,[d,p,q] Zaira R. Palacios Baena,[d,p,q] Elisa Rossi,[e] Jan Hasenauer,[c] Iris Lopes-Rafegas,[f] Elda Righi,[a] Natascia Caroccia,[g] Salvatore Cataudella,[e] Zeno Pasquini,[h] Thomas Osmo,[i] Lidia Del Piccolo,[j] Alessia Savoldi,[a] Samir Kumar-Singh,[k] Fulvia Mazzaferri,[a] Maria Giulia Caponcello,[d,p,q] Gerolf de Boer,[b] Gabriel Levy Hara,[l] ORCHESTRA Study Group,[t] Pasquale De Nardo,[a] Surbhi Malhotra,[k] Lorenzo Maria Canziani,[a] Jade Ghosn,[m,n] Aline-Marie Florence,[m,o] Nadhem Lafhej,[o] Bernardina T. F. van der Gun,[b] Maddalena Giannella,[g,h,s] Cédric Laouénan,[m,o,s] and Evelina Tacconelli[a,s,*]

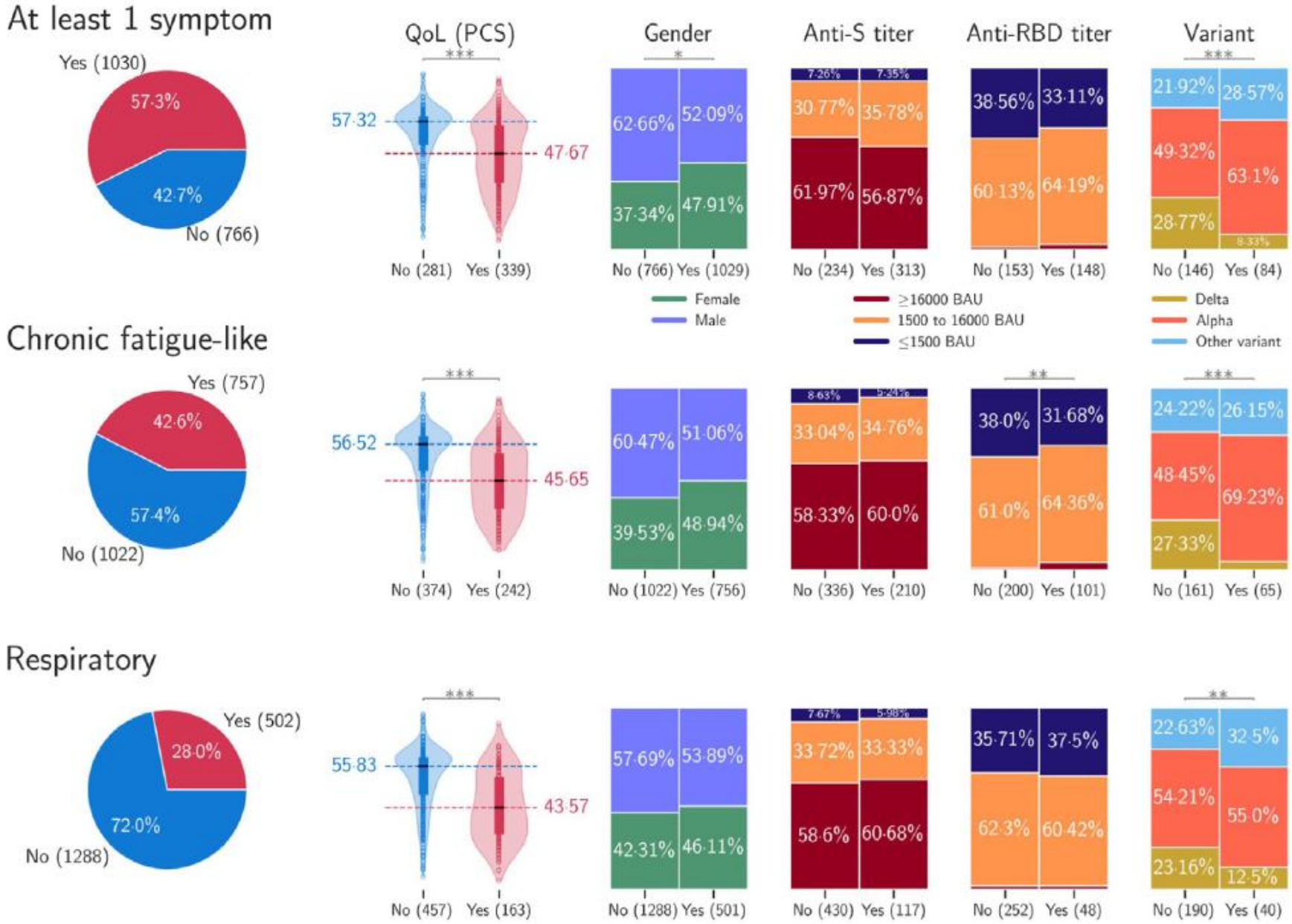
Variable	At least 1 symptom according to WHO definition of post-COVID-19 syndrome (N = 822)			
	OR	95% CI		p-value
		LB	UB	
Female sex	1.81	1.34	2.46	<0.001
Age	1.01	1.00	1.02	0.20
Neurological symptoms[a]	2.16	1.56	3.01	<0.001
Hospital admission[a]	0.62	0.37	1.02	0.06
Early therapy (monoclonal antibody)[b]	0.19	0.11	0.33	<0.001
Oxygen therapy[a]	1.54	0.96	2.46	0.07

OR: odd ratio; CI: confident interval; LB: lower bound; UB: upper bound; WHO: World Health Organization. The significant associations denoted with a bold font refer to p-values <0.05. [a]During the acute infection. [b]Monoclonal antibodies administered within the first three days of symptoms in high risk patients (see description in the Methods section of the manuscript): bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab.

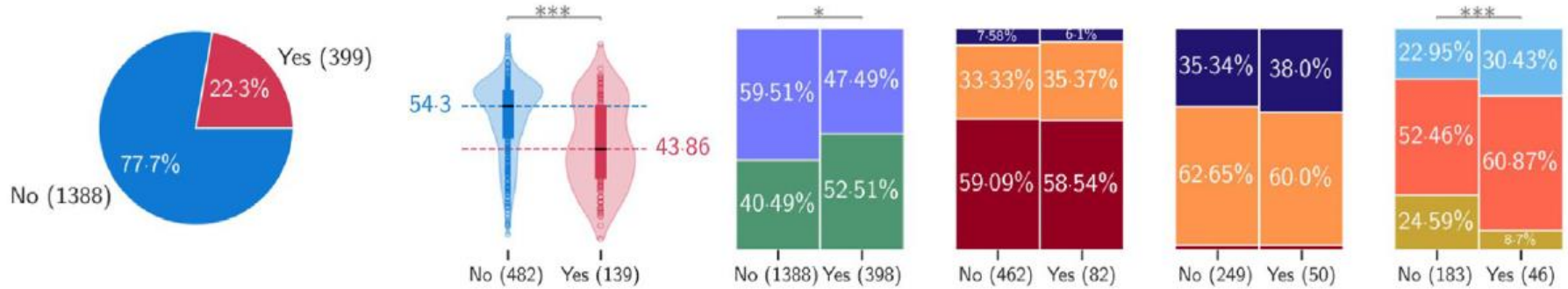
Table 1: Multivariable analysis of factors associated with at least one symptom at 12-month assessment (accuracy 0.66; balanced accuracy 0.65).



