

Sociedad Española de Neurología
Fundada en 1949



Neuro-COVID: an infectious and non-infectious nervous system disease

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Secondary Headache, Special Interest Group, International Headache Society

Infectious diseases panel, European Academy of Neurology

International Area, Spanish Society of Neurology

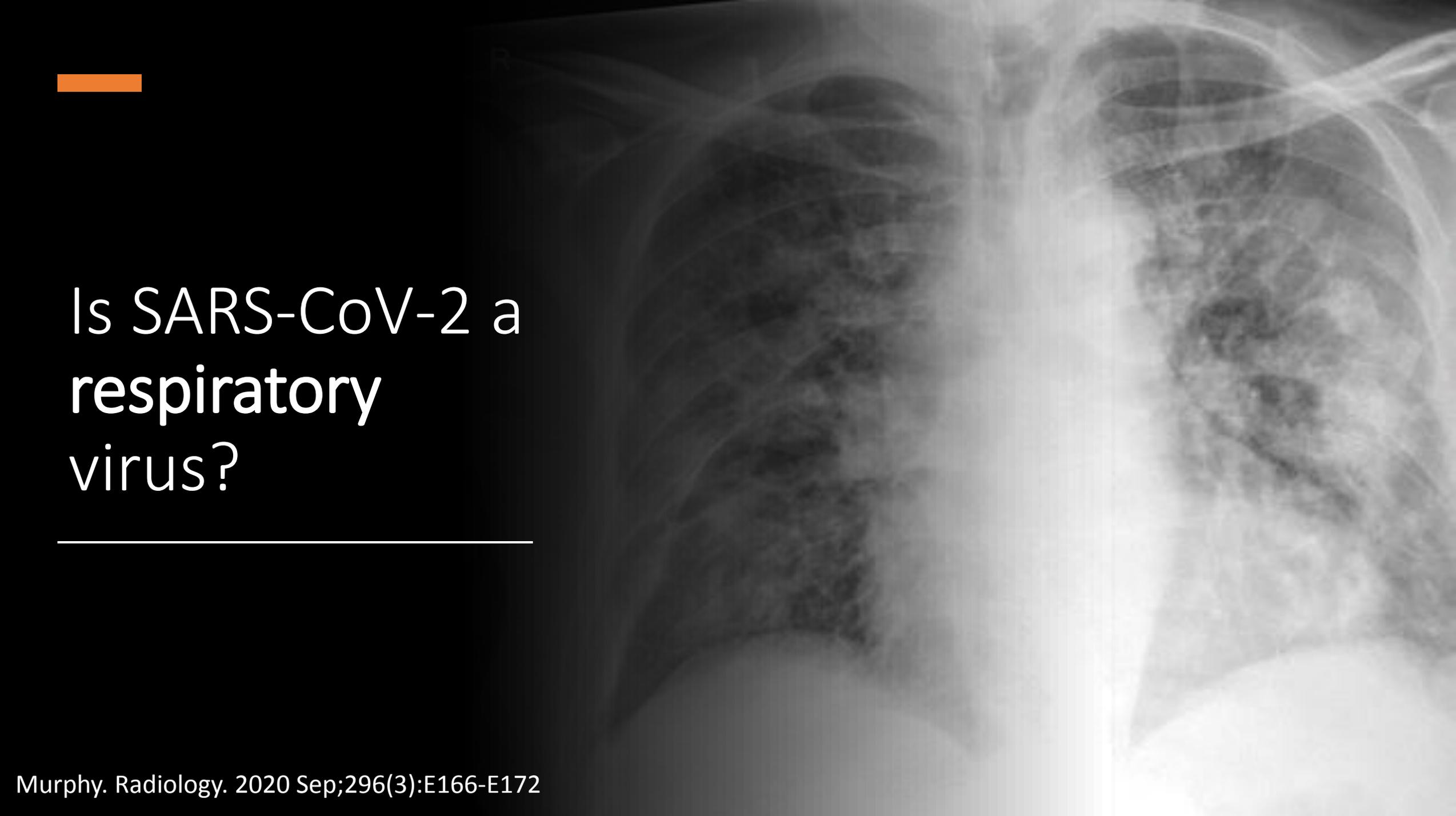


Disclosure

Clinical trials	Speaker honoraria	Events and travel support	Research projects
Teva, Eli Lilly, Amgen, Novartis, Allergan, Lundbeck	Teva, Novartis, Allergan, Chiesi, Eli Lilly	European Academy of Neurology, Teva, Allergan, Novartis, Eli Lilly	World Health Organization, International headache Society, Regional Health Administration Castilla y Leon, Spanish Society of Neurology

Outline: 4 questions – 10 statements

- Is SARS-CoV-2 a **respiratory** virus?
- Why are neurological symptoms so diverse?
- Which symptoms can be considered as non-infectious?
- How can we treat/prevent COVID?



