



  
**SITA**

Società Italiana di Terapia Antinfettiva  
Antibatterica Antivirale Antifungina

**13° CONGRESSO  
NAZIONALE**

PADOVA | 23-24 novembre 2023

## Long-Covid: cosa aspettarci?

Giovanni Guaraldi



**UNIMORE**

UNIVERSITÀ DEGLI STUDI DI  
MODENA E REGGIO EMILIA

1175

# Disclosures

- GG received research grant and speaker honorarium from Gilead, ViiV, MERCK, Jansen and Pfizer. He attended advisory boards of Gilead, ViiV, MERCK.

**Femmina 54**, Capo sala reparto di Pneumologia

**Infezione SARS Cov2:** 23/3/20 test molecolare. Non è stata ricoverata.

Trattata con paquenil e zitromax

Stato vaccinale COVID: non vaccinata

Cluster sintomatologici

cluster	sintomi	Impatto funzionale
<b>muscoloscheletrico</b>	Dolori muscolari, articolari, tendinei	Impossibilità di lavorare, non ha ripreso il lavoro
	Crampi, deficit di sensibilità alle mani	Difficoltà alla deambulazione, cadute
<b>neurocognitivo</b>	Deficit di memoria e concentrazione	Non riesce a tenere il filo di un discorso. Non ricorda il nome di persone famigliari

## **Nuove diagnosi post COVID**

05/2020 Pericardite, neuropatia delle piccole fibre

10/20 tenosinovite polso e spalla, orticaria recidivante

**Trattamenti:** Medrol a cicli, Metotrexate, probiotici

**Femmina 57**, Medico geriatra

**Infezione SARS Cov2:** 3/20 test molecolare negativo – ricoverata con polmonite in reparto COVID, trattata con steroide .

Stato vaccinale COVID: non vaccinata

Cluster sintomatologici

cluster	sintomi	Impatto funzionale
respiratorio	dispnea	O2 tp domiciliare per 1 anno
Muscoloscheletrico	Dolore diffuso, astenia	Sperimenta improvvisi cali di energia che la obbligano a riposarsi sdraiata. Ha orario di lavoro ridotto. Non può fare guardie
neurocognitivo	Deficit di memoria e concentrazione	riduzione della capacità e del tempo di concentrazione e nella necessità di compiere operazioni mentali singole

### **Nuove diagnosi post COVID**

Cambio ponderale da 55 a 70 Kg

Comparsa di sindrome metabolica

**Trattamenti:** HTN, citalopram

**Maschio 36**, medico infettivologo

**Infezione SARS Cov2:** (i) 01/20 polmonite interstiziale; (test non disponibile); (ii) 01/22 (test antigenico) paucisintomatico

Stato vaccinale COVID: vaccinato

Cluster sintomatologici

cluster	sintomi	Impatto funzionale
muscoloscheletrico	poliartrite	Impossibilità di rimanere in piedi
neurocognitivo	Deficit di memoria e concentrazione	Non riesce a seguire lezioni in inglese (master) Impossibilità di lavorare, non idoneo per attività clinica, lavora in un ufficio SDO
	Puntura lombare: iperproteinioracchia	

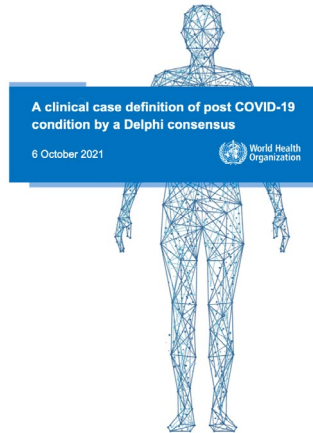
### **Nuove diagnosi post COVID**

04/23 neuropatia delle piccole fibre

valutazione neurocognitiva mostrava rallentamento del pensiero all'esecuzione di compiti esecutivo-strategici

**Trattamenti:** Maraviroc (sperimentazione)

# Definitions of post-acute COVID-19 syndrome (long COVID, PASC)



Post COVID-19 condition in individuals with **a history of probable or confirmed SARS- CoV-2** infection, may be present **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 and generally have an **impact on everyday functioning**.

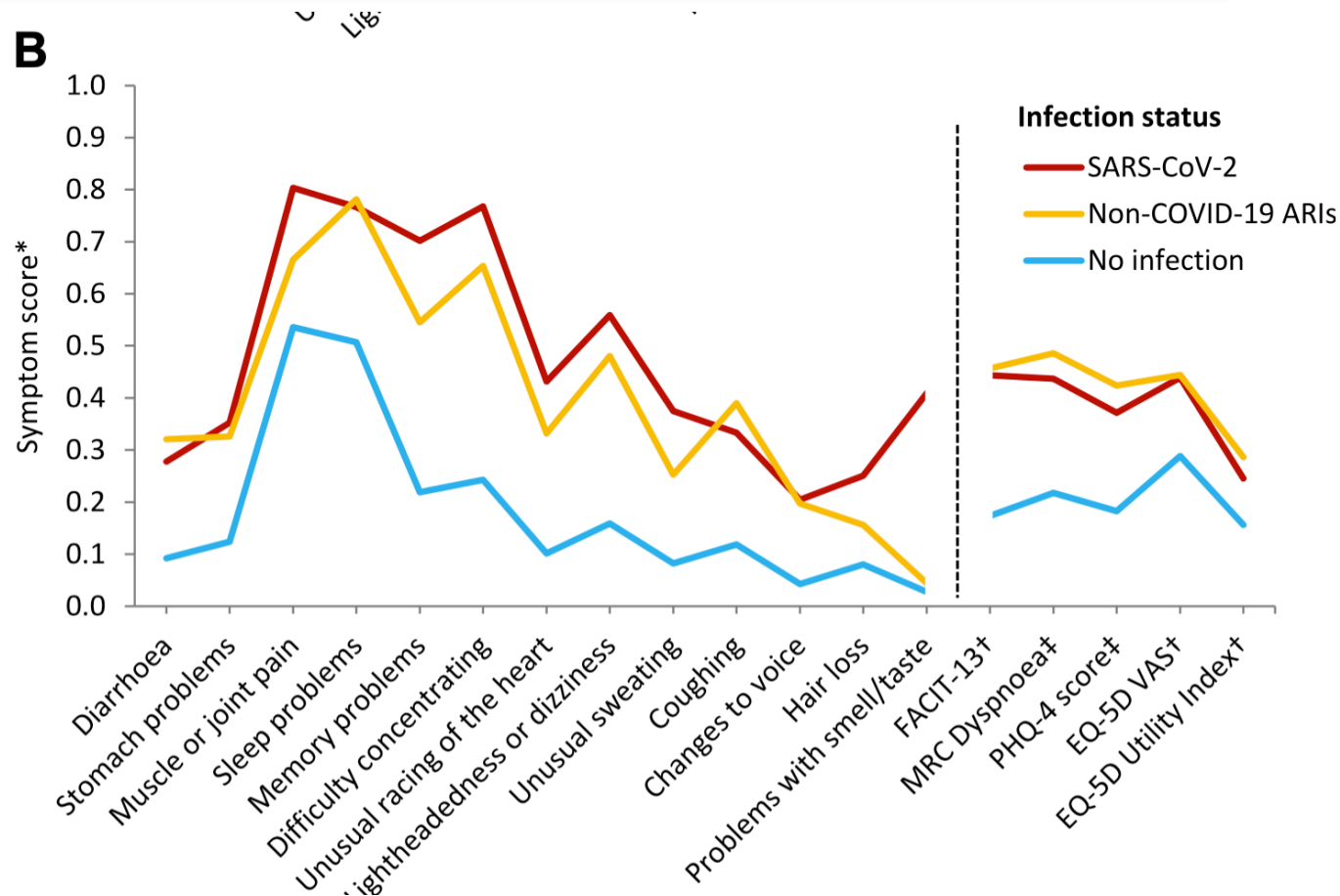
Symptoms may be **new onset** following initial recovery from an acute COVID-19 episode or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time”.

The term “post-COVID conditions” is **an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection**, including by patients who had initial mild or asymptomatic acute infection.