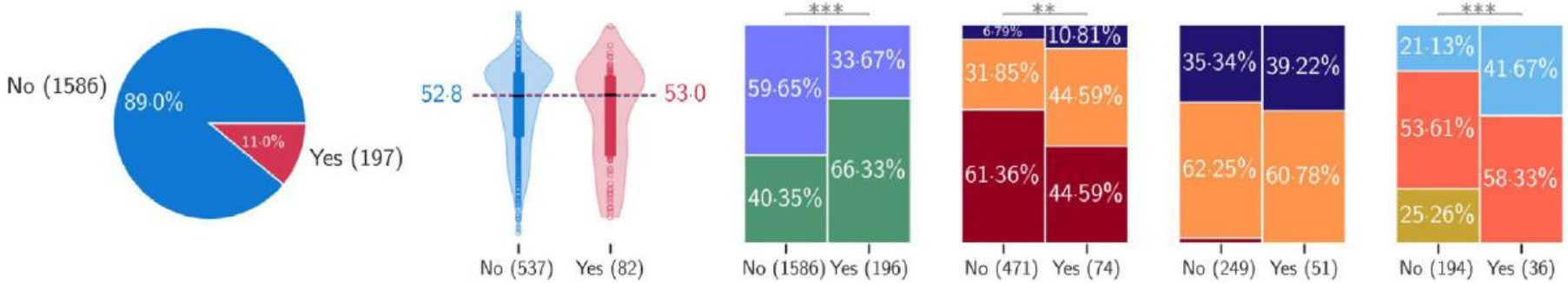
1030/1796 pts (57%) suffered from at least one symptom at 12 month


At least 1 symptom
Yes (1030)
57·3%
42·7%
No (766)
QoL (PCS)
***
57·32
47·67
No (281) Yes (339)
Gender
*
62·66%
52·09%
37·34%
47·91%
No (766) Yes (1029)
Female
Male
Anti-S titer
7·26%
7·35%
30·77%
35·78%
61·97%
56·87%
No (234) Yes (313)
≥16000 BAU
1500 to 16000 BAU
≤1500 BAU
Anti-RBD titer
38·56%
33·11%
60·13%
64·19%
No (153) Yes (148)
Variant
***
21·92%
28·57%
49·32%
63·1%
28·77%
8·33%
No (146) Yes (84)
Delta
Alpha
Other variant
Chronic fatigue-like
Yes (757)
42·6%
57·4%
No (1022)
***
56·52
45·65
No (374) Yes (242)
60·47%
51·06%
39·53%
48·94%
No (1022) Yes (756)
8·63%
9·64%
33·04%
34·76%
58·33%
60·0%
No (336) Yes (210)
**
38·0%
31·68%
61·0%
64·36%
No (200) Yes (101)
***
24·22%
26·15%
48·45%
69·23%
27·33%
No (161) Yes (65)
Respiratory
Yes (502)
28·0%
72·0%
No (1288)
***
55·83
43·57
No (457) Yes (163)
57·69%
53·89%
42·31%
46·11%
No (1288) Yes (501)
7·67%
5·98%
33·72%
33·33%
58·6%
60·68%
No (430) Yes (117)
35·71%
37·5%
62·3%
60·42%
No (252) Yes (48)
**
22·63%
32·5%
54·21%
55·0%
23·16%
12·5%
No (190) Yes (40)

