Condición Covid-19 persistente

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NARRATIVE MATTERS

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‘Long COVID’: Making The Invisible Visible

After recovering from acute COVID-19 infection, a physician is stricken with the debilitating symptoms of long COVID.

BY MARIA VICTORIA BOVO

breathing and only on breathing. After forty-eight hours of it taking an incredible amount of effort just to breathe, I surrendered to the most refreshing and healing sleep that I can recall. When I woke at dawn, the sea was still there, and so was I. And so was I.

It’s been a year and a half, and there are still days in which tiredness defeats me, and I can’t get up. But on the days I can do it, I go back to the sea, where I feel alive.

Every wave, with each withdrawal, takes my fears away, and when the wave returns, it brings hope.

It takes away tiredness and brings acceptance; it takes away uncertainty and brings patience.

And it reminds me that I’m here to tell what I have been living through.

Not Able To Do But Able To Be

For the first three months after I was home, I was bedbound. I never imagined myself like this—not being able to take care of myself and my family. I couldn't utter more than a sentence or walk more than five meters without sitting and resting. I even had to use a wheelchair sometimes because I was breathless. I wasn’t able to watch television or listen to music, and I couldn’t read more than a sentence because I felt tired and lacked focus and concentration. Feeling so vulnerable made me feel guilty and angry: I was supposed to be treating patients, not being a patient!

Learning To Live

This may be an “invisible disease” for others, but for me, it is constantly present, setting limits on my body and mind.

It is a relapsing-remitting condition in which progress is variable. I move forward, then feel I’m regressing. As if I wanted to come out from the ocean and a wave reaches me and drags me back in again. The sea, like fatigue, always wins.

I have felt fear. At the beginning, it was fear of death. Later it was fear of the persistent symptoms of the disease. While I was in hospital with COVID-19, feeling that death was close, I thought that I didn’t regret not having a doctorate, but I did feel regret for “not having lived.” I’ve learned that I know “something” about medicine and that I don’t know anything about living. I thought I was afraid of death, but, in fact, I was afraid of life. But nothing good comes

COVID-19 did not end my life, but it stopped me. It dragged me down from the high-velocity train on which I was riding. I stood up, fell down, and stood up again.

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DEFINICIÓN

Long-Covid

Post-COVID-19 manifestations

Covid persistent

Long-term COVID-19 effects

Prolonged COVID-19

Prolonged sequelae

Post-acute COVID-19 syndrome (PACS)

Chronic COVID syndrome

Post-acute sequelae SARS-CoV-2 infection (PASC)

Post-COVID-19 syndrome

Long Haulers

Post-acute COVID-19 persistent COVID-19 symptoms

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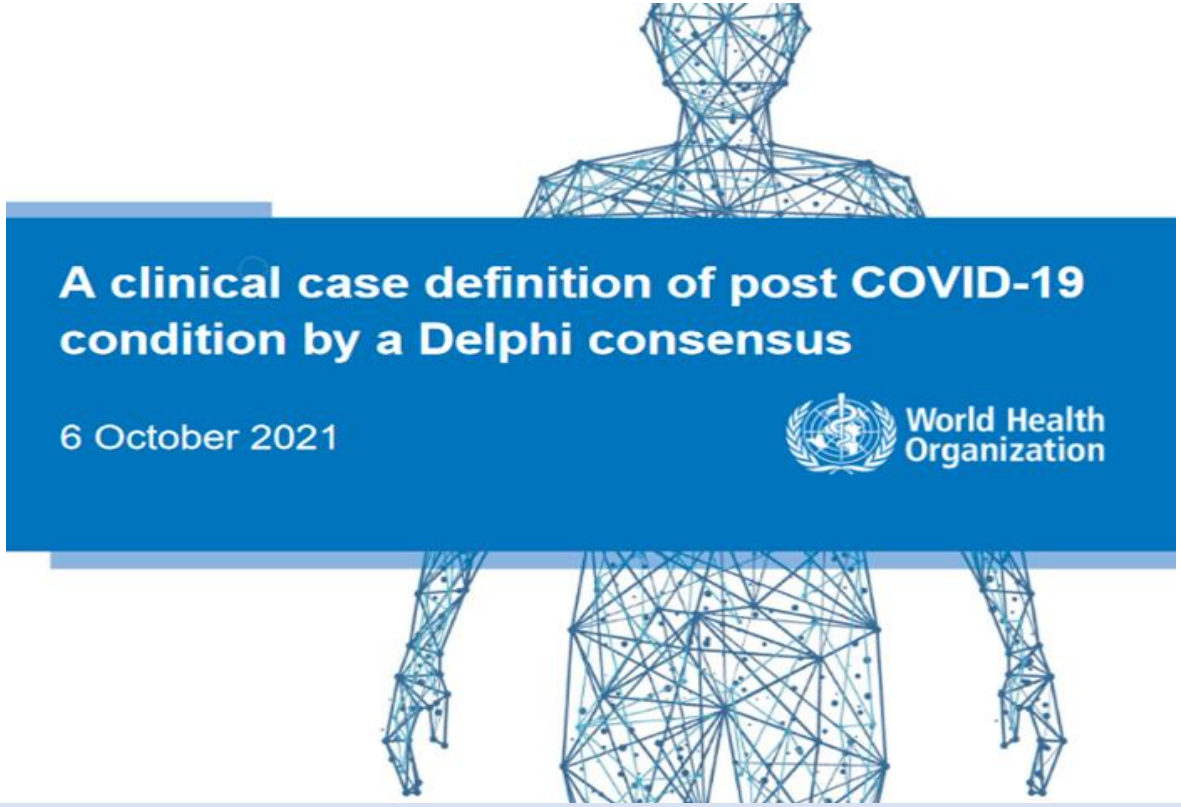
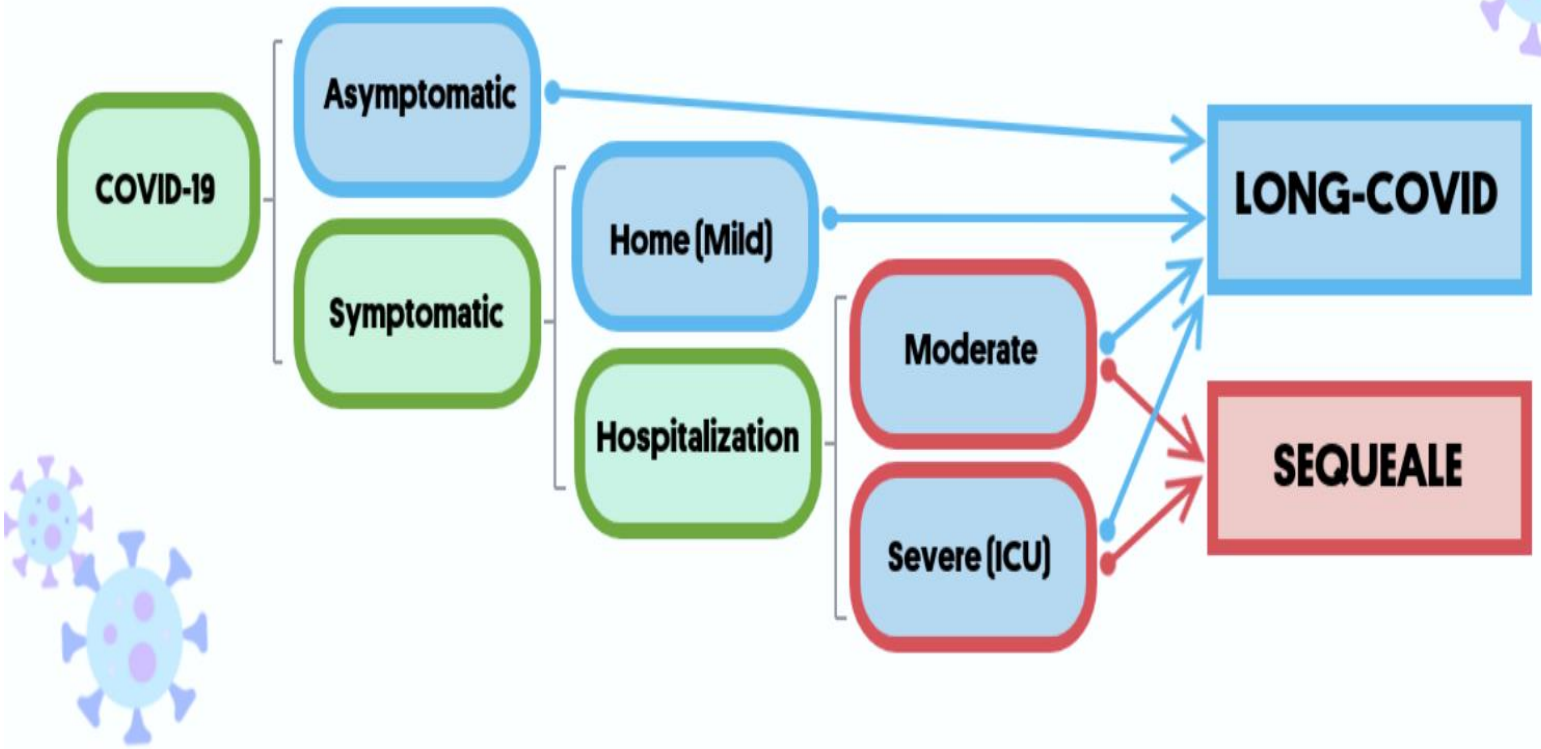
DEFINICIÓN



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.

*Soriano JB, et al. Lancet Infect Dis. 2022;22(4):e102-e107.

DEFINICIÓN



- **Post Intensive Care Syndrome.**
  Patients after ICU admission with target organ damage as part of the systemic inflammatory response. Example: lung, heart, renal damage and myopathy or neuropathy in critically ill patients.
- **Sequelae arising from post-thrombotic or haemorrhagic complications.**
  Such as cerebrovascular and thrombo-embolic events, myocardial infarction, and arterial ischaemia.
- **Sequelae resulting from immuno-mediated phenomena in the acute phase.**
  Such as Guillain-Barre syndrome, encephalitis, myelitis, idiopathic thrombocytopenic purpura or systemic autoimmune diseases.
- **MIS-C and MIS-A.**
  Multisystemic inflammatory syndrome in children (MIS-C) and adults (MIS-A) that can appear 3-4 weeks after viral infection, with high morbidity and mortality and significant risk of sequelae.

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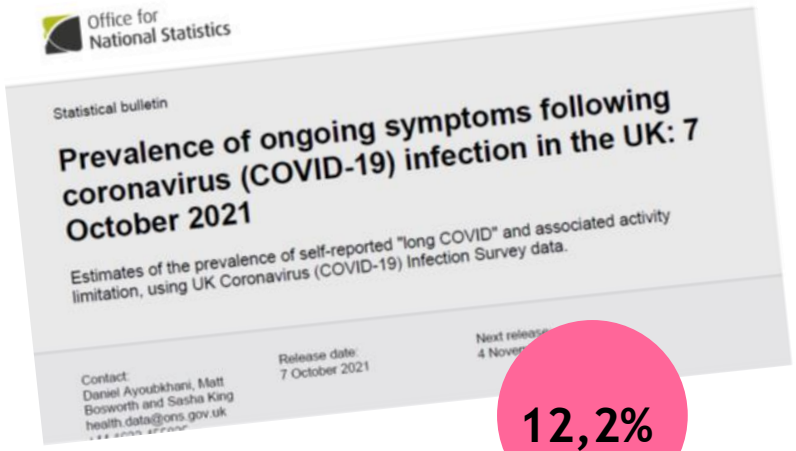
PREVALENCIA


Office for National Statistics

Statistical bulletin

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 7 October 2021

Estimates of the prevalence of self-reported "long COVID" and associated activity limitation, using UK Coronavirus (COVID-19) Infection Survey data.

Contact: Daniel Ayoubkhani, Matt Bosworth and Sasha King health.data@ons.gov.uk

Release date: 7 October 2021

Next release: 4 Nove

12,2%

1/8

Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study

*Aranka V Ballering, Sander K R van Zon, Tim C olde Hartman, Judith G M Rosmalen, for the Lifelines Corona Research Initiative**

España

13.755.956

>1millón

Mundo

674.063.615

65 millones

https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/alldatarelatingtoprevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk;
Ballering, Aranka V et al. Lancet 400,10350 (2022): 452-461. doi:10.1016/S0140-6736(22)01214-4
Long COVID: principals troballes, mecanismes i recomanacions
Hannah E. Davis , [1] Lisa McCorkell , [2] Julia Moore Vogel , [3] i Eric J. Topol

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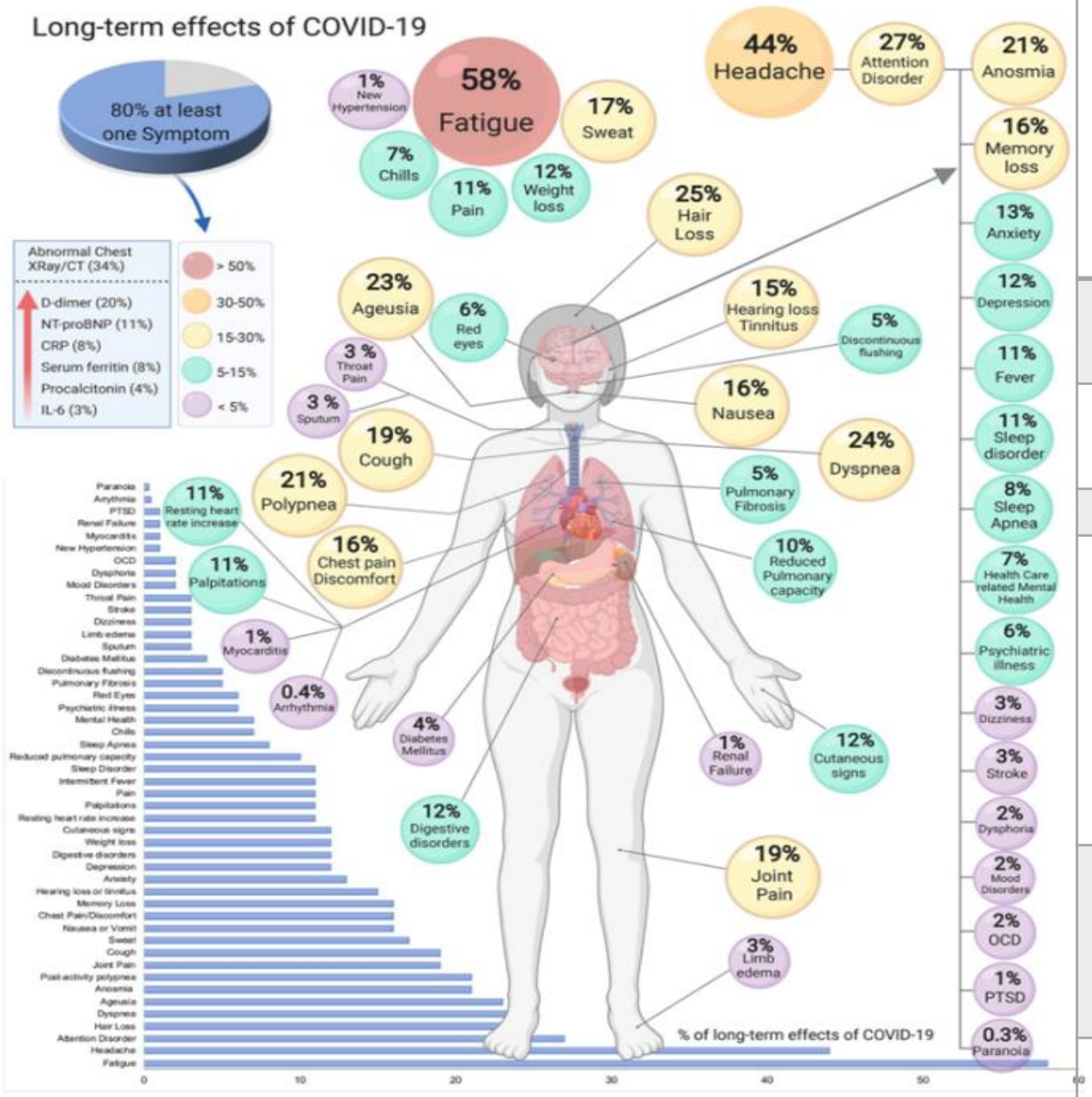
SÍNTOMAS