Many post-COVID conditions can be managed by primary care providers, **using patient-centered approaches to optimize the quality of life and function of affected patients**.

Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient’s well-being; **normal laboratory or imaging findings do not invalidate the existence, severity, or importance of a patient’s post-COVID symptoms or conditions**.

## Long-term symptom profiles after COVID-19 vs other acute respiratory infections: an analysis of data from the COVIDENCE UK study



**Symptom profiles among participants with the most severe symptoms, by infection status**

COVIDENCE UK is a prospective, population-based UK study of ARIs in adults

10,171 participants (1311 [12.9%] with SARS-CoV-2 infection, 472 [4.6%] with non-COVID-19 ARI). Both types of infection were associated with increased prevalence/severity of most symptoms and decreased HRQoL compared with no infection.

**Both SARS-CoV-2 and non-COVID-19 ARIs are associated with a wide range of symptoms more than 4 weeks after the acute infection. Research on post-acute sequelae of ARIs should extend from SARS-CoV-2 to include other pathogens.**

# PASC recovery definition

**PASC recovery was based on a medical judgment using the following criteria:**

- Resolution of symptoms or attenuation from moderate or severe to mild;
- Optimal management of new the diseases/conditions occurred after COVID-19 and the further follow-up from a specialized clinic;
- Return to a health status similar to the pre-COVID period evaluated by Clinical Frailty Scale (CFS).

A total of 1,012 people were evaluated,

70.8% were discharged since recovered,

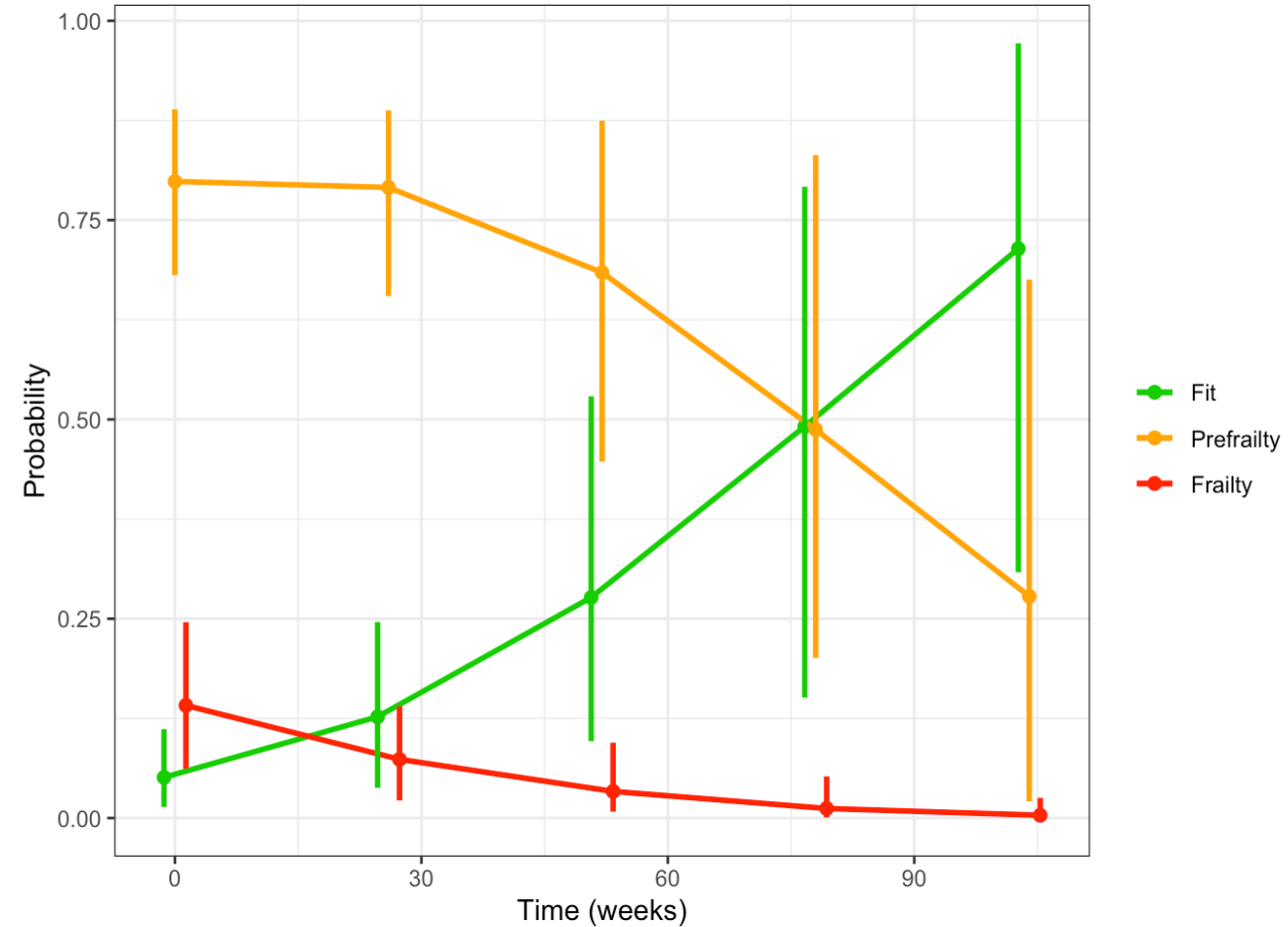
15.9% lost at follow-up

13.2% were still in charge after a mean of  $1.76 \pm 0.62$  years after the acute infection



# Frailty in PACS decreases over time

- We included 823 patients evaluated for PACS, 60.3% were males, with the mean age of 60.3 years.
- At baseline, overweight and obesity were present in 333 (40.5%) and 301 (36.6%), respectively.
- Frailty was diagnosed in 30.5% (203) of patients.