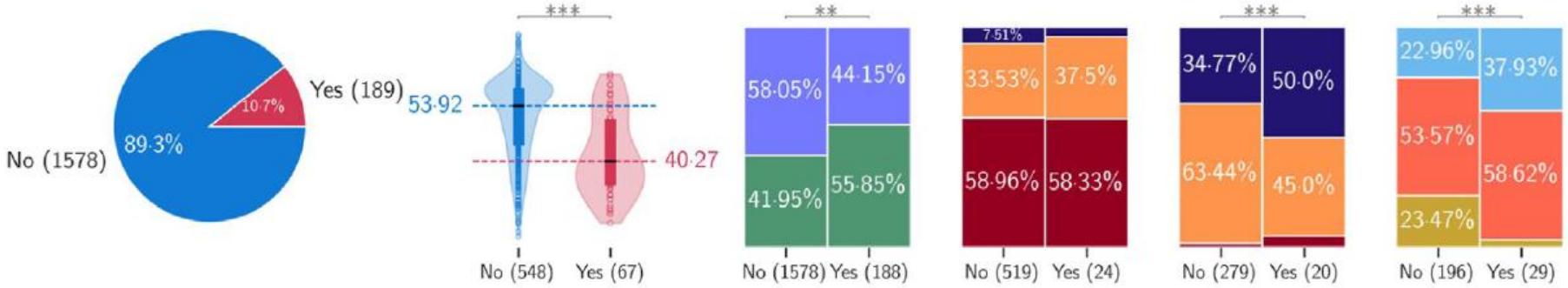
Chronic pain



Neurosensorial



Severe post-COVID



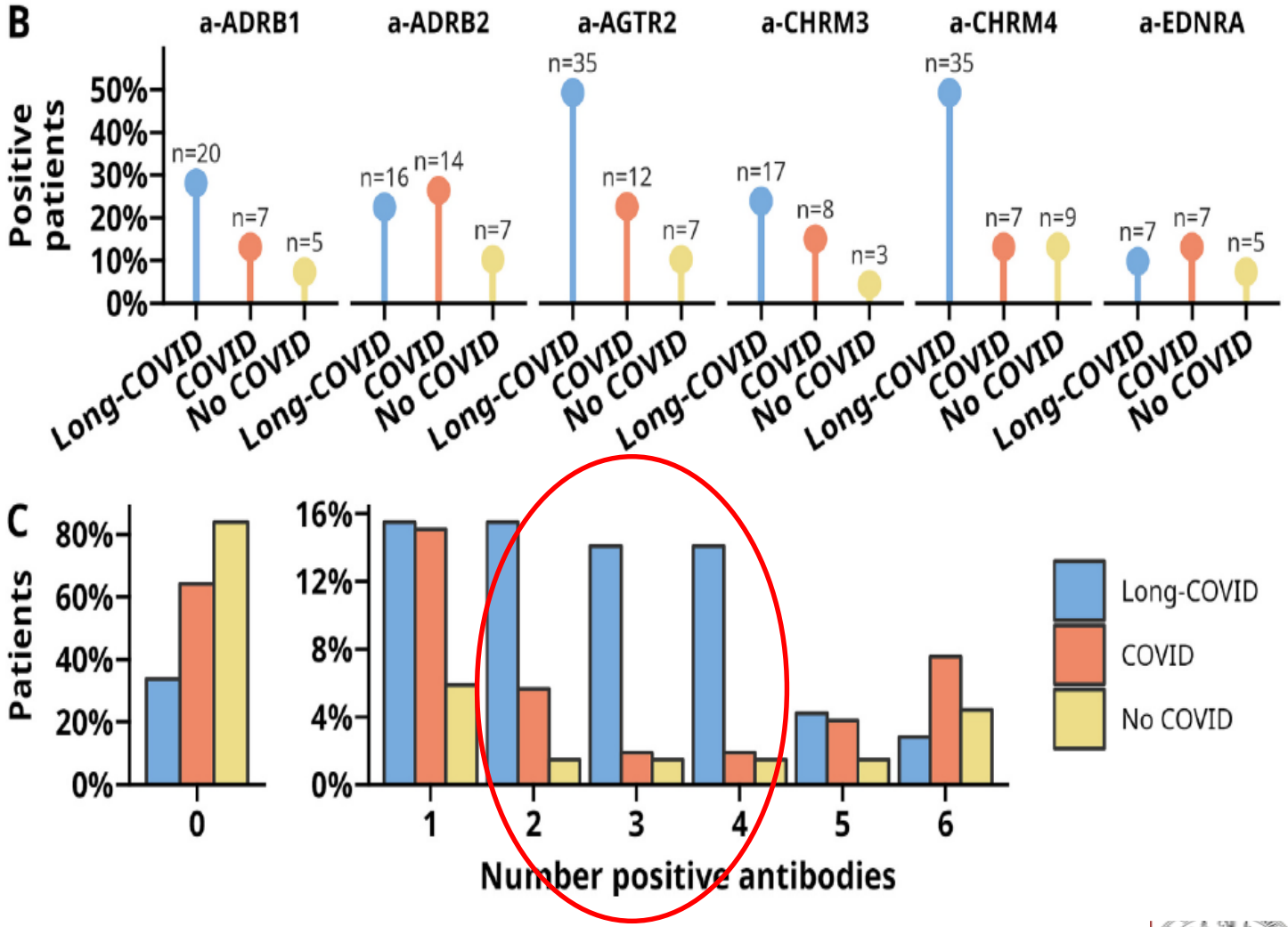
Severity of neurological Long-COVID symptoms correlates with increased level of autoantibodies targeting vasoregulatory and autonomic nervous system receptors

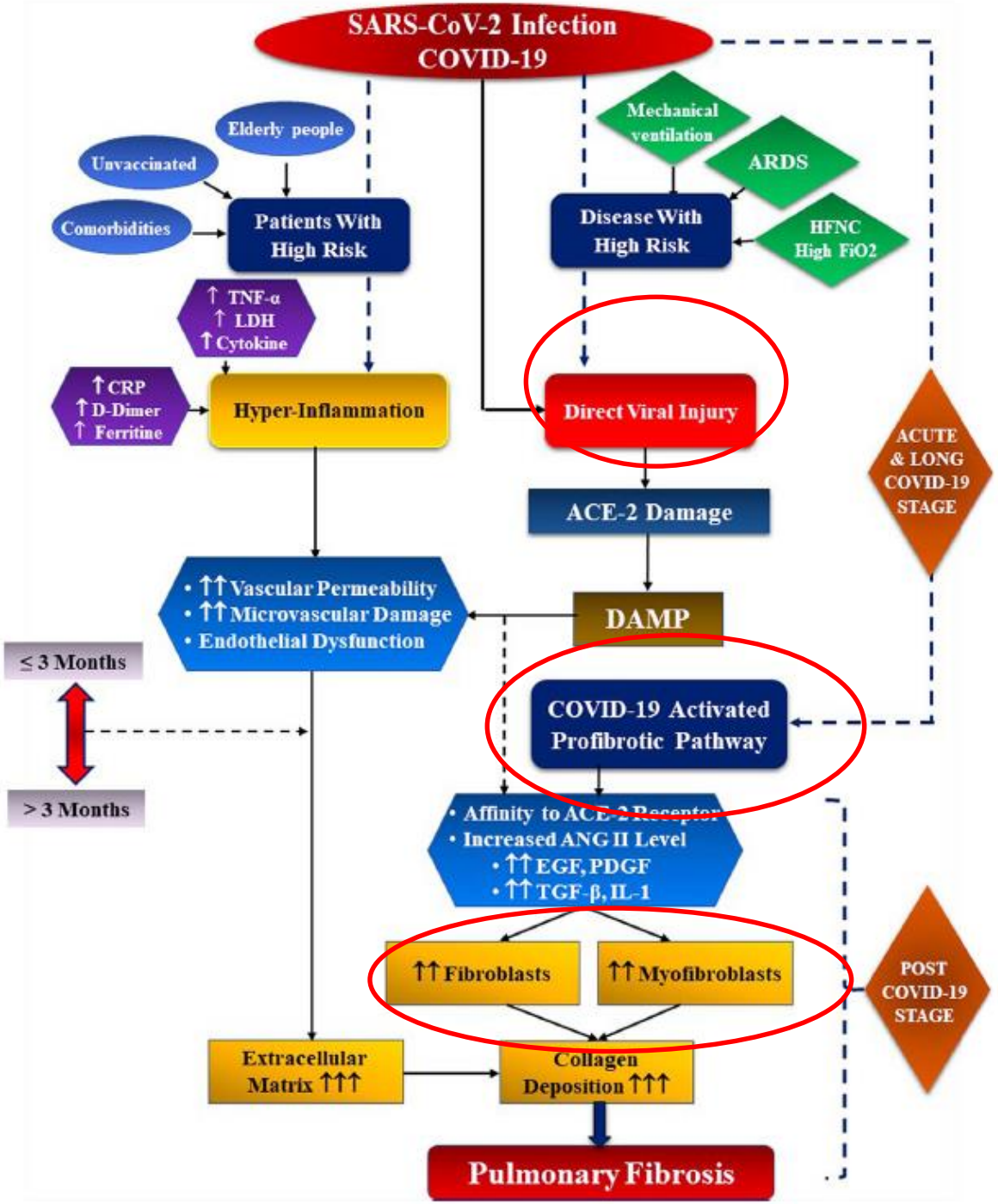
Felix S. Seibert [a], Ulrik Stervbo [b], Lea Wiemers [a], Sarah Skrzypczyk [b], Maximillian Hogeweg [a], Sebastian Bertram [a], Julia Kurek [b], Moritz Anft [b], Timm H. Westhoff [a,**,1], Nina Babel [b,c,*,1]