Síntomas generales	• **Fiebre/Febrícula/ Alteración de la percepción de la temperatura** • **Astenia/fatiga** • **Anorexia/Pérdida de peso** • **Pérdida del Cabello** • **Xerostomía o xeroftalmia** • **Alteraciones Cutáneas** • **Alteraciones visuales** • **Alteraciones en la menstruación** • **Disfunción eréctil**
Síntomas respiratorios	• Tos • Expectoración • Disnea
Síntomas cardiovasculares	• Dolor torácico • Taquicardia • Alteraciones en el control de la tensión arterial
Síntomas aparato locomotor	• Artralgias/Mialgias
Síntomas neurológicos/neurocognitivos	• Cefalea • Alteraciones neurosensitivas (parestesias, disestesias, fonofobia, fotofobia) • Niebla mental • Afectación neurocognitiva (pérdida de memoria, alteraciones en la atención/concentración, dificultad de planificación) • Sensación de inestabilidad (mareo, vértigo, inestabilidad) • Insomnio
Síntomas ORL	• Alteraciones del gusto /Alteraciones en el olfato • Disfonía • Disfagia • Odinofagía • Otalgia • Acúfenos
Síntomas digestivos	• Náuseas • Dolor abdominal/Diarrea/Estreñimiento

Lopez-Leon et et al, Scientific reports 2021

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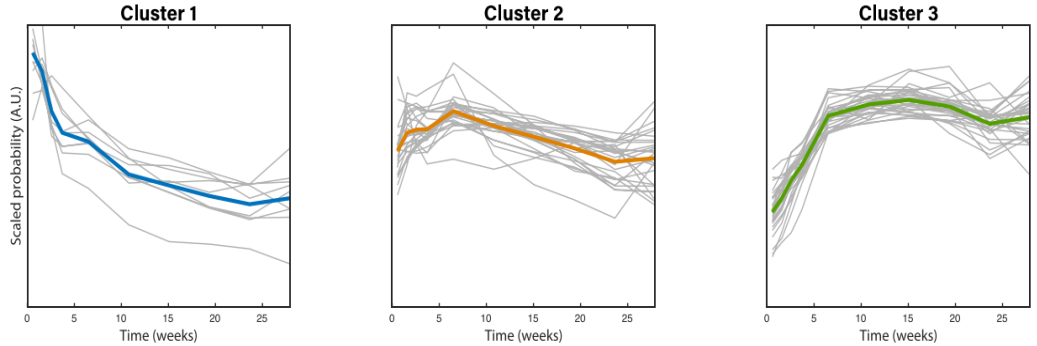
SÍNTOMAS



Cardiovascular		25. Fainting 19. Pain/burning in chest 33. Tachycardia	49. Bradycardia 38. Palpitations 64. Visibly inflamed/bulging veins
Dermatologic		30. COVID toe	53. Dermatographia 55. Other Skin and Allergy 42. Peeling skin 54. Petechiae 44. Skin rashes
Gastrointestinal	9. Diarrhea 2. Loss of Appetite 4. Vomiting	26. Abdominal pain 18. Nausea	45. Constipation 43. Gastroesophageal reflux
HEENT (Head, ears, eyes, nose, throat)	7. Runny nose 6. Sore Throat		48. Hearing loss 51. Other ear/hearing issues 39. Other eye symptoms 58. Tinnitus 59. Vision symptoms
Immunologic/ Autoimmune			65. New allergies 63. New anaphylaxis reaction
Musculoskeletal		32. Bone ache or burning 21. Muscle aches 15. Tightness of Chest	37. Joint pain 40. Muscle spasms
Neuropsychiatric		20. Acute (sudden) confusion/disorientation 12. Changes to sense of smell and taste 22. Dizzines, unsteadiness or balance issues 31. Hallucinations 29. Headaches and related symptoms 35. Insomnia 27. Other sleeping symptoms 34. Sleep apnea 36. Slurring words/speech	41. All sensorimotor symptoms 47. Brain fog 61. Memory issues 50. Neuralgia (nerve pain) 62. Speech/language issues 52. Tremors 56. Vibrating Sensations
Pulmonary/ Respiratory	3. Dry cough 5. Rattling of breath	14. Breathing difficulty (normal O2 saturation level) 17. Cough with mucus production 10. Coughing up Blood 24. Other Respiratory and Sinus 16. Shortness of Breath 13. Sneezing	
Reproductive/ Genitourinary/ Endocrine			60. All menstrual/period issues 46. Bladder control issues
Systemic	8. Elevated temperature (98.8-100.4F) 1. Fever (>= 100.4F)	11. Chills/flushing/sweats 28. Fatigue 23. Low temperature	39. Other temperature issues 57. Post Exertional Malaise

Davis et al, EClinicalMedicine 2021

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SÍNTOMAS

Mateu L, Teve C., Loste C., et al SEVERITY CLUSTERS AND LIKELIHOOD OF RECOVERY FROM POST-COVID-19 CONDITION
Croi 2023

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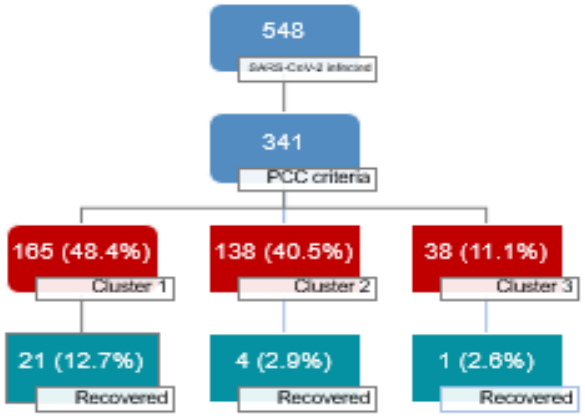
RESULTS

Study flowchart

Follow-up time, median (IQR): 23 months (16.5-23.5)

Time to recovery, median (IQR): 11.4 months (6.1-13.3)

All PCC participants, except 2, were SARS-CoV-2 infected prior vaccination



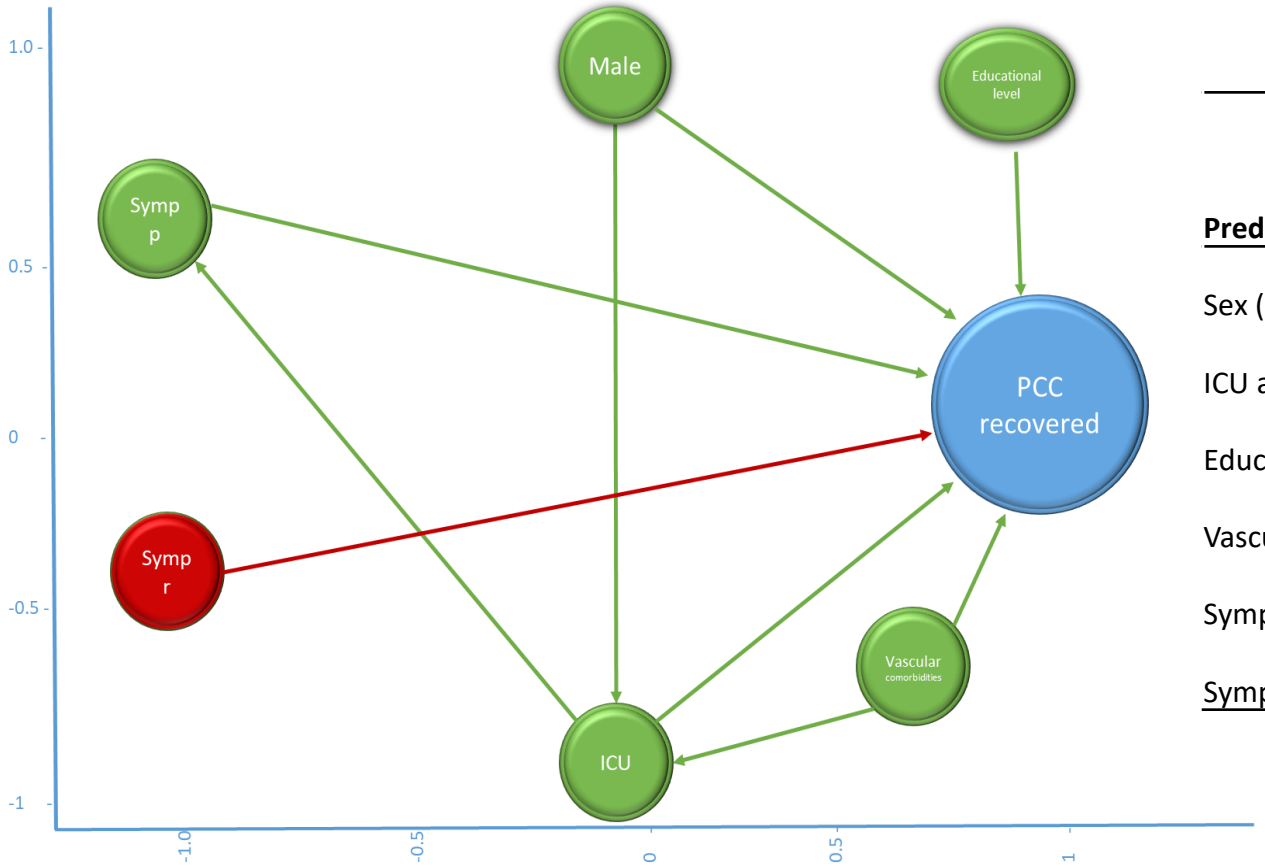
CHARACTERISTICS OF SEVERITY CLUSTERS

	CLUSTER A	CLUSTER B	CLUSTER C
	165 (48.4) N (%)	138 (40.5) N (%)	38 (11.1) N (%)
Age, median (IQR)	49 (40-56)	46 (38-55)	49.5 (43.5-56)
Sex, male	61 (37)	38 (27.5)	4 (10.5)
Hospitalization	37 (40.6)	51 (37)	12 (31.6)
Comorbidities			
Allergy	46(27.9)	45 (32.6)	16 (42.1)
Obesity	36 (21.8)	36 (26,1)	12 (31.6)
Dislypemia	39 (23.6)	32 (23.2)	11 (28.9)
Hypertension	39 (23.6)	22 (15.9)	6 (15.8)
Lung disease	26 (15.8)	22 (15.9)	10 (26.3)
Persistent symptoms			
Fatigue	93 (56.4)	128 (92.8)	28 (73.7)
Dyspnea	46 (27.9)	109 (79)	35 (92.1)
Neurocognitive complain	27 (16.4)	74 (53.6)	27 (71.1)
Headache	37 (22.4)	83 (60.1)	30 (78.9)
Myalgia	25 (15.2)	84 (61)	20 (52.6)
Arthralgia	20 (12.1)	81 (58.7)	27 (71.1)
Chest pain	19(11.5)	60 (43.5)	18 (47.4)
Tachycardia	16 (9.7)	53 (38.4)	28 (73.7)
Cough	23 (13.9)	36 (26.1)	31 (81.6)
Neurosensitive	8 (4.8)	33 (23.9)	24 (63.2)
Diarrhea	15 (9)	58 (42)	9 (23.7)
Low grade fever	20 (12.1)	22 (15.9)	11 (28.9)
Recovered	21 (12.7)	4 (2.9)	1 (2.6)

Main findings:

- 548 subjects were evaluated: **341 (62%) had PCC.**
- PCC participants were mostly **females** (69.8%) with mean age of **47.9 (SD 12.2) years**. Only 38.1% required hospitalization during acute COVID-19, and 9% required high-flow oxygen.
- Their **most frequent comorbidities** were allergy (31.4%), obesity (24.8%), dyslipidemia (24.0%) and hypertension (19.6%).
- At least **3 symptom clusters** with additive symptoms were identified: considering only symptoms present in >40% of subjects:
  - **Cluster A** was enriched in fatigue and dyspnea
  - **Cluster B** had Cluster A symptoms plus headache, arthralgia, chest pain and neurocognitive complains
  - **Cluster C** had Cluster B symptoms plus tachycardia, neurosensitive symptoms, and cough

Factores asociados a la recuperación de Covid-19 persisitente



Predictors		Risk Ratios	std. Error	Confidence Interval	*p-value*
Sex (Male)		3.24	1.21	1.56 – 6.75	***0.002***
ICU admission		8.34	4.51	2.84 – 24.27	***<0.001***
Educational level		2.34	0.94	1.08 – 5.09	***0.032***
Vascular comorbidities		1.99	0.69	1.01 – 3.92	***0.048***
Symptoms p		0.28	0.1	0.14 – 0.57	***<0.001***
Symptoms r		2.53	1.02	1.16 – 5.51	***0.02***

El dolor muscular, el déficit de atención, la disnea y la taquicardia en la fase aguda, relacionados inversamente proporcional con la recuperación (RR 2.53; CI 1.16-5.51)

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FISIOPATOLOGÍA

Hipótesis no excluyentes:

- Cambios fisiopatológicos causados directamente por SARS-CoV-2 (daño tisular)
- Persistencia viral
- Aberraciones inmunológicas y daños inflamatorios persistentes
- Reactivación de virus latentes
- Disbiosis
- Disfunción microvascular
- Respuesta autoinmune originada por una respuesta inmune alterada frente al SARS-CoV-2

Castanares et al, Pathophysiology and mechanism of long COVID: a comprehensive review Ann Med. 2022 Dec;54(1):1473-1487. doi: 10.1080/07853890.2022.2076901.