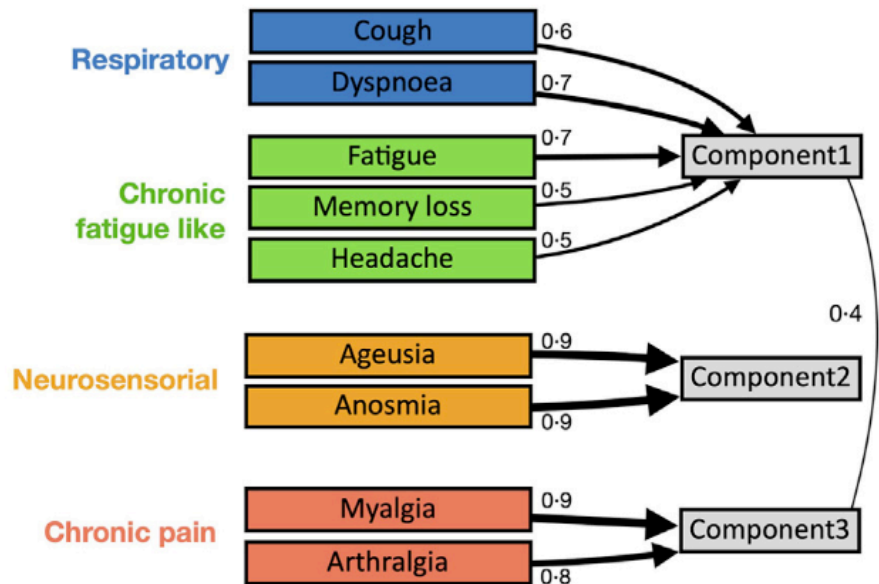
Modena PACS clinic, 2022

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

Gentilotti E, ...Tacconelli E. eClinicalMedicine 2023;62: 102107

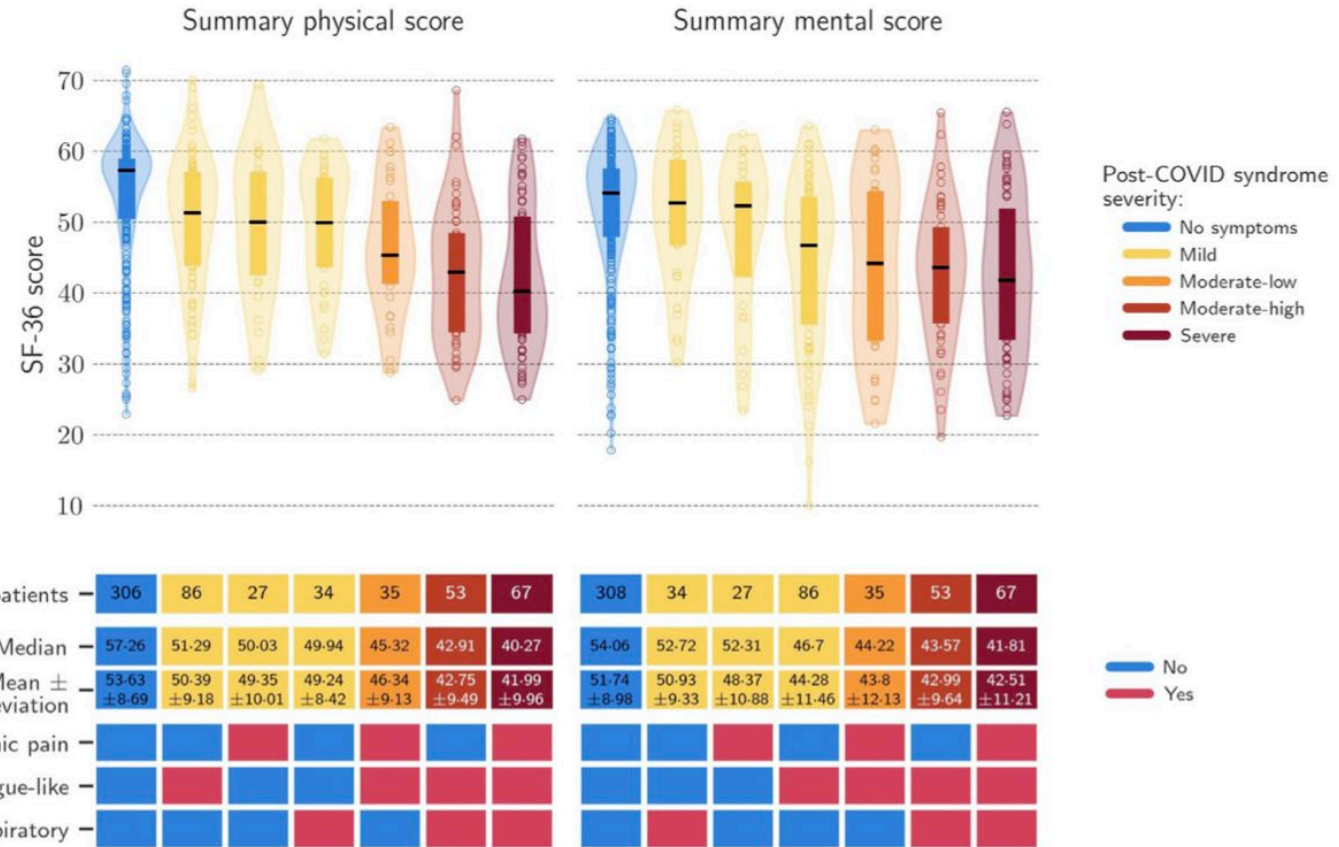


1030 people with PCS  
From 6 prospective cohort from 56 centers in 5 countries, followed at 3-, 6-, and 12-month



## Clusters of symptoms according to principal component analysis (PCA).

The numbers near the arrows are the loadings (only loadings >0.4 are depicted)



## Severity of post-COVID-19 syndrome by clinical phenotypes and quality of life measured with SF-36 questionnaire.

# COVID-19 Induced Postural Orthostatic Tachycardia Syndrome (POTS): A Review

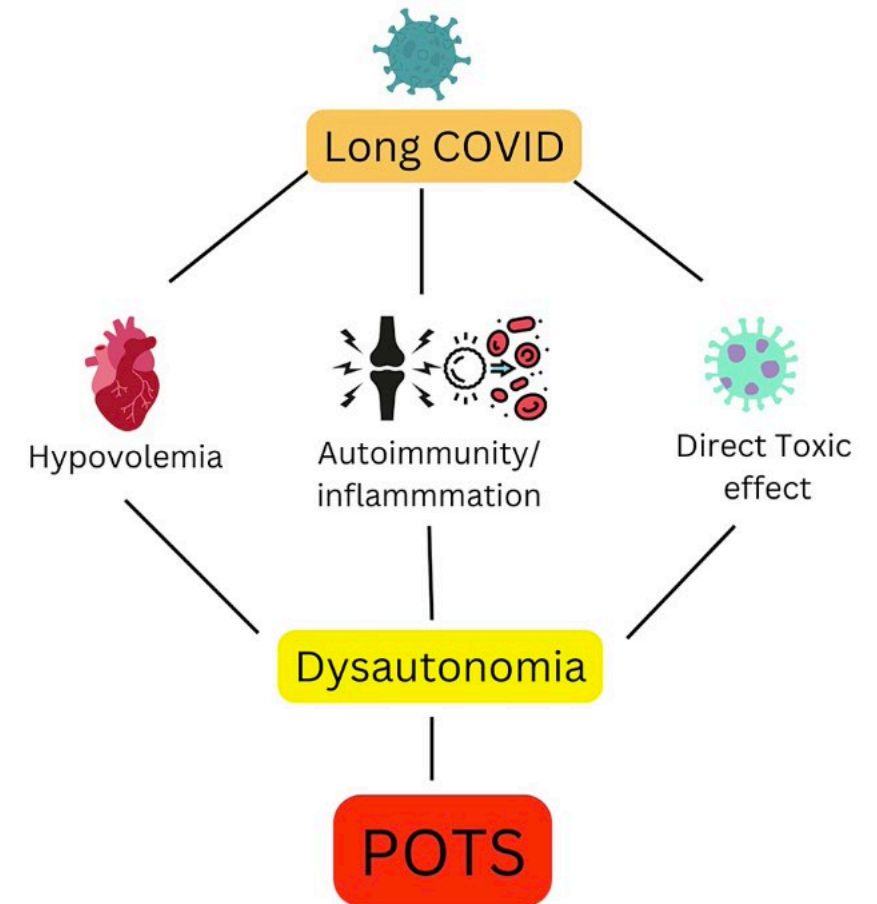
Deobrat Mallick <sup>1</sup>, Lokesh Goyal <sup>2</sup>, Prabal Chourasia <sup>3</sup>, Miana R. Zapata <sup>4</sup>, Kanica Yashi <sup>5</sup>, Salim Surani <sup>6, 7, 8, 9, 10</sup>

POTS (Postural Orthostatic Tachycardia Syndrome) is a multisystem disorder characterized by the abnormal autonomic response to an upright posture, causing orthostatic intolerance and excessive tachycardia without hypotension.