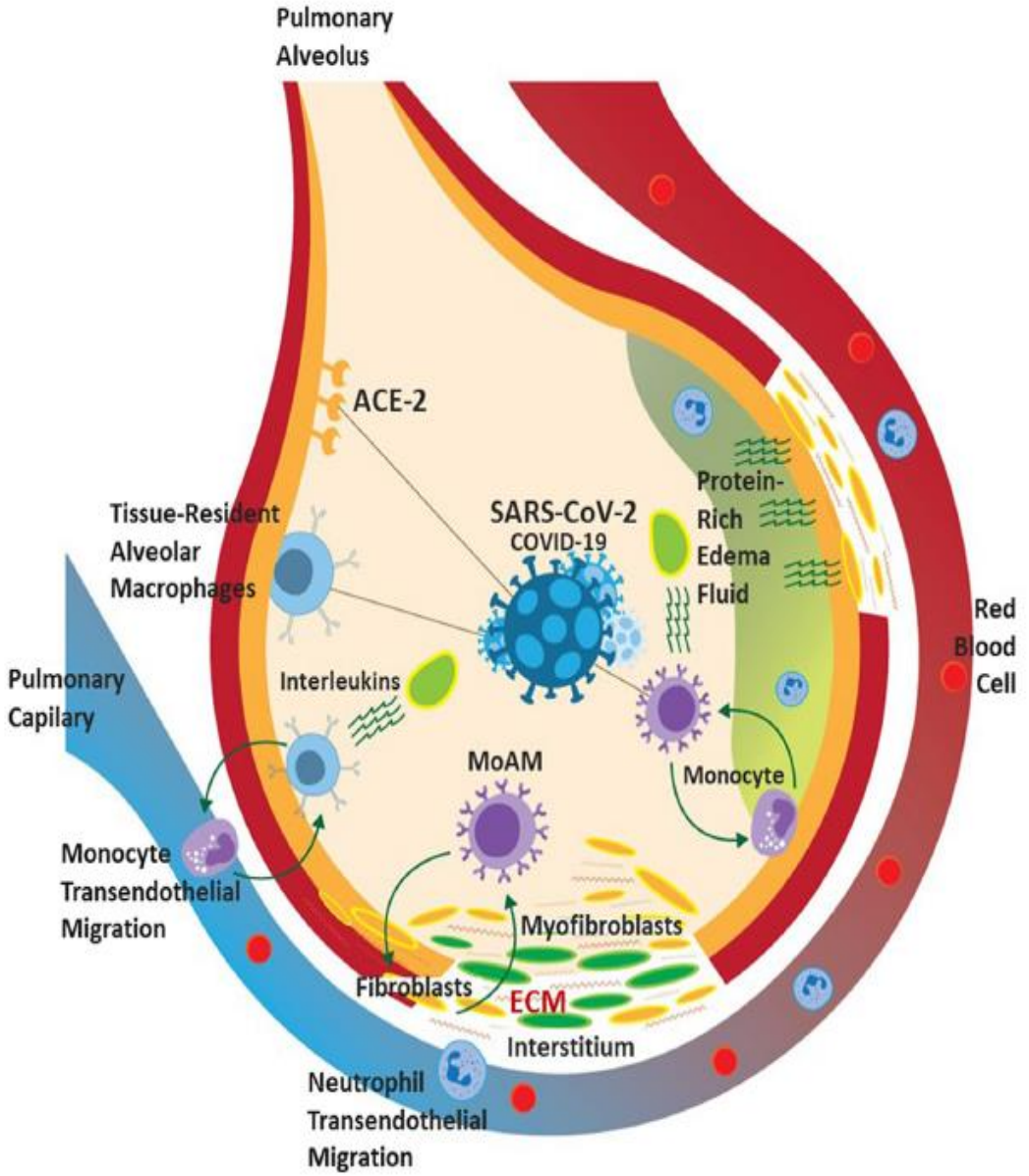
We recruited a total of 200 individuals: 72 patients were diagnosed with Long-COVID ("Long-COVID"); 58 patients had been infected by SARS-CoV-2 in the past without persisting symptoms ("COVID"). The second control group ("No COVID") encompassed 70 patients. The median age of the Long-COVID group was 48 years (interquartile range [IQR] 33–56), like the two control groups ($p = 0.64$). Patients of the

3.2. Measurement of GPCR autoantibodies

We measured autoantibodies to the Angiotensin-II-Receptor-1 (AGTR2), Beta-1 Adrenergic Receptor (ADRB1), Beta-2 Adrenergic Receptor (ADRB2), Endothelin Receptor (EDNRA), Muscarinergic Choline Receptor 3 (CHRM3), and Muscarinergic Choline Receptor 4 (CHRM4) (Fig. 1A). Antibody concentrations were generally higher in Long-COVID than in COVID, and healthy No COVID controls ($p < 0.001$). For several autoantibodies including a-ADRB1, a-AGTR2, a-CHRM3, and a-CHRM4, a stepwise decline with the ranking of Long-COVID > COVID > no COVID could be observed. a-ADRB2 and a-EDNRA showed no significant intergroup differences ($p > 0.05$).