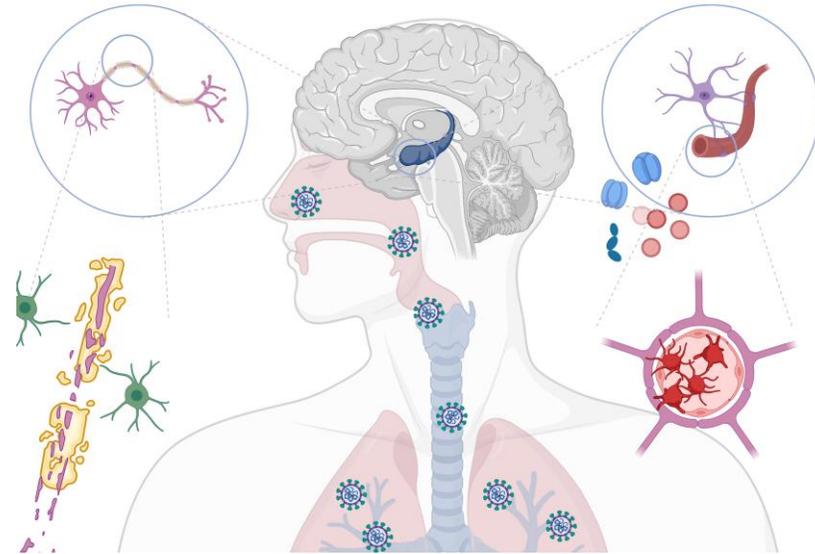
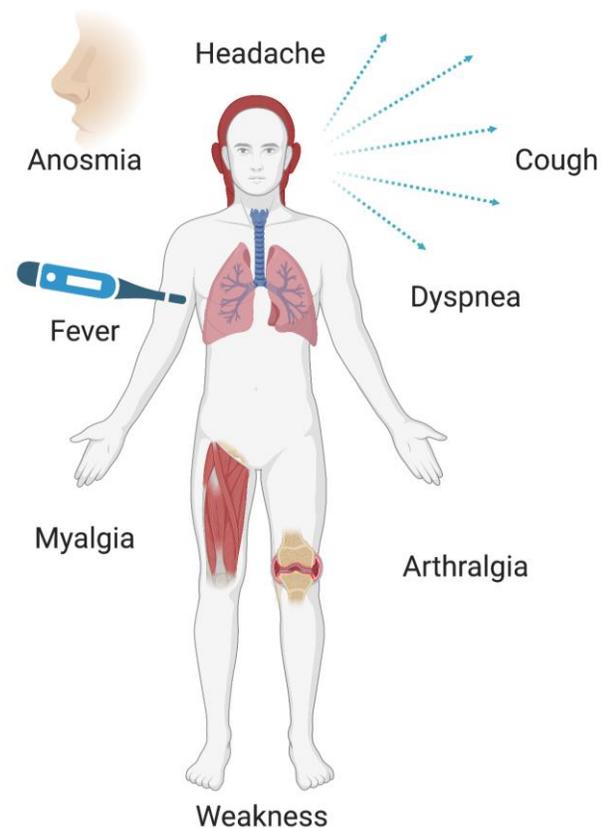
Is SARS-CoV-2 a
respiratory
virus?

Case #1:

- 45 year-old male with new—onset headache AND anosmia
 - Headache fulfilled the International Classification of Headache Disorders criteria for tension-type headache

1. SARS-CoV-2 is **not only** a respiratory virus^{1, 2}

- Severe acute **respiratory** syndrome coronavirus-2



Wang C. A novel coronavirus outbreak of global health concern. *Lancet*. 2020 Feb 15;395(10223):470-473.

Mao L. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020 Jun 1;77(6):683-690. doi: 10.1001/jamaneurol.2020.1127.