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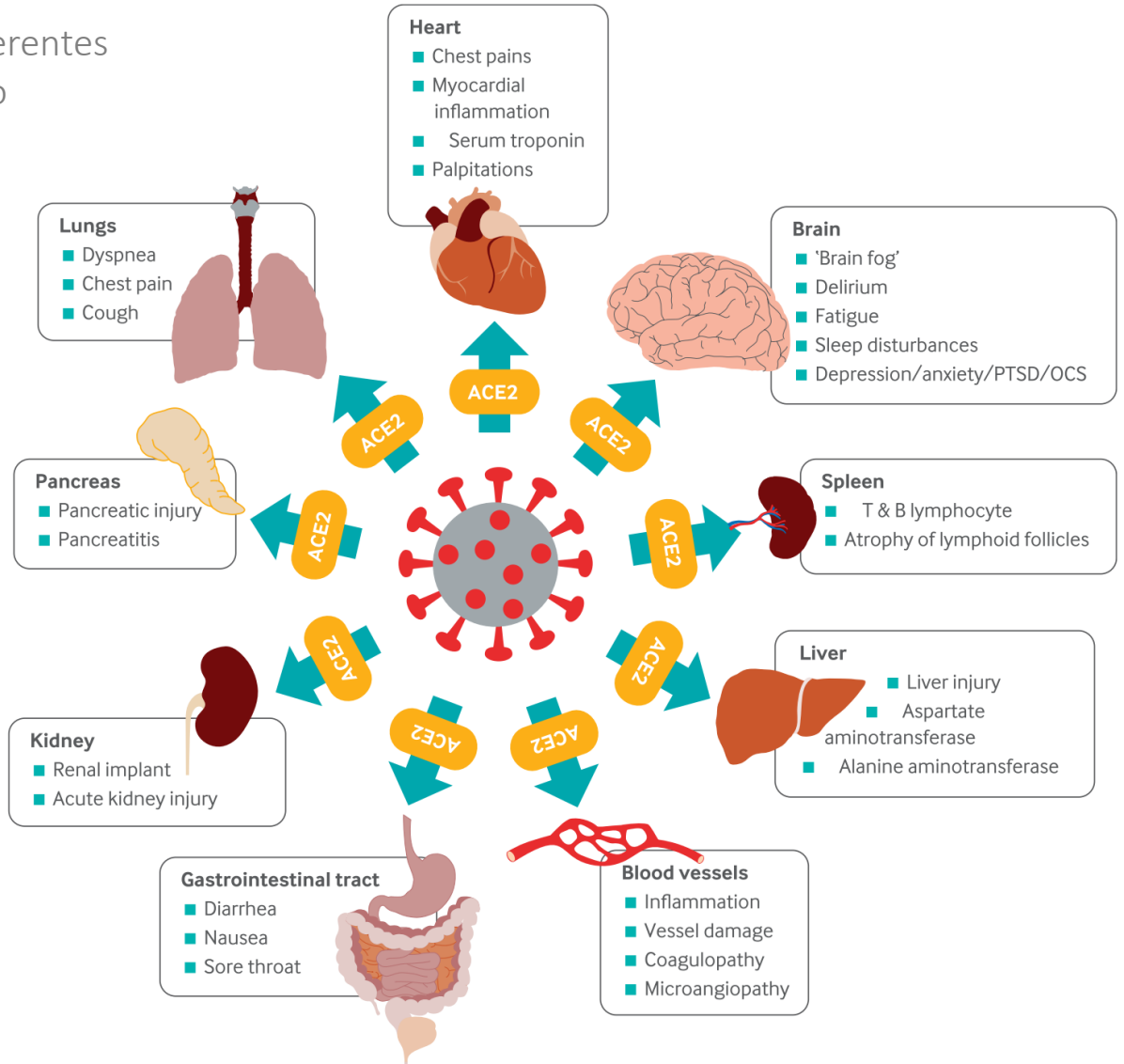
Cambios fisiopatológicos causados directamente por SARS-CoV-2 (daño tisular)

FISIOPATOLOGÍA

Gran expresión de ACE2 en diferentes celulas de todo el cuerpo



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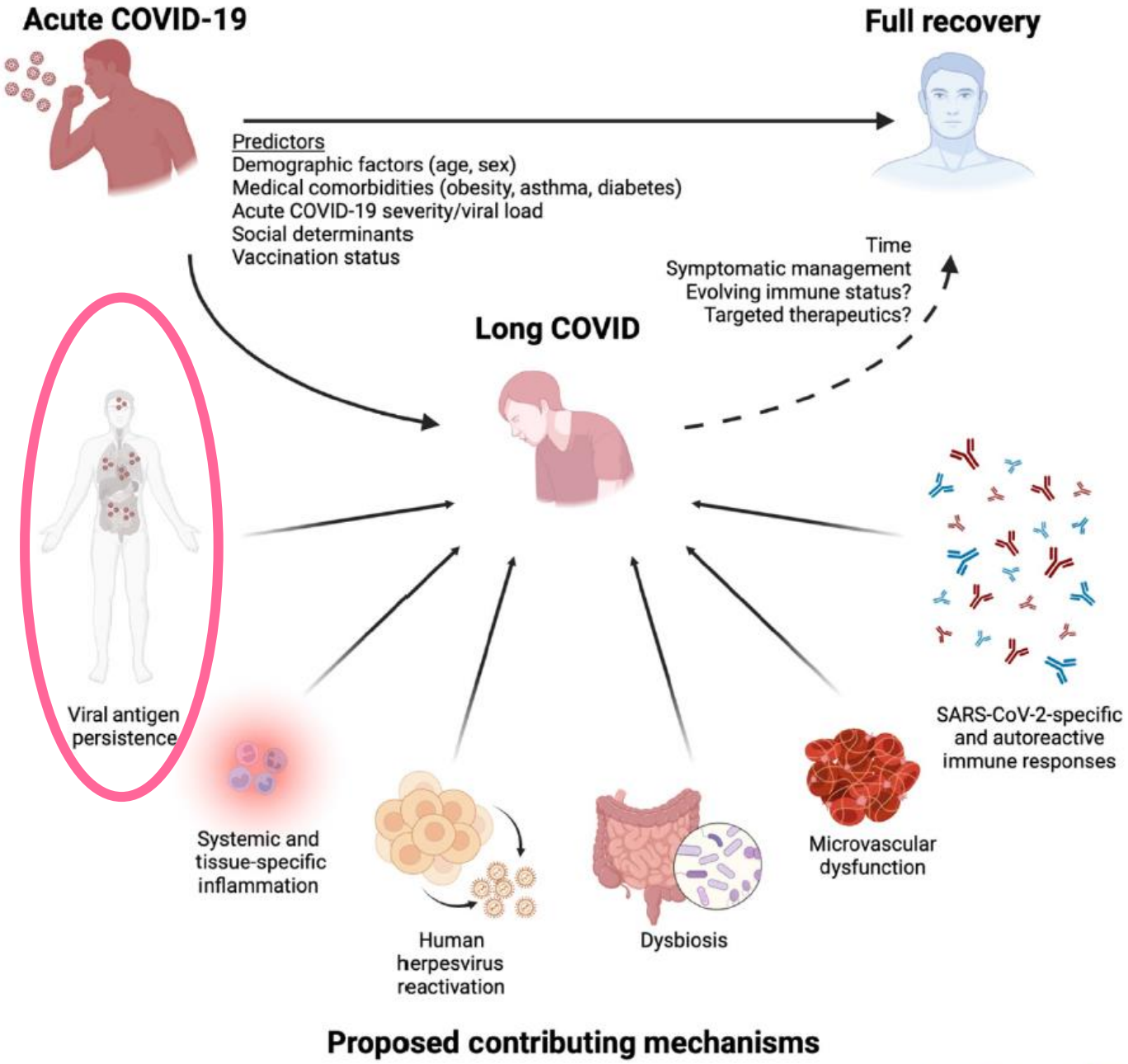
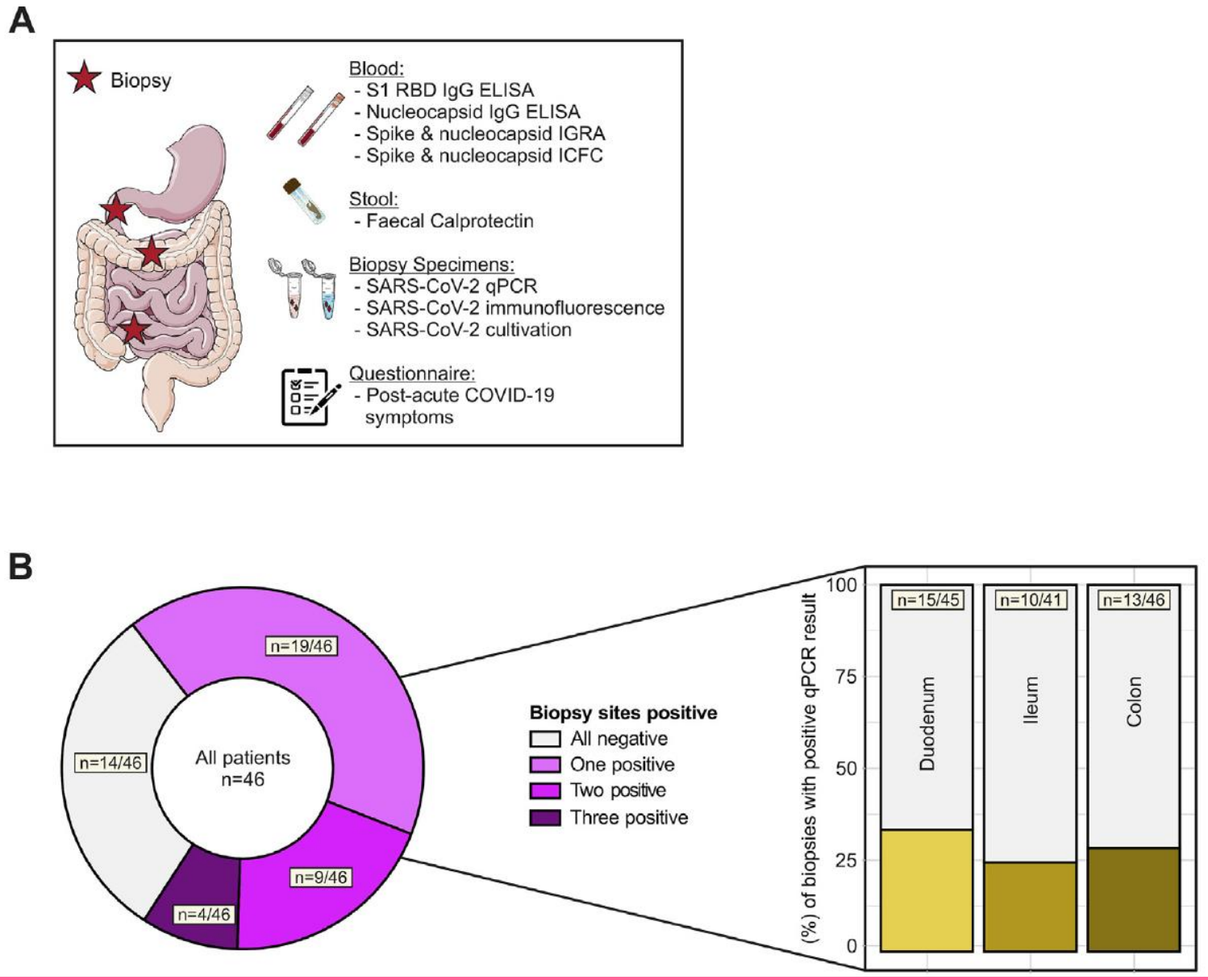
FISIOPATOLOGÍA



Peluso MJ, Deeks SG. *Trends Immunol*. 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008

Persistencia viral

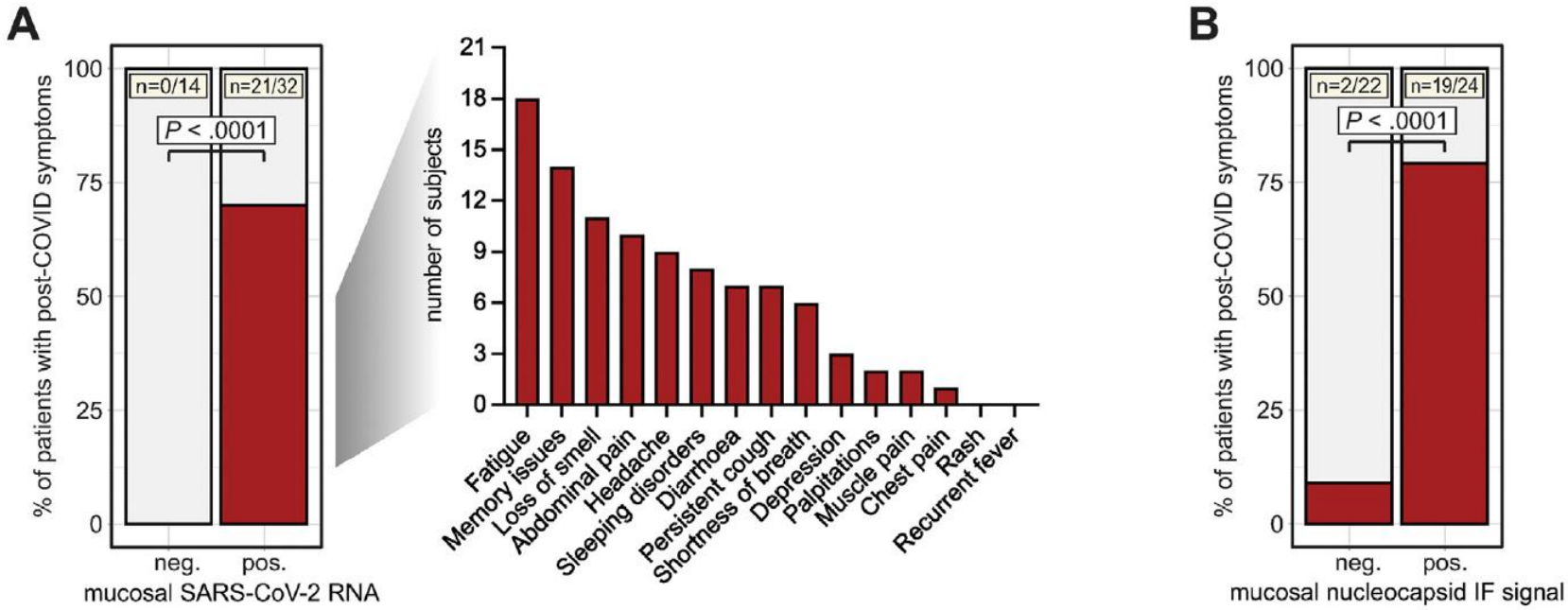
FISIOPATOLOGÍA



Zollner, A et al. *Gastroenterology* vol. 163,2 (2022): 495-506.e8. doi:10.1053/j.gastro.2022.04.037

Persistencia viral

FISIOPATOLOGÍA



Zollner, A et al. *Gastroenterology* vol. 163,2 (2022): 495-506.e8. doi:10.1053/j.gastro.2022.04.037