Duong-Quy S et al. Pulm Ther 2023;9:295-307

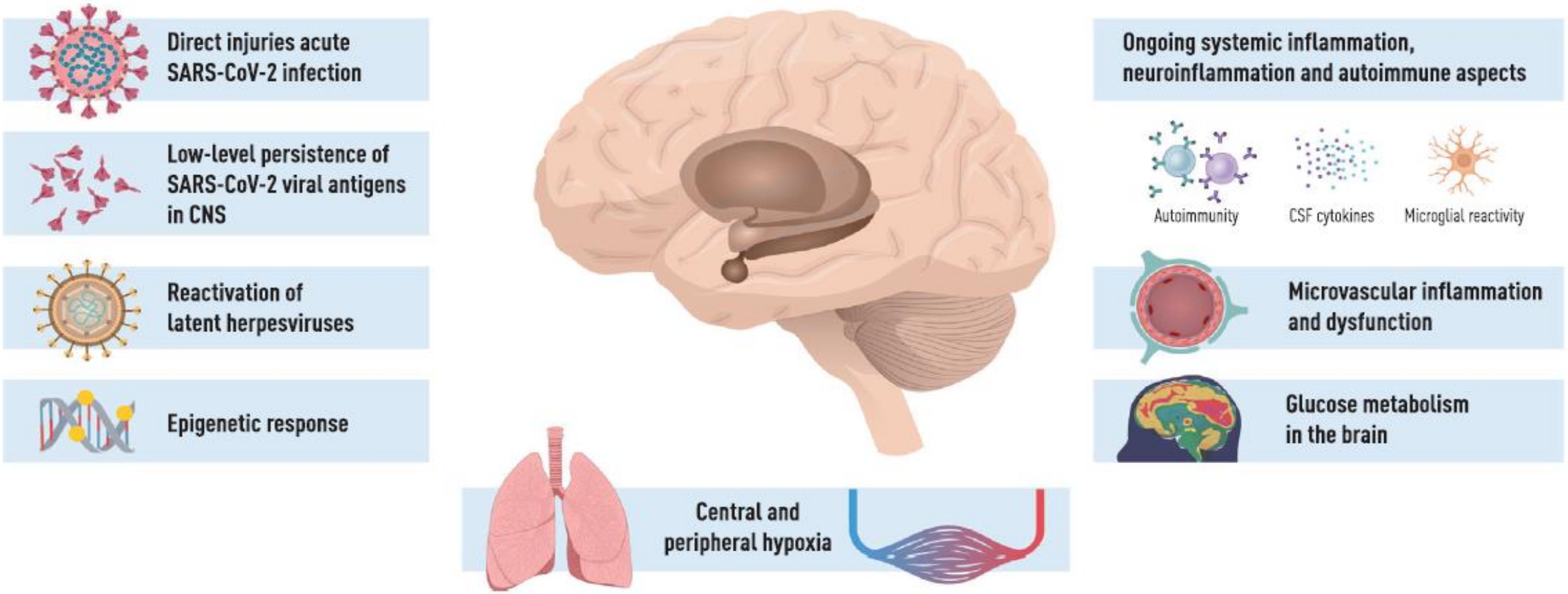
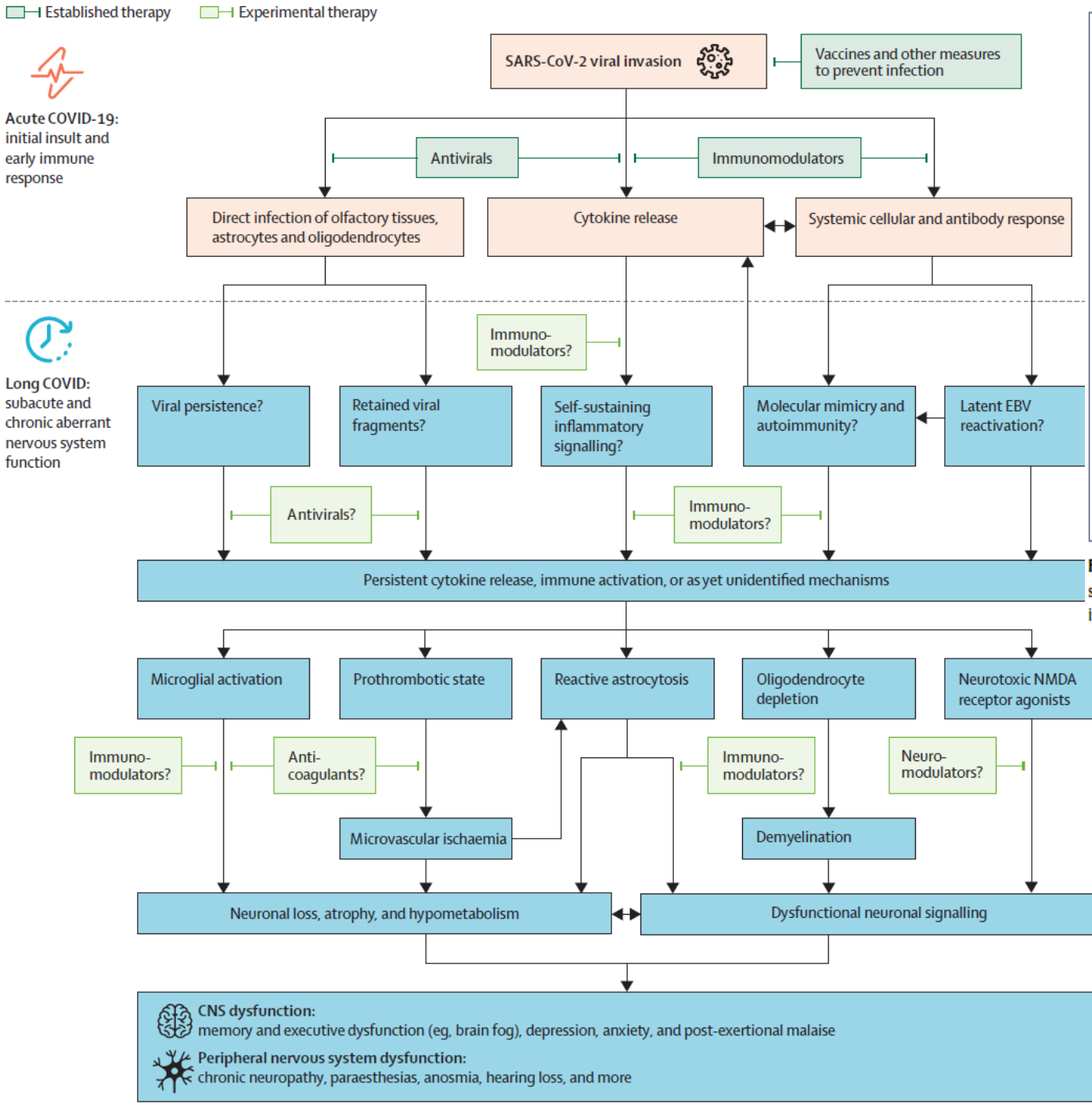


Fig. 1 *Possible pathophysiological mechanism in cognitive impairment of post-COVID-19 condition (PCC).*



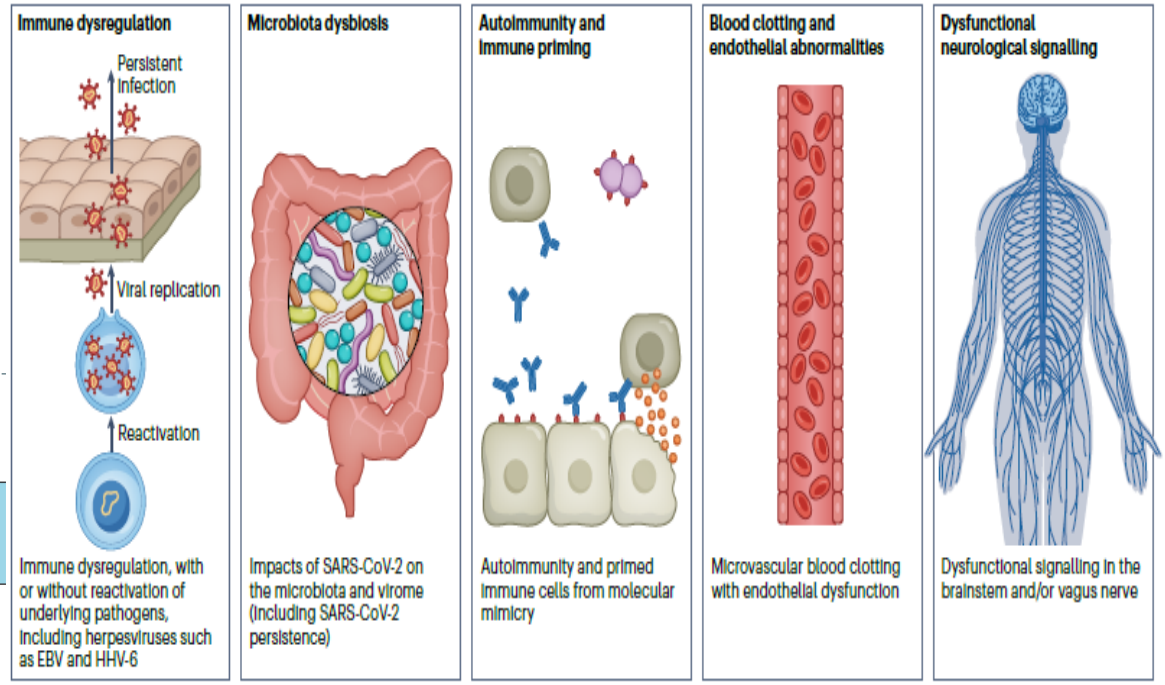


Fig. 3 | Hypothesized mechanisms of long COVID pathogenesis. There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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11: 726–38

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, *]

Who should be assessed for long COVID?

