



International
Headache Society



Sociedad Española de Neurología
Fundada en 1949



Neuro-COVID – Short & long term

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Africa Task-Force, European Academy of Neurology

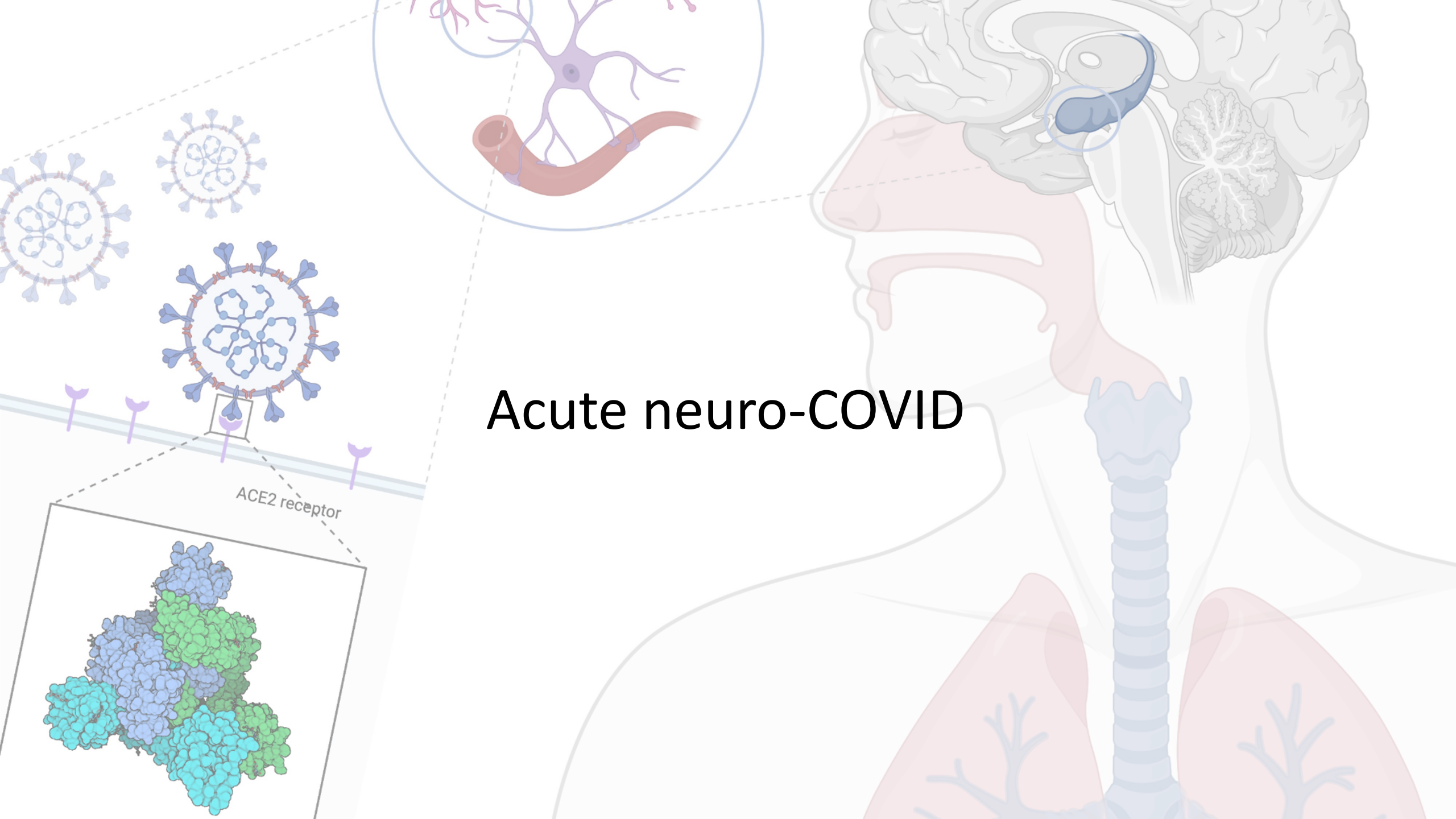
Chair, Secondary Headache Special Interest Group, International Headache Society

Secretary, Neurology Section, European Union of Medical Specialists

Chair, International Area, Spanish Society of Neurology Board



Universidad de Valladolid



Acute neuro-COVID

ACE2 receptor

Neurological manifestations are frequent

- >50% of patients¹
- Variable frequency^{2, 3}
- Commonest^{2, 3}:
 - Anosmia
 - Headache
 - Myalgia
 - Altered mental status

| | Number of studies (N) | Summary estimate (%) | 95% CI |
|---|-----------------------|----------------------|--------------|
| Smell disturbances | 17 | 35.8 | (21.4, 50.2) |
| Taste disturbances | 14 | 38.5 | (24.0, 53.0) |
| Headache | 54 | 14.7 | (10.4, 18.9) |
| Myalgia | 38 | 19.3 | (15.1, 23.6) |
| Disturbances in consciousness/altered mental status | 9 | 9.6 | (4.9, 14.3) |
| Dizziness | 12 | 6.1 | (3.1, 9.2) |
| Acute cerebrovascular disease | 8 | 2.3 | (1.0, 3.6) |
| Ischaemic stroke | 7 | 2.1 | (0.9, 3.3) |
| Hemorrhagic stroke | 7 | 0.4 | (0.2, 0.6) |
| Cerebral venous thrombosis | 2 | 0.3 | (0.1, 0.6) |
| Syncope | 3 | 1.8 | (0.9, 4.6) |
| Ataxia | 2 | 0.3 | (0.1, 0.7) |
| Seizure | 5 | 0.9 | (0.5, 1.3) |

| event | studies (N) | summary estimate (%) | 95% CI |
|-------------------------|-------------|----------------------|--------------|
| Malaise | 12 | 38.3 | [24.7, 52.9] |
| Fatigue | 147 | 33.6 | [29.5, 37.8] |
| Gustatory dysfunction | 74 | 27.2 | [22.3, 32.3] |
| Olfactory dysfunction | 89 | 26.4 | [21.8, 31.3] |
| Encephalopathy | 12 | 23.5 | [14.3, 34.1] |
| Myalgia | 154 | 21.4 | [18.8, 24.1] |
| Arthralgia | 34 | 19.9 | [15.3, 25.0] |
| Altered mental status | 30 | 17.1 | [12.3, 22.5] |
| Sleep disorder | 5 | 14.9 | [1.9, 36.8] |
| Headache | 176 | 14.6 | [12.2, 17.2] |
| Confusion | 13 | 14.2 | [6.9, 23.5] |
| Cerebrovascular disease | 28 | 9.9 | [6.8, 13.4] |
| Nausea | 100 | 9.8 | [8.1, 11.7] |
| Guillain-Barre syndrome | 7 | 6.9 | [2.3, 13.7] |
| Vomiting | 104 | 6.7 | [5.5, 8.0] |
| Dizziness | 50 | 6.7 | [4.7, 9.1] |
| Movement disorders | 9 | 5.2 | [1.7, 10.4] |
| Seizure | 24 | 4.05 | [2.5, 5.8] |
| Neuralgia | 7 | 2.4 | [0.8, 4.7] |
| Encephalitis | 8 | 0.6 | [0.2, 1.3] |

Romero-Sánchez CM. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020 Aug 25;95(8):e1060-e1070.

D V, Sharma A. Neurological Manifestations in COVID-19 Patients: A Meta-Analysis. *ACS Chem Neurosci*. 2021 Aug 4;12(15):2776-2797

Neurological manifestations present in combination²

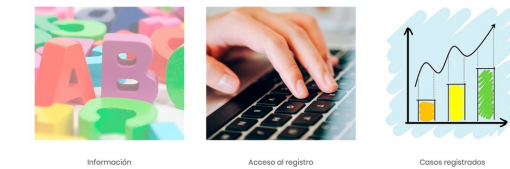
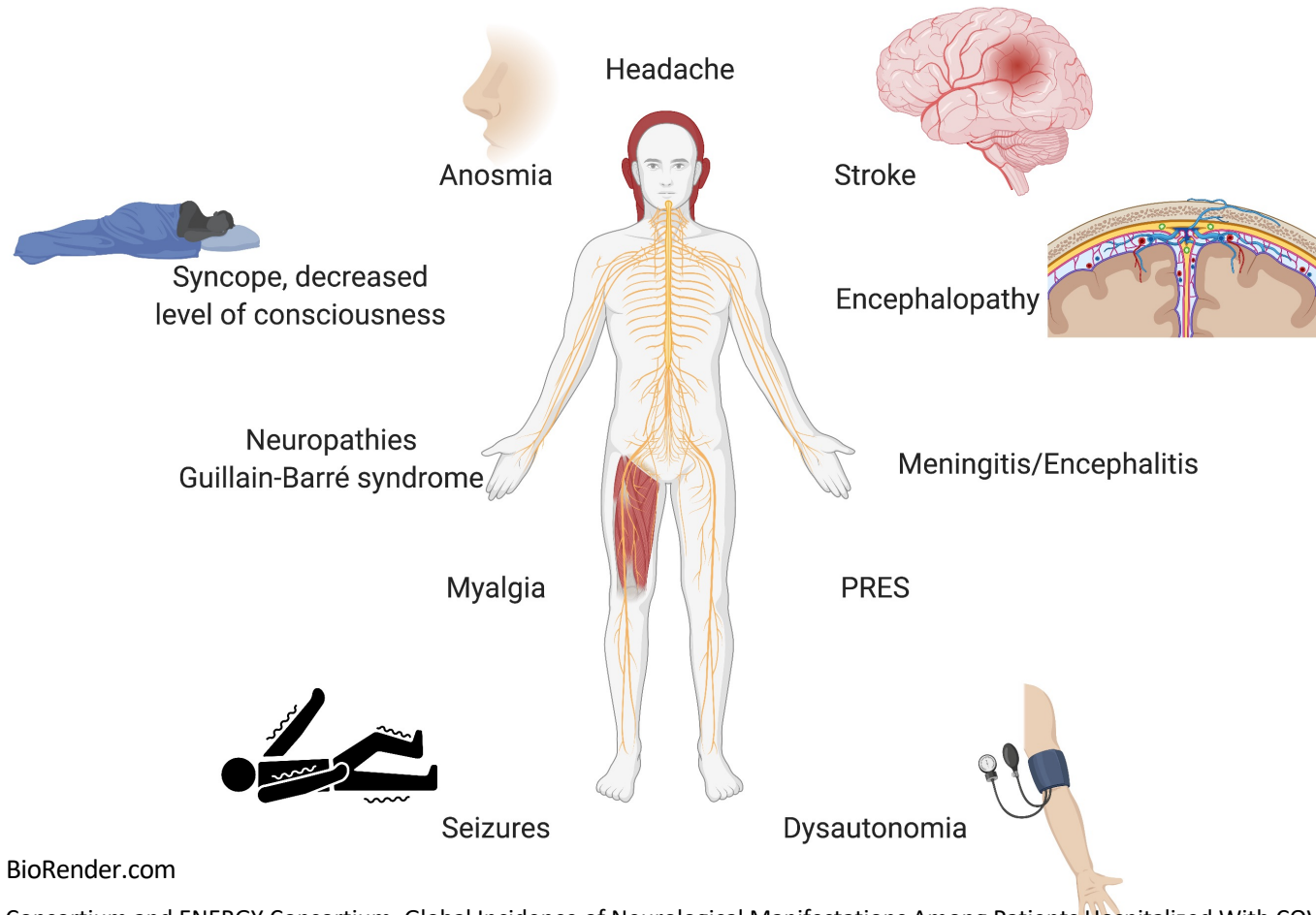


Figure created by David García-Azorín with BioRender.com

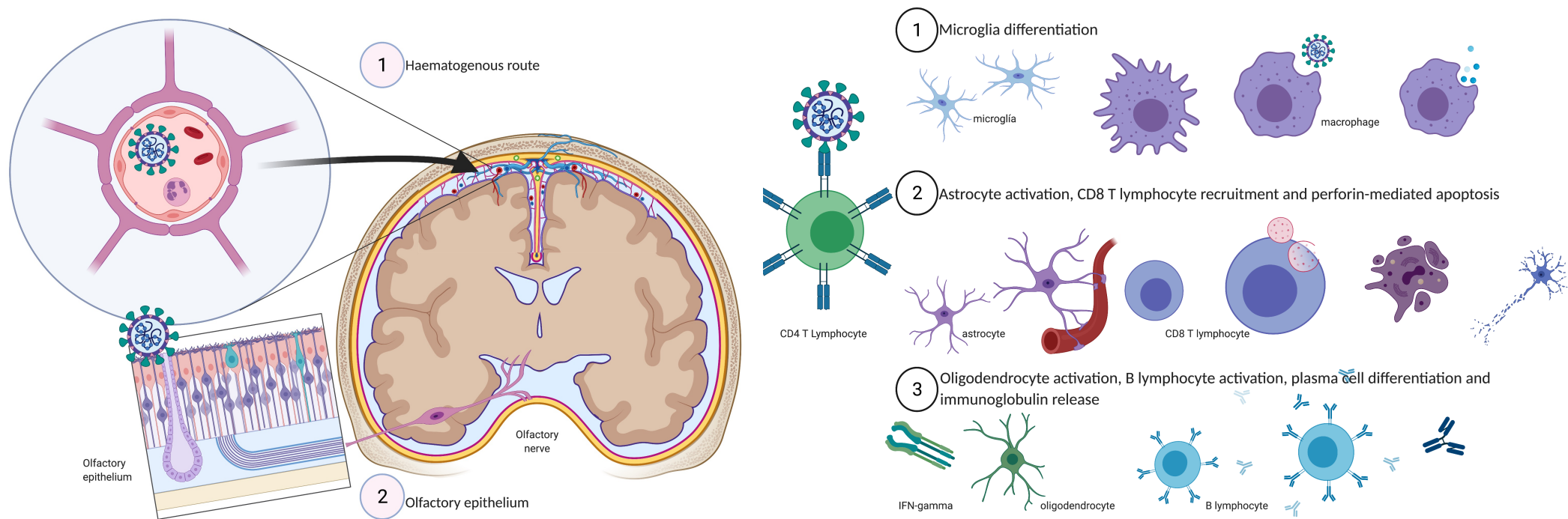
1. Chou SH, GCS-NeuroCOVID Consortium and ENERGY Consortium. Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19-A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open. 2021 May 3;4(5):e2112131.
2. García-Azorín D; Spanish neuroCOVID registry group. Neurological presentations of COVID-19: Findings from the Spanish Society of Neurology neuroCOVID-19 registry. J Neurol Sci. 2021 Apr 15;423:117283.
3. García-Azorín D. Neurological symptoms in Covid-19 patients in the emergency department. Brain Behav. 2021 Apr;11(4):e02058.

What is neuro-COVID pathophysiology?

Is neuro-
COVID caused
by neuro-
invasion?



- Neurological manifestations can be caused by the virus, the immune response or by organ dysfunction¹⁻³



Figures created by David García-Azorín with BioRender.com

- Finsterer J. Putative mechanisms explaining neuro-COVID. *J Neuroimmunol.* 2020 Dec 2;350:577453.
- Newcombe VFJ; Cambridge NeuroCovid Imaging Collaborators. Neuroanatomical substrates of generalized brain dysfunction in COVID-19. *Intensive Care Med.* 2021 Jan;47(1):116-118.
- Guerrero JI. Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. *BMC Infect Dis.* 2021 Jun 2;21(1):515.

- Caused by a prothrombotic state
Stroke, intracranial hemorrhage.

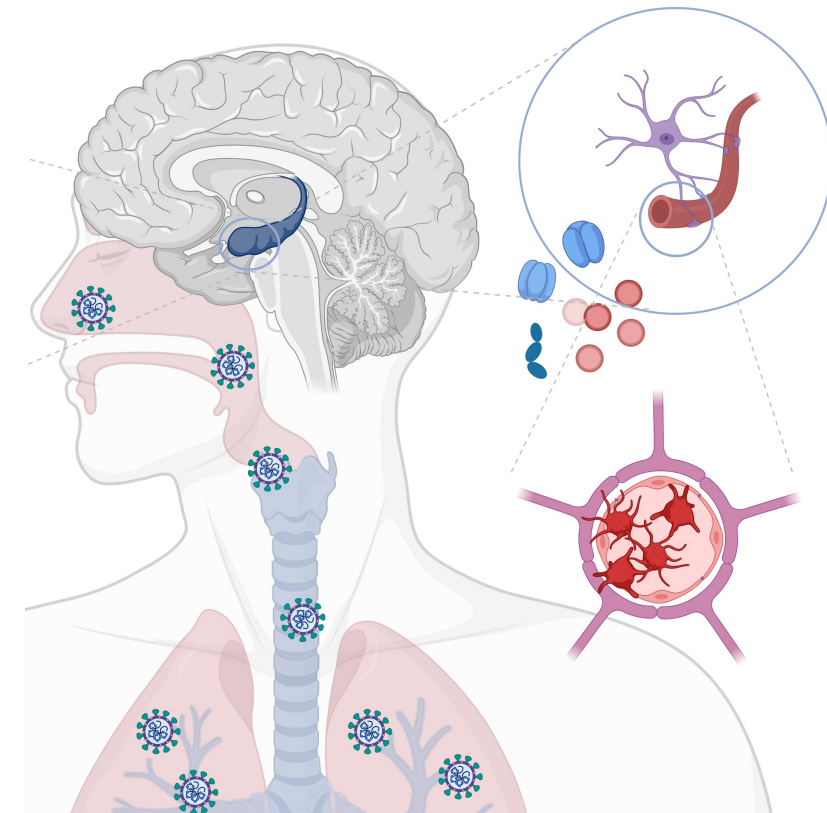
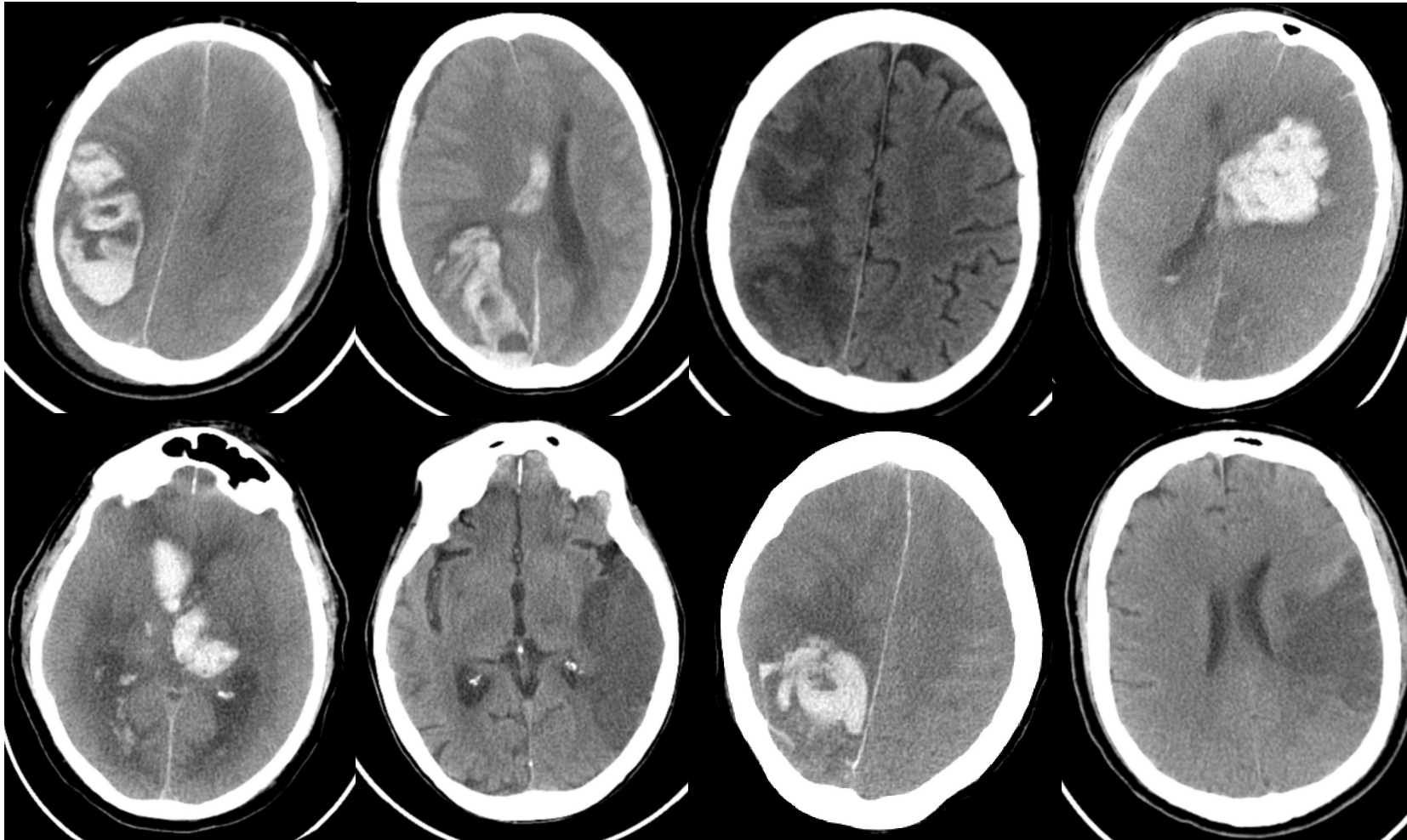