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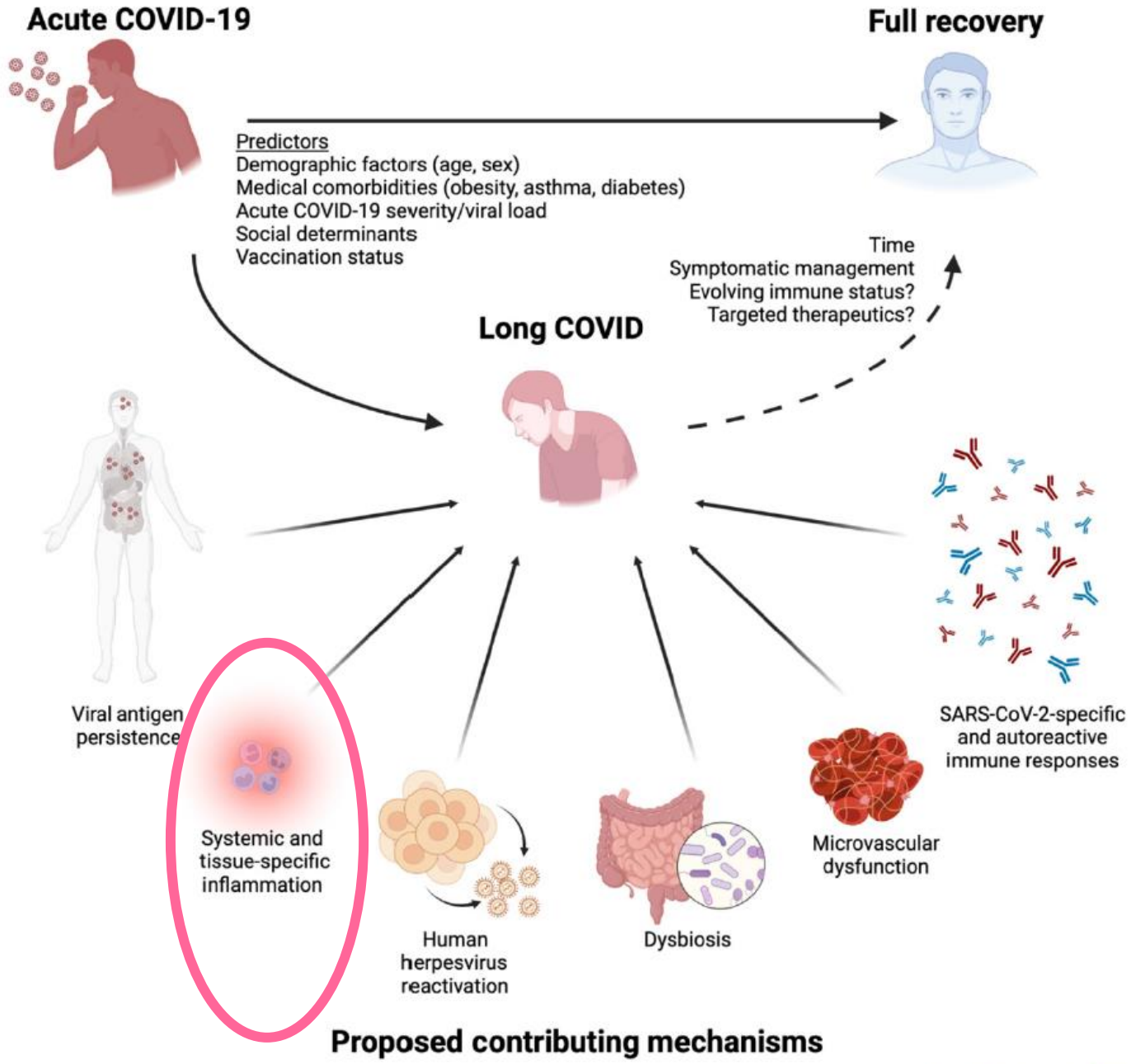
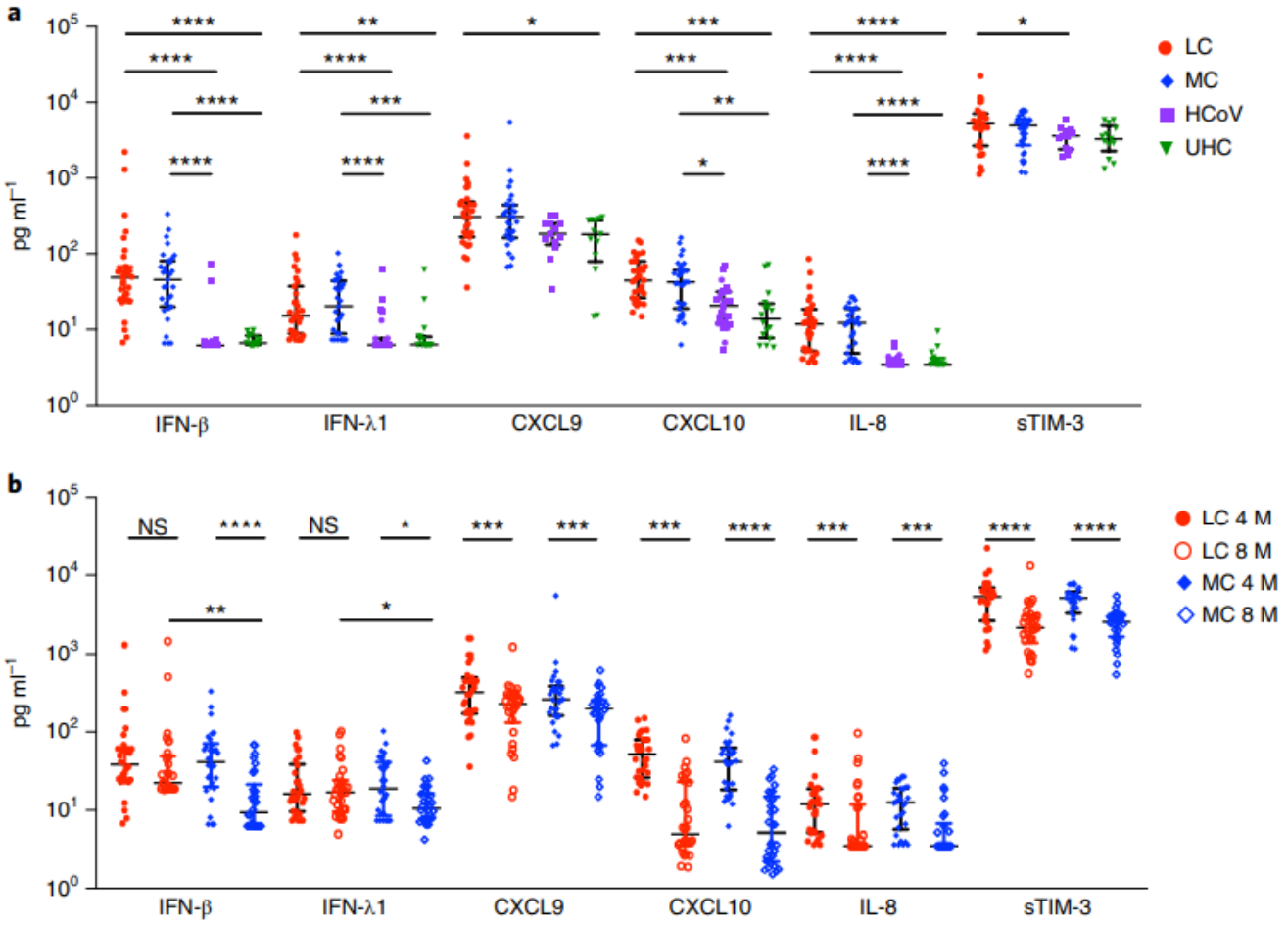
FISIOPATOLOGÍA



Peluso MJ, Deeks SG. OVID. *Trends Immunol*. 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008

Inflamación



- Long Covid (LC)
- Matched recovered individuals without LC (MC)
- Individuals infected with other coronaviruses (HCoV)
- Unexposed healthy controls (UHC)

Phetsouphanh, C., *et al.*. *Nat Immunol* **23**, 210–216 (2022). https://doi.org/10.1038/s41590-021-01113-x

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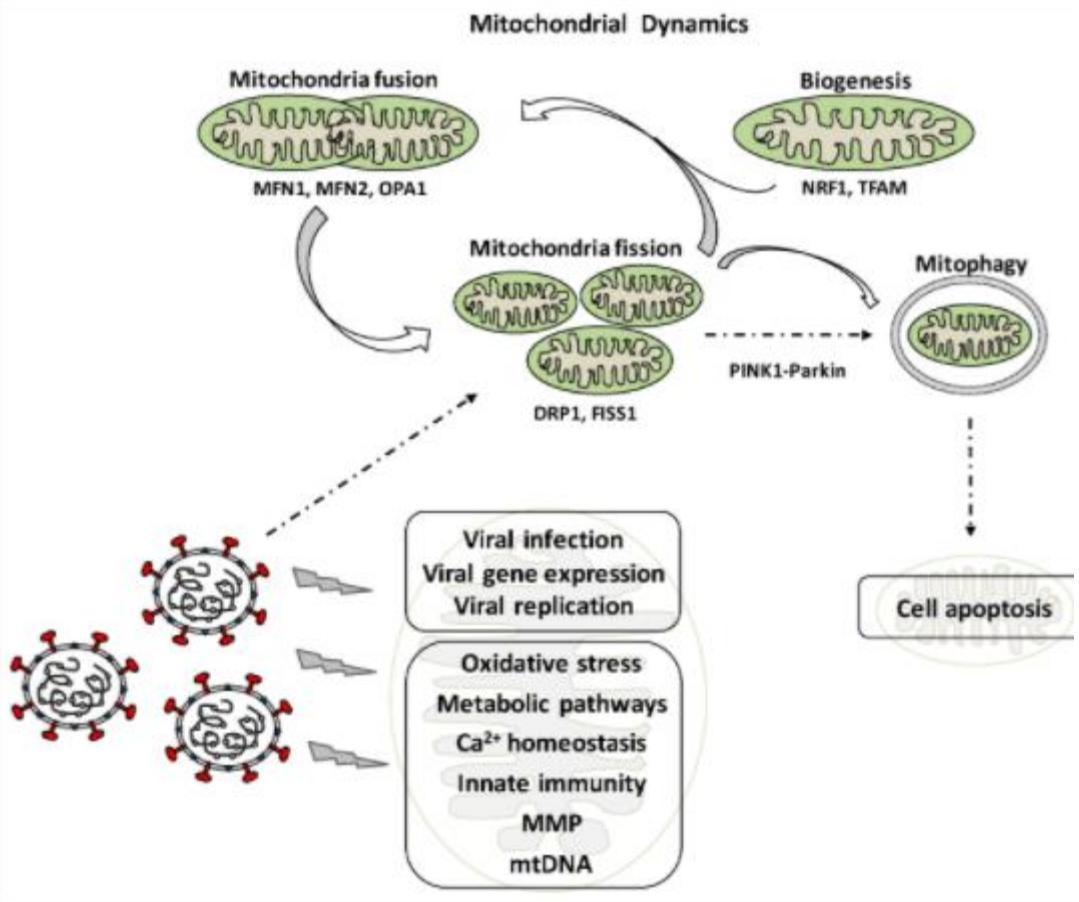
Figure 1. Effects of viral infection on mitochondrial dynamics, the viral life cycle, and various aspects associated with the internal metabolism of the mitochondria as well as its physiological processes.



Wood E, Hall KH, Tate W. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/chronic fatigue syndrome: A possible approach to SARS-CoV-2 'long-haulers'? Chronic Dis Transl Med. 2021 Mar;7(1):14-26. doi: 10.1016/j.cdtm.2020.11.002. Epub 2020 Nov 21. PMID: 33251031; PMCID: PMC7680046.

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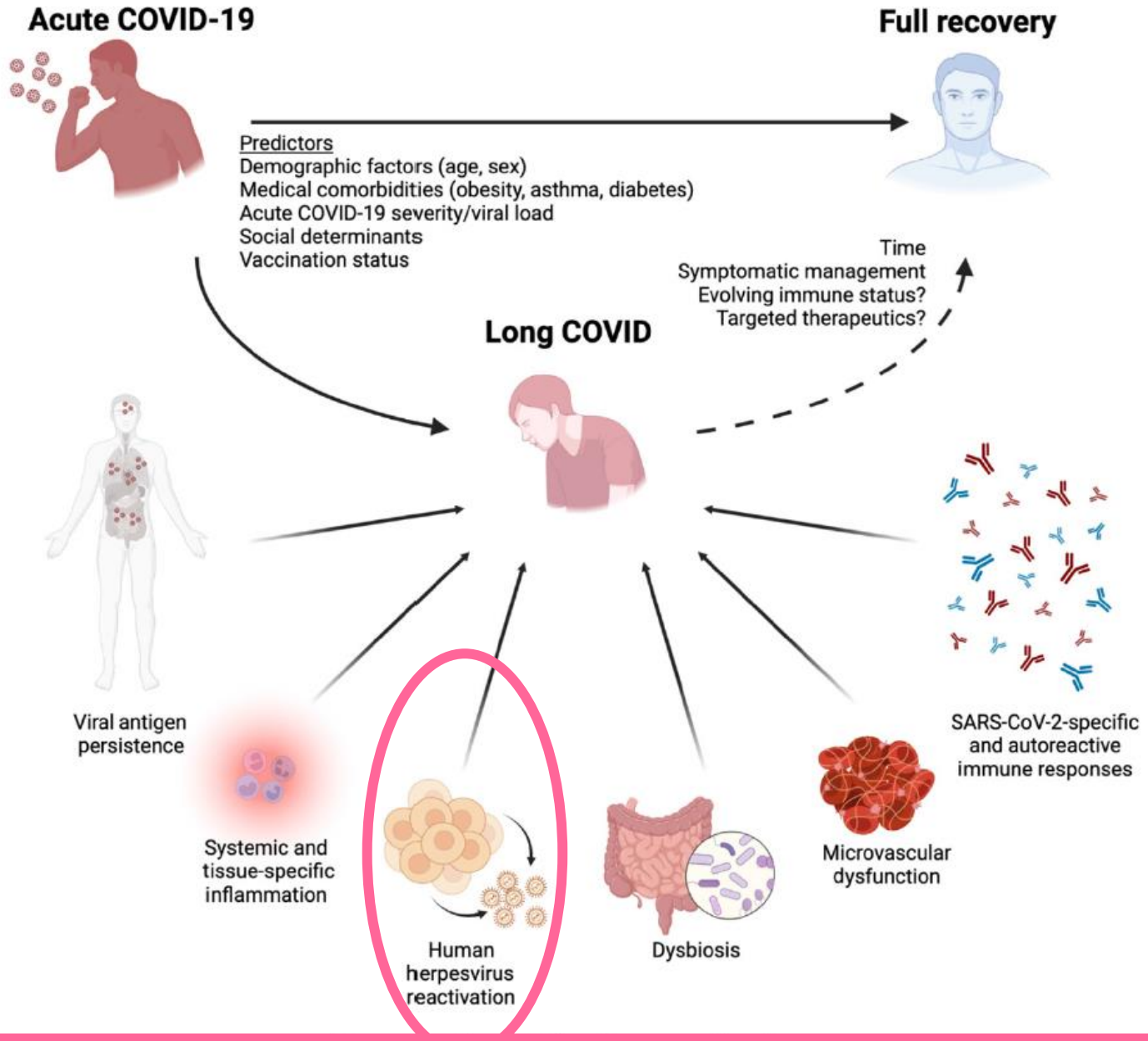
FISIOPATOLOGÍA