In symptomatic patients, other serious/life-threatening conditions should be ruled out prior to considering long COVID. These include prior overlooked conditions (e.g. malignancy) or complications of acute COVID-19 (e.g. thromboembolic events, myopericarditis, encephalitis). The investigation for other conditions should be guided by symptoms, signs, and other tests, performed according to the physician's discretion. Long COVID is a diagnosis of exclusion.

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, *]

Should post-discharge (extended) thromboprophylaxis be administered to patients with COVID-19?

Recommendation

Evidence is insufficient to provide a recommendation for or against the intervention. It is advisable to perform individualized risk stratification of the risk for thrombotic events vs. haemorrhagic events. Consider extended anticoagulation prophylaxis for patients with a low risk of bleeding and elevated risk for VTE (active malignancy, immobility, history of VTE, recent major surgery, thrombophilia).

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

Recommendation

Evidence is insufficient to provide a recommendation for or against the intervention specifically for COVID-19. No data regarding persistent long COVID were identified. Until further evidence accumulates, it is reasonable that clinicians follow available consensus statements regarding multidisciplinary rehabilitation in the post-acute stage [97].

How should persistent pulmonary symptoms/signs be managed?

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

How should persistent cough be managed?

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention. Due to its simplicity and safety, olfactory training should probably be suggested for all patients. Physicians should discuss the likelihood for spontaneous recovery with patients, and other interventions should be suggested only in clinical trials. Smoking cessation should be recommended.

How should fatigue be managed?

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

How should neurological/cognitive long-COVID sequelae be managed?

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

How should emotional/psychiatric long COVID sequelae be managed?

Clomipramine, a tricyclic antidepressant with anti-inflammatory action and penetrance to the central nervous system, has been suggested as a potential drug to prevent post-infectious mental complications. Further studies are needed [118].

Recommendation

Evidence is insufficient to provide a recommendation for or against any intervention.

Table 1 | Summary of candidate treatments and supporting evidence

Symptoms and/or biological mechanism	Treatments	Supporting evidence	Comments
Postexertional malaise	Pacing	ME/CFS literature	Exercise, cognitive behavioural therapy and graded exercise therapy are contraindicated
POTS	Pharmacological: β-blockers, pyridostigmine, fludrocortisone, midodrine	POTS and ME/CFS literature	Options can be prioritized on the basis of a specific constellation of symptoms
	Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings	POTS and ME/CFS literature	–
Immune dysfunction	Intravenous immunoglobulin	ME/CFS literature	Consider consulting an immunologist on implementation
Cognitive dysfunction	Cognitive pacing	ME/CFS literature	Consider implementation alongside pacing physical exertion
Cognitive dysfunction	Postconcussion syndrome protocols	ME/CFS and postconcussion syndrome literature	–
Fatigue	Coenzyme Q_{10}, D-ribose	ME/CFS literature	–
Pain, fatigue, neurological symptoms	Low-dose naltrexone	ME/CFS and other literature	Substantial anecdotal reports of success within the patient community
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole	ME/CFS literature	–
Autoimmunity	BC007	Long COVID case report	Neutralizes G protein-coupled receptor autoantibodies
Abnormal clotting	Anticoagulants	Long COVID pilot study	Additional trials in progress
Abnormal clotting	Apheresis	ME/CFS literature, long COVID pilot study	–
Viral persistence and antivirals (COVID-19)	Paxlovid	Long COVID case reports	No active trials, despite strong evidence for viral persistence
Viral persistence and antivirals (reactivations such as of EBV, HCMV and VZV)	Valaciclovir, famciclovir, valganciclovir and other antivirals	ME/CFS literature	–
Endothelial dysfunction	Sulodexide	Long COVID pilot study	–
Gastrointestinal symptoms	Probiotics	Long COVID pilot study	Resolved gastrointestinal and other symptoms
Dysautonomia	Stellate ganglion block	Long COVID case report	Effects may wane over time and require repeated procedures
Endothelial function, microcirculation, inflammatory markers and oxidative stress	Pycnogenol	COVID-19 pilot study	–
MCAS	H_1 and H_2 antihistamines, particularly famotidine	Long COVID case reports, MCAS literature	Expected to treat symptoms, not underlying mechanism
Autonomic dysfunction	Transcutaneous vagal stimulation	Long COVID pilot study	–

EBV, Epstein–Barr virus; HCMV, human cytomegalovirus; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome; VZV, varicella zoster virus.

Davis HE et al. Nat Rev Microbiol 2023;21:133-46

Systematic Review

Long COVID and Physical Therapy: A Systematic Review

Juan Carlos Sánchez-García [1,2], Andrés Reinoso-Cobo [3], Beatriz Piqueras-Sola [1,4], Jonathan Cortés-Martín [1,2,*], María José Menor-Rodríguez [5], Raquel Alabau-Dasi [3] and Raquel Rodríguez-Blanque [1,2,6]

Table 4. Results included in the systematic review.