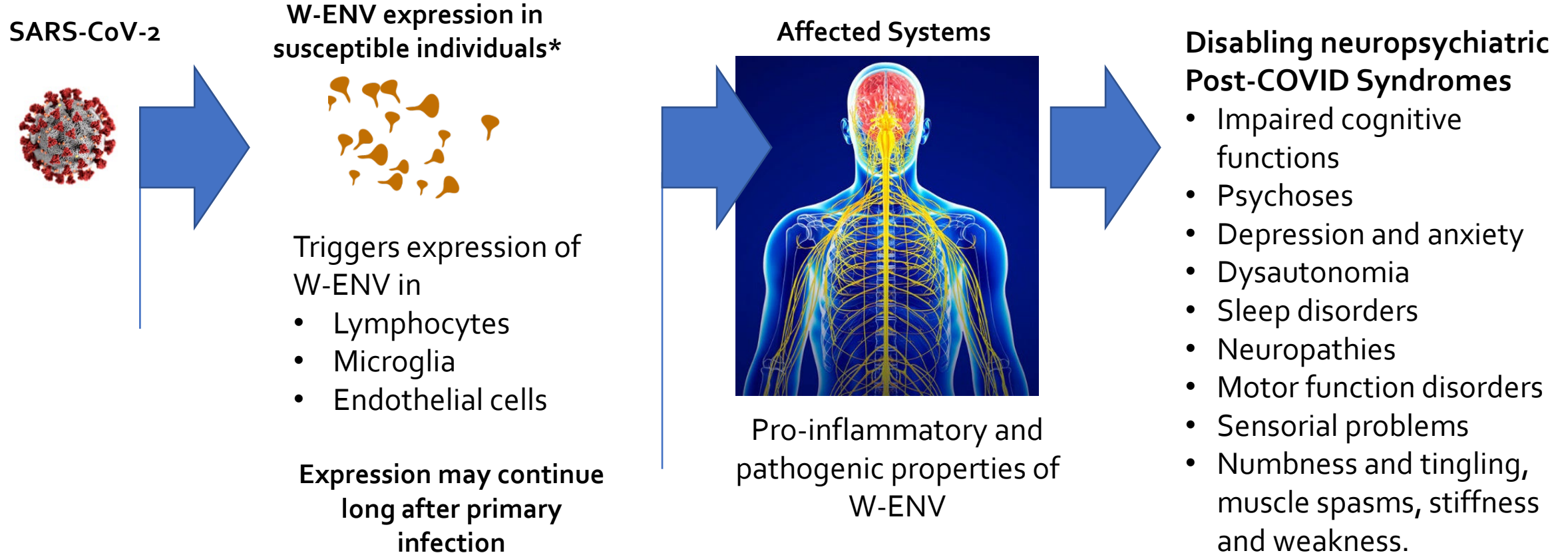
Prominent symptoms of POTS include fatigue, orthostatic intolerance, tachycardia, and cognitive impairment.

Diagnostic tests includes Tilt table

The management of COVID-19-related POTS requires a comprehensive approach. Most patients respond to initial non-pharmacological options, but when the symptoms become more severe and they do not respond to the non-pharmacological approach, pharmacological options are considered



# W-ENV as a key link between SARS-CoV-2 and disabling syndromes suffered by Post-COVID patients



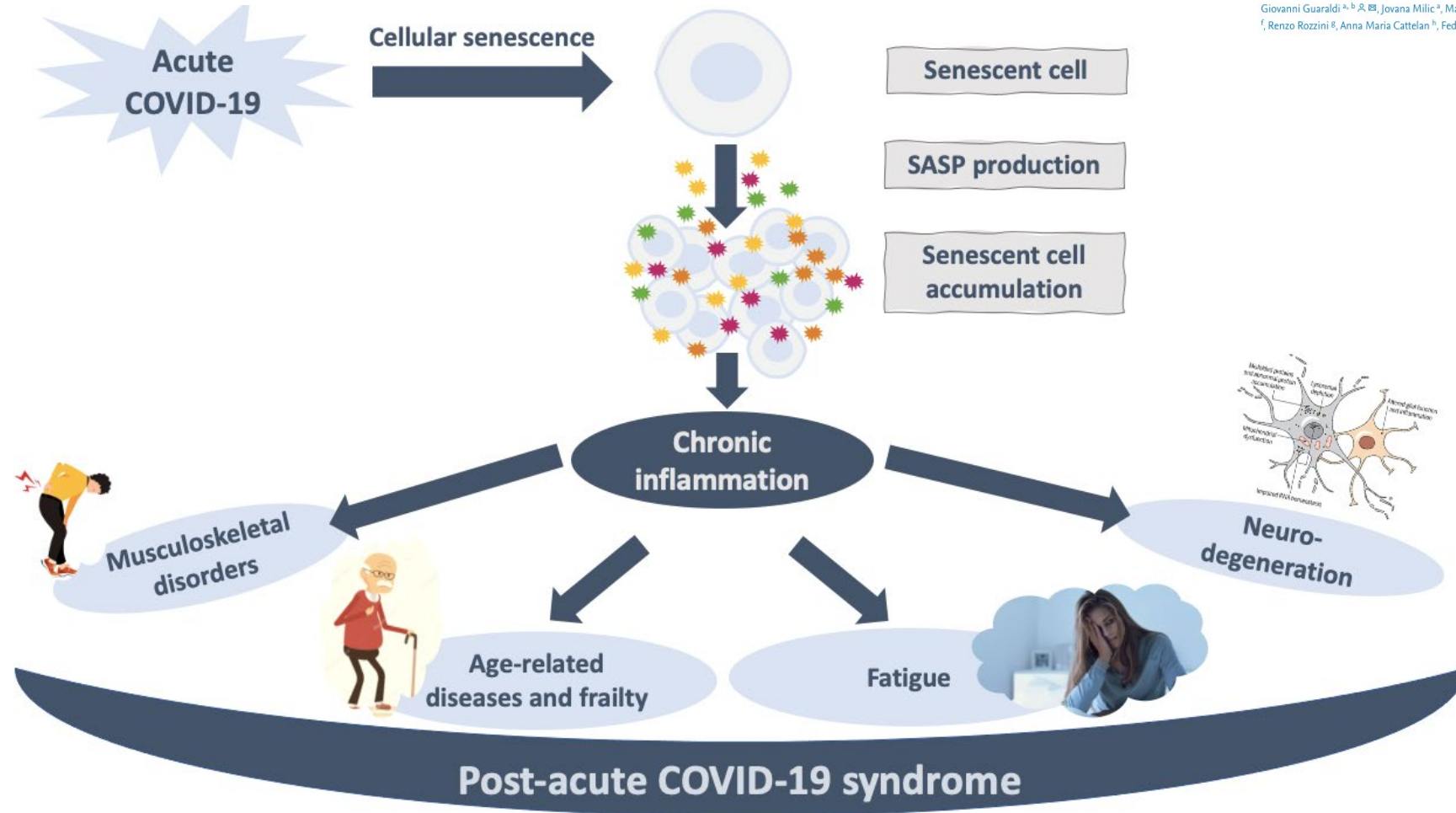
\* [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(21\)00134-1/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00134-1/fulltext)  
<https://www.medrxiv.org/content/10.1101/2022.01.18.21266111v2>  
[https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(21\)00156-0/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00156-0/fulltext)

# How to describe PASC Complexity

Review

The interplay of post-acute COVID-19 syndrome and aging: a biological, clinical and public health approach

Giovanni Guaraldi <sup>a, b, c, d, e</sup>, Jovana Milic <sup>a</sup>, Matteo Cesari <sup>c</sup>, Leonard Leibovici <sup>d</sup>, Federica Mandreoli <sup>e</sup>, Paolo Missier <sup>f</sup>, Renzo Rozzini <sup>g</sup>, Anna Maria Cattelan <sup>h</sup>, Federico Motta <sup>a</sup>, Cristina Mussini <sup>a, b</sup>, Andrea Cossarizza <sup>i</sup>



## Risk Factors Associated With Post–COVID-19 Condition

### A Systematic Review and Meta-analysis

Vasiliki Tsampasian, MD, MSc; Hussein Elghazaly, MBBS; Rahul Chattopadhyay, MBBS, MSc; Maciej Debski, MD, PhD; Thin Kyi Phyu Naing, MBBS; Pankaj Garg, PhD; Allan Clark, PhD; Eleana Ntatsaki, MD(Res), MA; Vassilios S. Vassiliou, MBBS, PhD

- 5334 records
- 255 articles underwent full-text evaluation
- 41 articles included
- total of 860 783 patients that were considered
- Data analysis preformed up to December 2022

## Factors associated with post-COVID-19 condition

	OR	95% CI
<b>Female sex</b>	<b>1.56</b>	<b>1.41 – 1.73</b>
<b>Age</b>	<b>1.21</b>	<b>1.11 - 1.33</b>
BMI >30 kg/m <sup>2</sup>	1.15	1.08 – 1.23
Smoking	1.10	1.07– 1.13
<b>Vaccination status</b>	<b>0.57</b>	<b>0.43 – 0.76</b>
Anxiety and/or depression	1.19	1.02 – 1.40
Asthma	1.24	1.15 – 1.35
Chronic kidney disease	1.12	0.98 – 1.28
Chronic obstructive pulmonary disease	1.38	1.08 – 1.78
Diabetes	1.06	1.03 – 1.09
Immunosuppression	1.50	1.05 – 2.15
Ischemic heart disease	1.28	1.19 – 1.38
Hospitalization	2.48	1.97 – 3.13
ICU admission	2.37	2.18 – 2.56