Figure created by David García-Azorín with BioRender.com

- Associated with multiple organ failure
Encephalopathy, seizures

| Pathology | Systemic cause | Investigations |
|---------------|---|---|
| Organ failure | Hypercapnia/hypoxia | Pulse oximetry, blood gas |
| | Hepatic failure | ALT, AST, GGT, ALP, ammonia |
| | Acute kidney injury | Creatinine, urea |
| | Thyroid disorders | TSH, T4 |
| | Cardiac failure | ECG, Echo, clinical examination |
| Metabolic | Hyper/hyponatremia | Plasma Na+ |
| | Hyper/Hypocalcemia | Corrected plasma ++ |
| | Hyper/hypoglycemia | Plasma / finger-prick glucose |
| | Hyperpyrexia/fever/hypothermia | Temperature/observations |
| | Cytokine release syndrome | IL-1, IL-6, TNF-alpha |
| Toxic | Sedatives, corticosteroids, hydroxychloroquine, lopinavir, ritonavir, tocilizumab, drugs, alcohol | Patient history, treatment review |
| Septic | Superinfection | Blood, urine, sputum cultures, serology |
| Vascular | Hypertensive encephalopathy/Severe hypotension | Blood pressure monitoring |
| Nutritional | Wernicke encephalopathy | Thiamine replacement, B12 |

- Immune-mediated manifestations
Guillain-Barré sd., myelitis, encephalitis

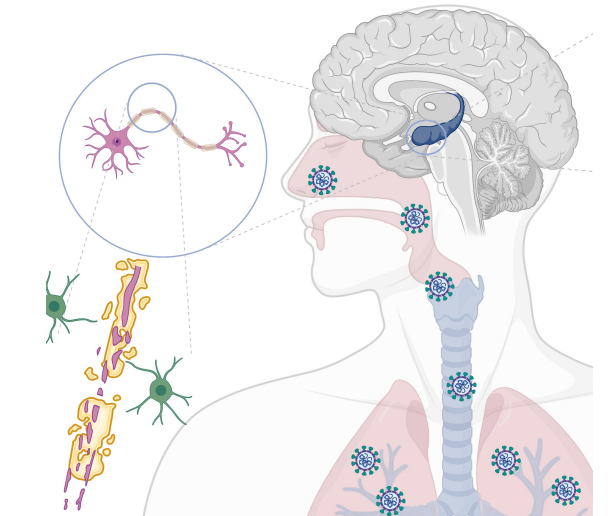
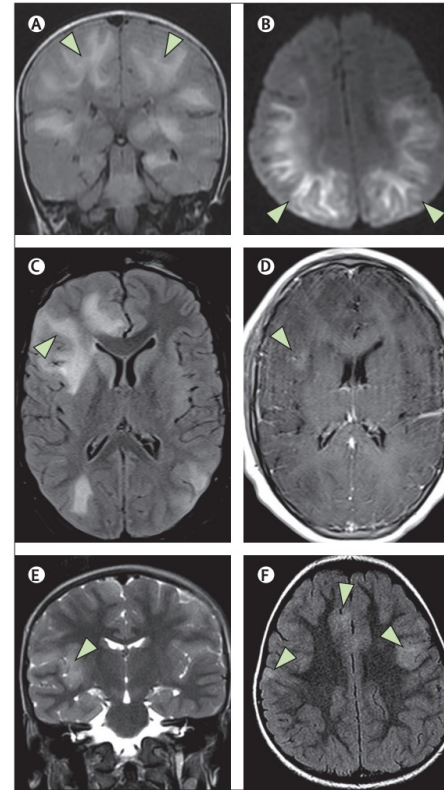
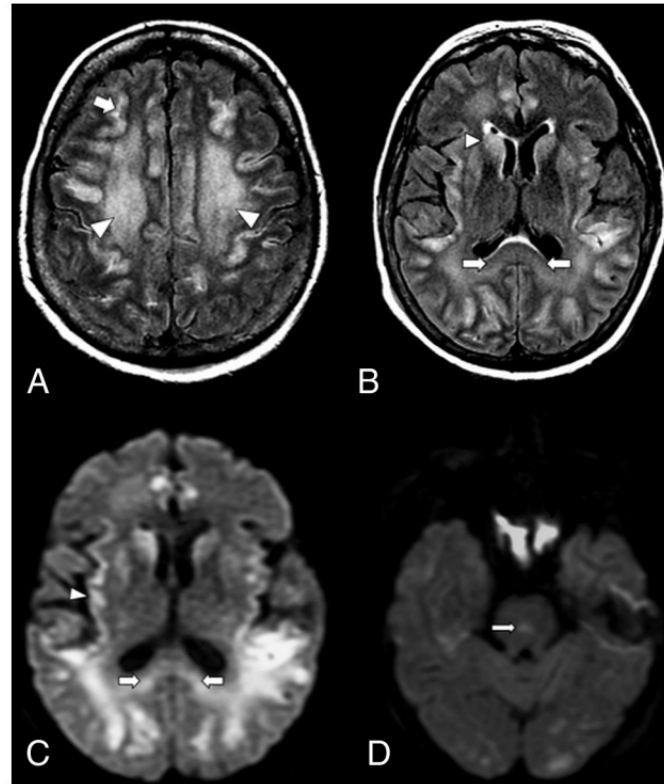
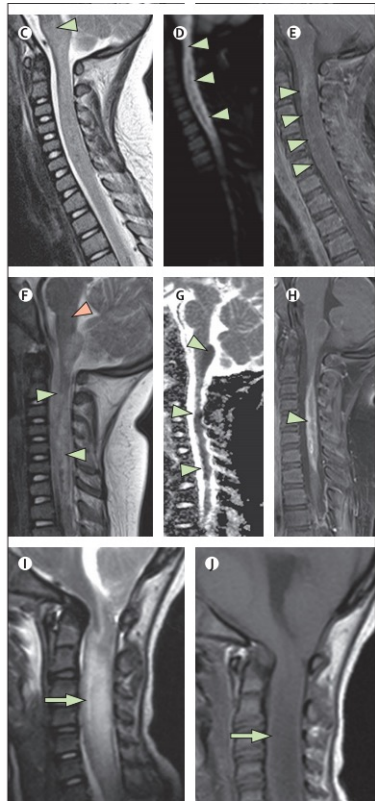


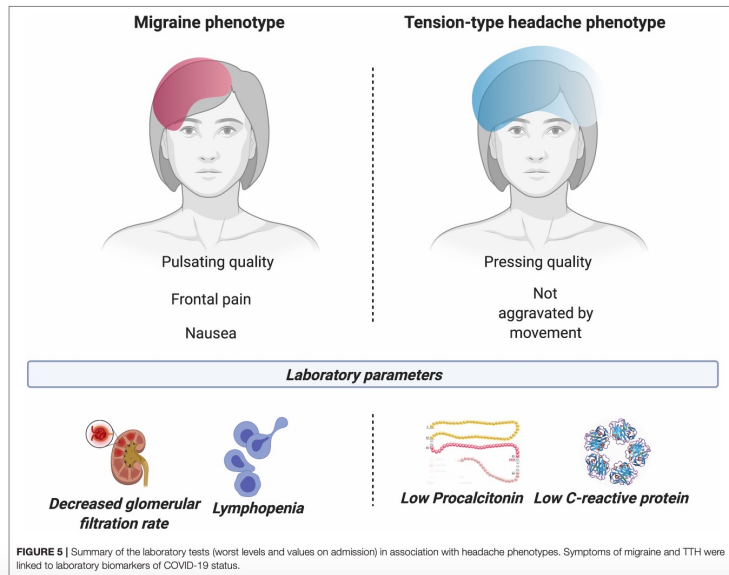
Figure created by David García-Azorín with BioRender.com

Lindan CE; ASPNR PECOBIG Collaborator Group. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. *Lancet Child Adolesc Health*. 2021 Mar;5(3):167-177.

Kihira S. Imaging Features of Acute Encephalopathy in Patients with COVID-19: A Case Series. *AJNR Am J Neuroradiol*. 2020 Oct;41(10):1804-1808.

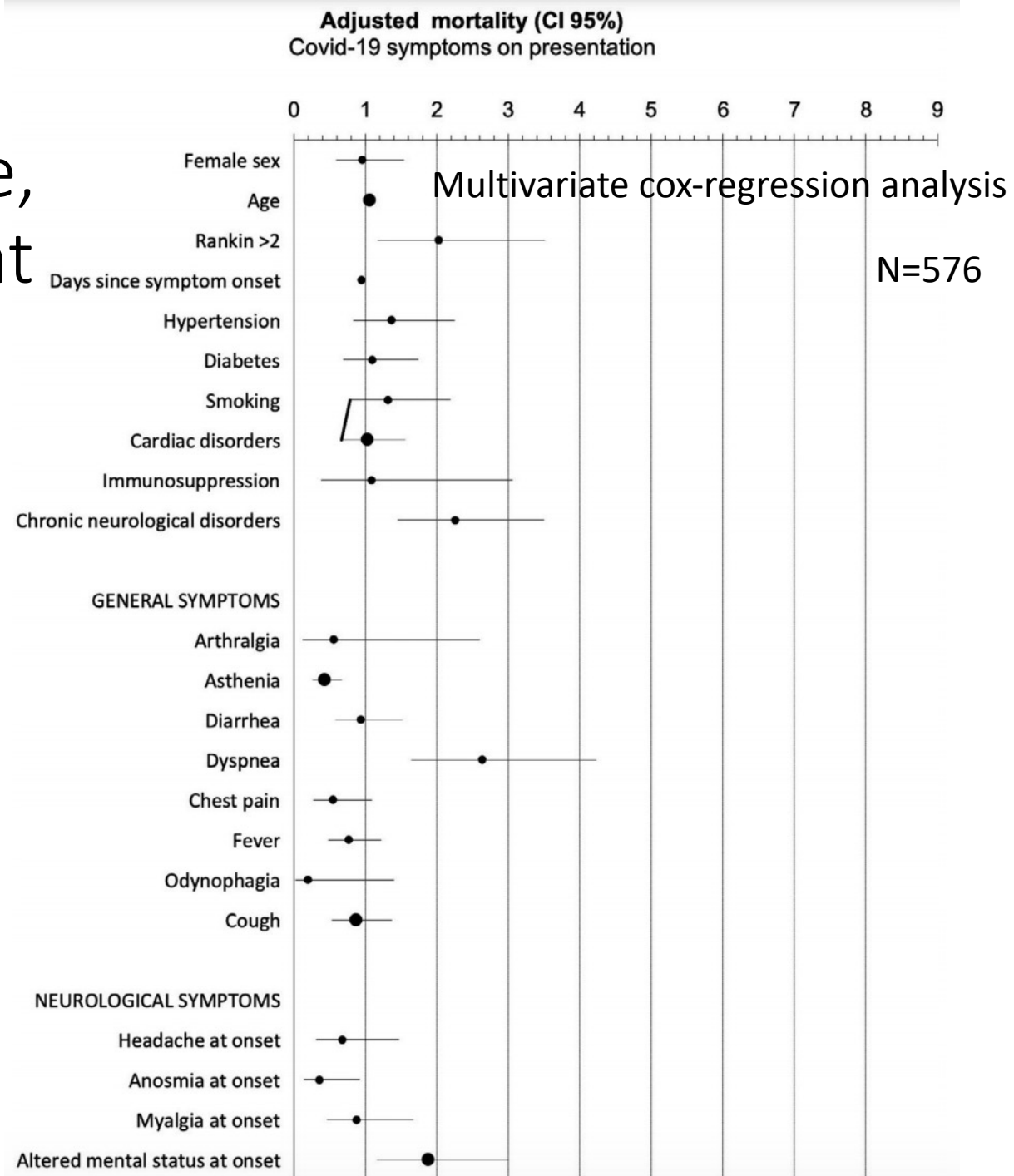
Some manifestations (headache, anosmia) reflect a more efficient immune response

- Lower **adjusted** mortality¹
- Related with the phenotype²



1. García-Azorín D. Neurological symptoms in Covid-19 patients in the emergency department. Brain Behav. 2021 Apr;11(4):e02058.

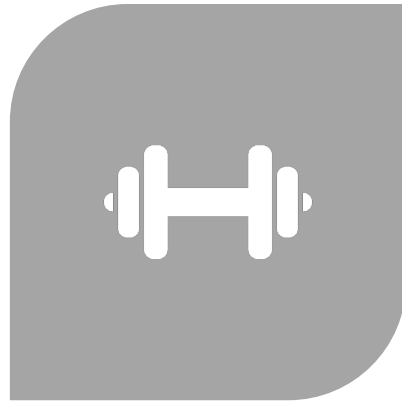
2. Planchuelo-Gómez Á. Deep Phenotyping of Headache in Hospitalized COVID-19 Patients via Principal Component Analysis. Front Neurol. 2020 Dec 17;11:583870.



Some specific manifestations



COGNITIVE SYMPTOMS



NEUROMUSCULAR



HEADACHE

Neuromuscular



Neuromuscular manifestations

Fatigue

- 69% of patients
- Multifactorial

Weakness, exercise intolerance

- 68% at 6 weeks
- 63% at 6 months

Myalgia

- 53% during the acute phase
- 56% experiences them again
- 93% fluctuating course

Neuromuscular manifestations

Paresthesia

- 40-60% of patients
- 38% during post-COVID

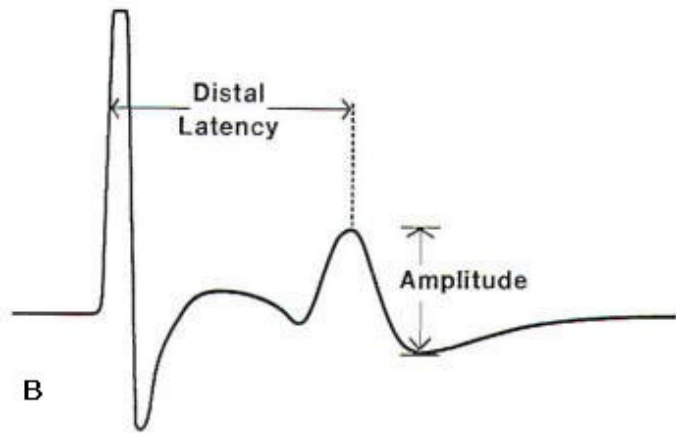
Neuropathic pain

- 15-50% of patients
- Unspecific distribution
- Fluctuating course

Postural Orthostatic Tachicardia syndrome (POTS)

- Orthostatic headache, syncope, hyperhidrosis, postural tachicardia, flushing.
- 59% of patients report symptoms
- 41% abnormal evaluation
- Also reported after other infections

Neuromuscular manifestations



- Not always a consistent relationship between COVID-19-severity and neuromuscular manifestations frequency/severity
- Frequently with no correlate in:
 - Laboratory (CPK)
 - Electromyography-electroneurography
 - Histology

A close-up photograph of a bronze statue, likely Auguste Rodin's 'The Thinker', showing the man's face and hand resting on his chin. The statue is set against a clear blue sky. The text 'Cognitive symptoms' is overlaid in white, centered on the man's face.

Cognitive
symptoms

A blue wireframe illustration of a human figure, composed of interconnected lines and dots, centered on the page. The figure is partially obscured by a blue rectangular banner that contains the title and date. The banner has a slight 3D effect with a lighter blue shadow on its top and bottom edges.

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

6 October 2021



**World Health
Organization**

Post COVID-19 condition

- *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 and*
 - *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.*

Case-control studies



Post-COVID-19 patients performed worse than controls



Attention, memory y executive function

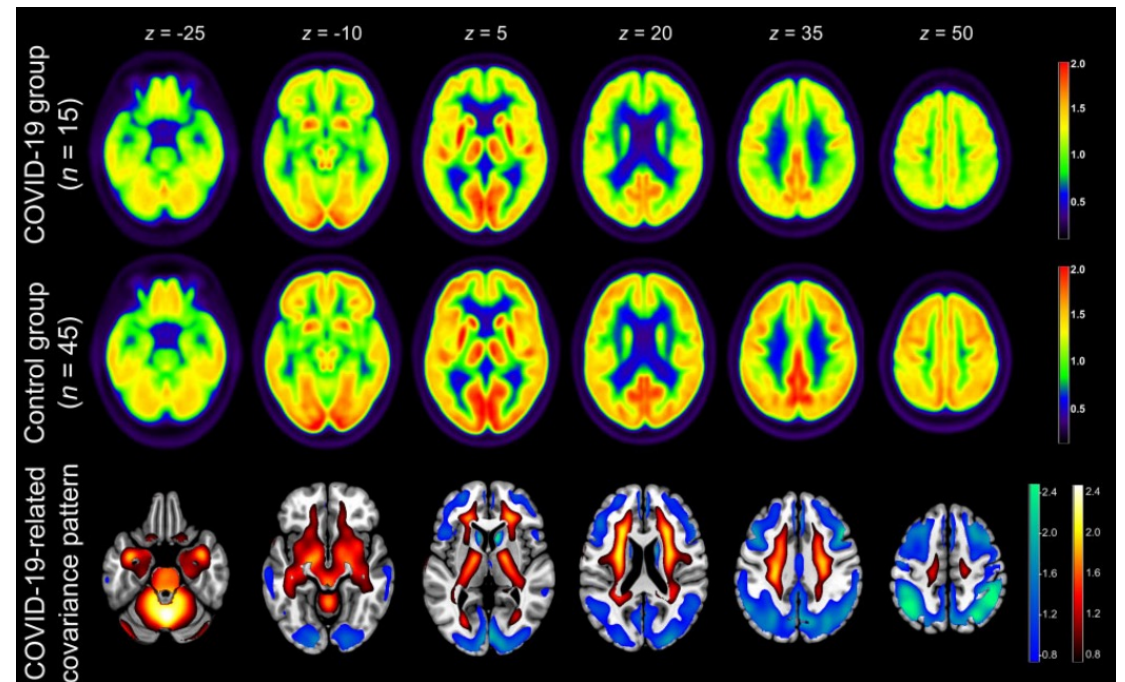
Cohort studies

Prevalence of cognitive complaints: 50-65%

- Attention, memory, semantic fluency, executive function.