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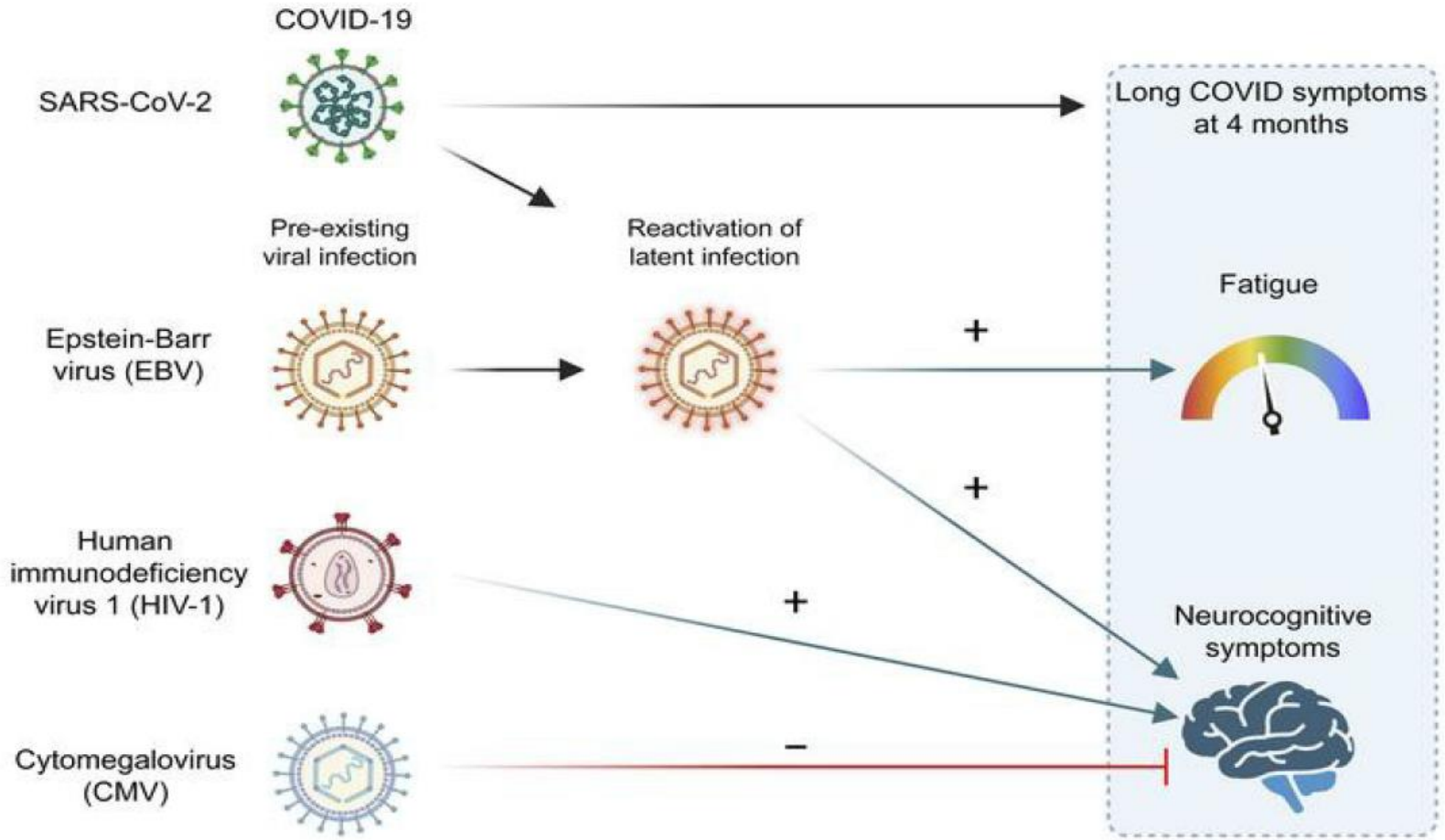

Peluso MJ, Deeks, Clinc.Invest. 2023

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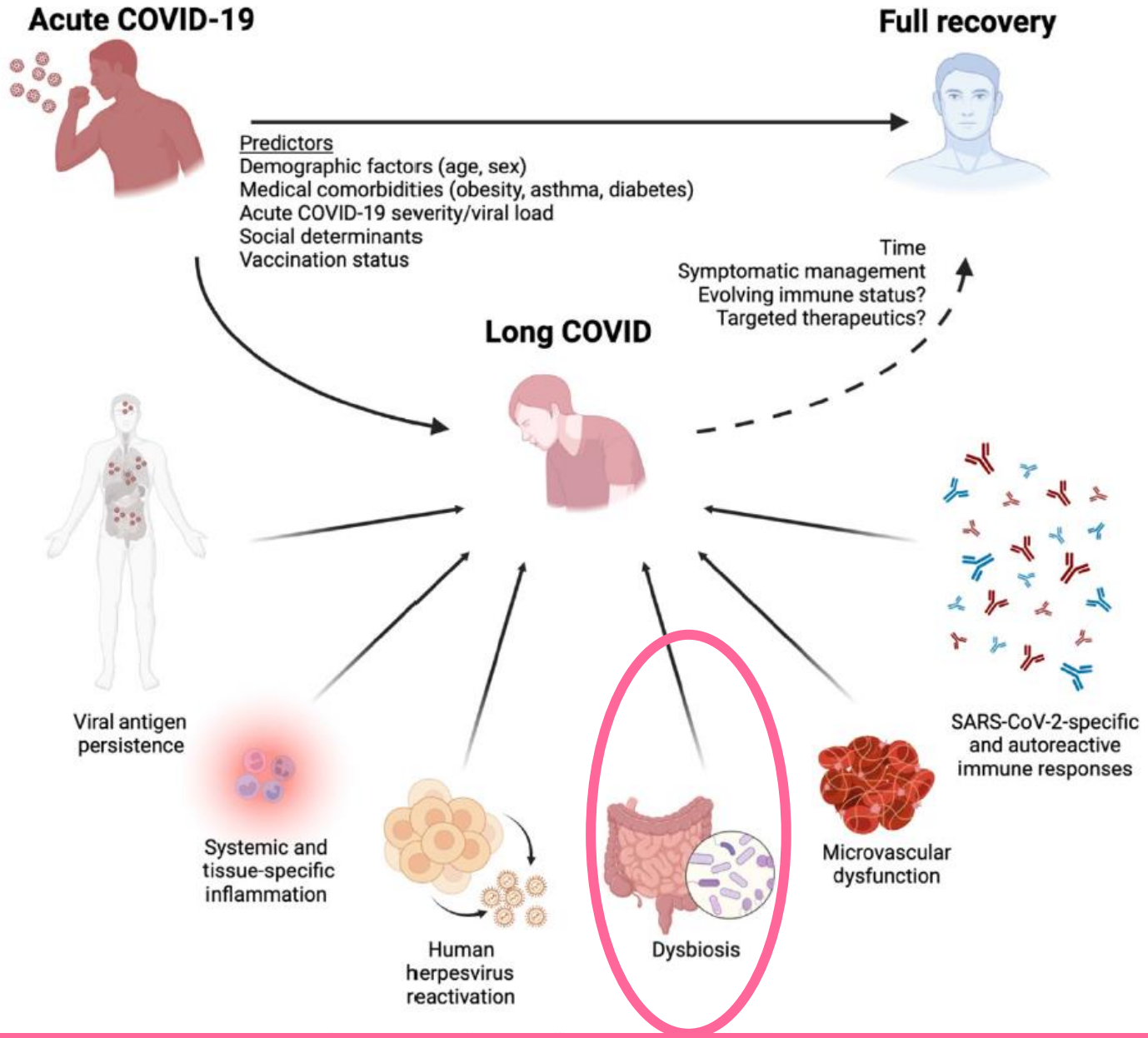
FISIOPATOLOGÍA



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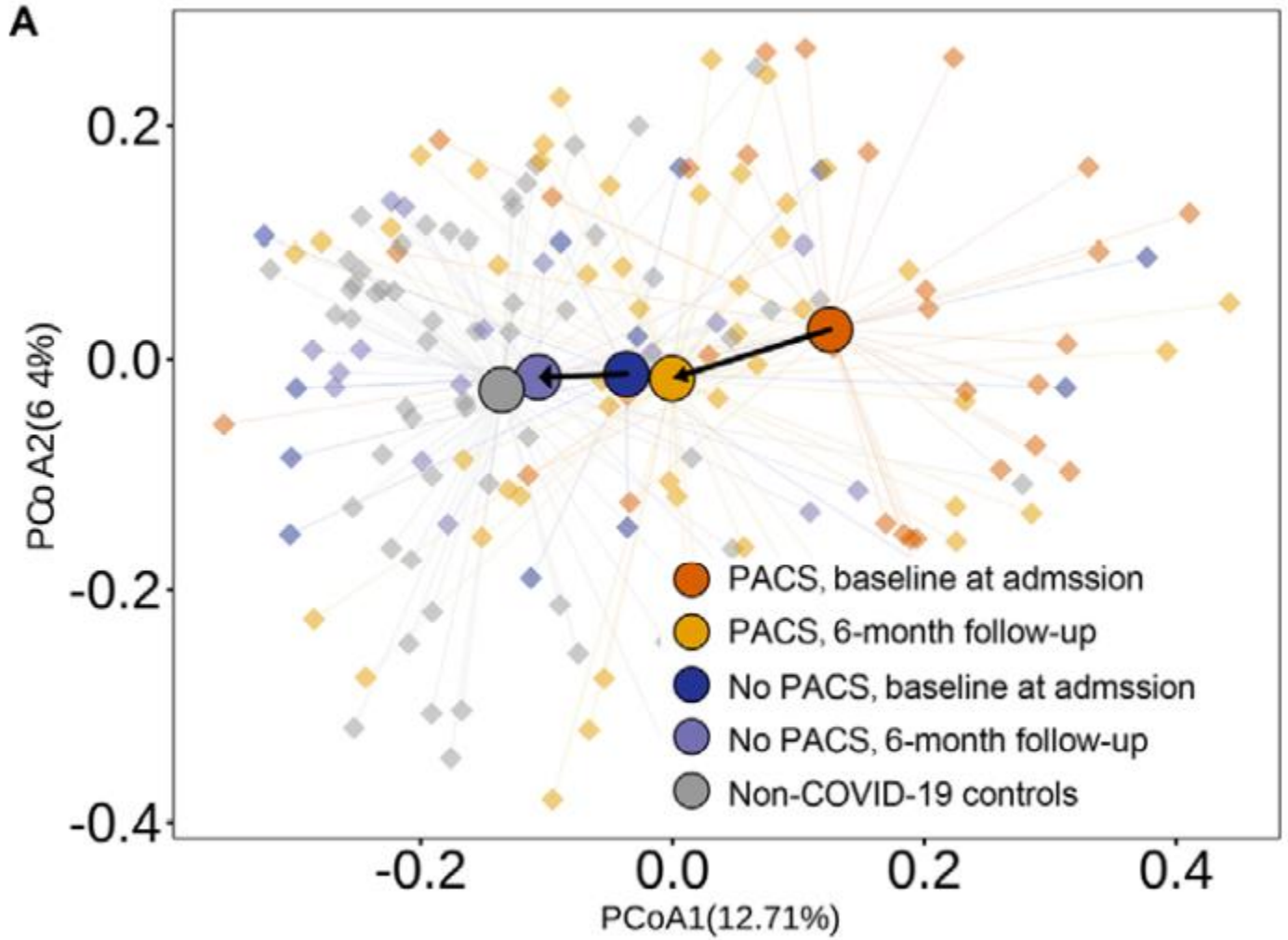
Inflamación

Diferencias entre la composición de la microbiota intestinal



Liu, Qin et al. *Gut* vol. 71,3 (2022): 544-552. doi:10.1136/gutjnl-2021-325989

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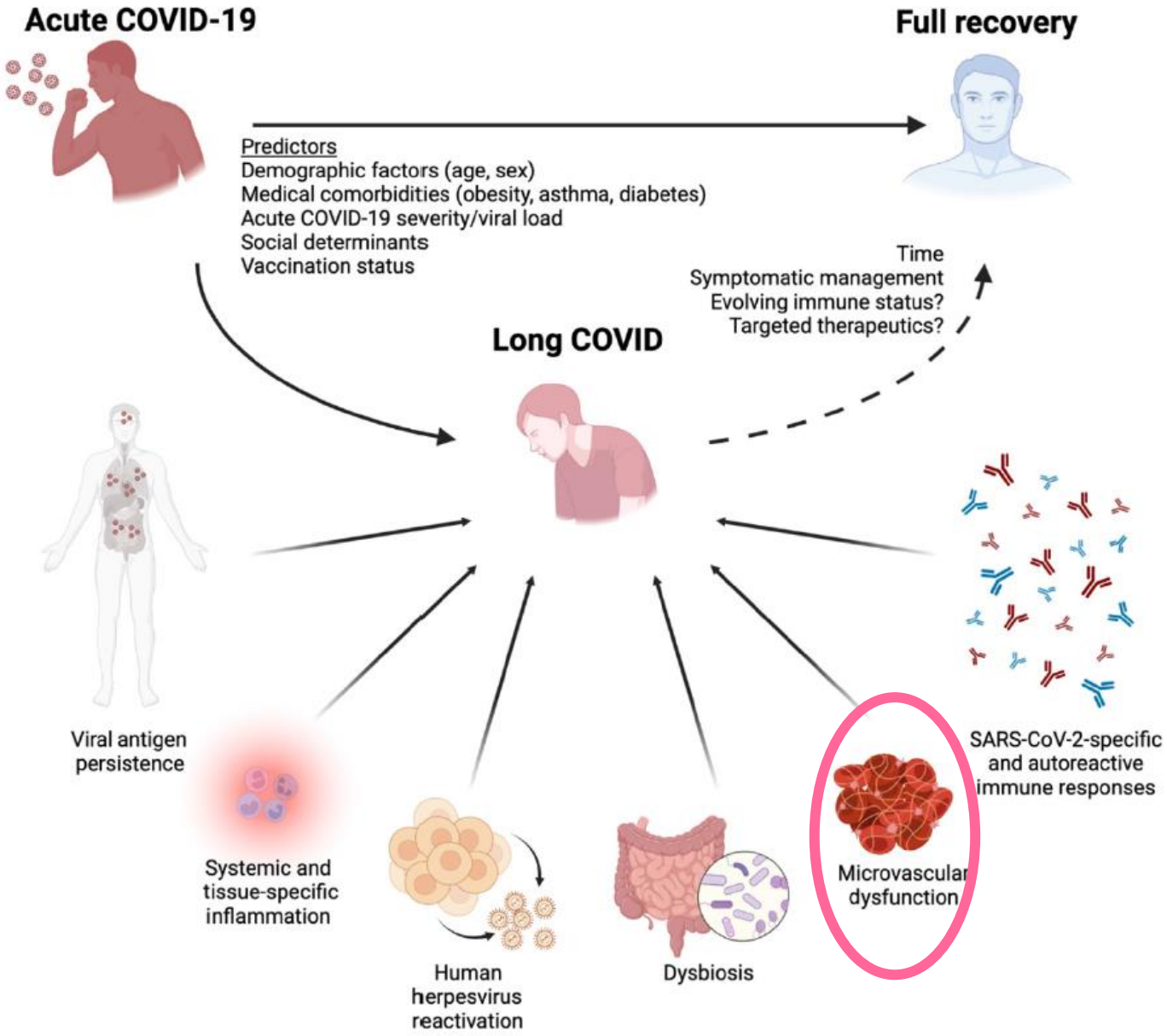
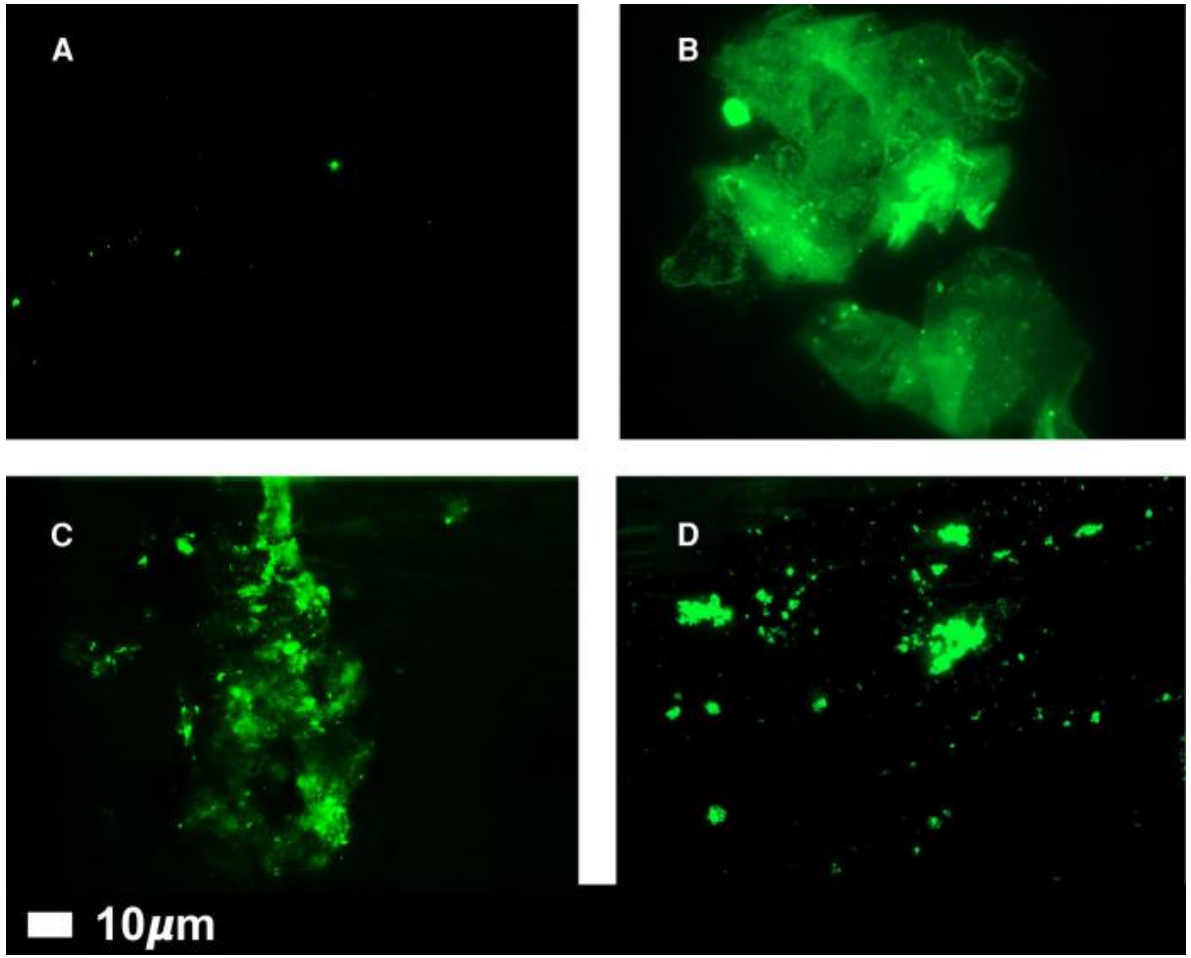
FISIOPATOLOGÍA