# A data-driven identification of people recovering from post-acute sequelae of SARS- CoV-2 infection (PASC)

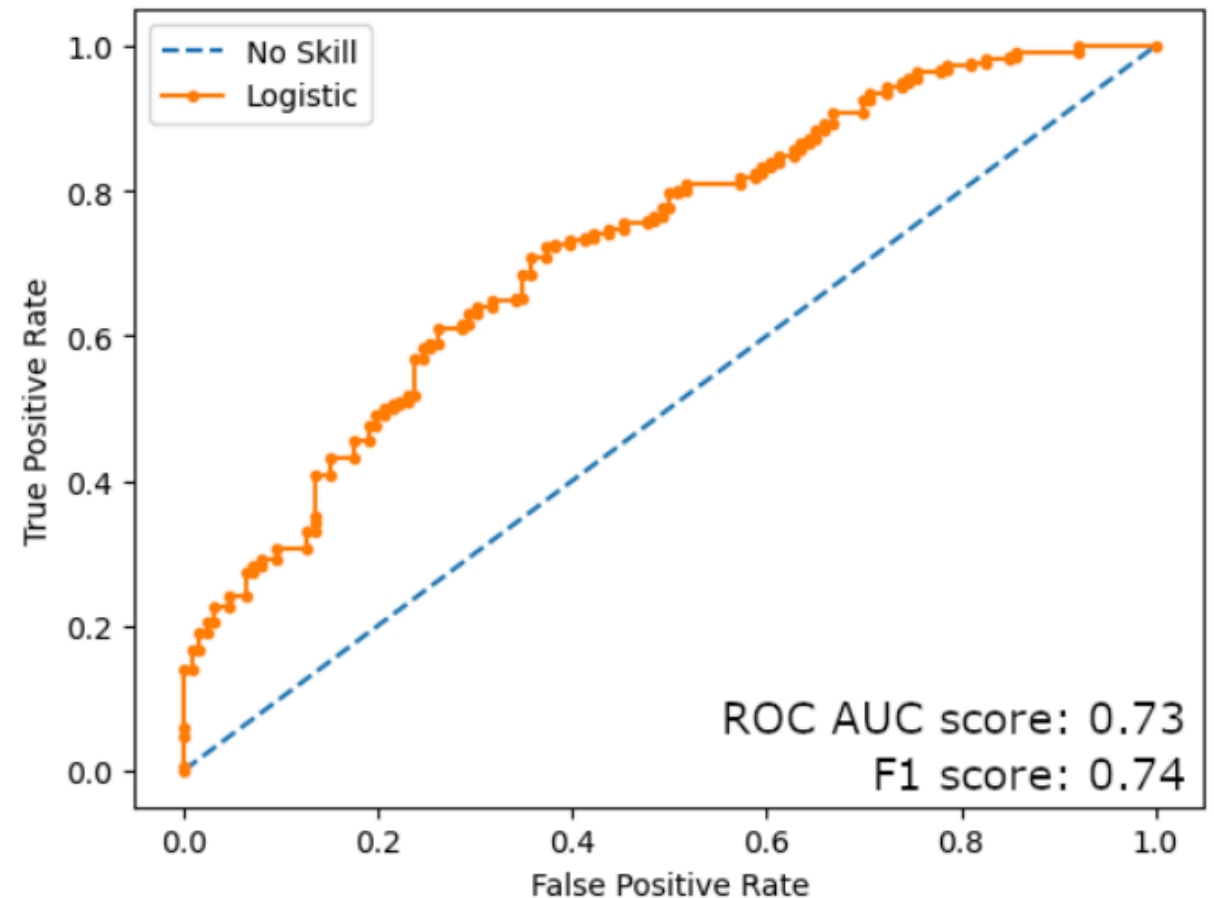
This study aims at identifying predictors of PASC recovery in terms of risks and protective factors by means of a novel machine learning approach applied to multi-faceted patient trajectories.

## Subjective attributes of PASC (TOPIC)

- PASC symptoms from the 51-item checklist.
- Each symptom was defined by intensity, i.e., mild, moderate or severe.

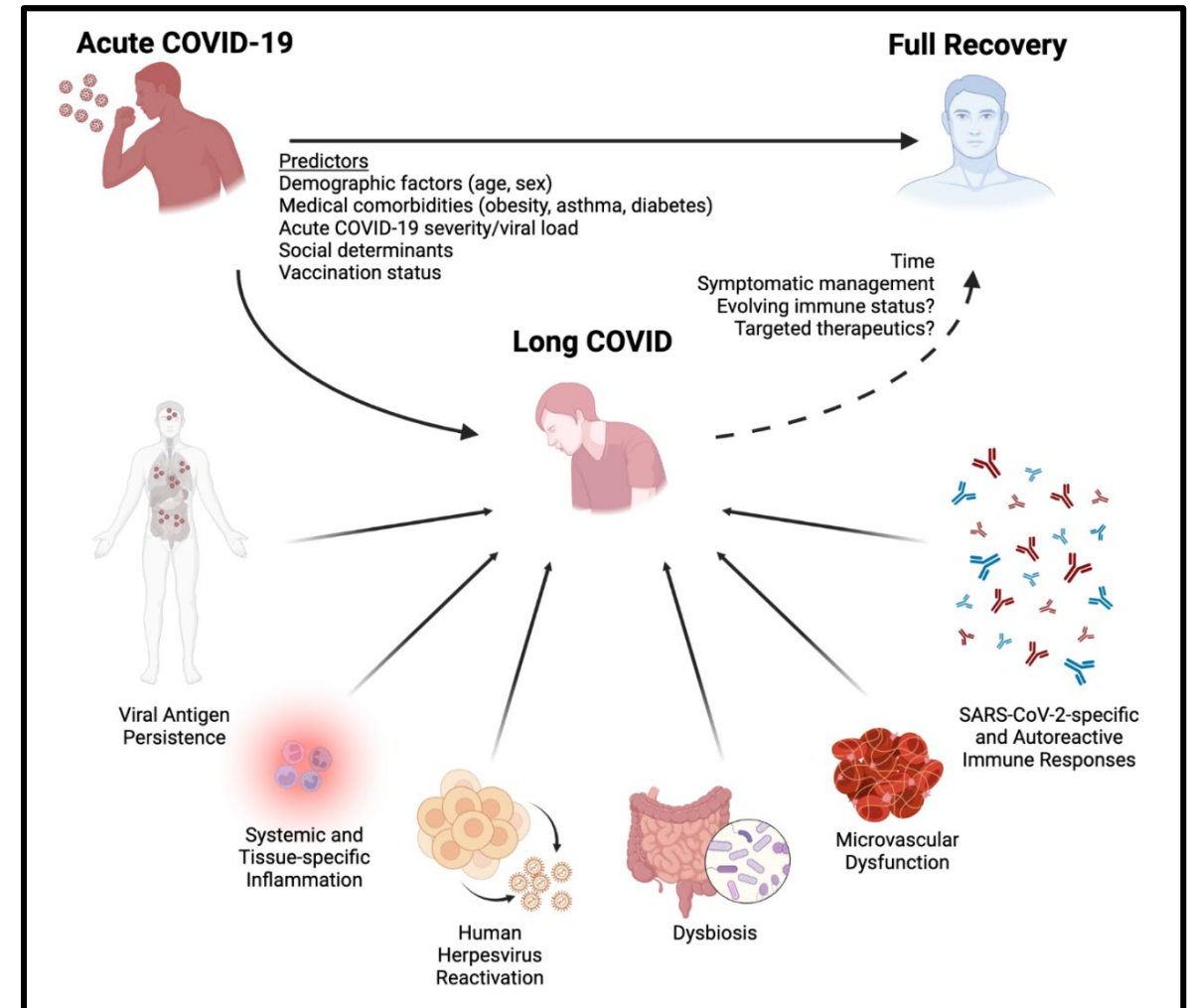
## Objective attributes of PASC included (CLUSTER):

- laboratory findings
- frailty (frailty phenotype)
- physical function (SPPB)
- cognitive function (Cogstate).