Findings in imaging

- No structural abnormalities
- Changes regarding grey matter volumen, white matter and brain metabolism



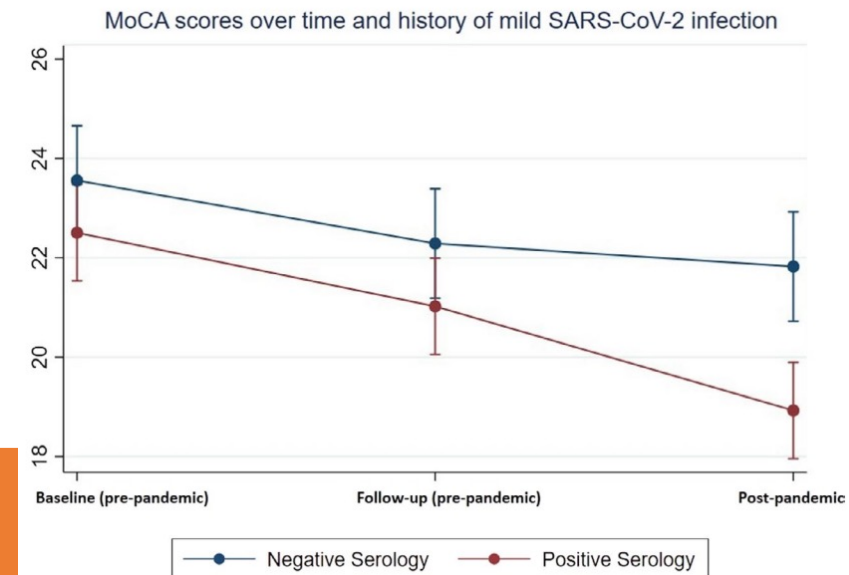
Longitudinal studies

Pre-pandemic data vs. 6-months after the infection¹

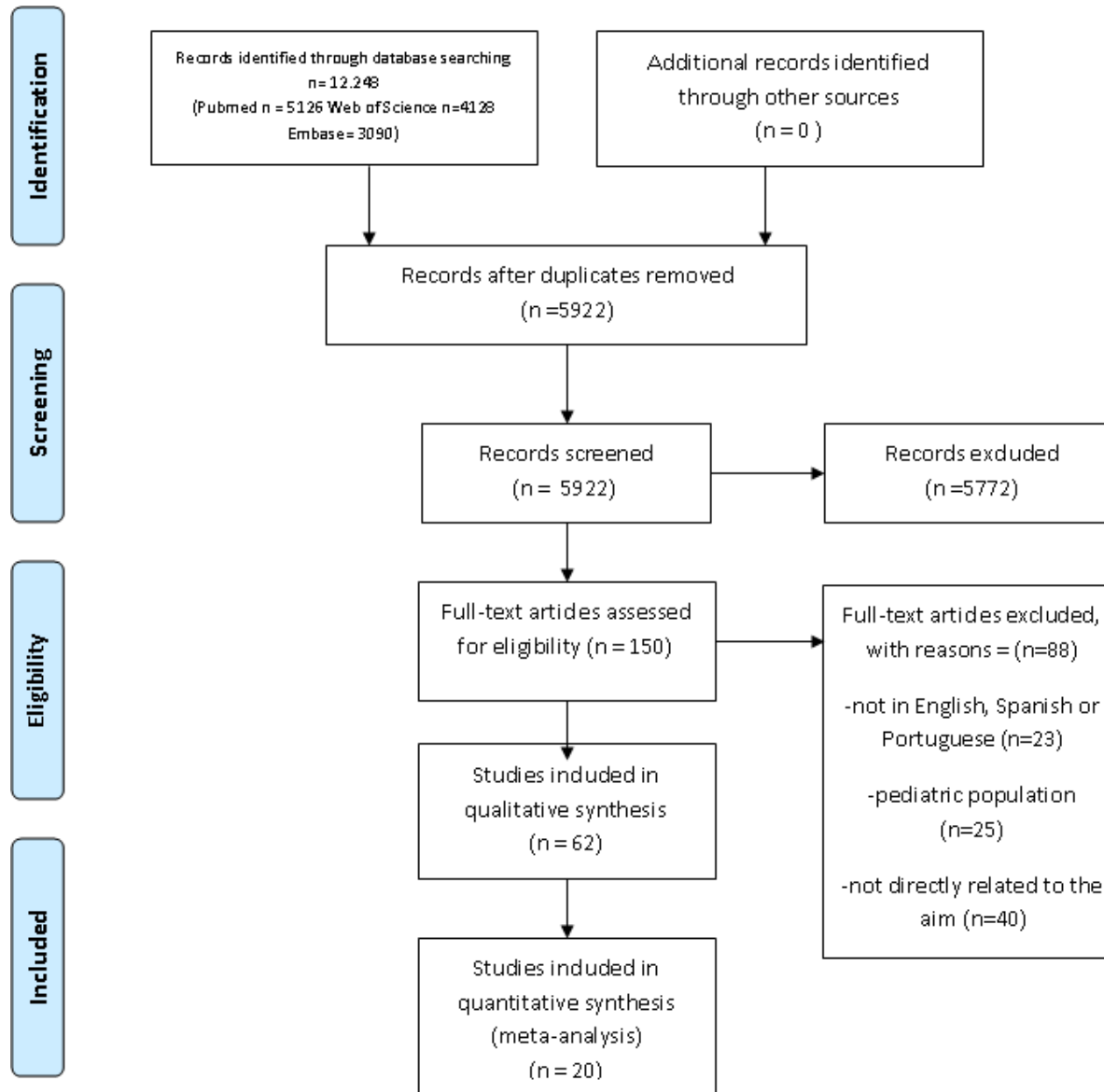
- Higher probability of having an abnormal MoCa test (21 vs. 2%)
- x18.1 higher risk of cognitive worsening
 - Adjusted for vascular risk factors, sleep disorders, mood disorders and education.

Data on admission and 1-month afterwards²

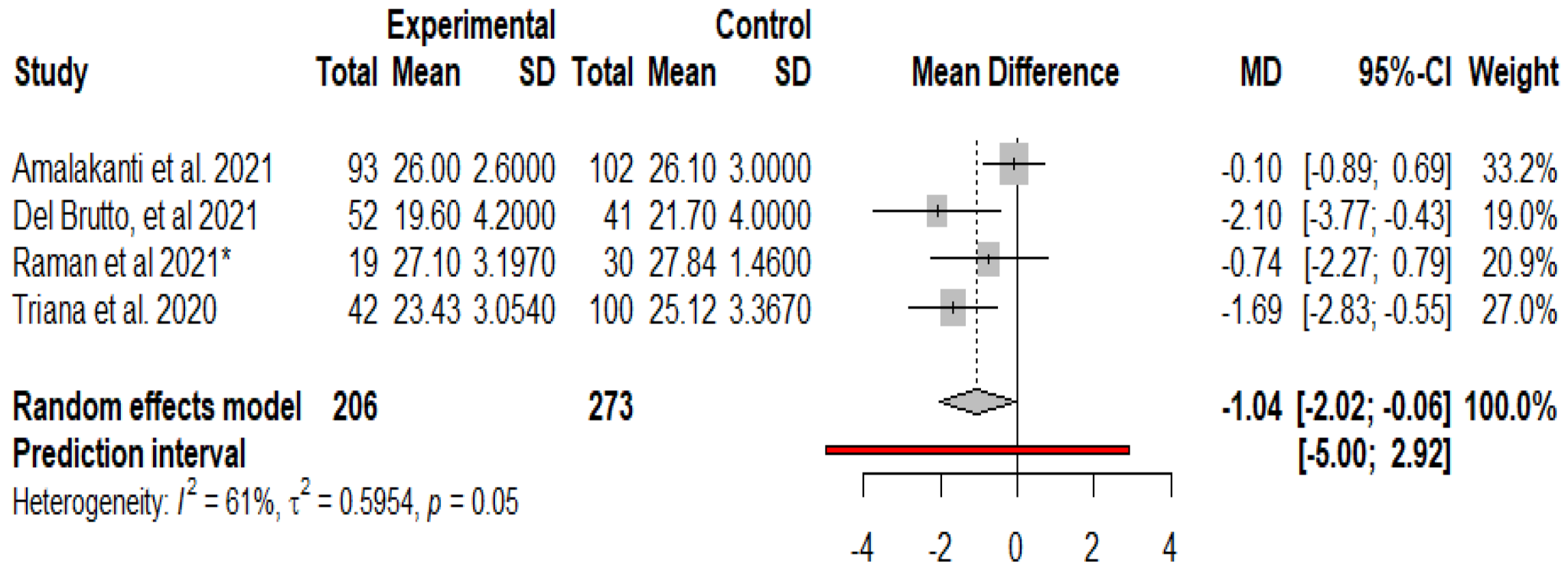
- Worsening of MoCa and MMSE



1. Del Brutto Eur J Neurol 2021;
2. Alemanno. PlosOne 2021;



Meta-analysis of studies reporting MoCA



MoCA test

MONTREAL COGNITIVE ASSESSMENT (MOCA) (EVALUACIÓN COGNITIVA MONTREAL)

NOMBRE:
Nivel de estudios:
Sexo:

Fecha de nacimiento:
FECHA:

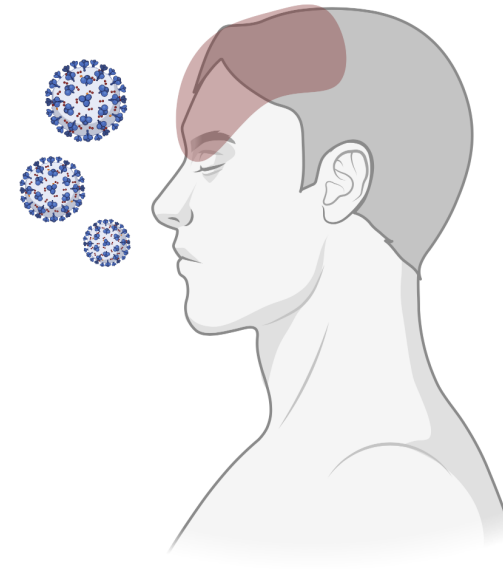
| VISUOESPACIAL / EJECUTIVA | | Copiar el cubo | | Dibujar un reloj (Once y diez) (3 puntos) | | | Puntos | | | | | | | |
|---------------------------|--|---|---------------------|---|--------|-----------------|--------|--------|--|-----|-------|-----|-----------|--------|
| | | | | <input type="checkbox"/> Contorno <input type="checkbox"/> Números <input type="checkbox"/> Agujas | | | ___/5 | | | | | | | |
| IDENTIFICACIÓN | | | | | | | | | | | | | | |
| | | | | | | ___/3 | | | | | | | | |
| MEMORIA | | Lea la lista de palabras, el paciente debe repetirlas. Haga dos intentos. Re cuérdese las 5 minutos más tarde. | | ROSTRO | SEDA | IGLESIA | CLAVEL | ROJO | Sin puntos | | | | | |
| | | 1er intento | | | | | | | | | | | | |
| | | 2º intento | | | | | | | | | | | | |
| ATENCIÓN | | Lea la serie de números (1 número/seg.) | | El paciente debe repetirla. [] 2 1 8 5 4 El paciente debe repetirla a la inversa. [] 7 4 2 | | | | ___/2 | | | | | | |
| | | Lea la serie de letras. El paciente debe dar un golpecito con la mano cada vez que se diga la letra A. No se asignan puntos si ≥ 2 errores. | | [] FBACMNAAJKLBAFAKDEAAAJAMOFAB | | | | ___/1 | | | | | | |
| | | Restar de 7 en 7 empezando desde 100. | | [] 93 | [] 86 | [] 79 | [] 72 | [] 65 | ___/3 | | | | | |
| | | | | 4 o 5 sustracciones correctas: 3 puntos, 2 o 3 correctas: 2 puntos, 1 correcta: 1 punto, 0 correctas: 0 puntos. | | | | | | | | | | |
| LENGUAJE | | Repetir: El gato se esconde bajo el sofá cuando los perros entran en la sala. [] | | Espero que él le entregue el mensaje una vez que ella se lo pida. [] | | | | ___/2 | | | | | | |
| | | Fluidez del lenguaje. Decir el mayor número posible de palabras que comiencen por la letra "P" en 1 min. | | [] _____ (N ≥ 11 palabras) | | | | ___/1 | | | | | | |
| ABSTRACCIÓN | | Similitud entre p. ej. manzana-naranja = fruta [] | | tren-bicicleta [] | | reloj-regla [] | | ___/2 | | | | | | |
| RECUERDO DIFERIDO | | Debe acordarse de las palabras SIN PISTAS | | ROSTRO | SEDA | IGLESIA | CLAVEL | ROJO | Puntos por recuerdos SIN PISTAS únicamente | | | | | |
| | | Pista de categoría | | [] | [] | [] | [] | [] | | | | | | |
| | | Pista elección múltiple | | | | | | | | | | | | |
| ORIENTACIÓN | | [] | Día del mes (fecha) | [] | Mes | [] | Año | [] | Día de la semana | [] | Lugar | [] | Localidad | ___/6 |
| | | | | | | | | | | | | | | ___/30 |
| | | | | | | | | | | | | | | ___/30 |



Headache

Headache is frequent in infections

- One of the commonest symptoms
 - Malaria, dengue, influenza
- Most people have experienced it
- Limited literature



Headache in influenza

- Up to 32-91% of cases¹⁻⁴
- Caused by cytokine release⁵
- May occur also after oseltamivir⁶
 - RR: 1.18 (95% CI: 1.05-1.33)

| Symptom | Patients With Laboratory-Confirmed Influenza, % (n = 2470) | Patients Who Tested Negative for Influenza, % (n = 1274) |
|--|---|--|
| Fever ($\geq 37.8^{\circ}\text{C}$)* | 68 | 40 |
| Feverishness* | 90 | 89 |
| Cough | 93 | 80 |
| Nasal congestion | 91 | 81 |
| Weakness | 94 | 94 |
| Loss of appetite | 92 | 86 |
| Sore throat | 84 | 84 |
| Headache | 91 | 89 |
| Myalgia | 94 | 94 |

*Fever was a body temperature of 37°C or higher, whereas feverishness was the patient's subjective feeling that they had a fever or chill.

1. Pedersen. *J Emerg Med* 2019
2. Eccles. *Pain Med* 2003
3. Monto. *Arch Intern Med* 2001
4. Eccles. *Lancet Infect Dis* 2005
5. Smith. *Med Hypotheses* 1992
6. Jefferson. *Cochrane Database Syst Rev* 2014

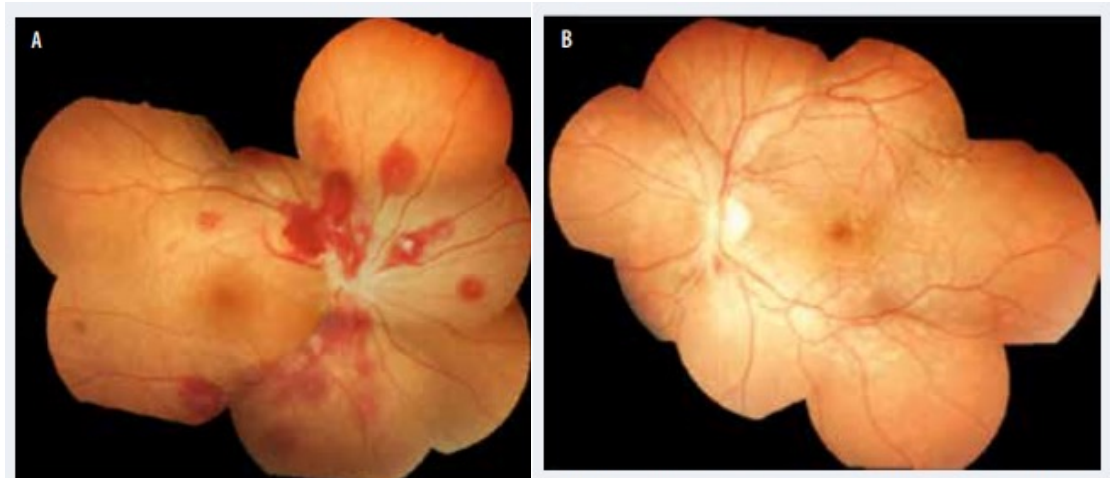
Dengue

- Sometimes becomes persistent (NDPH (0.67%))

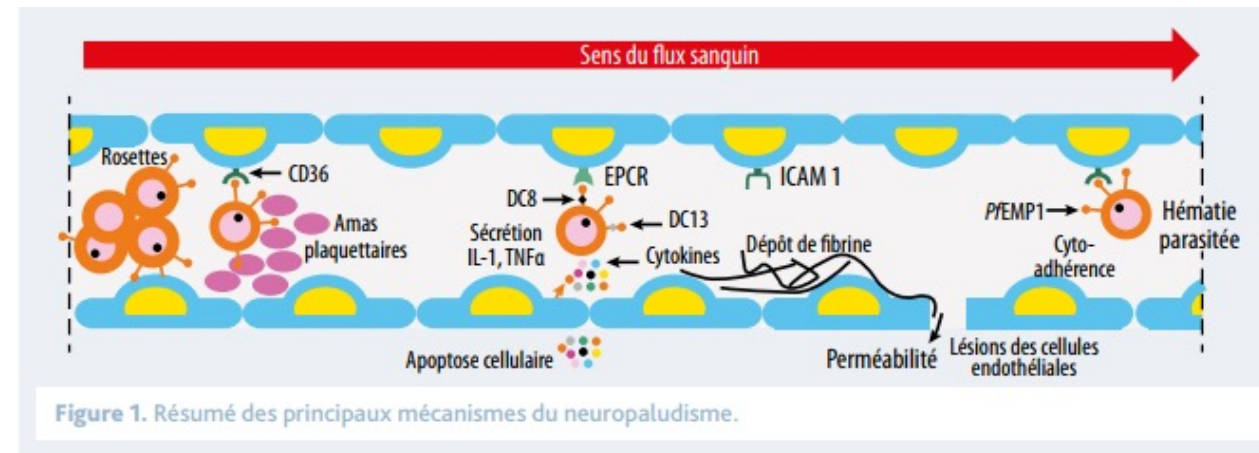
| Variables | No. studies meta-analyzed | Meta-analysis, pooled data (95% CI)* | | |
|-------------------------|---------------------------|--------------------------------------|-------------------------------------|---------------------|
| CONSTITUTIONAL | | | MUCOCUTANEOUS | |
| Fever | 88 | 98.1 (97.2–98.7) | Rash | 83 29.6 (26.1–33.3) |
| Chills | 14 | 65.3 (58.3–71.6) | Pruritus | 5 24.1 (19.8–29.0) |
| Myalgia | 65 | 64.2 (58.1–69.8) | Exanthema | 5 33.7 (11.2–67.1) |
| Arthralgia | 53 | 53.6 (46.0–61.0) | Itching eruption | 6 24.0 (18.7–30.2) |
| Lethargy | 5 | 67.1 (32.6–89.6) | CARDIORESPIRATORY | |
| Malaise | 9 | 76.0 (64.1–84.9) | Cough | 29 22.9 (17.8–28.8) |
| Asthenia | 6 | 74.3 (45.8–90.8) | Pleural effusion | 23 8.3 (4.5–14.9) |
| Body-ache | 13 | 67.2 (55.2–77.3) | Myocarditis | 5 5.7 (1.2–22.5) |
| Back pain | 9 | 57.3 (32.2–79.1) | Hypotension | 14 12.5 (7.7–19.7) |
| Sore throat | 12 | 19.7 (13.4–28.1) | Respiratory disorders | 13 8.7 (5.3–13.9) |
| Eye pain | 6 | 27.8 (13.7–48.1) | NEUROLOGICAL | |
| Retro-orbital pain | 38 | 35.1 (27.0–44.2) | Headache | 83 75.7 (69.5–81.0) |
| Lymphadenopathy | 13 | 9.2 (4.4–18.2) | Dizziness | 9 22.8 (11.7–39.7) |
| GASTROINTESTINAL | | | Seizure | 7 2.7 (1.8–3.9)** |
| Vomiting | 36 | 39.8 (35.0–44.9) | Shock | 12 9.5 (4.2–20.0) |
| Nausea | 22 | 42.0 (34.0–50.4) | Convulsion | 5 6.1 (2.9–12.5) |
| Diarrhea | 36 | 20.7 (17.3–24.7) | Encephalopathy | 8 5.0 (1.9–12.4) |
| Anorexia | 17 | 47.8 (34.9–61.0) | HEMORRHAGIC MANIFESTATIONS | |
| Ascites | 25 | 10.2 (5.3–18.8) | Gingivorrhagia | 16 9.7 (6.0–15.2) |
| Icterus/Jaundice | 13 | 2.8 (1.5–5.2) | Epistaxis | 25 11.8 (7.6–17.9) |
| Abdominal pain | 61 | 32.4 (27.9–37.2) | Hematuria | 16 5.0 (3.0–8.1) |
| Hepatomegaly | 41 | 18.9 (12.7–27.1) | Melena | 13 16.9 (8.1–31.8) |
| Splenomegaly | 20 | 7.7 (5.2–11.3) | Petechiae | 30 22.3 (16.5–29.3) |
| Hepatosplenomegaly | 5 | 17.5 (8.3–33.3) | Hematemesis | 18 13.4 (8.0–21.6) |
| | | | Bleeding/Hemorrhagic manifestations | 58 25.8 (21.0–31.1) |

1. Guo. *Front Cell Infect Microbiol* 2017
2. Volpe de Abreu. *Headache* 2020

Malaria



- *P. Falciparum*
- Up to 10% mortality, 30% sequelae
 - Children, immunosuppression, pregnancy
- Clinical presentation (apart from headache):
 - Fever (not consistent)
 - Altered level of consciousness
 - No meningeal irritation syndrome
 - Seizures
 - Altered mental status
 - Anemia



1. Wiwanitkit. *Acta Neurol Taiwan* 2009
2. Albrecht-Schgoer. *Front Immunol* 2022

How frequent is
COVID-related headache?