Peluso MJ, Deeks SG. OVID. *Trends Immunol*. 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008

Disfución microvascular

- **Microscopía de fluorescencia** de micrografías representativas que muestran **microcoágulos** en la circulación de controles (A) y en pacientes con **Covid-19 persisitente (B-D).**
- **Ausencia de microcoágulos de amiloide** significativos en el plasma de **individuos "normales"** y su presencia significativa en el plasma de individuos Covid-19 persisitente.



Pretorius E,, et al. *Cardiovasc Diabetol*. 2021;20(1):172. Published 2021 Aug 23. doi:10.1186/s12933-021-01359-7

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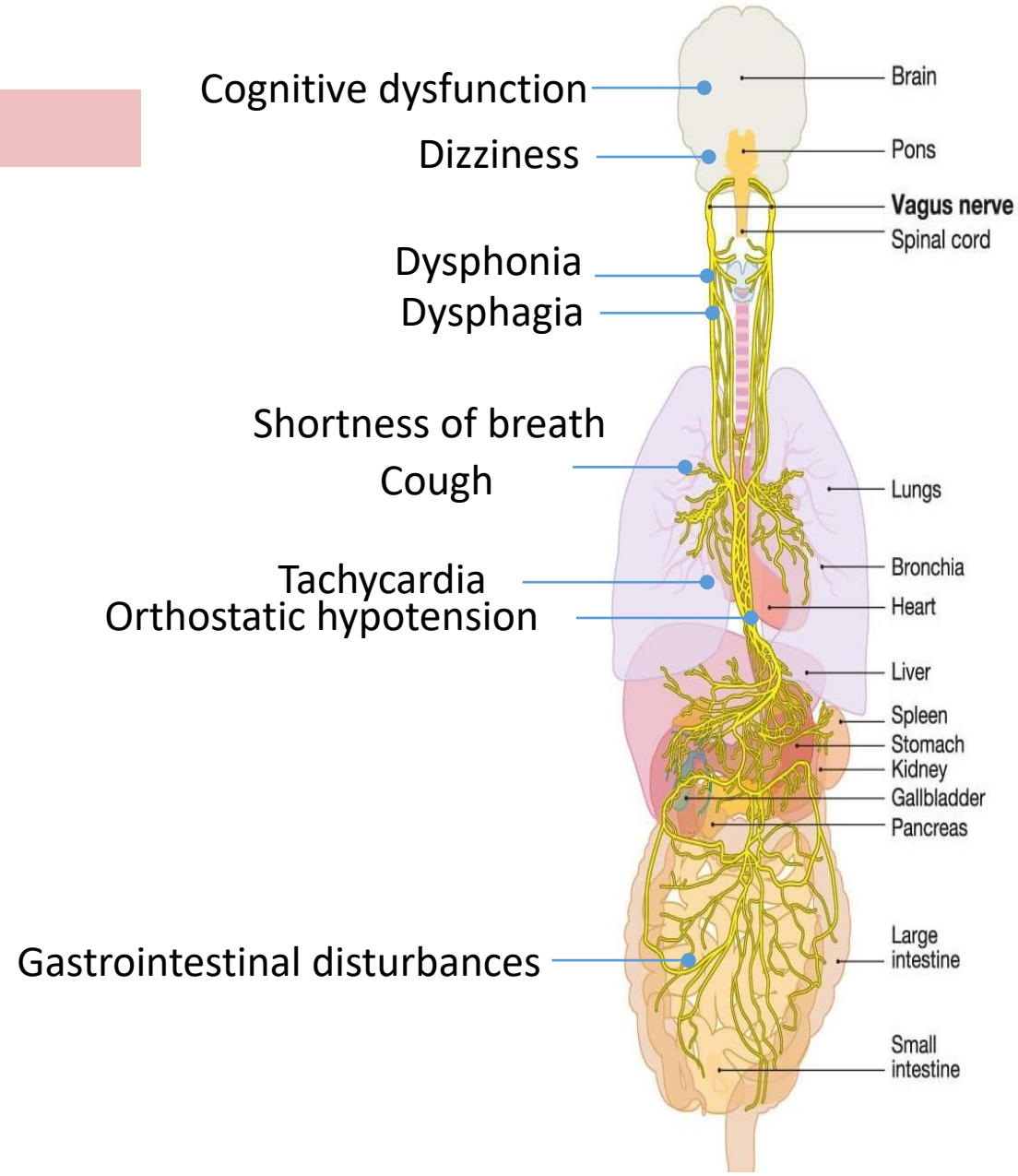
Alteraciones N. vago

FISIOPATOLOGÍA



https://www.dreamstime.com/illustration-showing-brain-vagus-nerve-tenth-cranial-nerve-cn-human-organs-vagus-nerve-labeled-human-organs image215358799#:~:text=%C2%A9-,Axel%20Kock,-%7C%20Dreamstime.com

Alteraciones N. vago

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PCC: Post COVID-19 Condition
VND: Vagus Nerve Dysfunction

*Prospective observational cohort of SARS-CoV-2 exposed participants

N= 691 from King cohort*

N=108 Uninfected
N= 205 Without persistent symptoms
N= 36 Unknown/lost of follow up

N= 342 Patients with PCC

Inclusion criteria:
- 18 years
- Confirmed SARS-CoV-2 infection
- Symptoms compatible with VND (≥1):
  - -Dysphonia
  - -Dysphagia
  - -Cough
  - -Dyspnea
  - -Tachycardia
  - -Orthostatic hypotension
  - -Dizziness
  - -Gastrointestinal dysfunction

N = 228 (67%) Patients with at least 1 VND-related symptom

Exclusion criteria (diabetes mellitus, pregnancy, dementia)

The first 30ª patients were selected

N= 30 PCC

N= 16 Recovered

N= 14 Uninfected

March 2021-March 2022

Alteraciones N. vago

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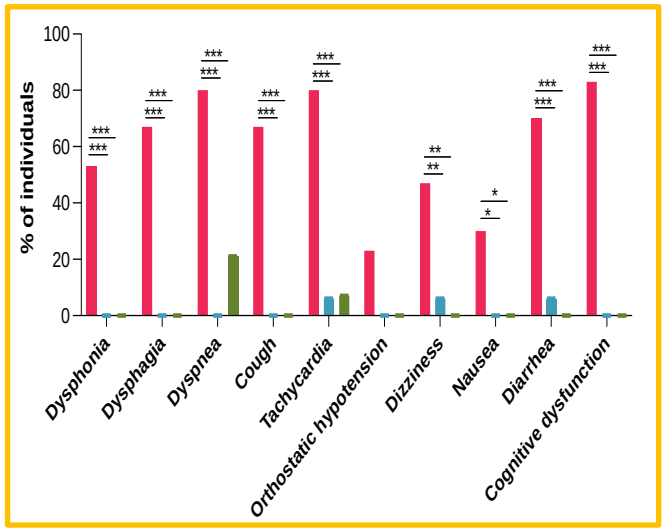
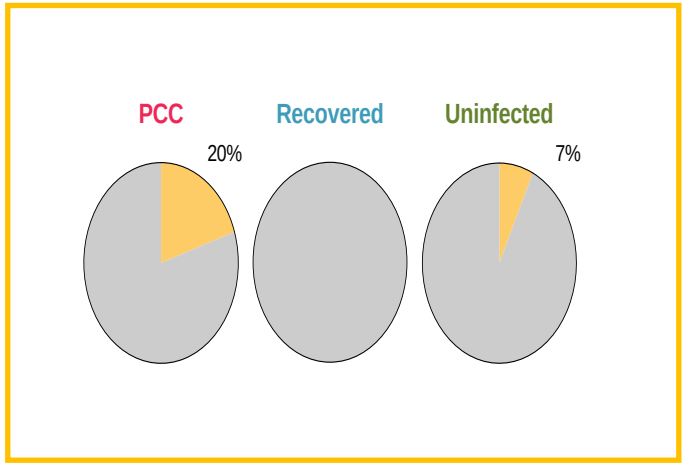
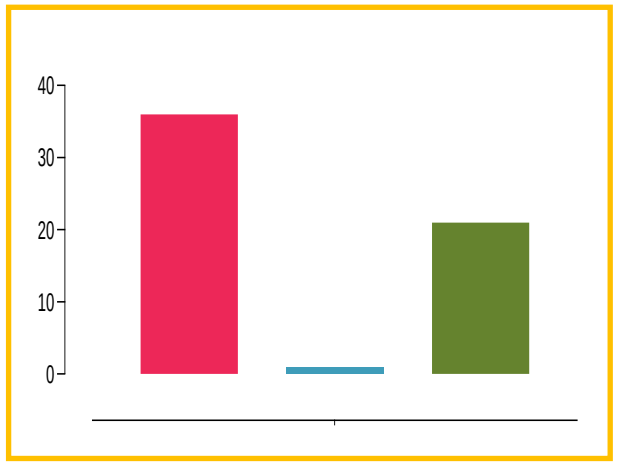
1 Síntomas



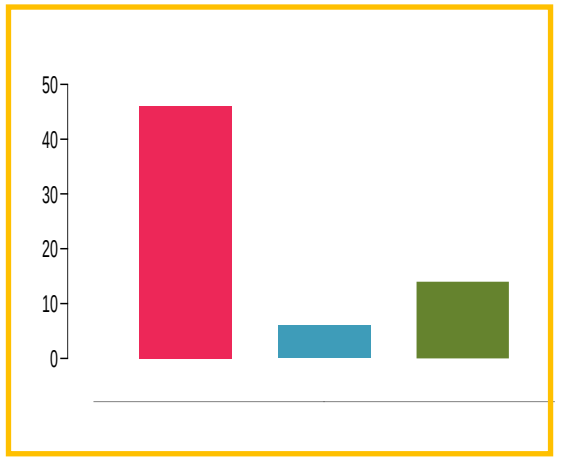
2 Ecografía de nervio vago



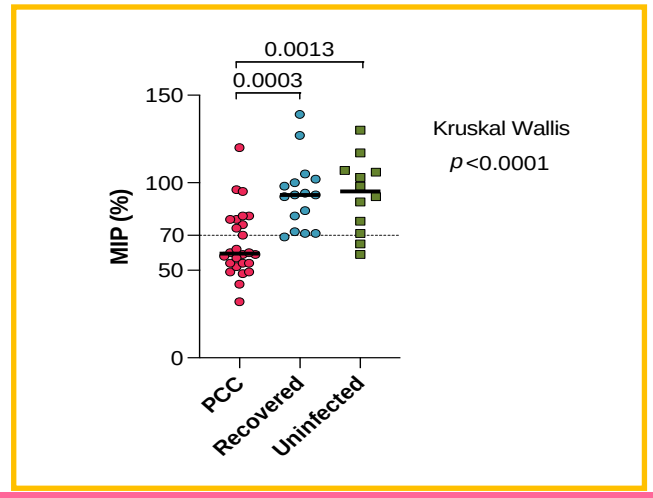
3 Disminución del persistaltismo esofágico



4 Disminución de la movilidad diafragmática



5 PIM <70%



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Taquicardia sinusal inapropiada

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	Inappropriate sinus tachycardia (Group 1) N = 40	Fully recovered (Group 2) N = 19	Uninfected (Group 3) N = 17	*P* value
Demographic and clinical characteristics				
Age (years)	40.1 ± 10	42.2 ± 11	39.5 ± 13	0.243
Males, n (%)	6 (15)	2 (11)	2 (12)	0.655
Body mass index, mean ± SD	25.2 ± 6.1	24.5 ± 3.6	22.5 ± 2.3	0.374
Smoking, n (%)	1 (3)	1(5)	0	0.623
Hypertension, n (%)	3(8)	0	0	0.589
Hyperlipidemia, n (%)	3 (8)	0	0	0.589
Diabetes mellitus, n (%)	0	0	0	NA
Asthma, n (%)				
Environmental allergy, n				
Symptoms of the acute				
Palpitations, n (%)				
Dyspnea, n (%)				
Myalgia and joint pain, n				
Chest pain, n (%)				
Fever, n (%)	29 (73)	16 (84)	–	0.462
Headache, n (%)	29 (73)	7 (37)	–	**0.007**
Dizziness, n (%)	21 (53)	1 (5)	–	**0.002**
Diarrhea, n (%)	21 (53)	3 (16)	–	**0.003**
Anosmia, n (%)	19 (48)	15 (79)	–	**0.03**
Ageusia, n (%)	19 (48)	8 (42)	–	0.454
Dermatologic alterations, n (%)	14 (35)	1 (5)	–	**0.009**
Severity of clinical presentation				
Mild	33 (83)	16 (84)	–	0.387
Moderate	6 (15)	3 (16)	–	0.550
Intensive care management	1 (3)	0	–	0.254

Table 1. Demographic and clinical characteristics of the cases and their matched controls. Values are expressed as mean ± standard deviation unless otherwise stated. A P value of < 0.05 is considered statistically significant. Significant values are in [bold].