Author	Participants	Interventions	Outcomes	Conclusion	Finding
Palau et al., 2022 [15]	26 post-discharged patients with long COVID	They assessed a 12-week home-based IMT program in 26 post-discharge COVID-19 patients	At 12 weeks, the mean pp-peakVO_2 was higher in the IMT group compared to controls	IMT significantly increased pp-peakVO_2 in post-COVID patients versus controls	↑ sig increase
Sharma et al., 2022 [24]	30 post-COVID patients with respiratory complications and chronic COVID	They evaluated a pulmonary tele-rehabilitation program including breathing exercises and therapeutic exercises in 30 post-COVID patients with respiratory complications and chronic COVID compared to conventional care	Patients receiving tele-rehabilitation showed significant improvement in dyspnea, fatigue, and ability to rehabilitate at home versus conventional care	Pulmonary tele-rehabilitation was a valuable service for post-COVID patients with respiratory complications	↑ sig increase
Jimeno-Almazán et al., 2023 [20]	80 non-hospitalized adults with post-COVID-19 conditions	They compared two 8-week exercise programs in 80 non-hospitalized adults with post-COVID conditions: (1) multicomponent exercise with concurrent resistance and endurance training versus (2) a program combining inspiratory muscle training, physical exercise and self-management	The multicomponent exercise program elicited significant improvement in fatigue, depression, fitness, quality of life, symptoms, dyspnea, strength, and severity versus the other program	Multicomponent exercise with concurrent training showed more effectiveness than the other program in post-COVID conditions	↑ sig increase
Jimeno-Almazán et al., 2022 [21]	39 patients	They compared 10 weeks of tailored supervised therapeutic exercise versus self-management recommendations in the WHO rehabilitation leaflet in 39 patients with post-COVID conditions	Supervised exercise showed significantly better cardiovascular fitness, strength, quality of life, fatigue, depression, and functional status than self-management controls	Supervised therapeutic exercise was a more effective intervention than self-management in post-COVID conditions	↑ sig increase
Philip et al., 2022 [23]	192 people with long COVID	They assessed a 6-week online breathing and well-being program developed for 192 people with long COVID experiencing breathlessness	The online breathing program improved the mental component of HRQoL and breathlessness VAS while running versus controls	The online breathing program improved mental HRQoL and breathlessness in people with persisting post-COVID symptoms	↑ sig increase
Mcnarry et al., 2022 [22]	281 adults recovering from self-reported COVID-19	They compared IMT versus control in 281 adults recovering from self-reported COVID-19	No difference between groups in KBILD total score but clinically meaningful IMT improvements in breathlessness, chest symptoms, and respiratory muscle strength	IMT may represent an important home-based post-COVID rehabilitation strategy, improving breathlessness, chest symptoms, respiratory muscle strength and estimated aerobic fitness	↓ sig decrease

↑—Means increase; ↓—Means decreaseIMT—inspiratory muscle training; pp-peakVO2—post-COVID peak oxygen uptake; KBILD—King's Brief Interstitial Lung Disease; HRQoL—health-related quality of life; VAS—visual analogue scale.

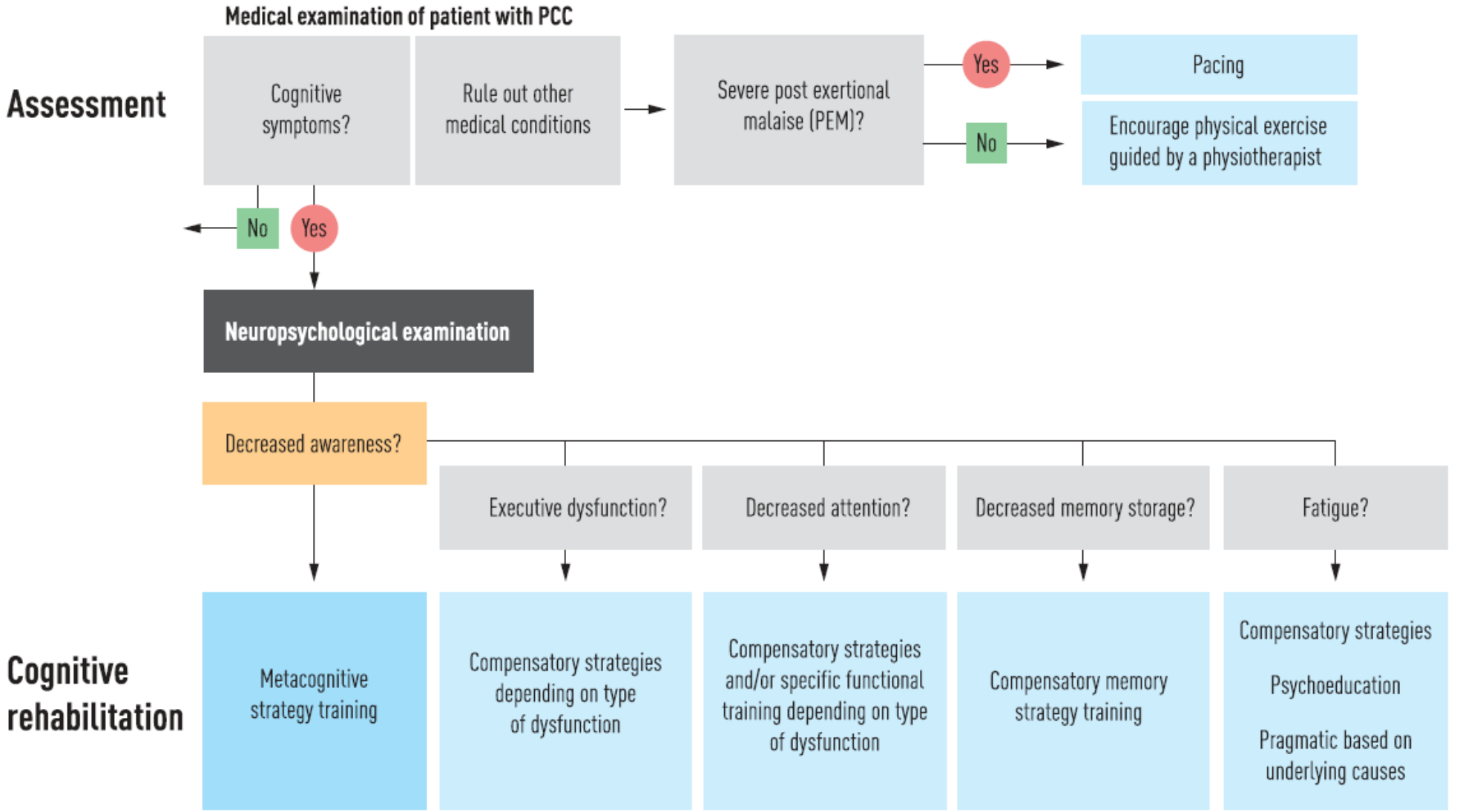

Fig. 2 *Flowchart on proposed assessments and rehabilitation interventions for patients with post-COVID-19 condition (PCC) with cognitive symptoms and fatigue.*

Fatigue

Compensatory strategies

Increase self-awareness for fatigue by

- identifying fatigue patterns (e.g. by using a diary)
- identifying individual triggers and how to avoid them

Regulate activity by

- learning to set realistic goals for achievements
- learning about pacing and activity regulation
  - prioritizing, planning, and scheduling
  - taking breaks regularly before fatigue kicks in
  - recognizing time limits
  - giving extra time between tasks
  - allowing rest after a demanding activity
  - avoiding doing too much when feeling better
  - avoiding multitasking
  - delegating
  - breaking down large tasks into smaller components
  - avoiding crowded/messy environments
  - wearing earplugs, headphones, sunglasses, cap if sensitive to environmental stimuli
- mindfulness
- physical exercise in absence of Post Exertional Malaise (PEM)

Post exertional malaise

Compensatory strategies

Stabilization of symptoms

Pacing strategies

Executive dysfunctions

Compensatory strategies

Protocols for formal problem-solving strategies

Go-Plan-Do-Review techniques

Stop-Think-Act strategies

Goal Management Training (GMT)