March-
April 2020



n=458

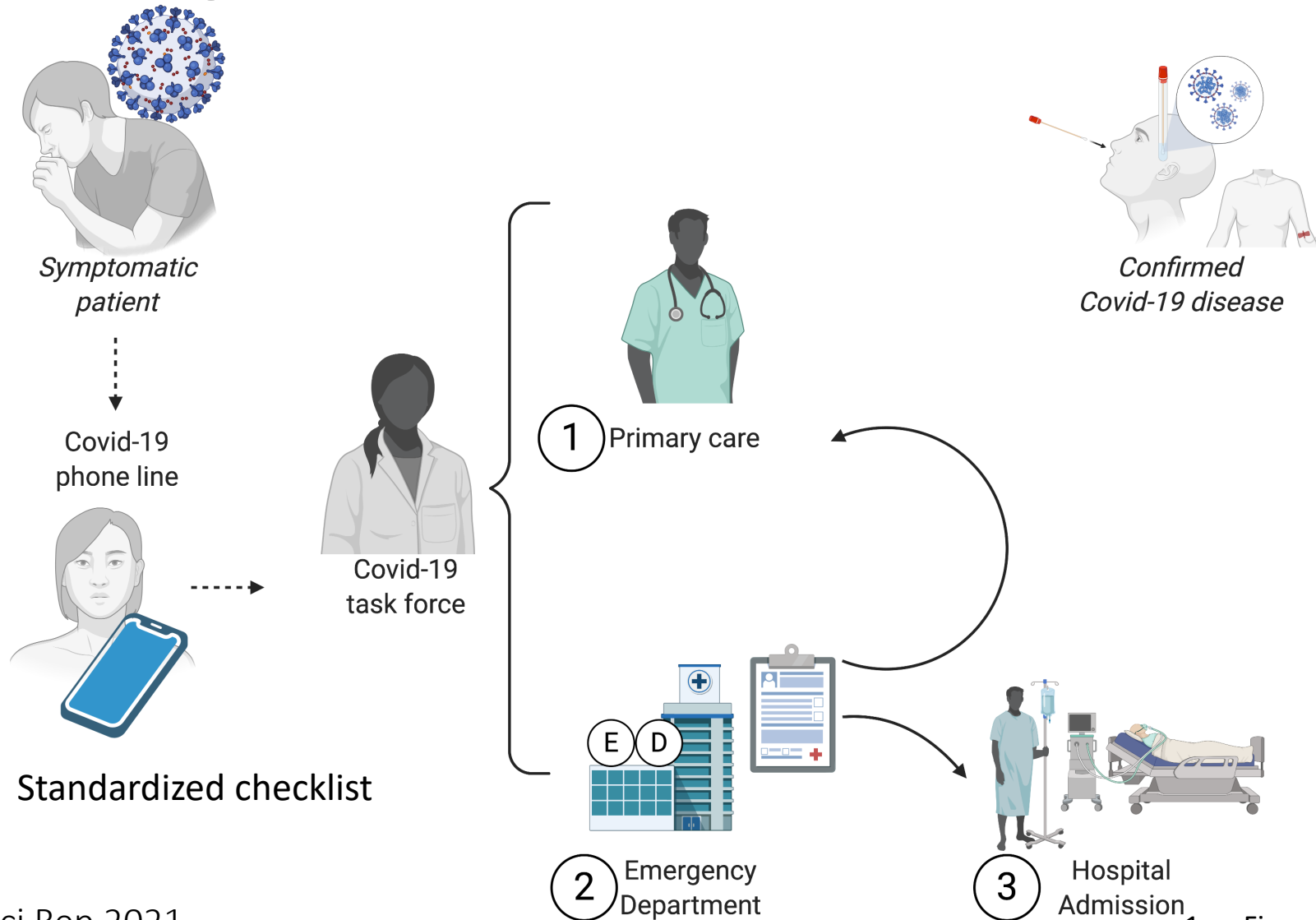
OPEN

Frequency and phenotype of headache in covid-19: a study of 2194 patients

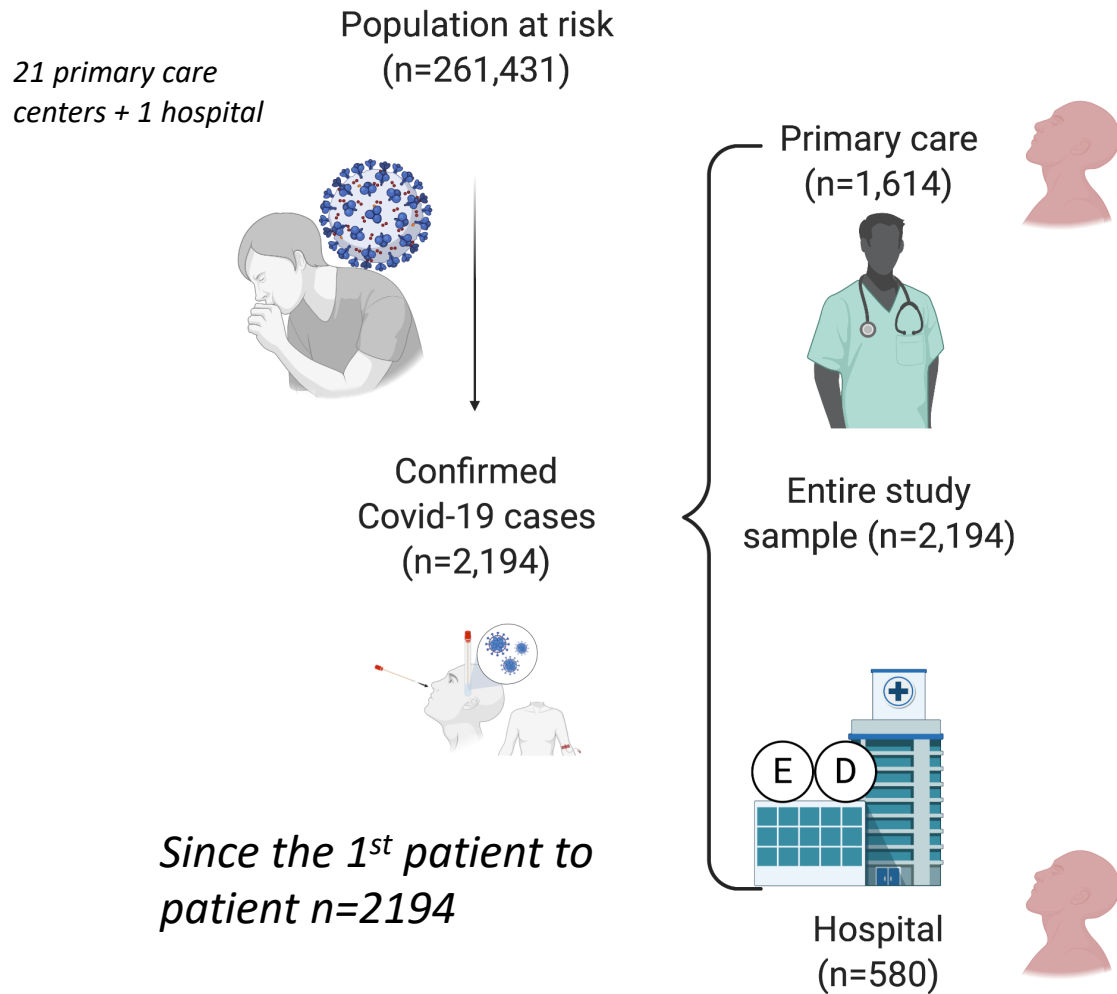
David García-Azorín¹  [✉], Álvaro Sierra¹, Javier Trigo¹, Ana Alberdi², María Blanco², Ismael Calcerrada², Ana Cornejo², Miguel Cubero², Ana Gil², Cristina García-Iglesias², Ana Guiomar Lozano², Cristina Martínez Badillo², Carol Montilla², Marta Mora², Gabriela Núñez², Marina Paniagua², Carolina Pérez², María Rojas², Marta Ruiz², Leticia Sierra², María Luisa Hurtado² & Ángel Luis Guerrero Peral^{1,3}

Study design

Valladolid Study



Frequency of headache



Frequency of Headache

ITT analysis: 383/1,614 (23.7%; 95% CI: 21.7-25.9%)

PP analysis: 383/1,525 (25.1%; 95% CI: 23.0-27.4%)

ITT analysis: 514/2,194 (23.4%; 95% CI: 21.7-25.3%)

PP analysis: 514/2,099 (24.5%; 95% CI: 22.7-26.4%)

23%

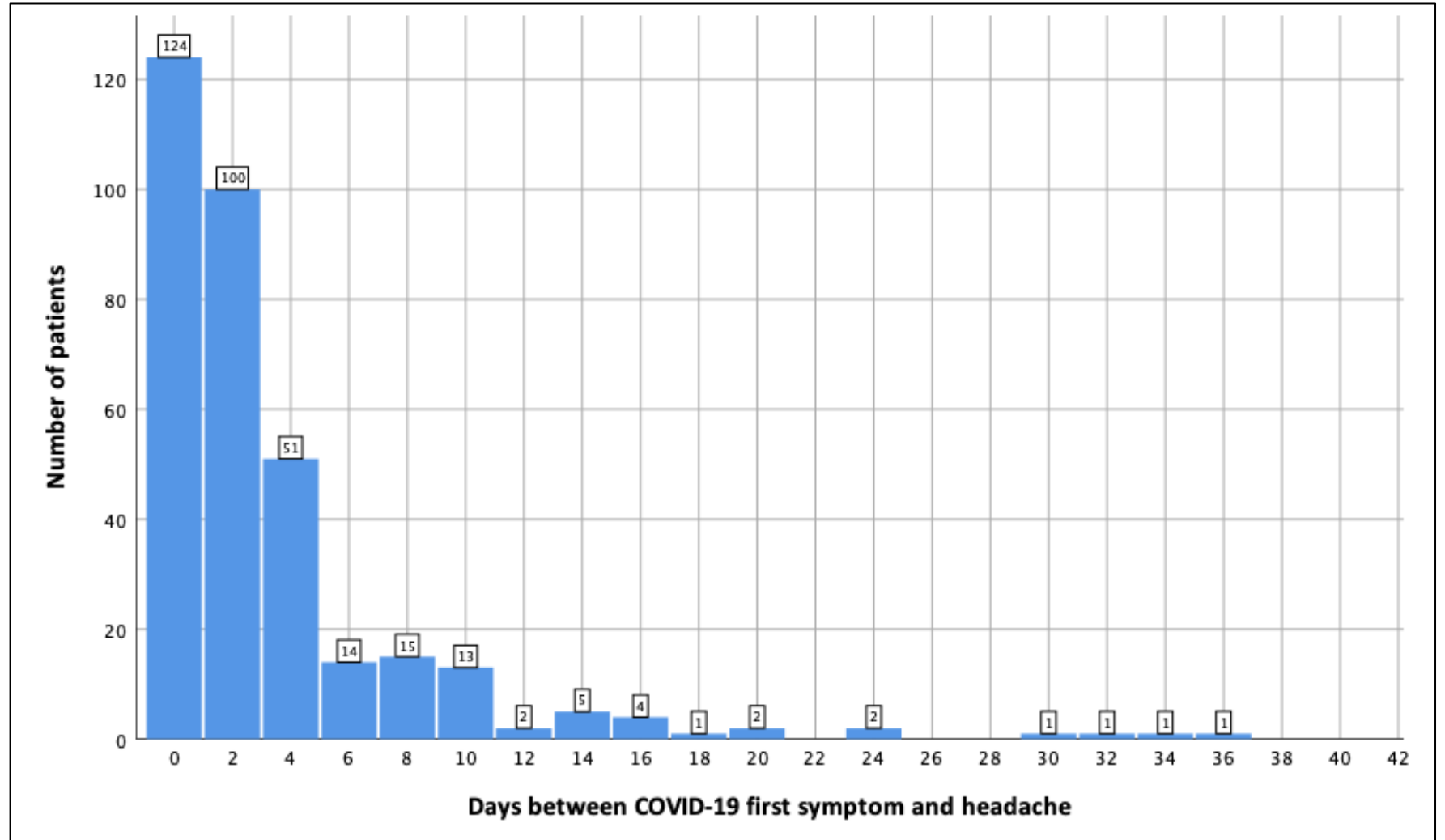
ITT analysis: 131/580 (22.6%; 95% CI: 19.3-26.2%)

PP analysis: 131/574 (22.8%; 95% CI: 19.5-26.5%)

Headache and anosmia are early symptoms

1st symptom: 27.9%

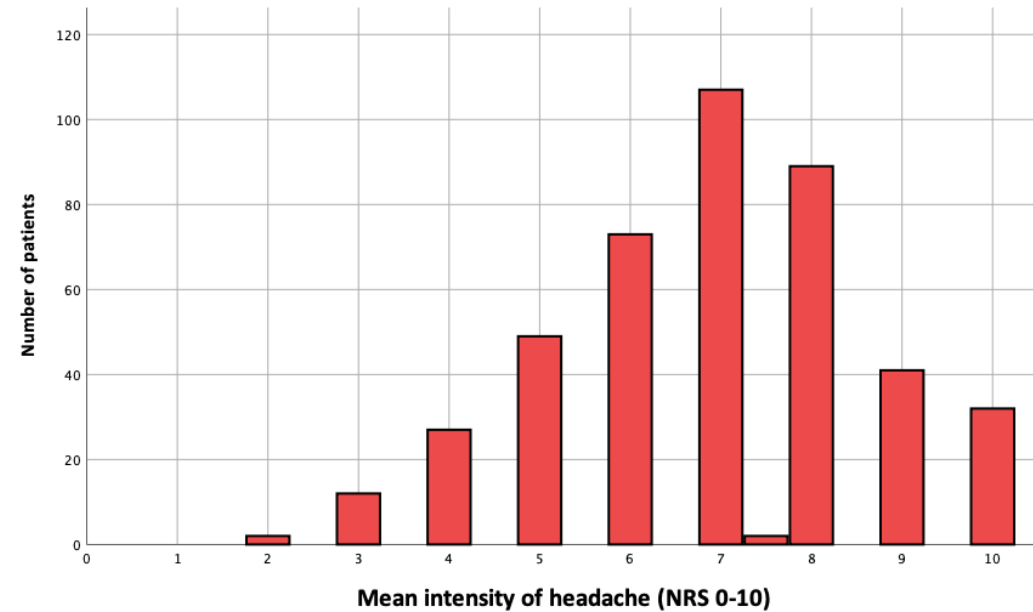
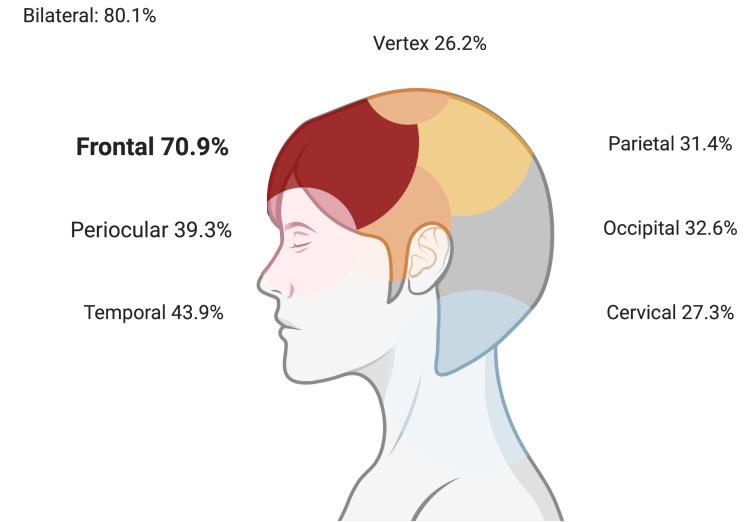
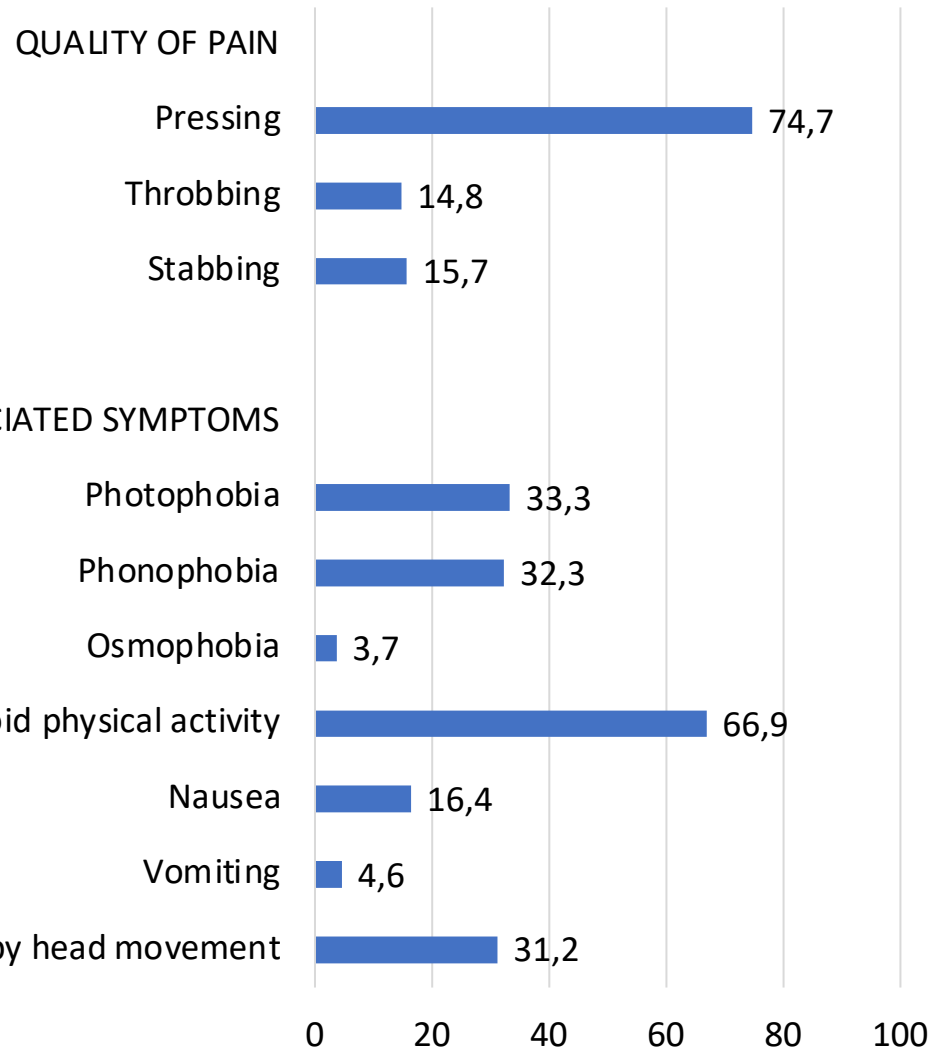
<24h: 42%
<48h: 53%
<72h: 67%
<96h: 77%



(n=458)

How does COVID-related headache
present?