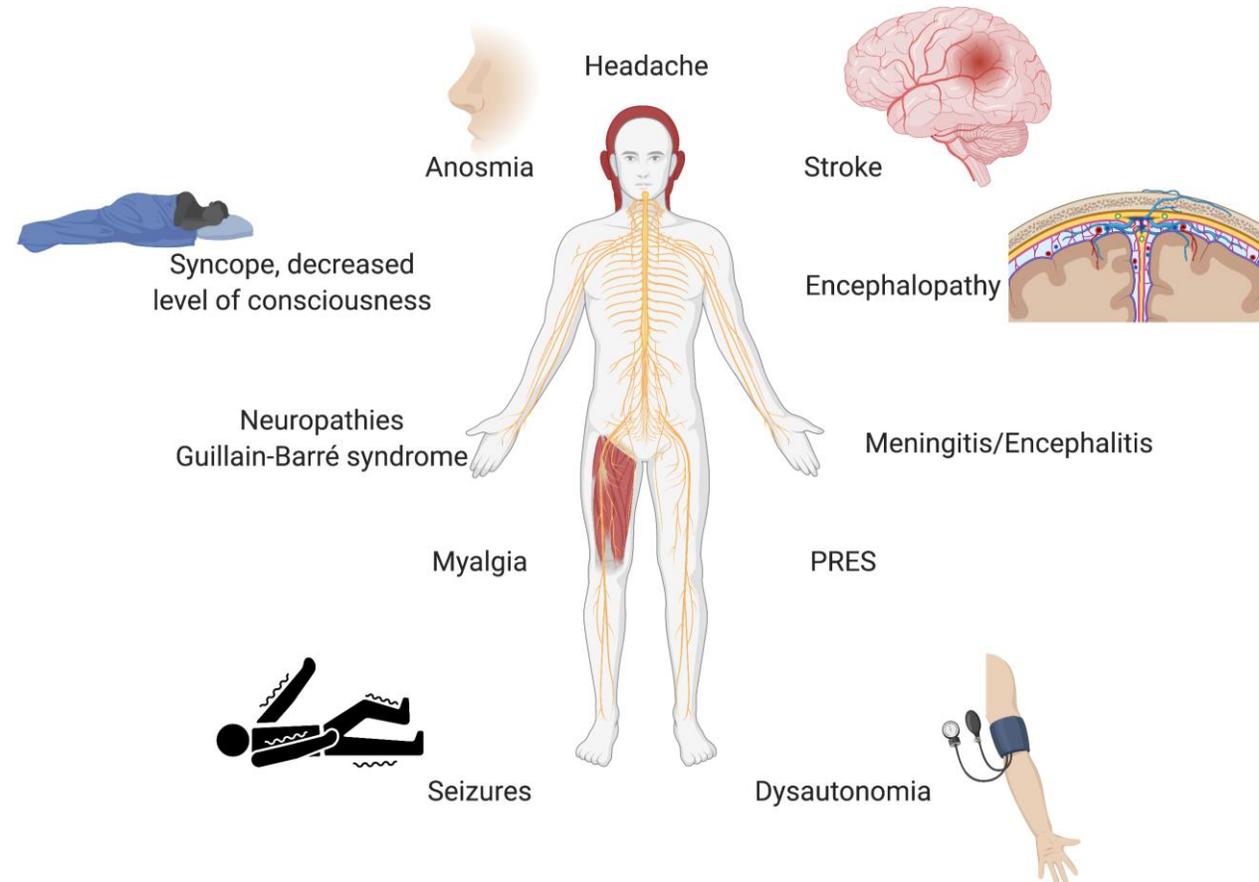
2. Neurological manifestations are frequent

- >50% of patients¹
- Prevalence varies from manifestation to manifestation^{2, 3}
- Non-specific (anosmia, headache, myalgia, altered mental status) > frequent than specific^{2, 3}

	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]