De los 200 pacientes con PCS, 40 (20%) fueron diagnosticados de taquicardia inusual inapropiada (media de edad de 40.1 ± 10 años, 85% mujeres, 83% COVID-19 leve)

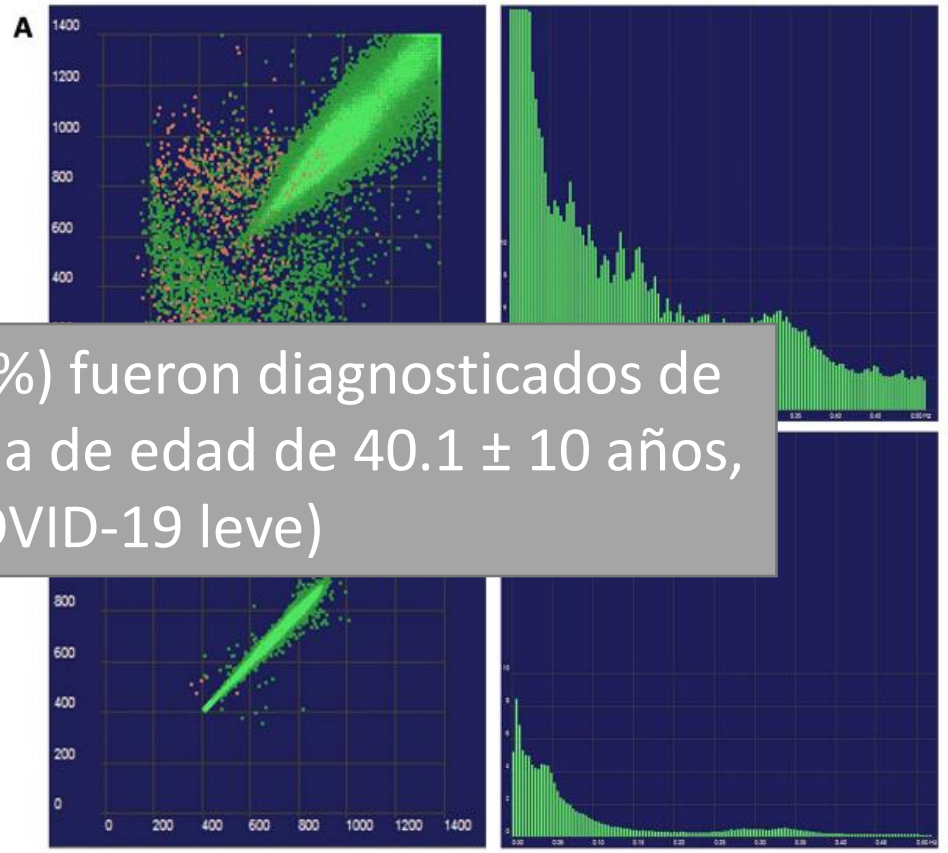

Figure 2. (**A**) Uninfected subject. Poincaré plot of 24-hour ECG monitoring showing the beat-to-beat variability from an uninfected subject and histogram of the frequencydomain parameters. (**B**) IST patient. Poincaré plot of 24-h ECG monitoring and histogram of the frequency-domain parameters from a patient with IST. A lower heart rate variability in comparison with the uninfected subject and an overall decrease is observed throughout all bands, being more manifest at the high frequency band (HF, 0.15–0.40 Hz), are both apparent.

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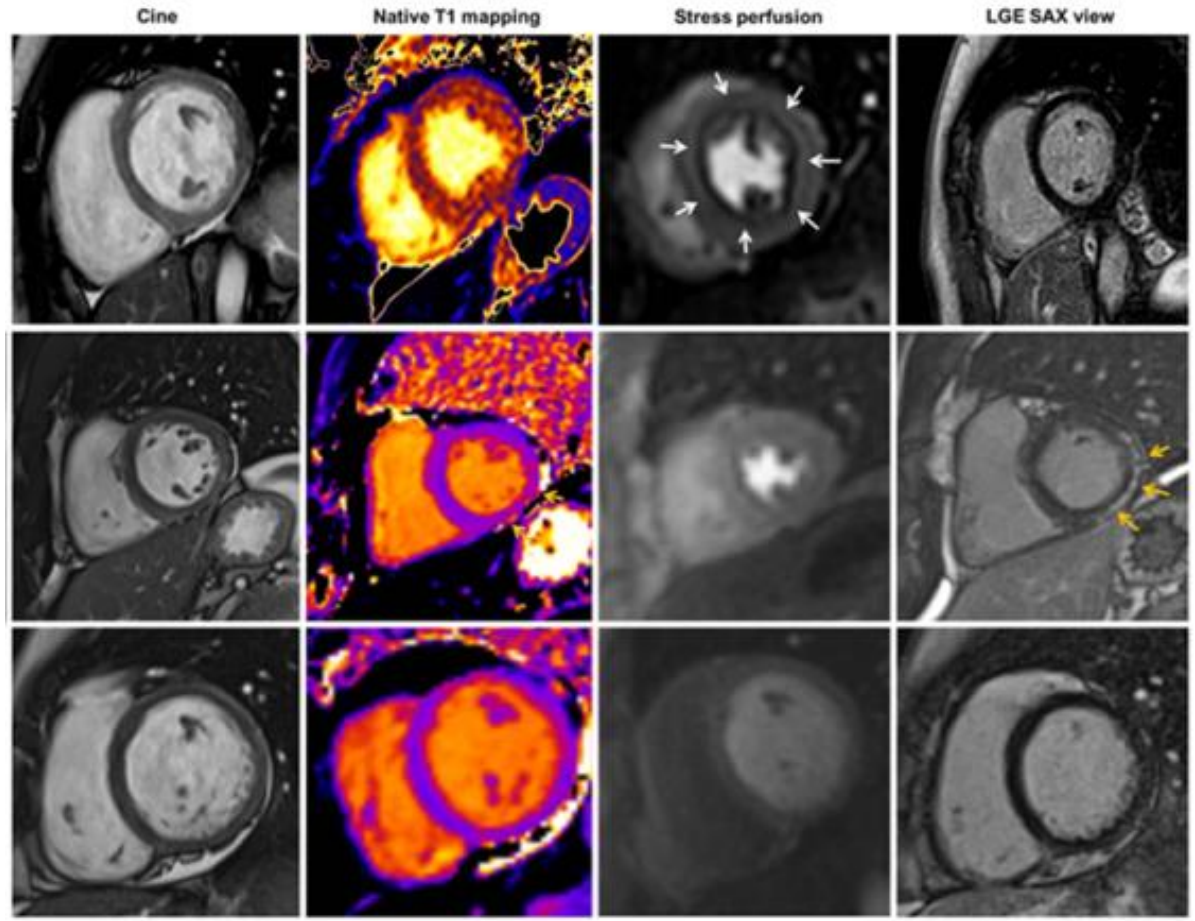
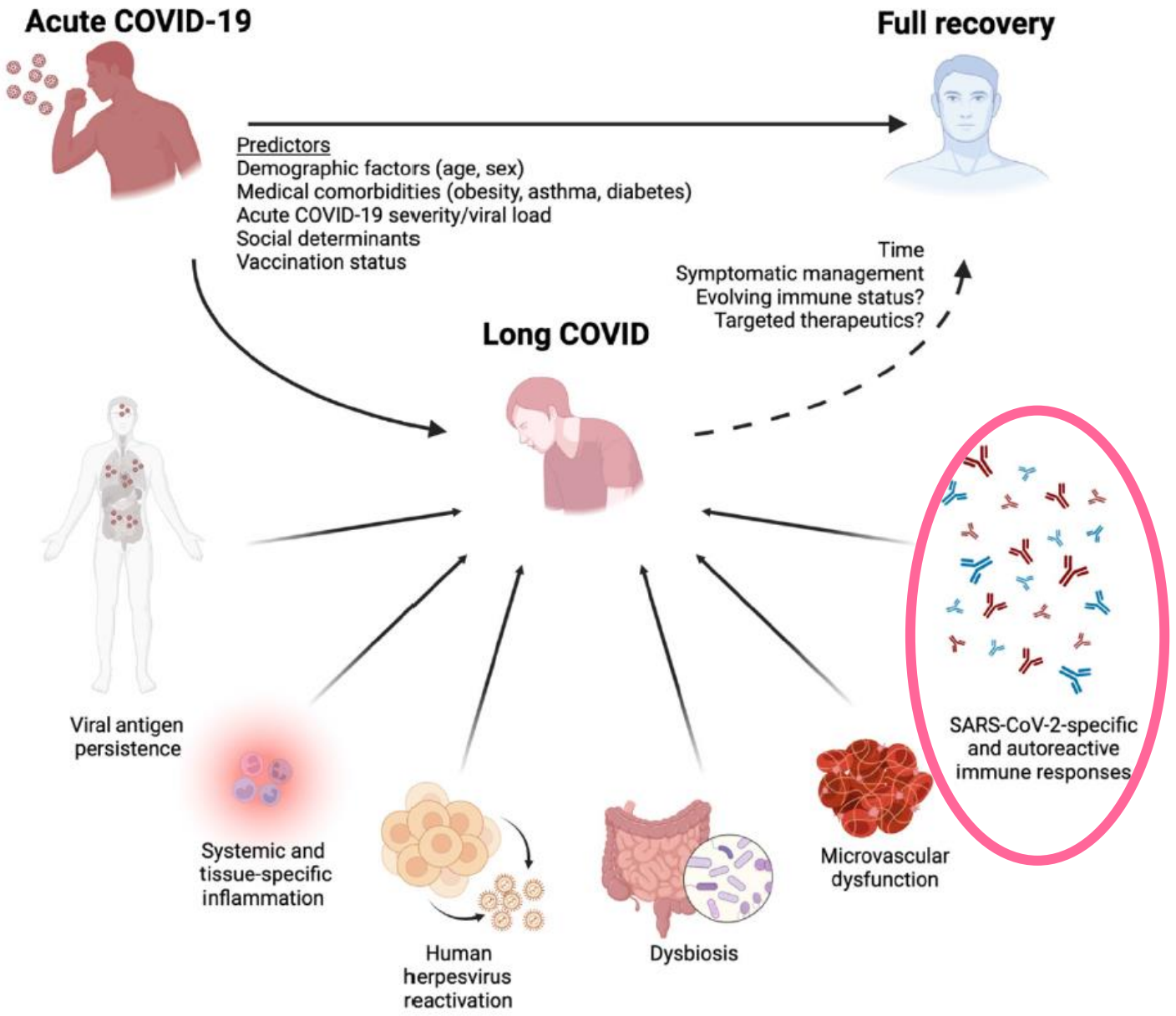
Defectos de perfusión subendocárdica en pacientes con dolor de características anginosas



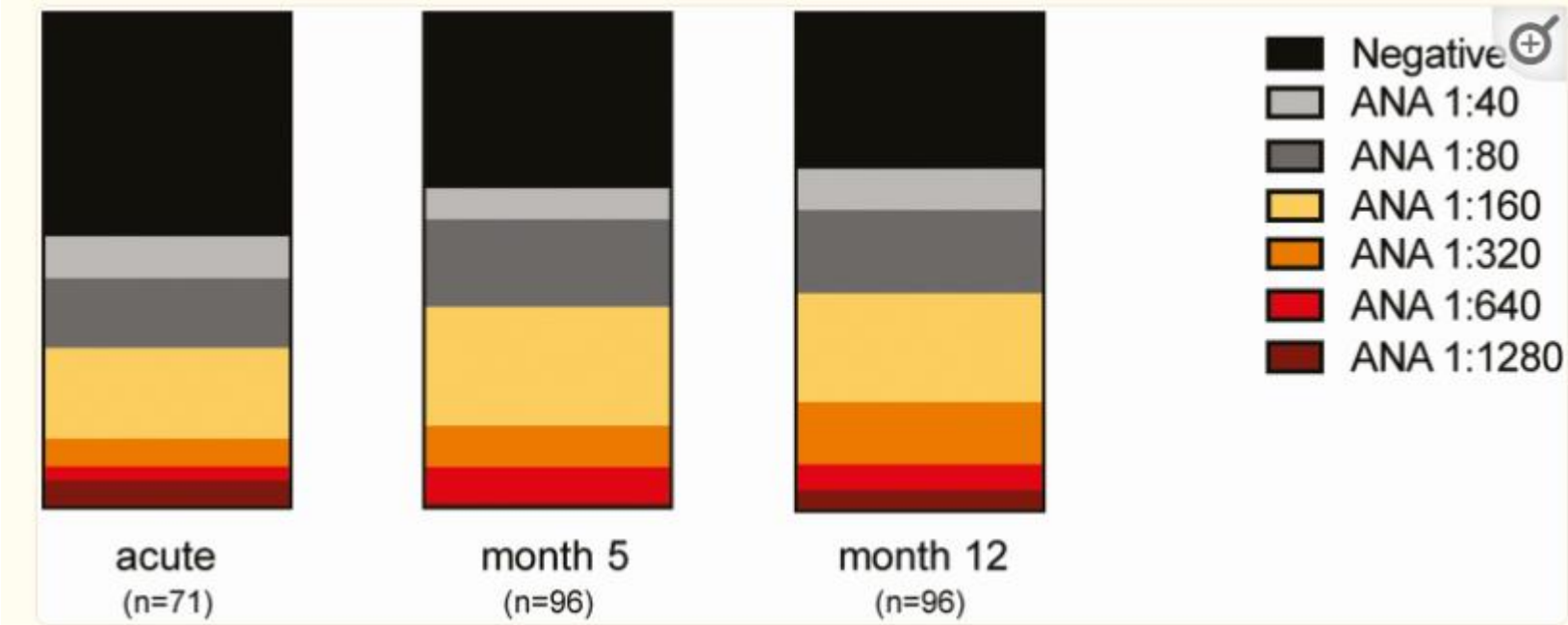
FISIOPATOLOGÍA



Peluso MJ, Deeks SG. OVID. *Trends Immunol*. 2022;43(4):268-270. doi:10.1016/j.it.2022.02.008

Autoinmunidad

FISIOPATOLOGÍA



Al año, ANAs ≥1:160 en el 43,6% de los pacientes
Grupo ANAs ≥1:160 con significativamente más síntomas en comparación con el grupo con ANAs <1:160

Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, Müller B, Merle U. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis. 2022 Apr 9;74(7):1191-1198. doi: 10.1093/cid/ciab611. PMID: 34223884; PMCID: PMC8394862.