Clinical phenotype



Can we **misdiagnose**
patients with **COVID-19**
as a **primary headache** disorder?

Diagnosis of secondary headache is based on the presence of red flags^{1, 2}

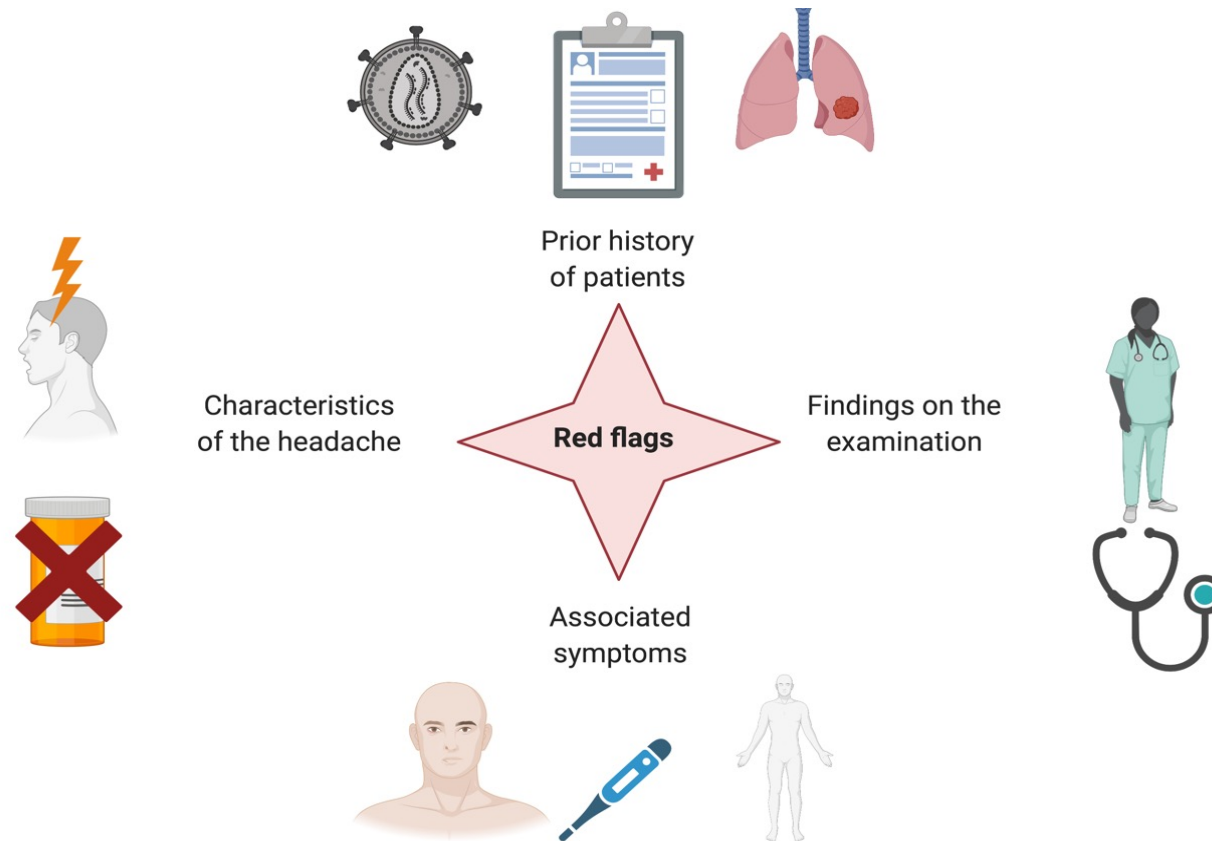


Figure created by David García-Azorín with BioRender.com

1. Friedman. *Neurol Clin* 2012
2. Do. *Neurology* 2019




Can we **misdiagnose** patients with **COVID-19** as a **primary headache** disorder?

- All consecutive hospitalized patients (1st to patient 576) - Valladolid
- Interviewed by a headache expert
- Structured interview



Research Submissions

Frequency and Type of Red Flags in Patients With Covid-19 and Headache: A Series of 104 Hospitalized Patients

David García-Azorín, MD ; Javier Trigo, MD; Blanca Talavera, MD; Enrique Martínez-Pías, MD ; Álvaro Sierra, MSci; Jesús Porta-Etessam, MD, PhD ; Juan F. Arenillas, MD, PhD; Ángel L. Guerrero, MD, PhD

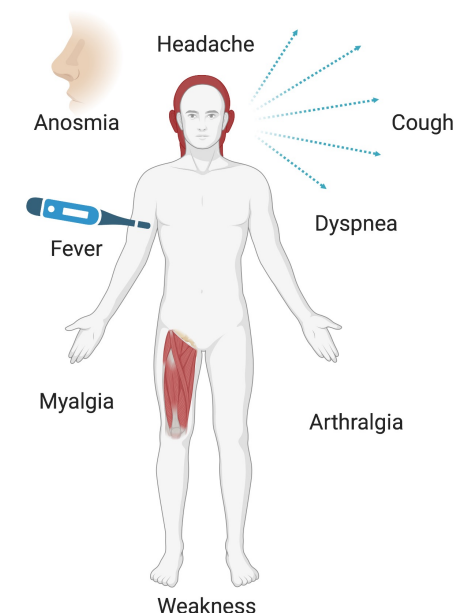
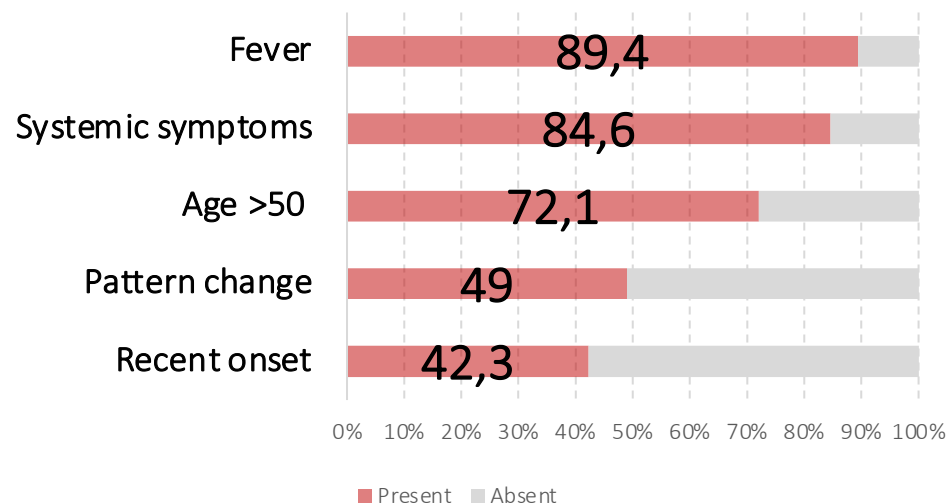


n=104

- **Red flags frequency: 100%**

- 76% prior medical history
- 95% headache phenotype
- 100% systemic symptoms
- Abnormal labs: 94%.

Most frequent red flags



But still, may
COVID-19 headache
phenotype mimic a
primary headache?



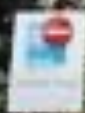
espacio de
salud

espacio de
respeto

espacio
sin tabaco

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de la Ley 28/2005 de 26 de noviembre
de los derechos de los consumidores
y usuarios de bienes y servicios



Phenotypic characterization of acute headache attributed to SARS-CoV-2: An ICHD-3 validation study on 106 hospitalized patients

Javier Trigo López¹ , David García-Azorín^{1,2} ,
Álvaro Planchuelo-Gómez³ , Cristina García-Iglesias¹,
Carlos Dueñas-Gutiérrez⁴ and Ángel L Guerrero^{1,2,5} 

Cephalalgia

2020, Vol. 40(13) 1432–1442

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DOI: 10.1177/0333102420965146

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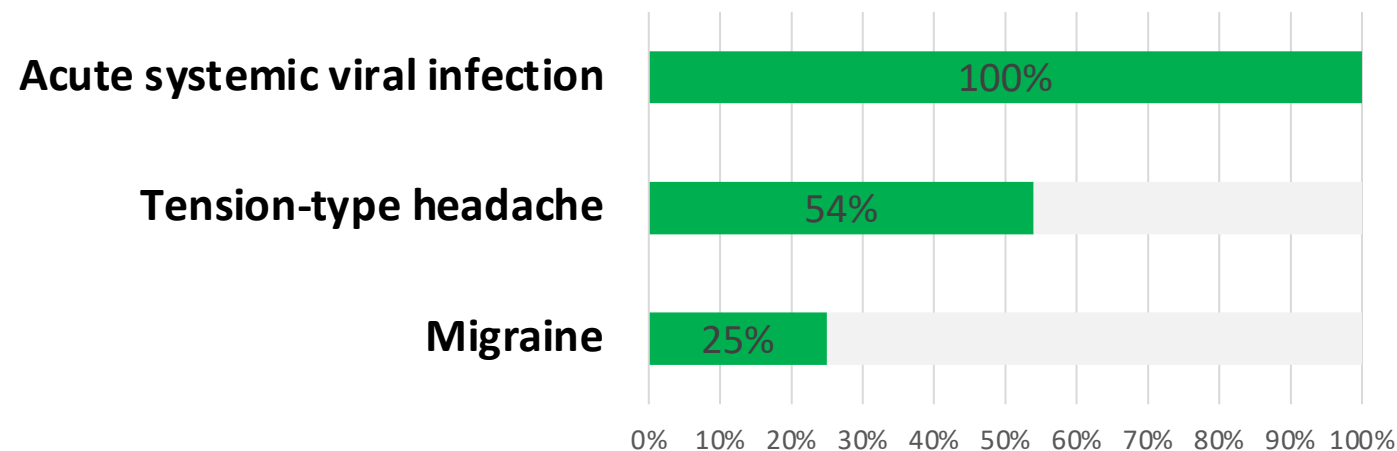


May 2020



n=106

Percentage of patients that fulfilled phenotypic ICHD-3 criteria for:

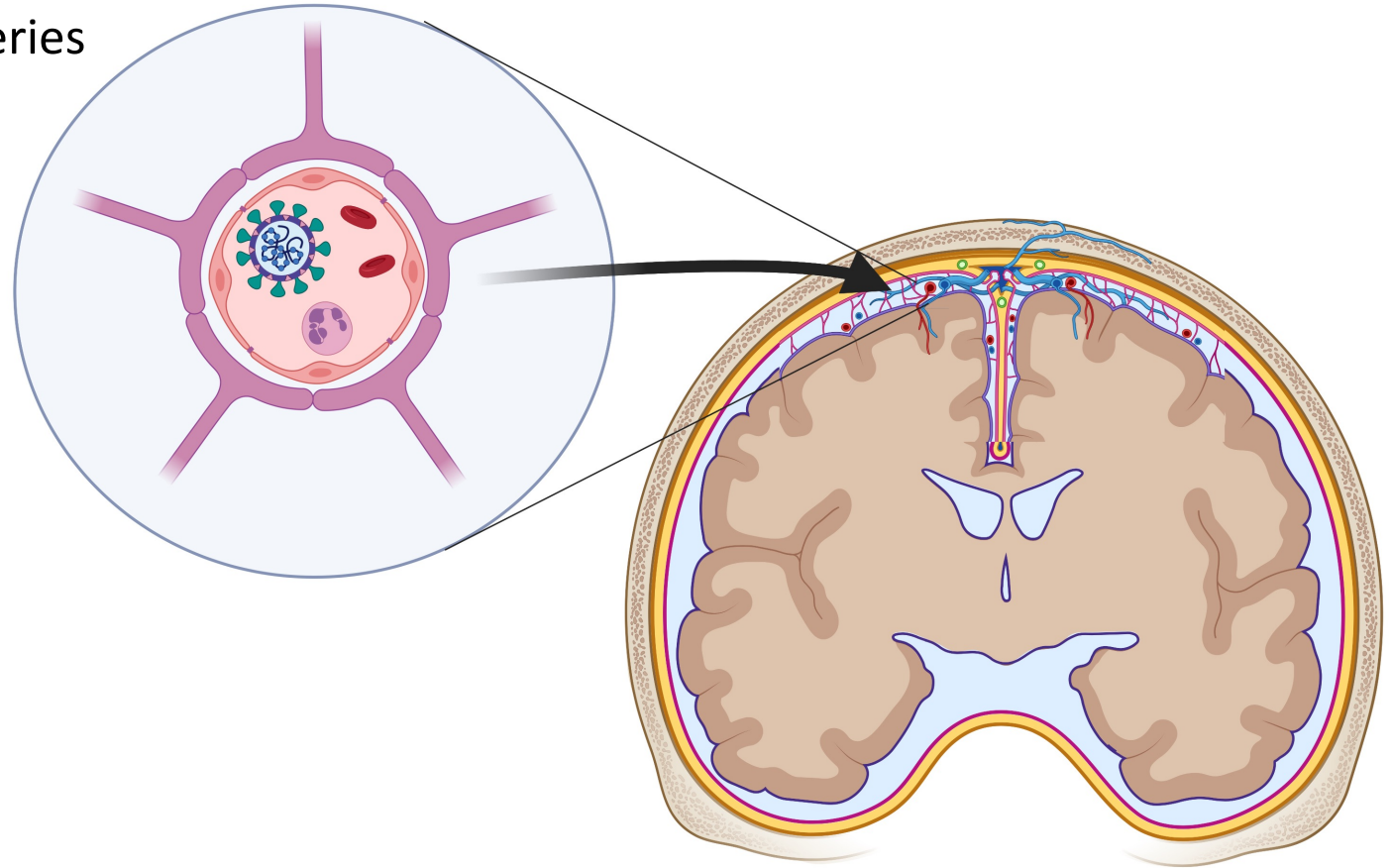




Which is the cause of
headache?

Does COVID-19 invade CNS? Positive PCR on CSF

- Not reported in most of the large series
- Few selected case reports
- *Neurotuturism?*



1. Mao *JAMA Neurol* 2020;
2. Romero-Sánchez. *Neurology* 2020
3. Moriguchi. *Int J Infect Dis* 2020
4. Helms. *N Engl J Med* 2020
5. Romoli. *Eur J Neurol* 2020
6. García-Azorín. *J Neurol Sci* 2020
7. Frontera. *J Neurol Sci* 2020

Demographical profile

| Author | García-Azorín | Magdy | Porta-Etessam | Membrilla | Caronna | Poncet-Megemont |
|----------------------------------|---------------|------------|---------------|-------------|----------------|-----------------|
| n | 458 | 172 | 112 | 99 | 97 | 82 |
| Age | 51 [42-61] | 33 [27-42] | 43 (SD: 11) | 43 (SD: 11) | 51 (SD: 15) | 47 (SD: 14) |
| Female sex | 72% | 63% | 81% | 36% | 67% | 67% |
| Prior history of headache | 49% | 53% | 27% | 33% | 20% (migraine) | NS |

1. García-Azorín. *Sci Rep* 2021
2. Magdy. *Cephalalgia* 2020
3. Porta-Etessam. *Headache* 2020
4. Membrilla. *Headache* 2020
5. Caronna. *Cephalalgia* 2020
6. Poncet-Megemont *Headache* 2020

July 2020


RESEARCH ARTICLE

Open Access

Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study



n=136

Javier Trigo¹, David García-Azorín^{1*} , Álvaro Planchuelo-Gómez², Enrique Martínez-Pías¹, Blanca Talavera¹, Isabel Hernández-Pérez¹, Gonzalo Valle-Peñacoba¹, Paula Simón-Campo¹, Mercedes de Lera¹, Alba Chavarría-Miranda¹, Cristina López-Sanz¹, María Gutiérrez-Sánchez¹, Elena Martínez-Velasco¹, María Pedraza¹, Álvaro Sierra¹, Beatriz Gómez-Vicente¹, Juan Francisco Arenillas^{1,3,4} and Ángel L. Guerrero^{1,3}

- Patients with headache **are different from** patients without headache
- The direct calculation **must be adjusted** for:
 - Age, sex, prior medical history, and other posible confounders.



Same prognosis?

Causes of the headache (n=576)

- 56 variables included in the univariate model¹.
 - 39 had a P value <0.1 → included in a multivariate model.
 - 11 variables were statistically significant.
 - 10 variables remained significant after adjusting for multiple comparisons by using False-Discovery Rate².