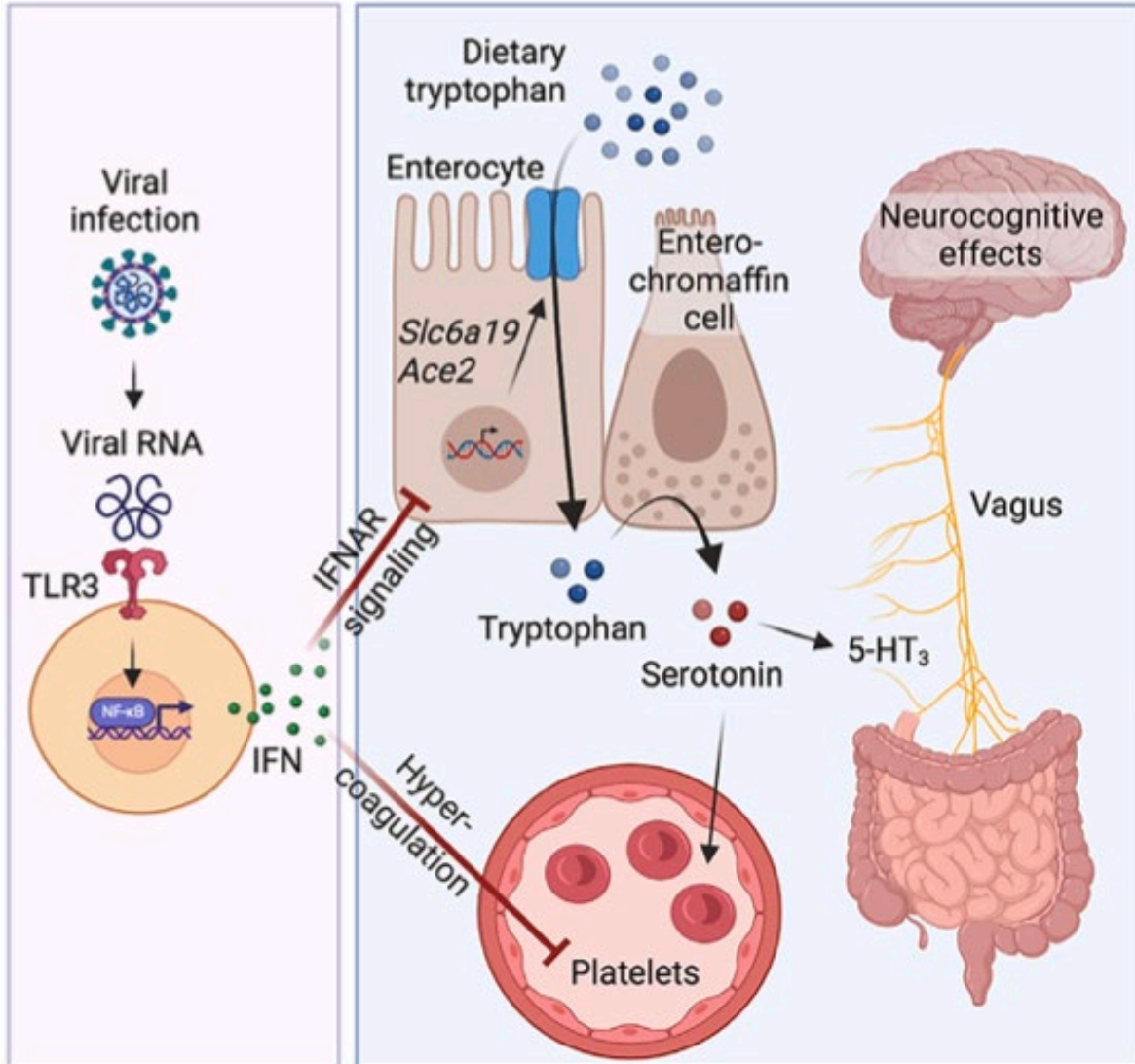
# Possible pathogenetic mechanisms of PACS

- Persistent viral infection and ongoing tissue harm
- Inflammation
  - Direct: SARS-CoV-2
  - Indirect: EBV/CMV reactivation, dysbiosis
  - Immune dysfunction
- Auto-antibodies
- Microvascular disease (clotting, endotheliitis)





## Serotonin reduction in post-acute sequelae of viral infection



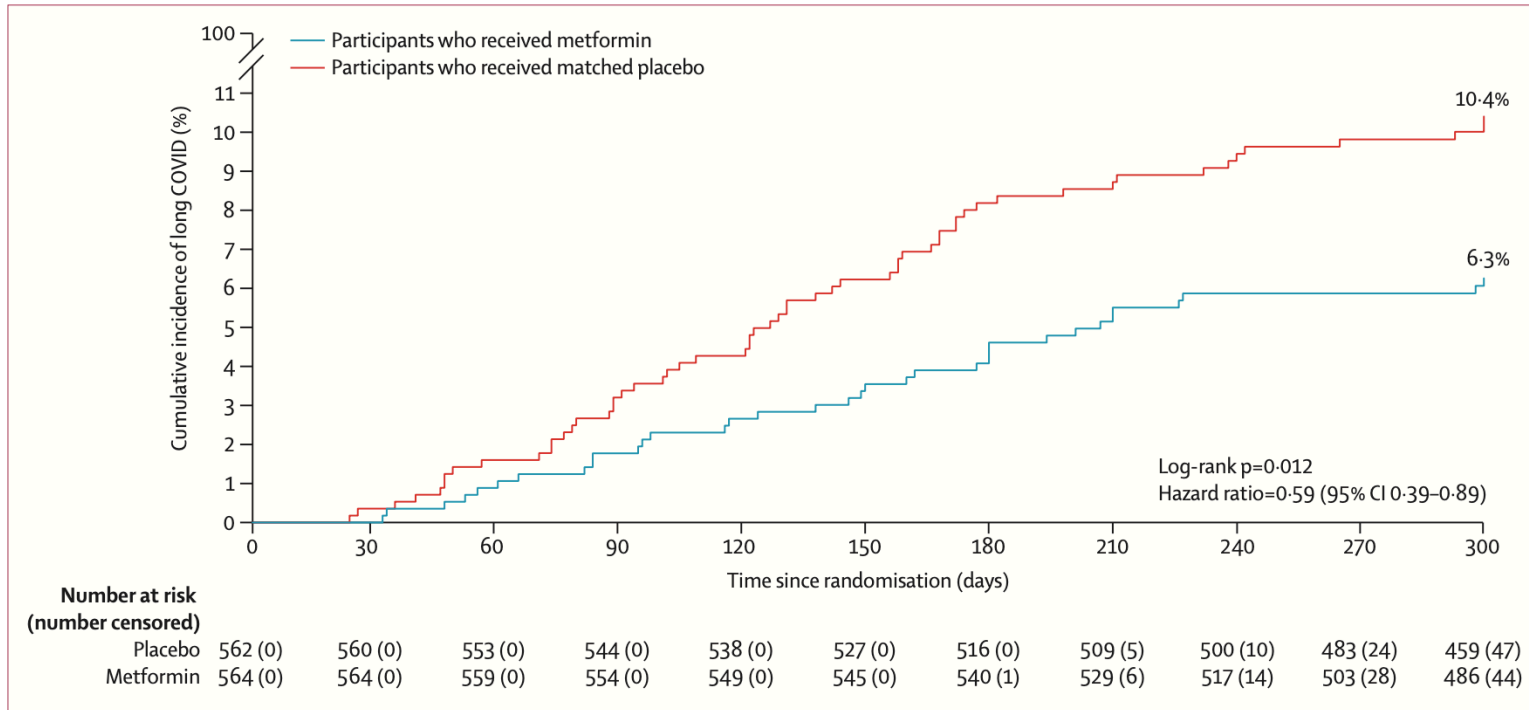
## Long COVID is associated with reduced circulating serotonin levels

- ✓ Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs) through
  1. diminished intestinal absorption of the serotonin precursor tryptophan;
  2. platelet hyperactivation and thrombocytopenia, which impacts serotonin storage;
  3. enhanced MAO-mediated serotonin turnover.
- ✓ Peripheral serotonin reduction impedes the activity of the vagus nerve and thereby impairs hippocampal responses and memory

# Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial



Caveat: The primary method for ascertaining long COVID was participant-reported receipt of a long COVID diagnosis from a medical provider, in follow-up surveys on days 180, 210, 240, 270, and 300.



**Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomisation**

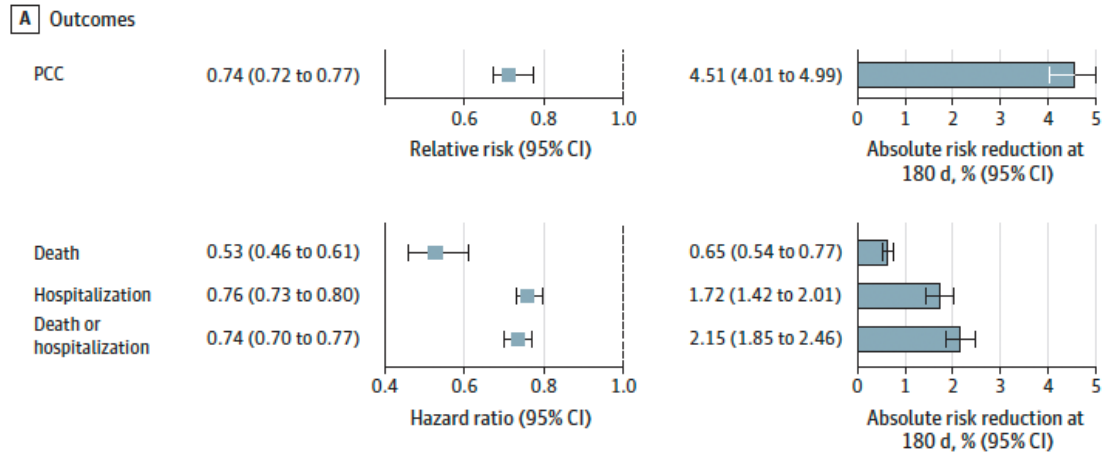
- ✓ Outpatient treatment with metformin reduced long COVID incidence by about 41%, with an absolute reduction of 4.1% (6.3% vs 10.4%), compared with placebo.
- ✓ Metformin has clinical benefits when used as outpatient treatment for COVID-19 and is globally available, low-cost, and safe.

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

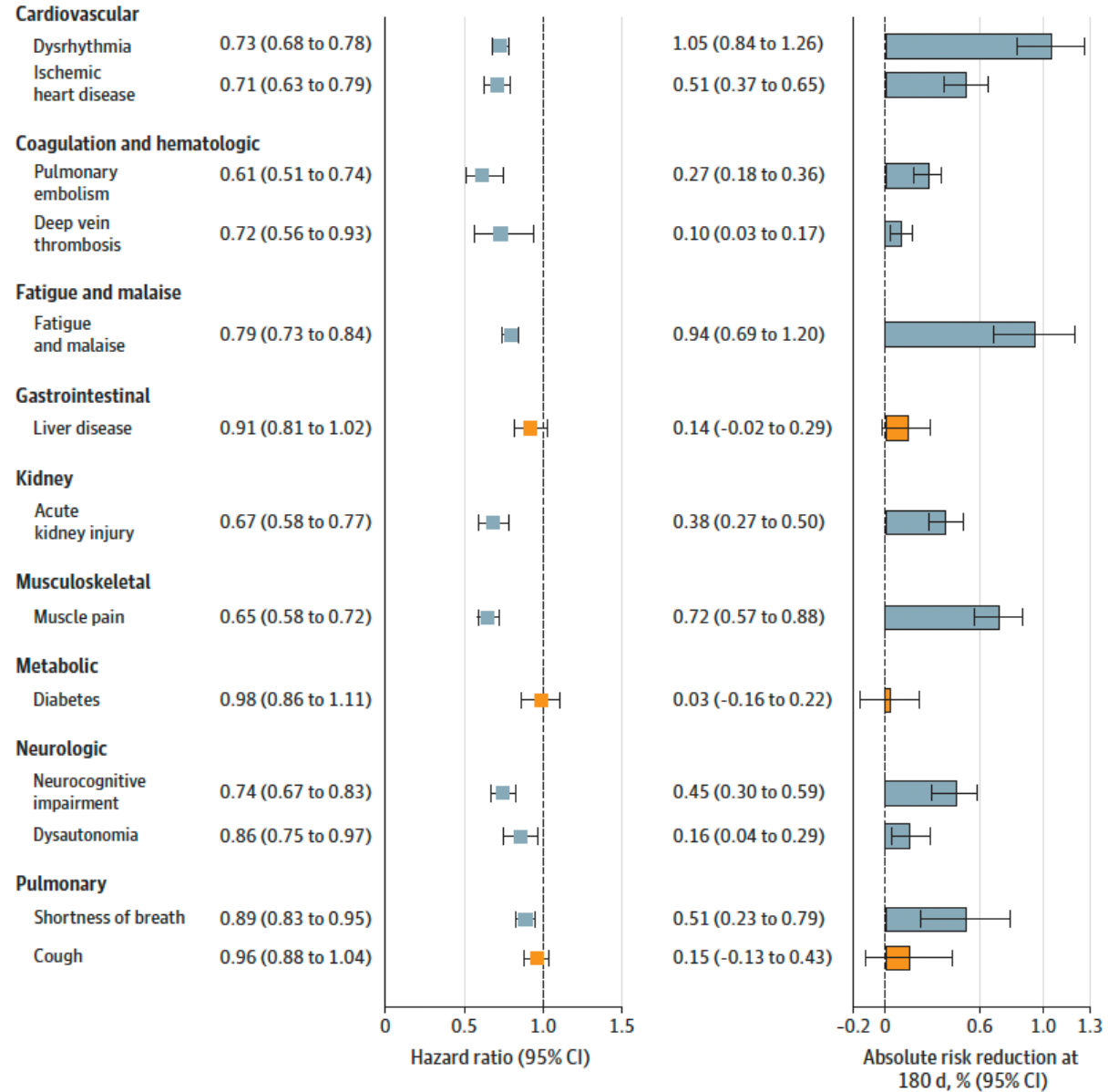
Yan Xie, PhD; Taeyoung Choi, MPH; Ziyad Al-Aly, MD

A total of **281 793 patients** (mean age **61.99 years; 86% were male**) who had a positive SARS-CoV-2 test result and had at least 1 risk factor for progression to severe COVID-19 illness were studied.