Memory problems

Compensatory strategies

Associative techniques (in mild impairment)

Organization techniques

Mobile phone reminders or checklists

Routines and schedules

Memory notebooks

Diaries

Attention dysfunctions

Training on functional level

Attention Process Training (APT)

(computerized) working memory training with a coach specialized in neurorehabilitation

Time Pressure Management (TPM)

Compensatory strategies

Stimuli reduction

Establishing routines

Scheduling of activities

Avoiding time constraints

Avoiding working in an open office landscape

Wearing earplugs or sunglasses in case of noise or light sensitivity

Fig. 3 *Rehabilitation strategies for fatigue and different cognitive dysfunctions.*

A synbiotic preparation (SIM01) for post-acute COVID-19 syndrome in Hong Kong (RECOVERY): a randomised, double-blind, placebo-controlled trial

Raphaela I Lau, Qi Su*, Ivan S F Lau, Jessica Y L Ching, Martin C S Wong, Louis H S Lau, Hein M Tun, Chris K P Mok, Steven W H Chau, Yee Kit Tse, Chun Pan Cheung, Moses K T Li, Giann T Y Yeung, Pui Kuan Cheong, Francis K L Chan†, Siew C Ng†*

acute COVID-19 syndrome (PACS). SIM01 is a synbiotic preparation of three lyophilised *Bifidobacteria* strains and three prebiotic compounds derived from our metagenomics dataset. In a pilot study, we showed that, in COVID-19 patients staying in hospital, SIM01 improved gut dysbiosis, hastened antibody formation, and decreased nasopharyngeal viral load and plasma pro-inflammatory immune markers.

The present study did not identify a significant difference in quality of life and physical activity between the two groups at 6 months. Quality of life indices commonly cover a broad range of domains, including personal, social, political, cultural, economic, and environmental aspects. Time spent on physical activity is determined by multiple factors in addition to physical health. Our primary outcome focused mainly on physical symptoms, which only partly contribute to the assessment of quality of life and time spent on physical activity.

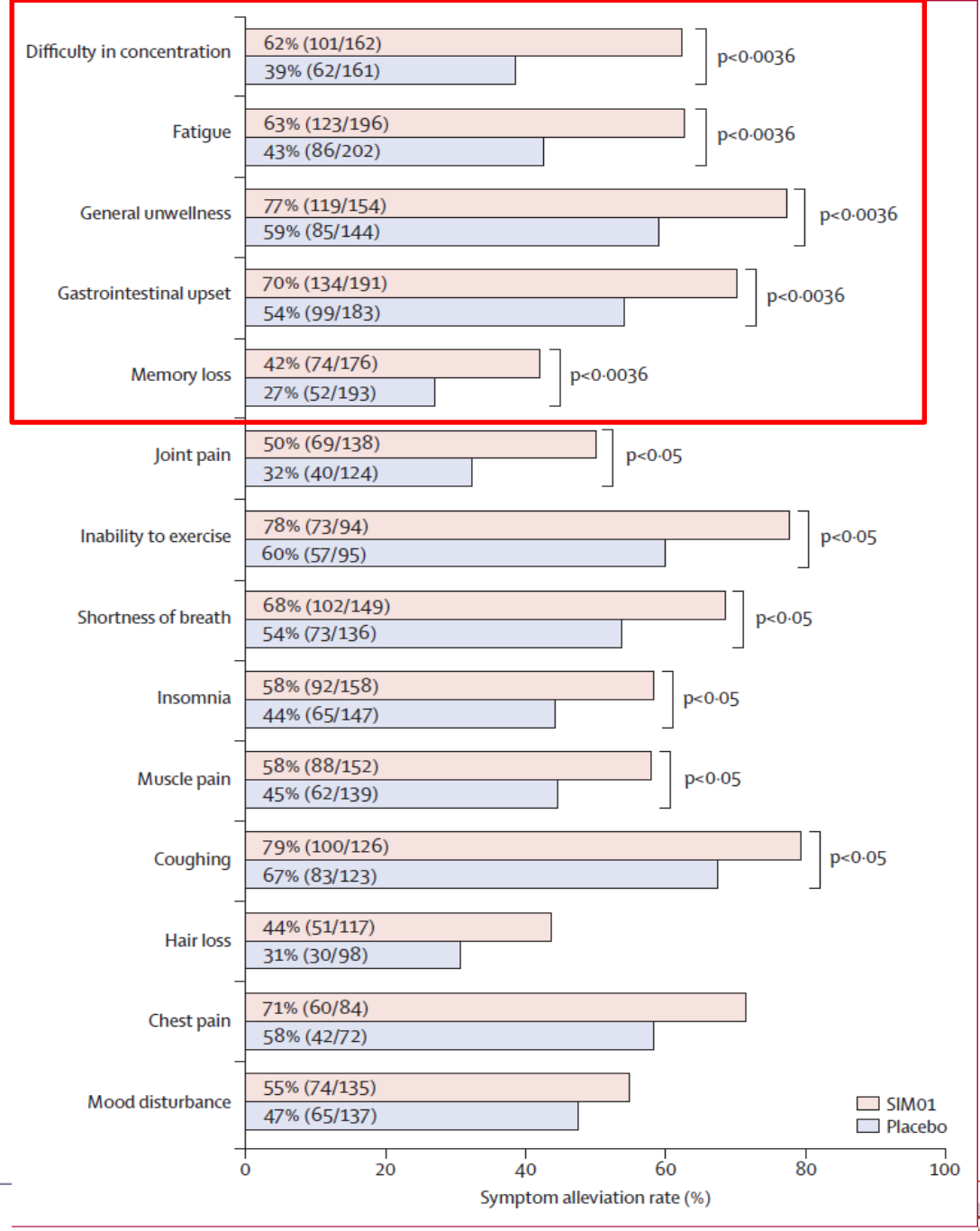

Figure 2: **Proportion of PACS symptoms alleviation by 6 months**
p<0·0036 represents the significance level set by Bonferroni correction.

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Sistema Socio Sanitario

Regione Lombardia

ASST Fatebenefratelli Sacco

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MILANO

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email:

MILANO, 15/01/2024

SI CERTIFICA CHE / It is hereby certified that:

il sig. **ANTINORI SPINELLO DOMENICO**
Nato a **GENOVA** il **03/04/1959**, codice fiscale **NTNSNL59D03D969N**
[redacted]

HA EFFETTUATO LE SEGUENTI VACCINAZIONI / Has received the following vaccinations

COVID 19 *COVID 19*	**1 - 04/01/2021** SARS-CoV-2 COMIRNATY EL1484-28-001	**2 - 25/01/2021** SARS-CoV-2 COMIRNATY EJ6797-28-04	**3 - 05/11/2021** SARS-CoV-2 COMIRNATY FG4686	**4 - 16/11/2022** SARS-CoV-2 COMIRNATY GH9545
	5 - 18/10/2023 SARS-CoV-2 COMIRNATY HJ2834			