1. Trigo. *J Headache Pain* 2020
2. Benjamini. *Stat Soc Ser B* 1995

Causes

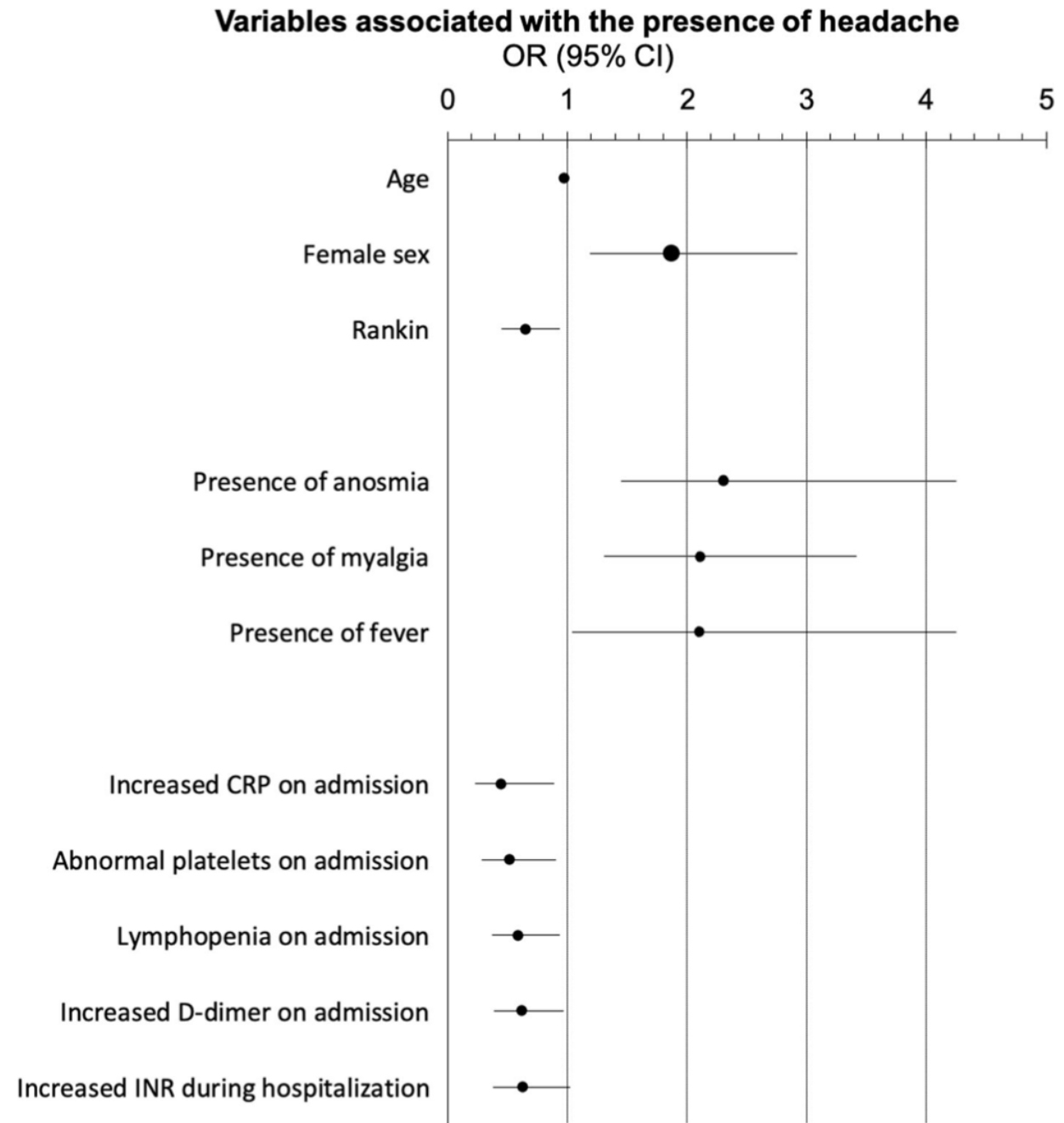


Fig. 1 Odds ratio and 95% confidence interval of variables associated with the presence of headache

RESEARCH ARTICLE

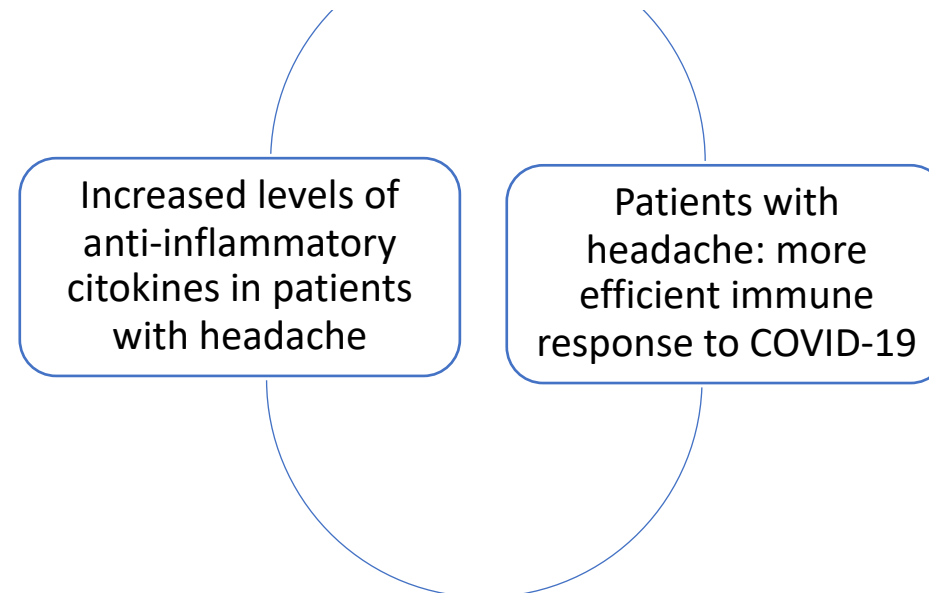
Open Access

Cytokine and interleukin profile in patients with headache and COVID-19: A pilot, CASE-control, study on 104 patients



n=104

Javier Trigo¹, David García-Azorín¹, Álvaro Sierra-Mencía¹, Álvaro Tamayo-Velasco², Pedro Martínez-Paz^{3*} , Eduardo Tamayo^{3,4}, Angel Luis Guerrero^{1,5} and Hugo Gonzalo-Benito⁶



Is the clinical **phenotype** of the headache
linked to the **severity** of the COVID-19?

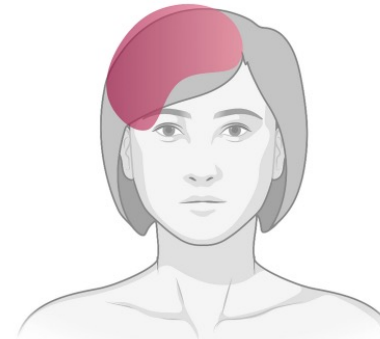


Deep Phenotyping of Headache in Hospitalized COVID-19 Patients *via* Principal Component Analysis

Álvaro Planchuelo-Gómez¹, Javier Trigo², Rodrigo de Luis-García¹, Ángel L. Guerrero^{2,3,4*}, Jesús Porta-Etessam⁵ and David García-Azorín^{2,3}

¹ Imaging Processing Laboratory, Universidad de Valladolid, Valladolid, Spain, ² Headache Unit, Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, ³ Neuroscience Research Unit, Institute for Biomedical Research of Salamanca, Salamanca, Spain, ⁴ Department of Medicine, Universidad de Valladolid, Valladolid, Spain, ⁵ Headache Unit, Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain

Migraine phenotype

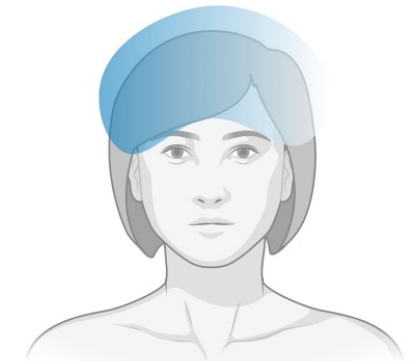


Pulsating quality

Frontal pain

Nausea

Tension-type headache phenotype



Pressing quality

Not
aggravated by
movement

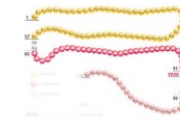
Laboratory parameters



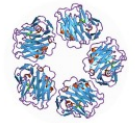
Decreased glomerular
filtration rate



Lymphopenia



Low Procalcitonin



Low C-reactive protein

FIGURE 5 | Summary of the laboratory tests (worst levels and values on admission) in association with headache phenotypes. Symptoms of migraine and TTH were linked to laboratory biomarkers of COVID-19 status.

- Migraine-like phenotype → correlated with:
 - More severe clinical course
 - Altered inflammatory markers
 - Higher intensity and disability



How frequent is headache
after COVID-19?

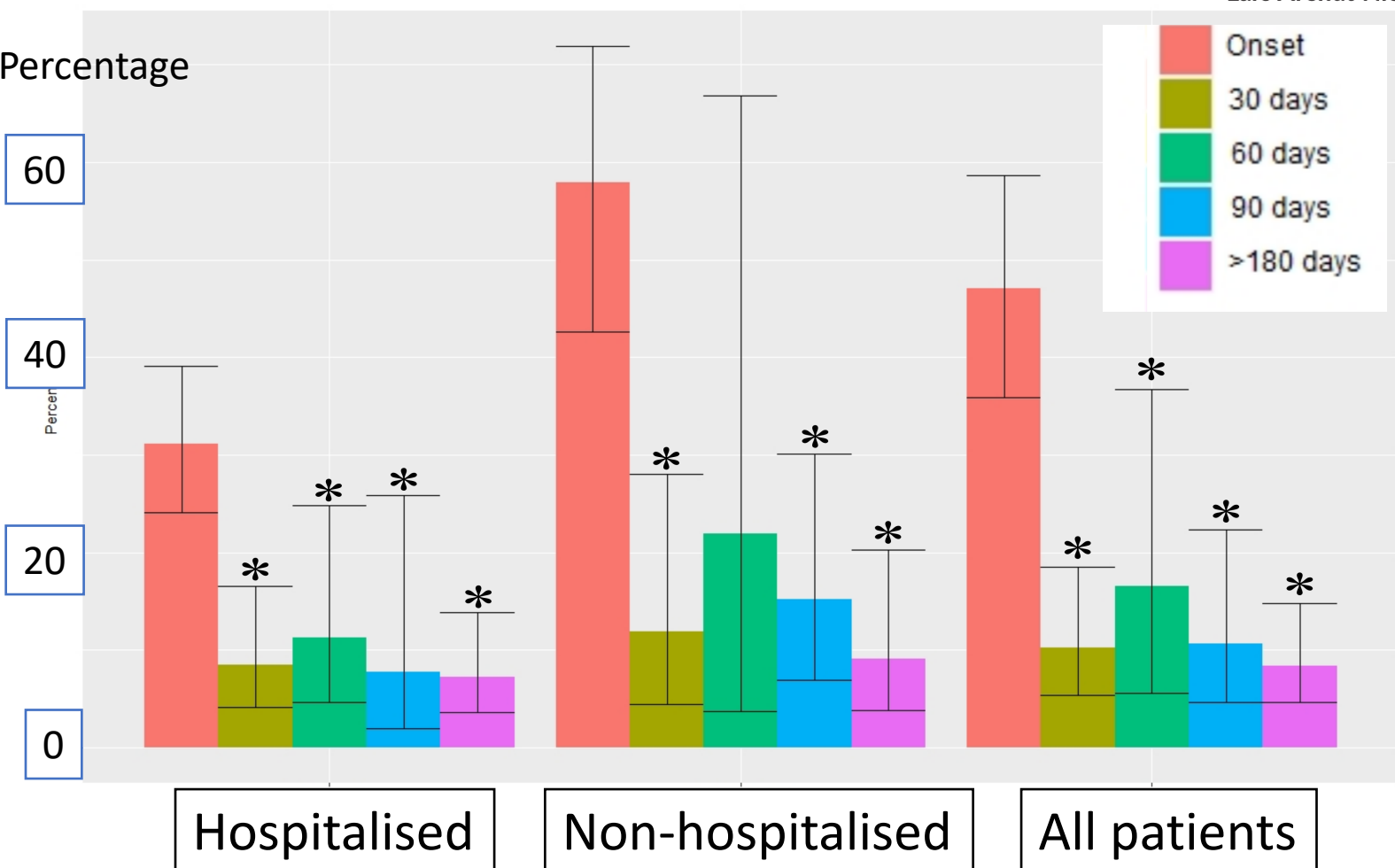
SHORT COMMUNICATION

- As of July 2021
- 35 studies
- N=28.438 COVID survivors
- 6 months

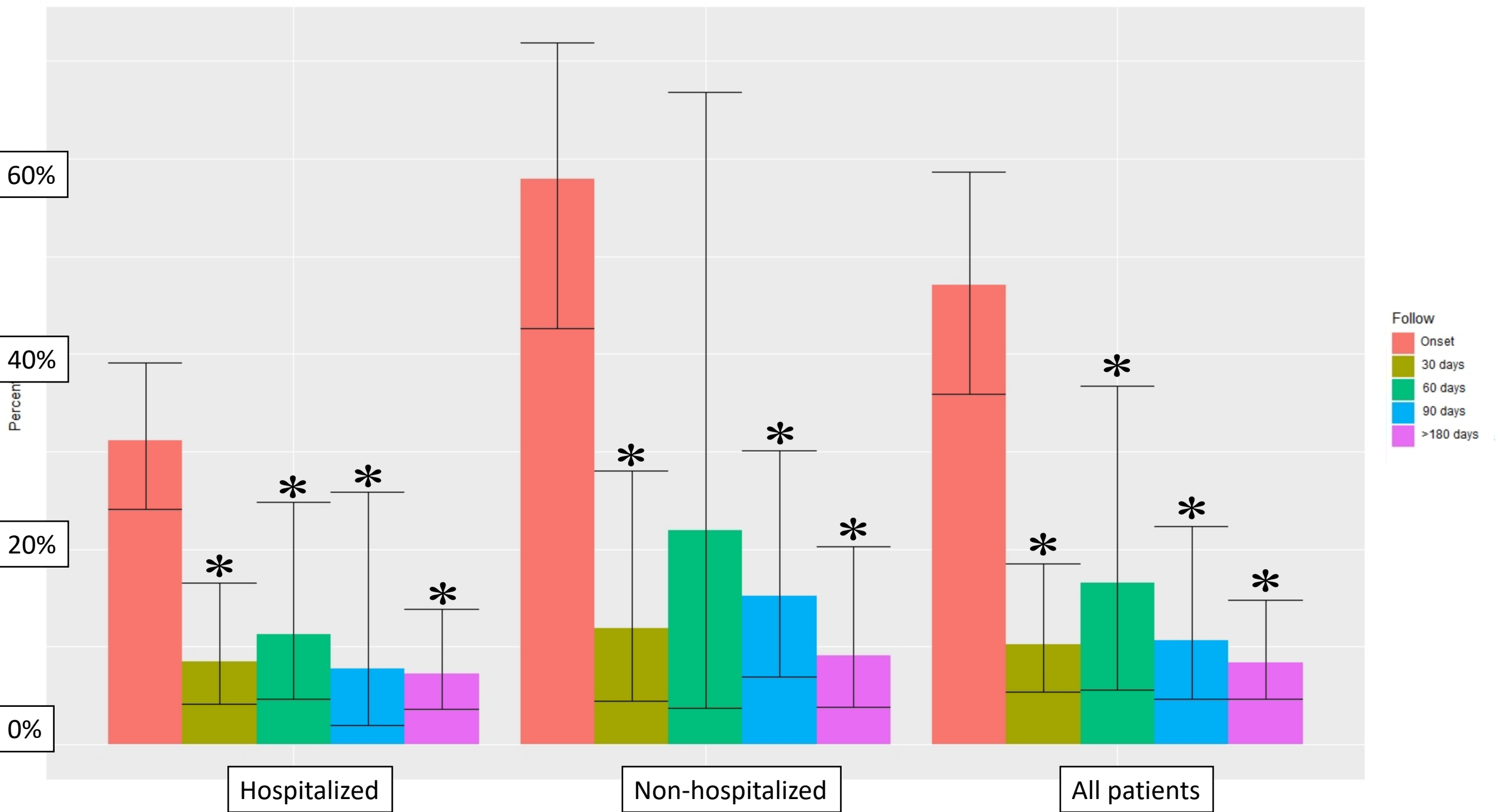
Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: A meta-analysis of the current literature

César Fernández-de-las-Peñas^{1,2} | Marcos Navarro-Santana³ |
Víctor Gómez-Mayordomo⁴ | María L. Cuadrado^{4,5} | David García-Azorín^{6,7} |
Lars Arendt-Nielsen^{2,8} | Gustavo Plaza-Manzano^{3,9}

1. Department of Neurology, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain
2. Department of Neurology, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain
3. Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark
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5. Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
6. Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
7. Institute for Biomedical Research of Salamanca, Salamanca, Spain
8. Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
9. Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain



Between 10-20% of COVID patients present headache during post-COVID



Post-COVID-19 persistent headache: A multicentric 9-months follow-up study of 905 patients

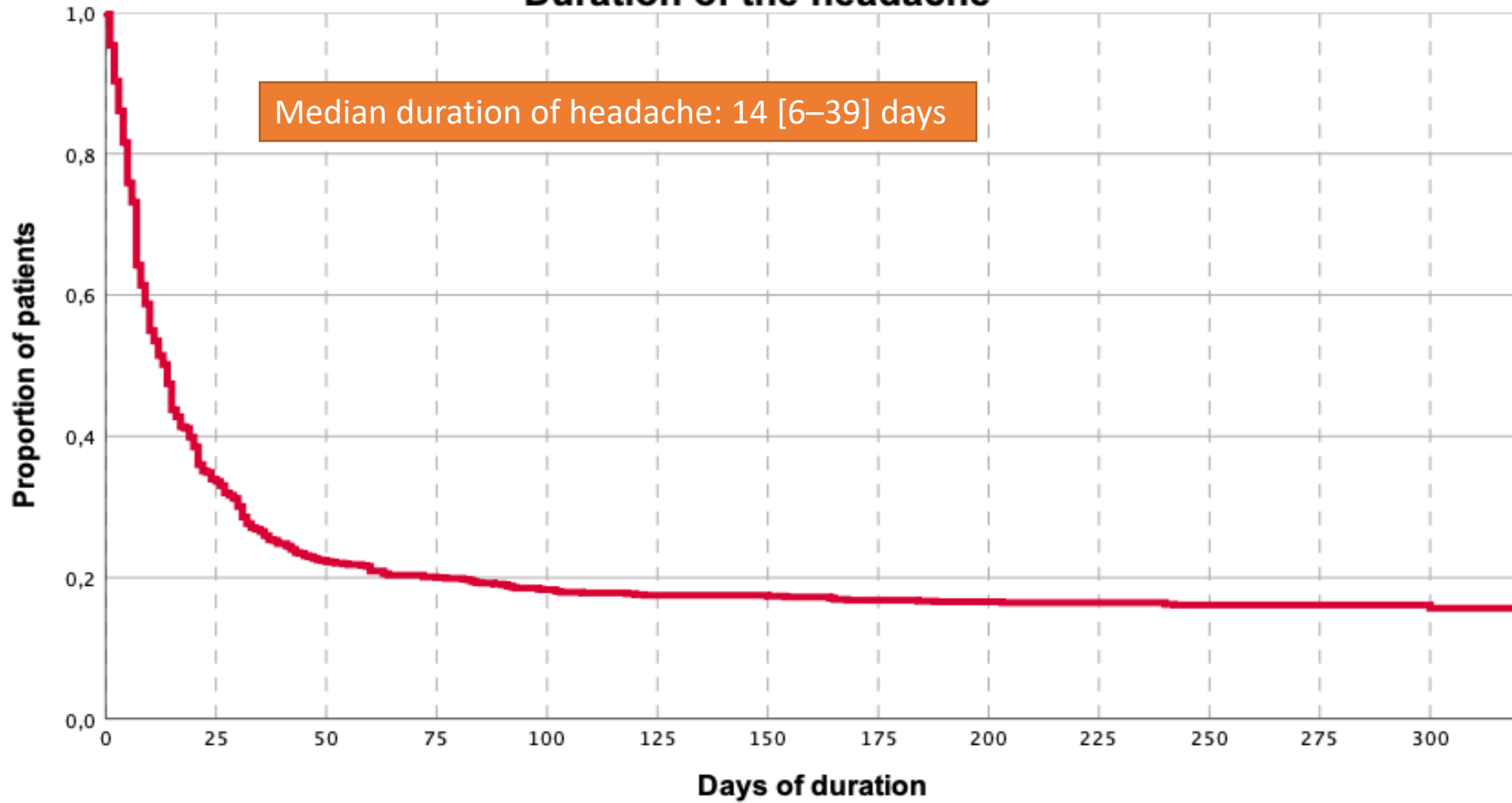
Cephalalgia 0(0) 1-6 © International Headache Society 2022 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/03331024211068074 journals.sagepub.com/home/cep SAGE

David Garcia-Azorin¹, Almudena Layos-Romero², Jesús Porta-Etessam^{3,4,5}, Javier A Membrilla^{6,7}, Edoardo Caronna^{8,9}, Alicia Gonzalez-Martinez¹⁰, Álvaro Sierra Mencía¹, Tomás Segura², Nuria Gonzalez-García^{3,4,5}, Javier Díaz-de-Terán^{6,7}, Víctor J Gallardo⁹, Ana Beatriz Gago-Veiga¹⁰, Alejandro Ballvé⁸, Javier Trigo López¹, María Sastre-Real^{6,7}, Arnau Llauro⁸, Ana Cornejo¹¹, Iñigo de Lorenzo^{6,7}, Ángel Guerrero-Peral^{1,12} and Patricia Pozo-Rosich^{8,9}

- May-April 2020 → 9 months follow-up
• Data from 6 cohorts
• Hospitalized and non-hospitalized



Duration of the headache



N=905

| Days | 0 | 25 | 50 | 75 | 100 | 125 | 150 | 175 | 200 | 225 | 250 | 275 | 300 |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Number of patients | 874 | 296 | 195 | 175 | 160 | 153 | 152 | 147 | 144 | 143 | 141 | 141 | 140 |

Duration of the headache



N=905

| | | | | | | | | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Days | 0 | 25 | 50 | 75 | 100 | 125 | 150 | 175 | 200 | 225 | 250 | 275 | 300 |
| Number of patients | 874 | 296 | 195 | 175 | 160 | 153 | 152 | 147 | 144 | 143 | 141 | 141 | 140 |

Predictors of more prolonged duration

| Variable | OR | 95% CI |
|-----------------------------------|------|-----------|
| Female sex | 0.85 | 0.74-0.98 |
| Headache intensity | 0.62 | 0.56-0.69 |
| Pressing quality of the headache | 1.29 | 1.18-1.48 |
| Throbbing quality of the headache | 0.76 | 0.64-0.8 |
| Photophobia / Phonophobia | 0.83 | 0.72-0.95 |
| Worsening by physical activity | 0.82 | 0.71-0.94 |



**Is migraine a risk factor
for persistent post-COVID
headache?**



Previous History of Migraine Is Associated With Fatigue, but Not Headache, as Long-Term Post-COVID Symptom After Severe Acute Respiratory SARS-CoV-2 Infection: A Case-Control Study



César Fernández-de-las-Peñas^{1*}, Víctor Gómez-Mayordomo², David García-Azorín^{3,4}, Domingo Palacios-Ceña¹, Lidiane L. Florencio¹, Angel L. Guerrero^{3,4,5}, Valentín Hernández-Barrera⁶ and María L. Cuadrado^{2,7}

February-
may 2020



n=201

57 patients with migraine+ 144 controls.
Evaluated 7 months after the acute phase



COVID patients with prior
history of migraine



Higher frequency of post-COVID symptoms
Higher frequency of fatigue

No higher frequency of post-COVID headache

The presence of headache at onset in SARS-CoV-2 infection is associated with long-term post-COVID headache and fatigue: A case-control study

Cephalalgia
0(0) 1–10

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DOI: 10.1177/03331024211020404

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n=615



César Fernández-de-las-Peñas¹ ,
Víctor Gómez-Mayordomo² , **María L Cuadrado^{2,3}** ,
Domingo Palacios-Ceña¹, **Lidiane L Florencio¹**,
Angel L Guerrero^{4,5,6} , **David García-Azorín^{4,5}** ,
Valentín Hernández-Barrera⁷ and **Lars Arendt-Nielsen⁸**

205 patients with headache vs 410 controls.
Evaluated 7 months after the acute phase



Headache during COVID



Higher frequency of symptoms during post-COVID
Higher frequency of fatigue during post-COVID
Presence of headache with a tensión-type phenotype

What is the effect of
vaccination on post-
COVID headache?