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



**B Components**

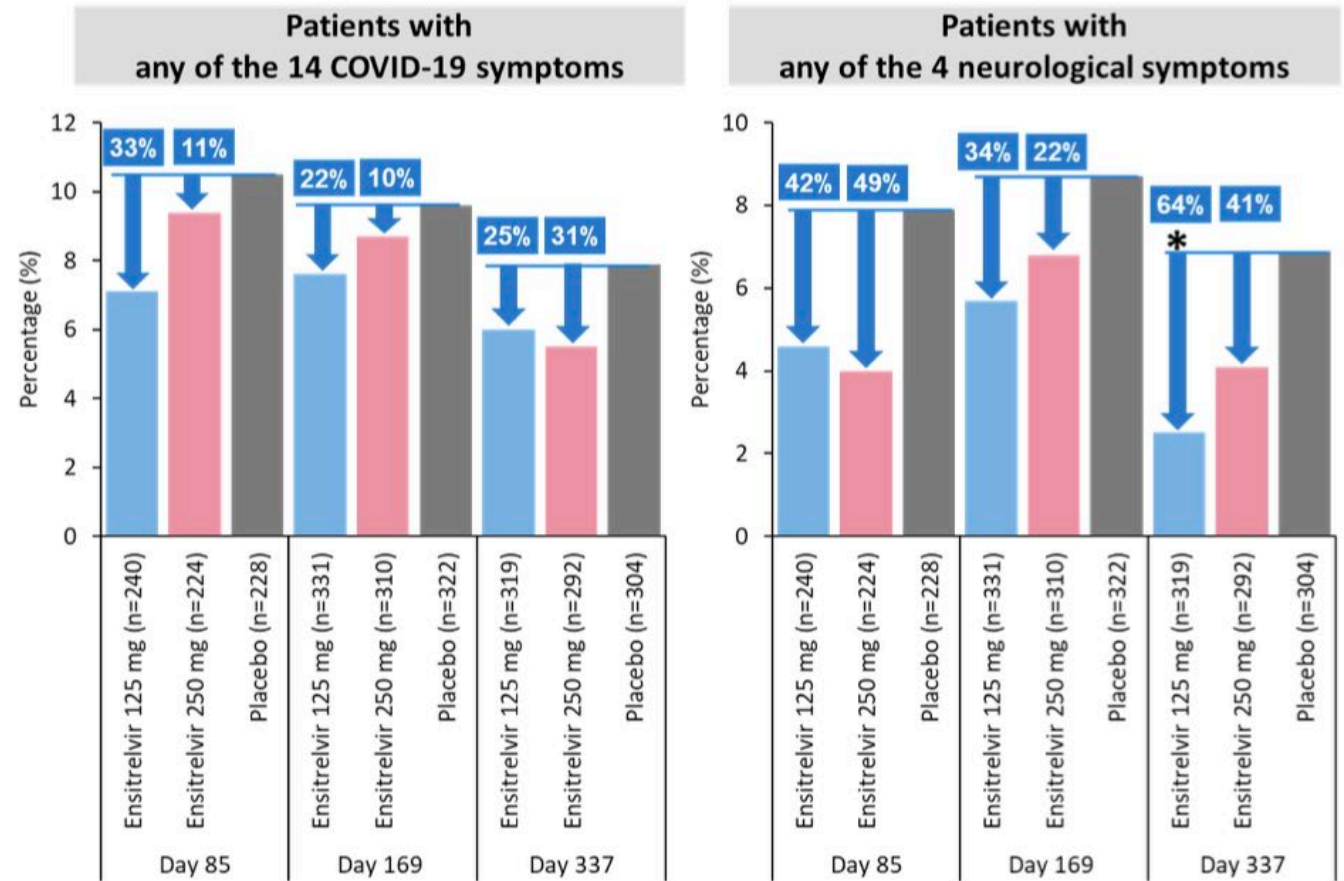


# Effect of Ensitrelvir on Long COVID in Patients with Mild-to-Moderate COVID-19: A Post-Hoc Analysis of the Phase 3 SCORPIO-SR Study

CORPIO-SR is a multicenter, randomized, double-blind, placebo-controlled, phase 2/3 study.

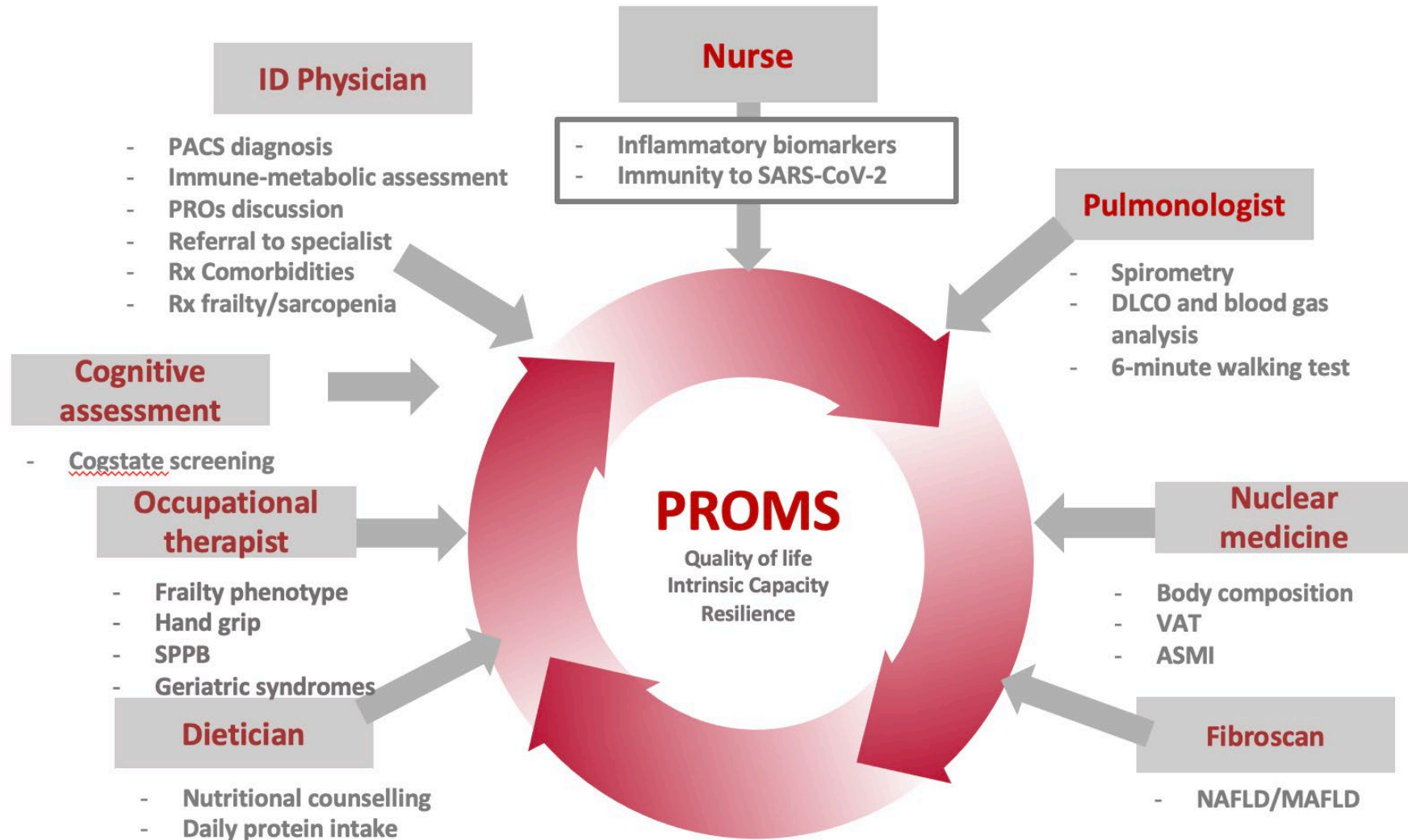
Eligible patients were randomized (1:1:1) to orally receive once-daily ensitrelvir 125 mg (375 mg on Day 1), 250 mg (750 mg on Day 1), or placebo for 5 days

- Long COVID assessments were performed during the exploratory period (Days 85, 169, and 337) using the PASC questionnaire



# Health care model of Modena PACS Clinic

## Multidisciplinary and multidimensional assessment and health care model



# Long-Covid: che cosa aspettarci?

- Occorre demistificare il PASC: è reale ma non è una malattia ma una sindrome
- Lo studio del PASC aprirà nuovi scenari all'interpretazione delle sequele di diverse malattie (chronic fatigue)
- Si individueranno biomarcatori associati non al PASC ma a specifici elementi patogenetici/sintomatologici che lo costituiscono
- Occorrerà lavorare maggiormente con le associazioni dei pazienti per caratterizzare meglio la sindrome e ottenere risorse dalle istituzioni
- I numeri dei pazienti diminuiranno e saranno necessari centri di riferimento macroregionali
- Una migliore definizione dei pazienti a rischio di PASC rappresenterà un criterio di utilizzo dei farmaci antivirali nella fase acuta (Emsitrelvir, Nirmatrelvir)