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Autoinmunidad

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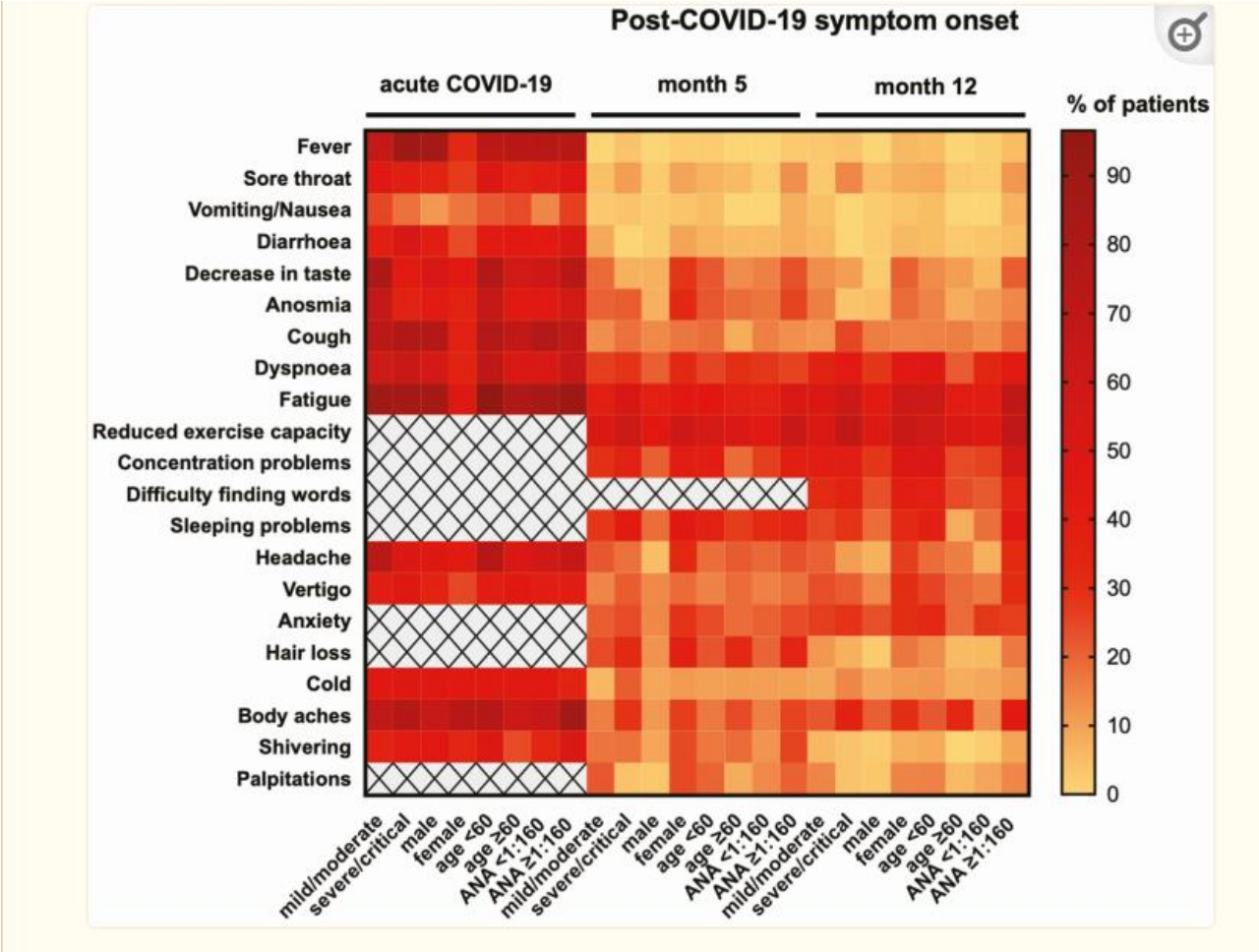
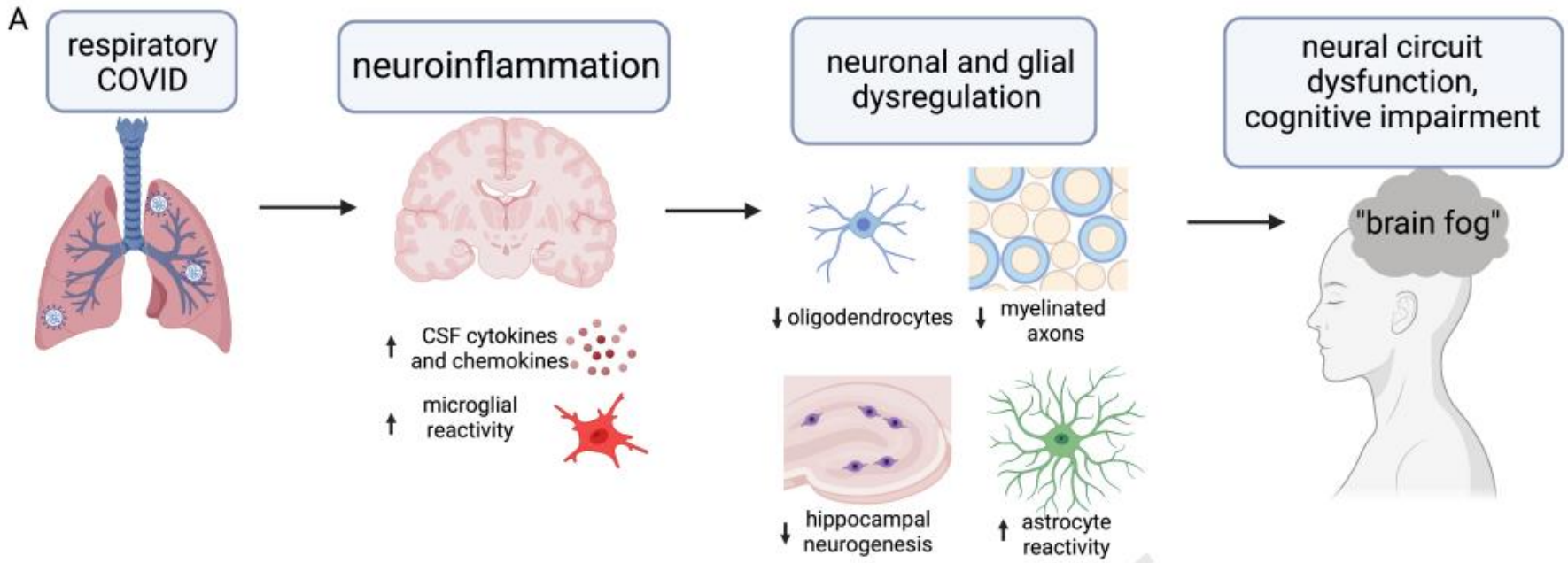


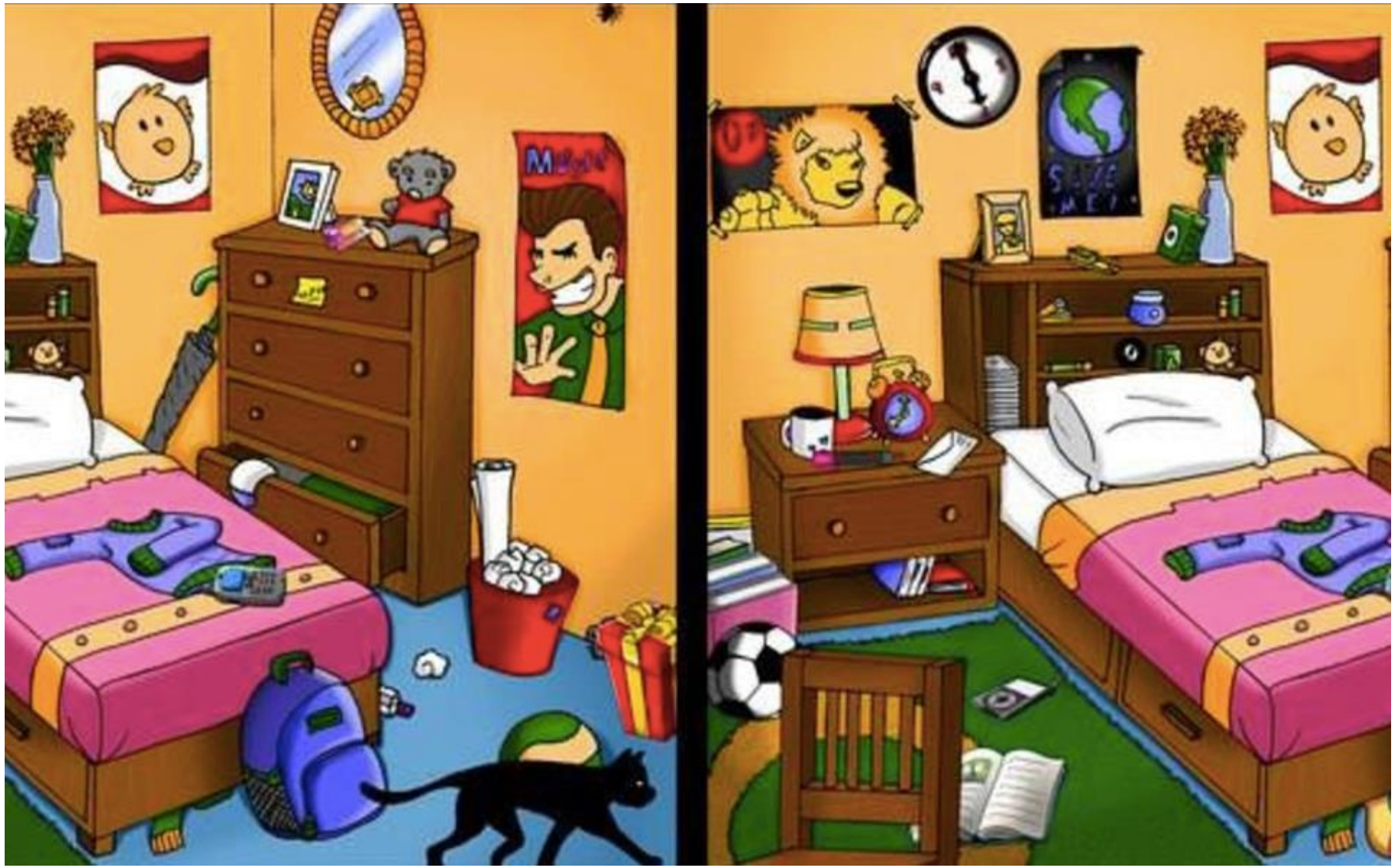
Grupo ANAs ≥1:160 con significativamente más síntomas en comparación con el grupo con ANAs <1:160

Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, Müller B, Merle U. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis. 2022 Apr

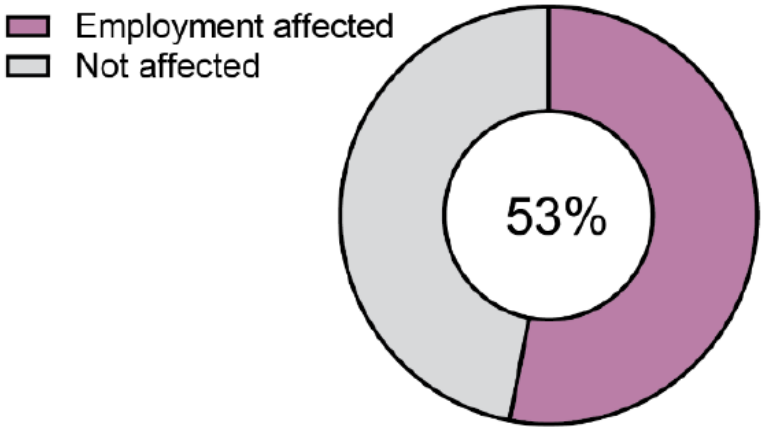


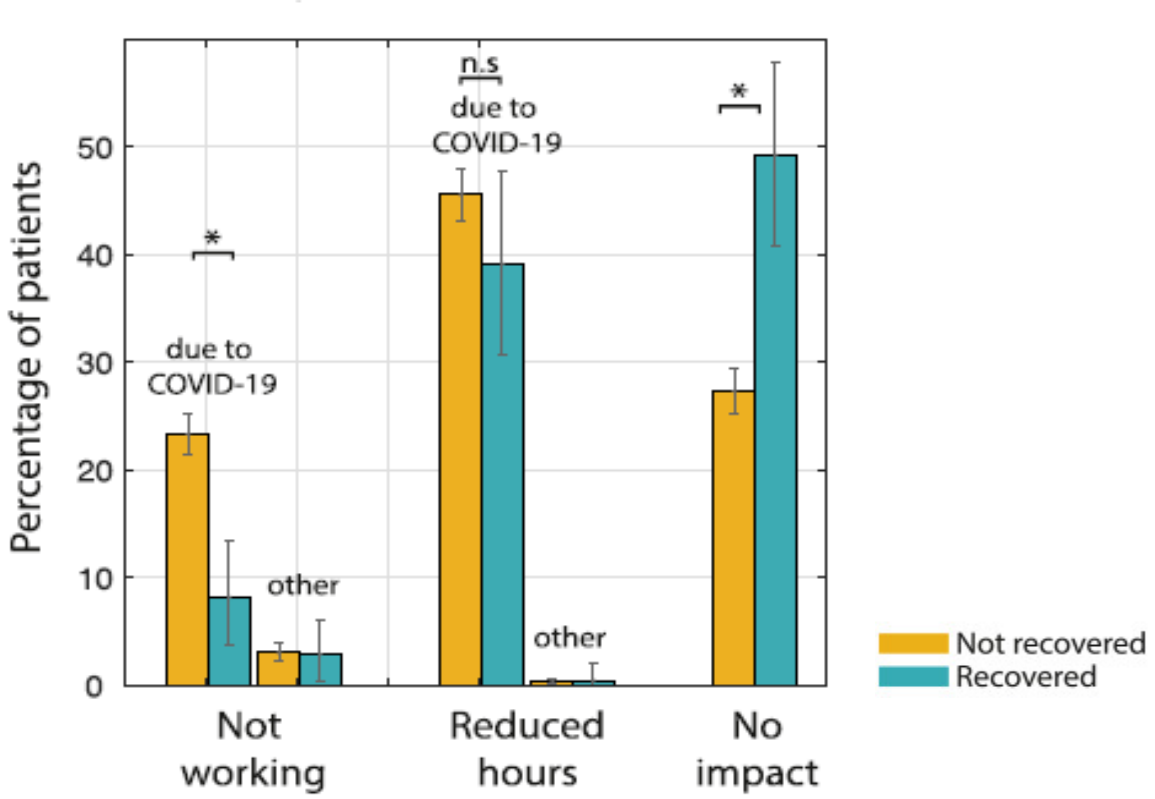
Monje, M., Iwasaki, A., Neuron (2022), doi:https://doi.org/10.1016/j.neuron.2022.10.006

¿Por qué no conocemos aún la fisiopatología?



¿debemos esperar a conocer la fisiopatología para encontrar dianas terapéuticas?





22,3% Sin poder trabajar
45,2% Reducción de jornada

Vaes AW, et al. J Clin Med. 2020; Davis HE, et al. EClinicalMedicine. 2021.; Klein J et et al, medRxiv **doi:** https://doi.org/10.1101/2022.08.09.22278592

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TRATAMIENTO

Sintomático

Rehabilitación

- Respiratoria
- Motora
- Logopedia
- Terapia ocupacional
- Neurocognitiva

Ningún tratamiento ha mostrado su eficacia en tratar la causa del Covid persistente

↓

ENSAYOS CLÍNICOS!!!!

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Conclusiones

- Múltiples síntomas que se correlacionan con diferentes clusters.

- Diferentes hipótesis sobre la fisiopatología no excluyentes entre ellas:
  - Persistencia viral.
  - Inflamación.
  - Autoinmunidad.
  - Alteraciones en la microbiota.
  - Disfunción microvascular.

- Problema de salud pública con gran impacto social y económico.

- Tratamientos sintomáticos, centrados en la rehabilitación.

- Asistencia e investigación de la mano.

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IrsiCaixa
Institut de Recerca de la Sida

Germans Trias i Pujol Hospital

Muchas gracias!!

REiCOP
Red Española de Investigación en COVID Persistente

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COVID19
PERSISTENT