- Patients that had **COVID** after being adequately **vaccinated** and had **headache** during the acute phase
- N=104

Non vaccinated (n=350)
Vaccinated (n=104)

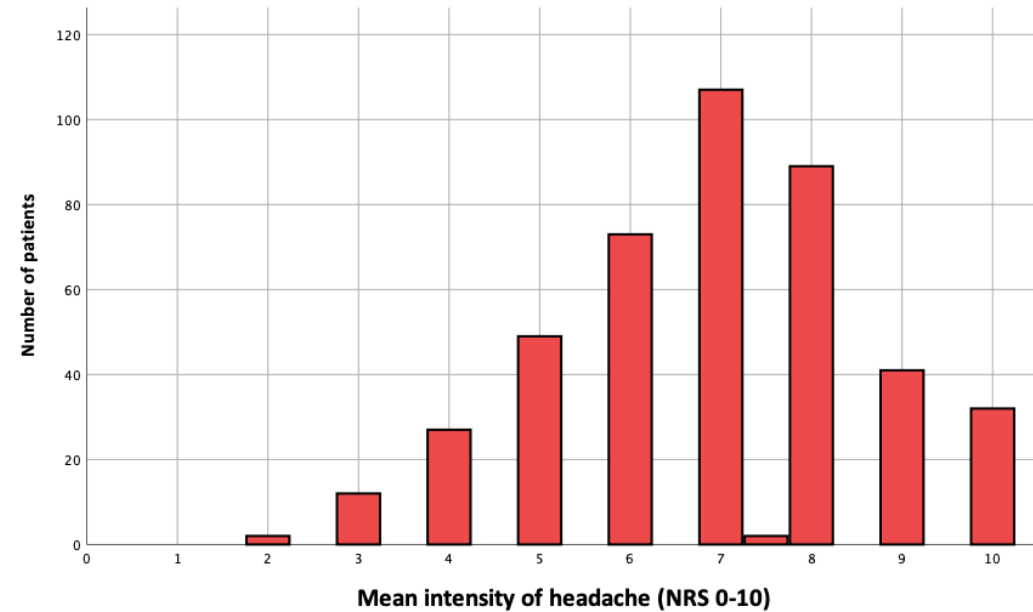
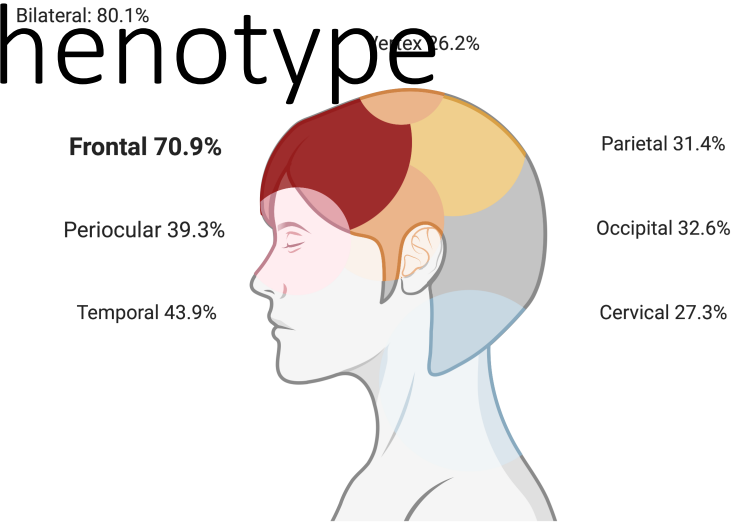
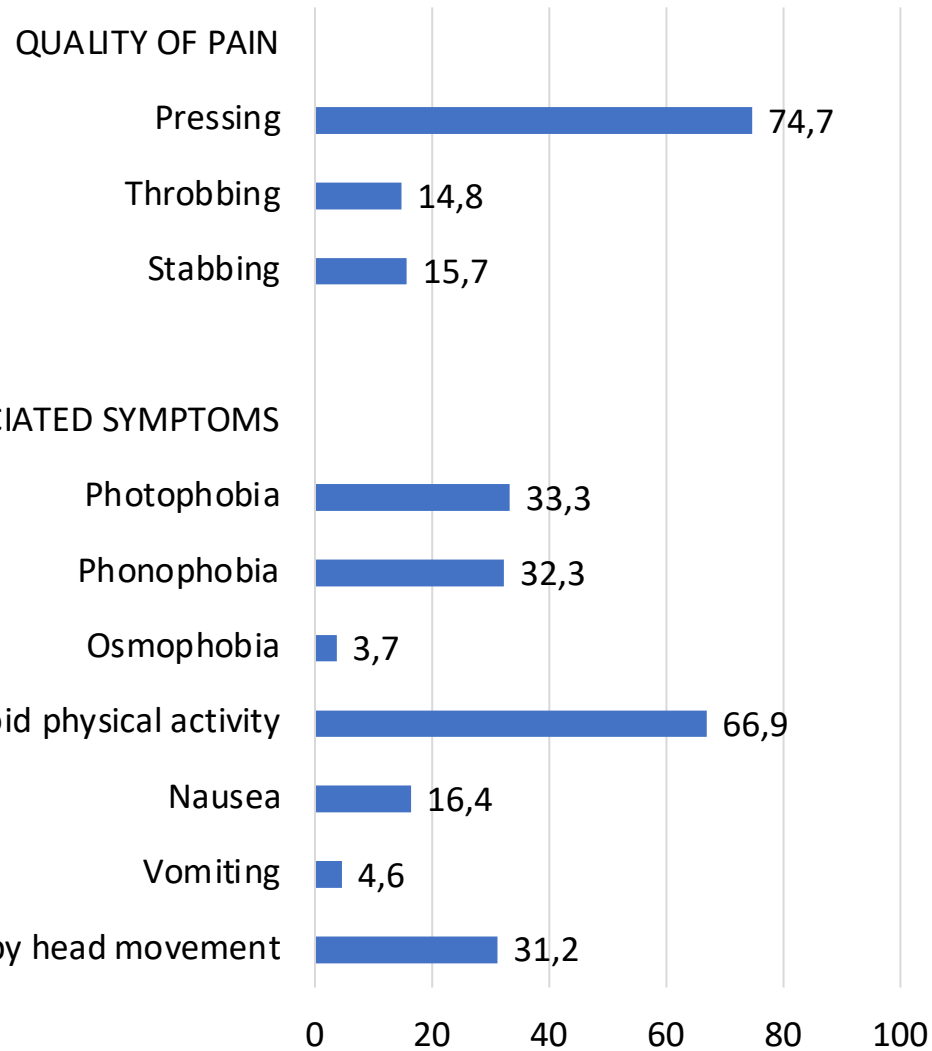
Duration of 4 [IQR: 2-8] days in vaccinated vs. 8 [IQR 4-21] days in non-vaccinated, ($p < 0,001$).



Treatment?

What about post-COVID
headache **treatment**?

Remember the clinical phenotype





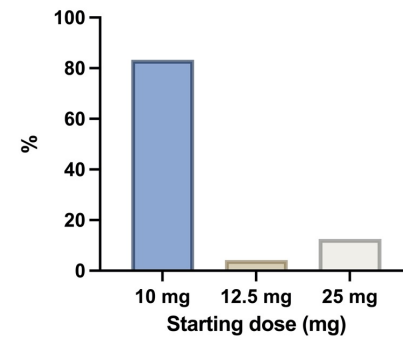
March-
April 2021



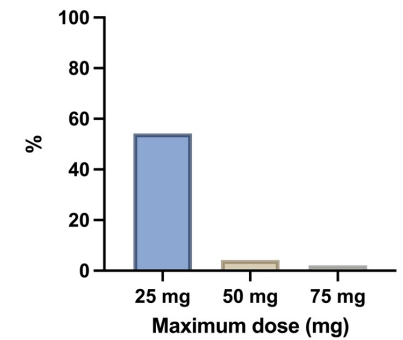
n=48

N=48 patients treated with amitriptyline

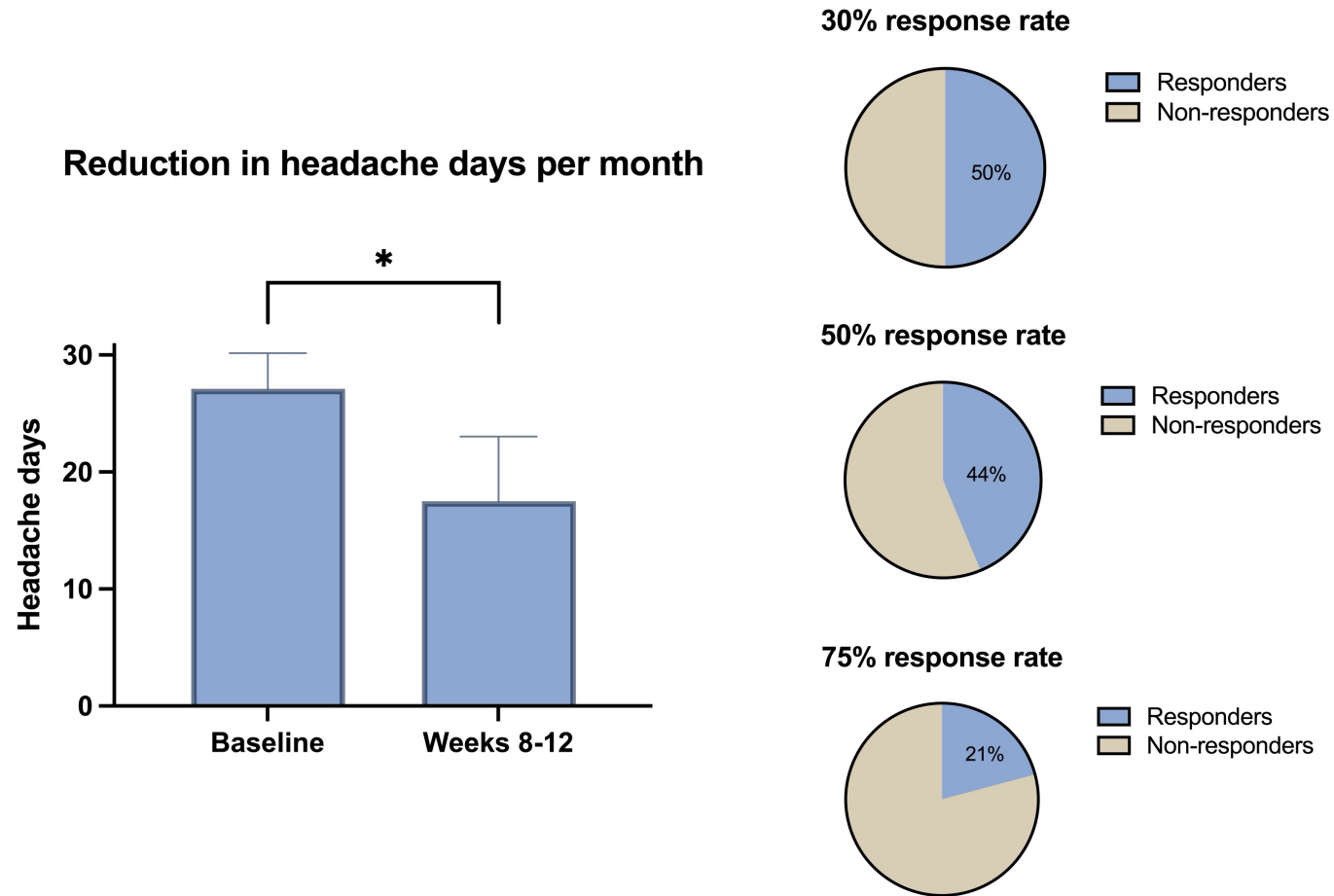
AMT starting dose



AMT maximum dose



Response to amitriptyline

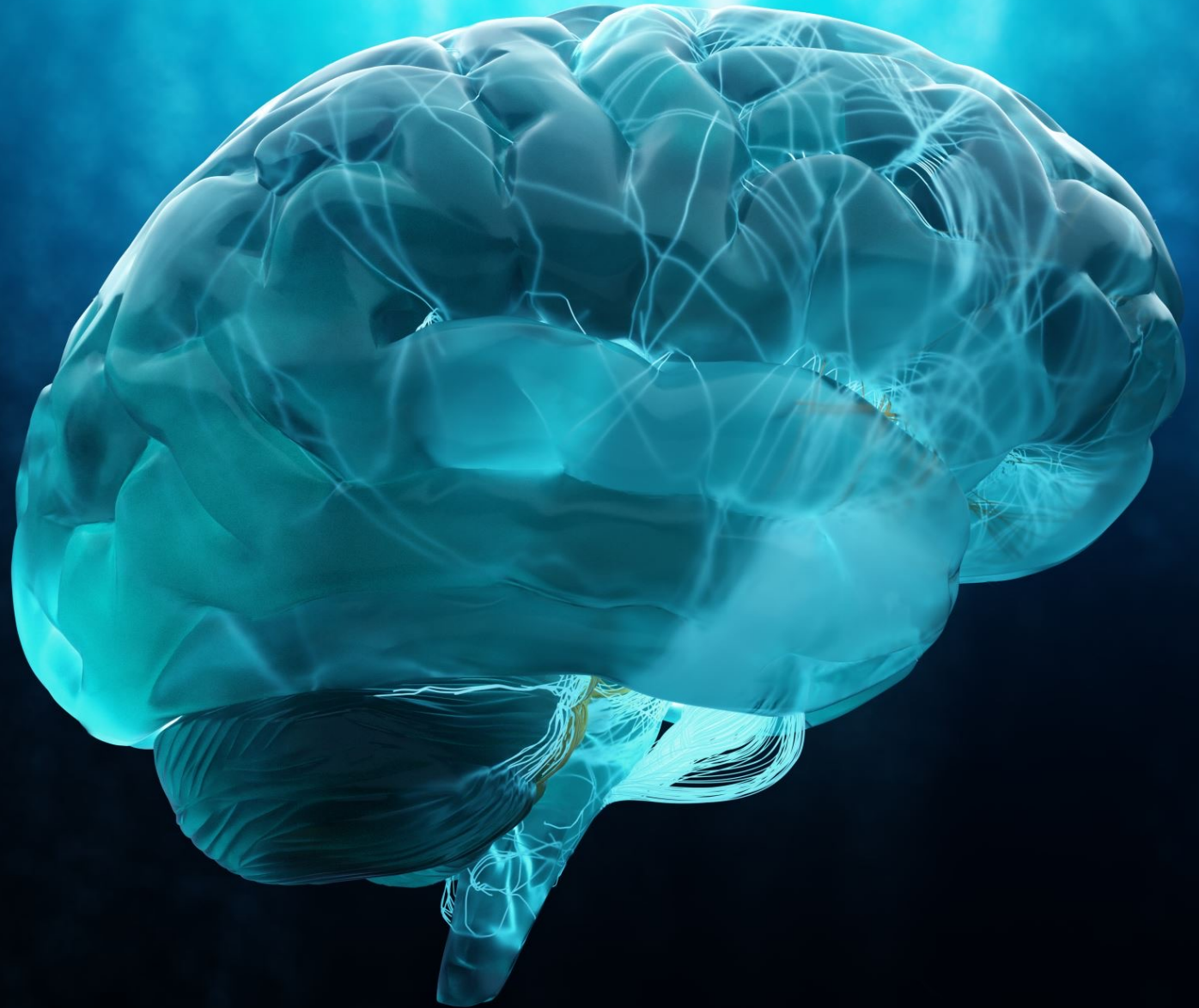


Predictors of amitriptyline response

| VARIABLE | ANÁLISIS | OR | 95% CI LOWER LIMIT, CI UPPER LIMIT | P VALUE |
|--|--------------|--------|------------------------------------|---------|
| Months from COVID-19 to treatment | Univariate | -0.641 | (-1.402, -0.042) | 0.036* |
| | Multivariate | -0.429 | (-1.253, 0.395) | 0.299 |
| Prior history of TTH | Univariate | 11.535 | (1.555, 21.515) | 0.024* |
| | Multivariate | 10.966 | (1.316, 20.617) | 0.027* |
| Prior history of anxiety or depression | Univariate | 7.862 | (0.558, 15.167) | 0.035* |
| | Multivariate | 2.778 | (-4.661, 10.216) | 0.455 |
| Prior history of insomnia | Univariate | 7.037 | (-0.342, 14.415) | 0.061 |
| | Multivariate | 1.687 | (-5.916, 9.290) | 0.656 |
| Nausea | Univariate | -9.531 | (-15.756, -3.307) | 0.003* |
| | Multivariate | -8.547 | (-14.624, -2.470) | 0.007** |
| Initial dose of Amitriptyline (mg) | Univariate | -0.633 | (-1.257, -0.009) | 0.047* |
| | Multivariate | -0.322 | (-0.909, 0.265) | 0.275 |



What happens in the brain of patients with persistent post-COVID headache?





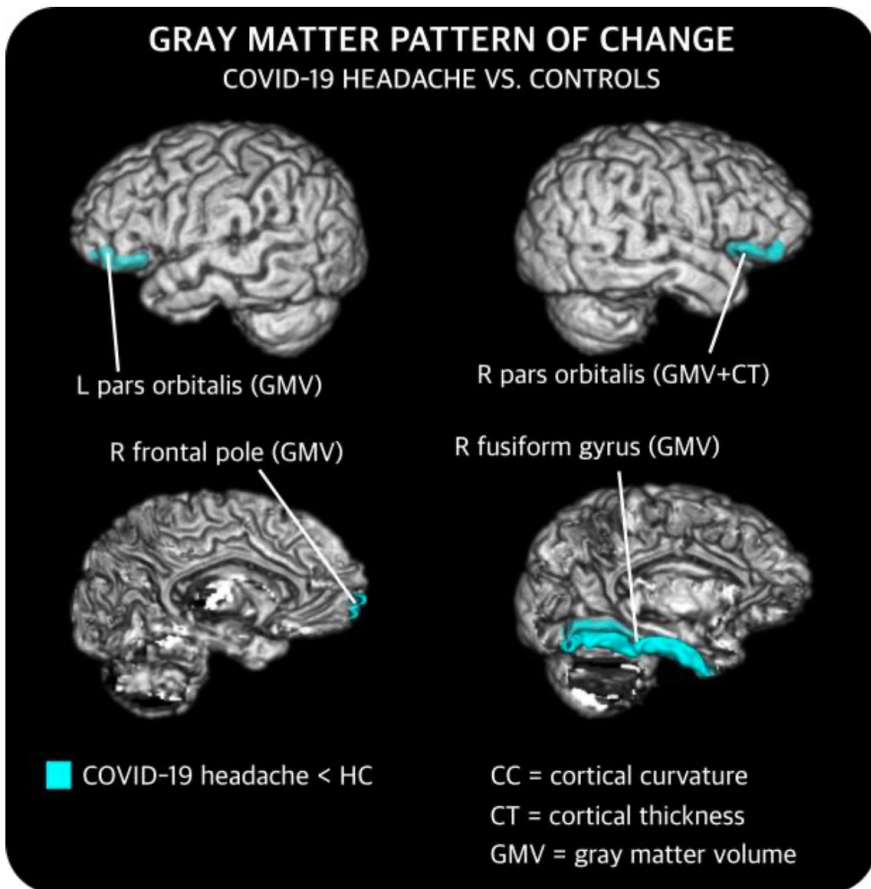
Structural brain changes in patients with persistent headache after COVID-19 resolution

Álvaro Planchuelo-Gómez^{1,2}  · David García-Azorín^{3,4}  · Ángel L. Guerrero^{3,4}  · Margarita Rodríguez⁵  · Santiago Aja-Fernández¹  · Rodrigo de Luis-García¹ 

Received: 10 August 2022 / Revised: 21 September 2022 / Accepted: 22 September 2022
© The Author(s) 2022

- n=42 patients with persistent post-COVID headache (6 months) with no prior history of headache
- n=42 healthy controls (prior to COVID era)
- n=43 episodic migraine patients (prior to COVID era)
- n=43 chronic migraine patients (prior to COVID era)

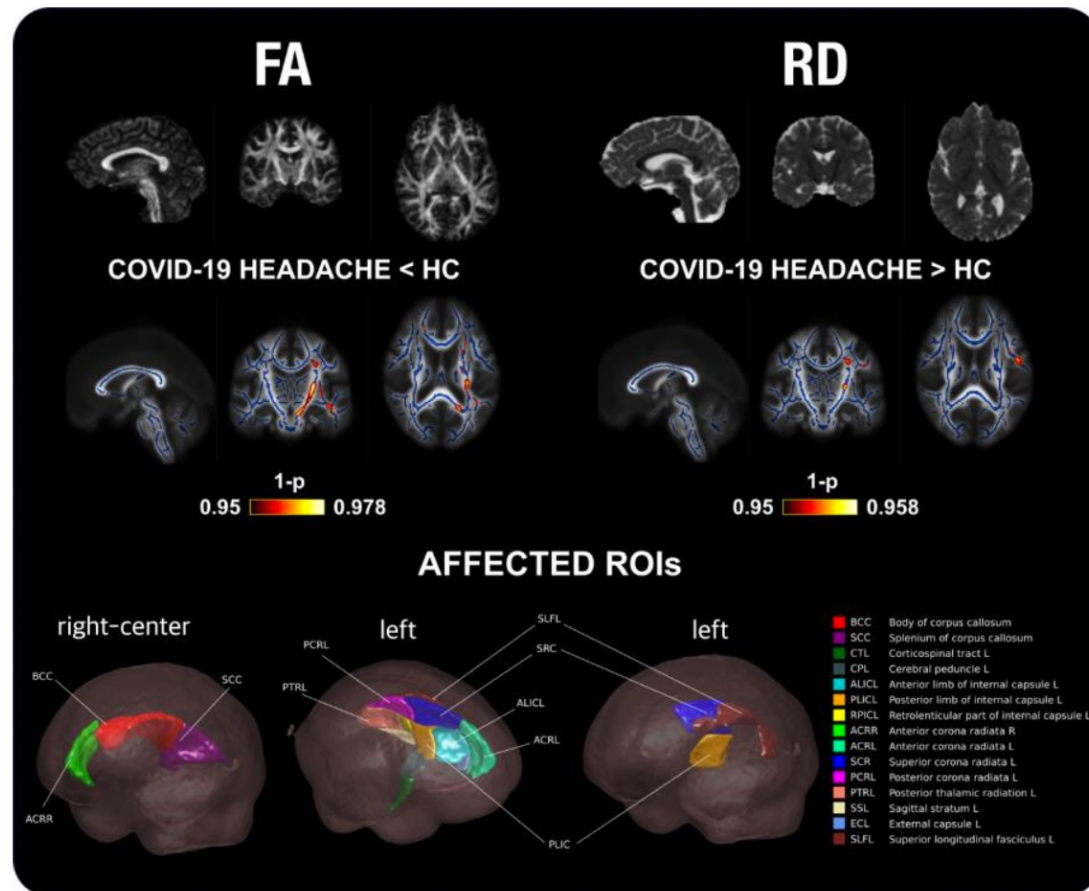
Structural brain changes in patients with persistent post-COVID headache



| Desikan-Killiany atlas | HC | | | | EM | | | | CM | | | |
|---|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| | CC | CT | SA | GMV | CC | CT | SA | GMV | CC | CT | SA | GMV |
| L banks of the superior temporal sulcus | | | | | | | | | | 0.79 | | |
| L caudal middle frontal | | | | | | | | | | | | 0.68 |
| L cuneus | | | | | | | | | 0.79 | | | |
| L paracentral | | | | | | 0.78 | | | | 0.79 | | 0.59 |
| L pars orbitalis | | | | 0.67 | | | | | | | | |
| L rostral anterior cingulate | | 0.74* | | | | | | | | | | |
| L posterior cingulate | | | | | | | | | | | | 0.54 |
| L accumbens | | | | | | | | 0.64 | | | | |
| R thalamus | | | | | | | | 0.50 | | | | |
| R fusiform | | | | 0.64 | | | | | | | | |
| R pars orbitalis | | 0.76 | | 0.59 | | | | | | | | |
| R precuneus | | | | | | | | | 0.76 | | | |
| R frontal pole | | | | 0.66 | | | | | | | | |
| Total | 0 | 2 | 0 | 4 | 0 | 1 | 0 | 2 | 2 | 2 | 0 | 3 |

■ COV <
■ COV >
■ Right
■ Left

Structural brain changes in patients with persistent post-COVID headache



Widespread white matter changes, with a pattern that resembles that of migraine, but more subtle.

Questions



Are these changes COVID-specific? Headache-specific?



Is the headache-phenotype relevant?



Are the changes persistent?

Neurological symptoms following vaccination to prevent COVID-19



Vaccination may be associated with neurological manifestations

- 1 CVT per 100,000-1,000,000 non-replicant adenovirus vector-based vaccines¹
- 227 cases of GBS out of 51M doses of AstraZeneca vaccine²
- But **COVID is even worse:**
 - RR CVT in COVID: 14.3 (95% CI: 3.9-36.8) to 1589 (95% CI: 192-5740)^{3, 4}
 - RR Guillain-Barré syndrome in COVID: 6.30 (95% CI: 3.2-12.5)⁵

CVT: Cerebral Venous Thrombosis, GBS: Guillain-Barre syndrome, M: Million, RR: Relative risk, CI: Confidence Interval.

1. WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

2. European Medicines Agency. Pharmacovigilance Risk Assessment Committee meeting 5-8 July 2021.

3. Mahammedi A. Brain and Lung Imaging Correlation in Patients with COVID-19: Could the Severity of Lung Disease Reflect the Prevalence of Acute Abnormalities on Neuroimaging? A Global Multicenter Observational Study. *AJNR Am J Neuroradiol.* 2021 Jun;42(6):1008-1016. doi: 10.3174/ajnr.A7072. Epub 2021 Mar 11. PMID: 33707278; PMCID: PMC8191655.

4. Koh JS. Neurology of COVID-19 in Singapore. *J Neurol Sci.* 2020 Nov 15;418:117118. doi: 10.1016/j.jns.2020.117118. Epub 2020 Sep 3. Erratum in: *J Neurol Sci.* 2021 May 15;424:117406. PMID: 32977228; PMCID: PMC7470792.

5. SIESTA (Spanish Investigators in Emergency Situations Team) network. Incidence, clinical, risk factors and outcomes of Guillain-Barré in Covid-19. *Ann Neurol.* 2021 Mar;89(3):598-603.

Thrombosis with thrombocytopenia syndrome

1. TTS is a rare syndrome observed following non-replicant adenovirus vector-based vaccines
2. 1 case per 100,000-1,000,000 vaccine doses
 1. 1st dose, > Younger patients
3. Caused by anti-platelet factor 4 antibodies

WHO classification of TTS



Thrombosis

Uncommon location

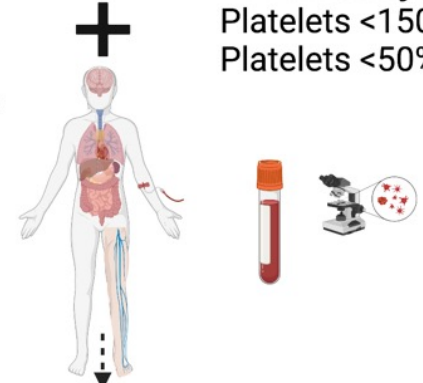
Cerebral venous sinus thrombosis
Splanchnic thrombosis
Multiple organs

Common location

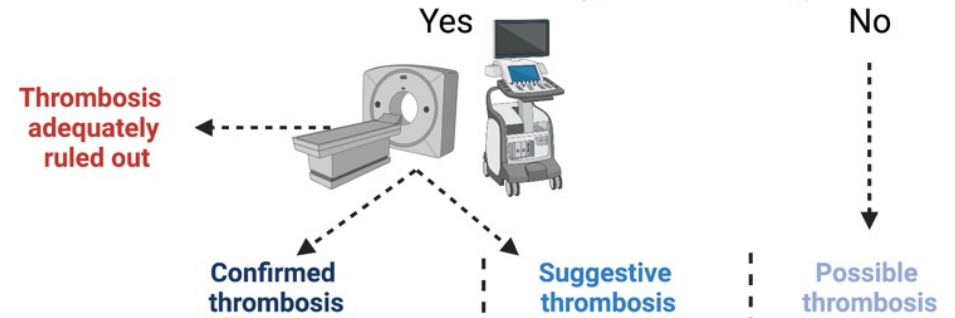
Ischemic stroke
Pulmonary embolism
Myocardial infarction
Deep vein thrombosis

Thrombocytopenia

Platelets $<150 \times 10^9/L$
Platelets $<50\%$ baseline



Imaging studies available?



Uncommon location | Common location

| | | | | |
|--|----------------------|---------------------|---------------------|---------------------|
| Severe thrombocytopenia Platelets $<50 \times 10^9/L$ | Confirmed TTS | Probable TTS | Possible TTS | Possible TTS |
| Mild-to-moderate thrombocytopenia Platelets $<150 \times 10^9/L$ | Probable TTS | Possible TTS | Possible TTS | Possible TTS |

WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

TTS Work-up

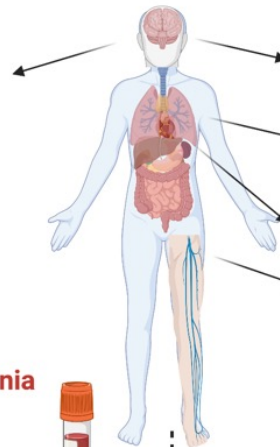
Vaccination against COVID-19 in the last 30 days



Clinical suspicion of thrombosis

Pre-TTS syndrome

Delayed-onset headache with progressive worsening, resistance to treatment, worsening with supine position, exertion or coughing



Uncommon location thrombosis

Cerebral venous sinus thrombosis: headache, visual disturbances, seizures, focal neurological symptoms, decreased level of consciousness

Splanchnic thrombosis: abdominal pain, bloating, nausea, vomiting, diarrhoea, fever, bleeding, anorexia

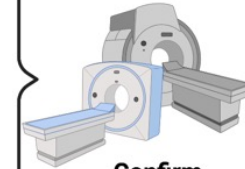
Common location thrombosis

Ischemic stroke: sudden onset focal neurological symptoms of cerebral origin

Pulmonary embolisms: dyspnea, chest pain, haemoptysis, syncope, palpitations, sudden impairment of physical performance

Myocardial infarction: chest pain, shortness of breath, cyanosis, sudden death

Limb vein thrombosis: unilateral or bilateral swelling, pain, tenderness, redness



Confirm diagnosis of thrombosis by imaging, pathology or surgery

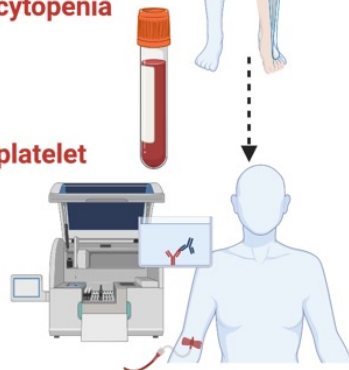
Laboratory work-up

Evaluation of thrombocytopenia

Platelet count
Platelets $<150 \times 10^9/L$
Platelets $<50\%$ baseline

Determination of anti-platelet factor 4 antibodies

ELISA
Not with rapid tests

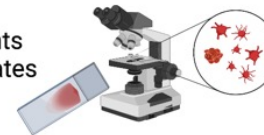


Other supporting laboratory parameters

D-dimer $> 4000 \mu g/L$ FEU

Peripheral smear

Reduced platelet counts
Small platelet aggregates
No platelet clumping



Early treatment

Clinical suspicion of thrombosis and diagnosis confirmation

Laboratory diagnosis of thrombocytopenia and TTS

Treatment of TTS



Patients should be hospitalized and closely monitored



Avoid platelet transfusions

In all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe, and platelet transfusion is required to be able to proceed with emergency surgery



Avoid heparin based anticoagulation

For individuals with TTS following vaccination with a COVID-19 vaccine



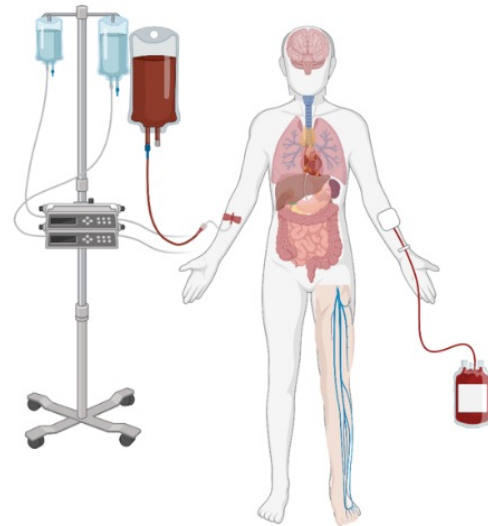
Administer non-heparin based anticoagulants

Argatroban, bivalirudine, fondaparinux, danaparoid, rivaroxaban, apixaban, dabigatran



Consider IV Immunoglobulins

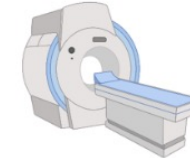
1 g/kg x 2 days or 0.4g/kg x 5 days



PCR test for COVID-19



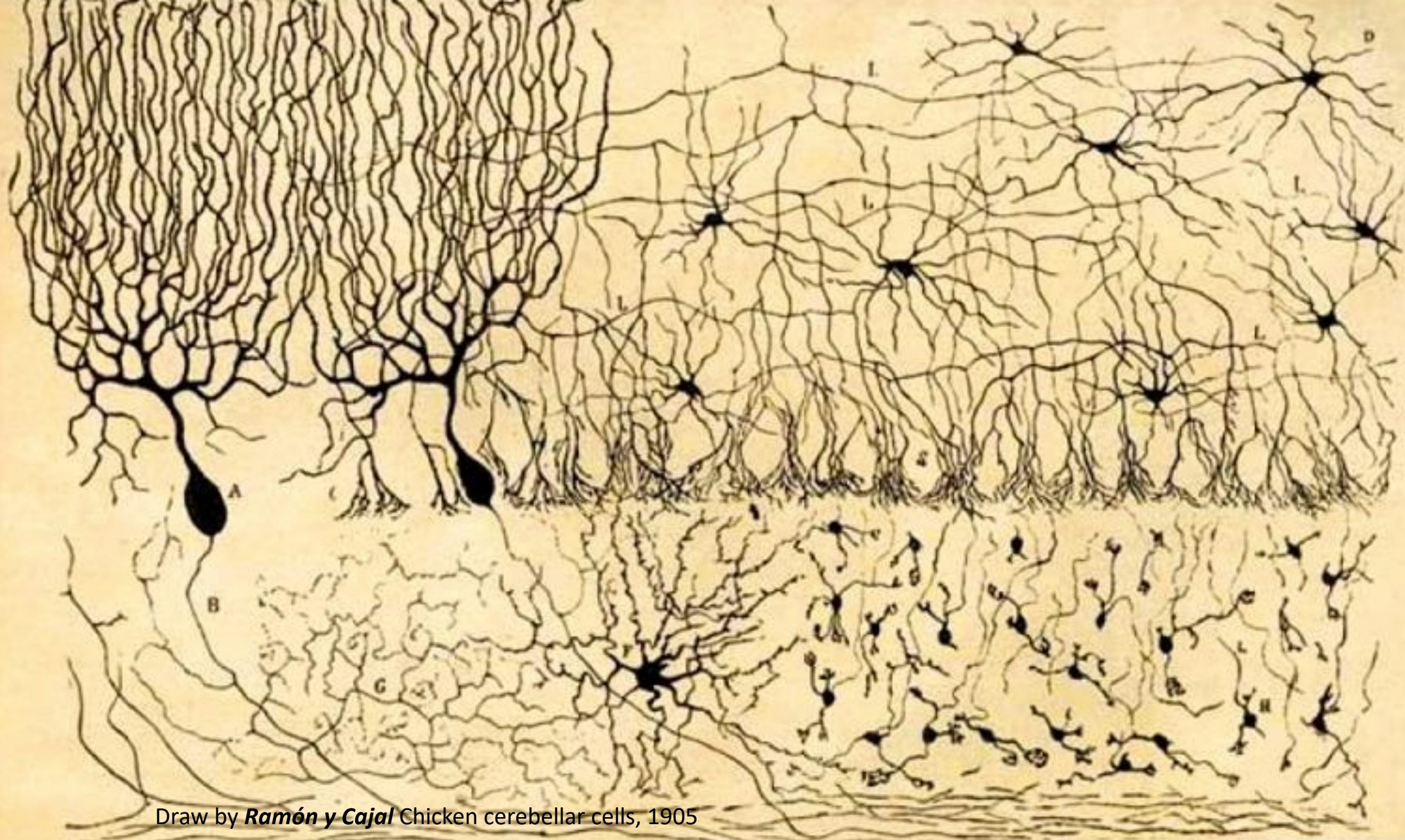
Monitor platelet count



Complete examinations per patient



Report the case



Draw by **Ramón y Cajal** Chicken cerebellar cells, 1905

Conclusions

1. COVID is polymorph: Include it in the differential diagnosis
2. Symptoms can be related with the virus, the immune response or the presence of systemic complications
3. Manifestations may arise after the acute phase or persist
4. Do treat the treatable manifestations



Thank you!

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