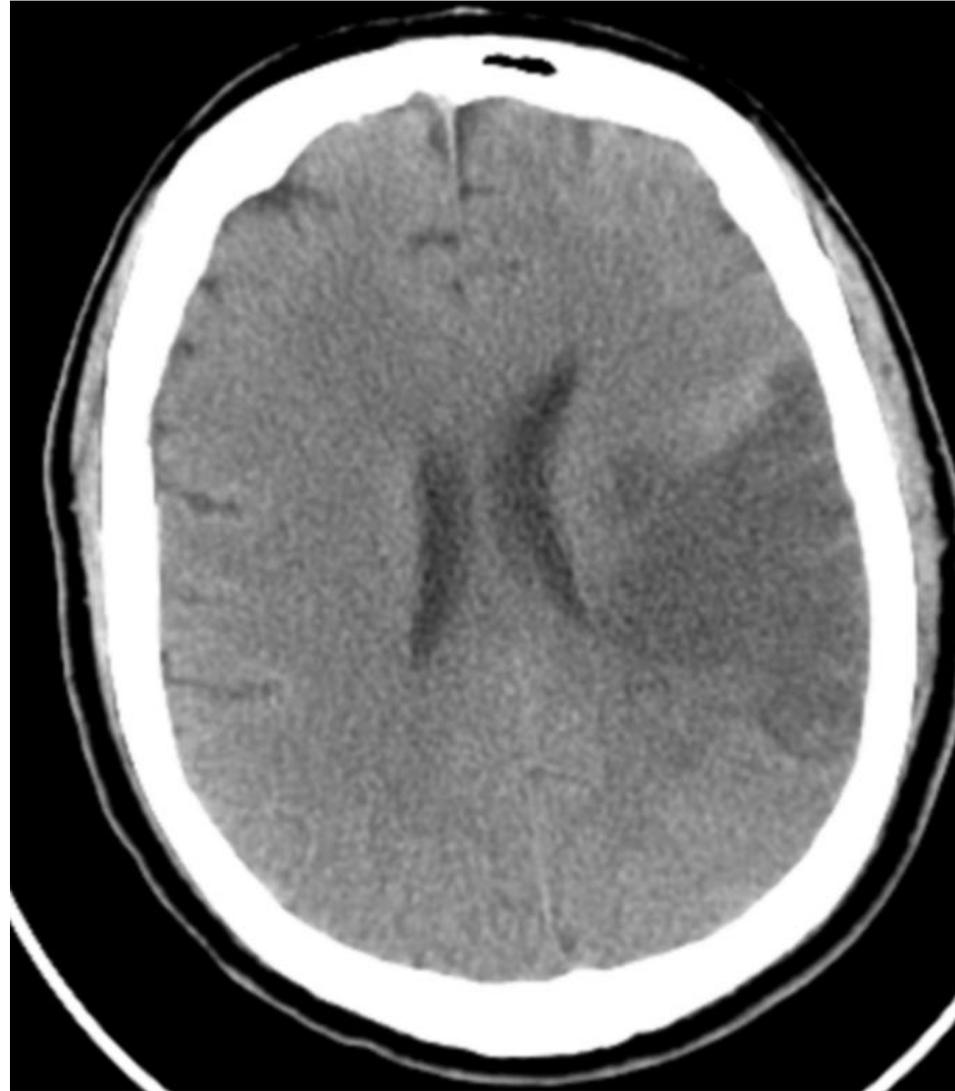
3. Neurological manifestations are diverse¹, and in most cases accompanied by other symptoms²



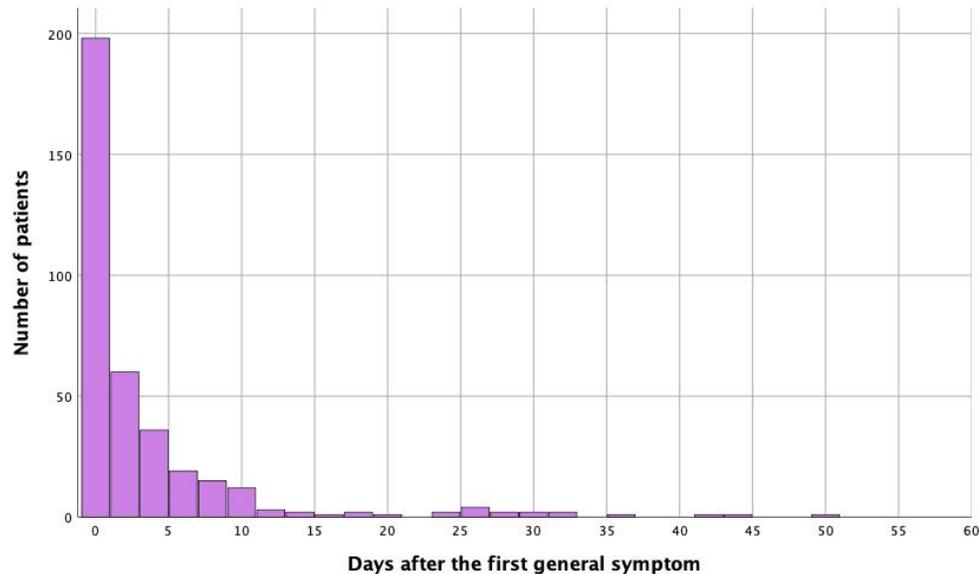
1. Chou SH, GCS-NeuroCOVID Consortium and ENERGY Consortium. Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19-A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open. 2021 May 3;4(5):e2112131.
2. García-Azorín D; Spanish neuroCOVID 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.

Case #2:

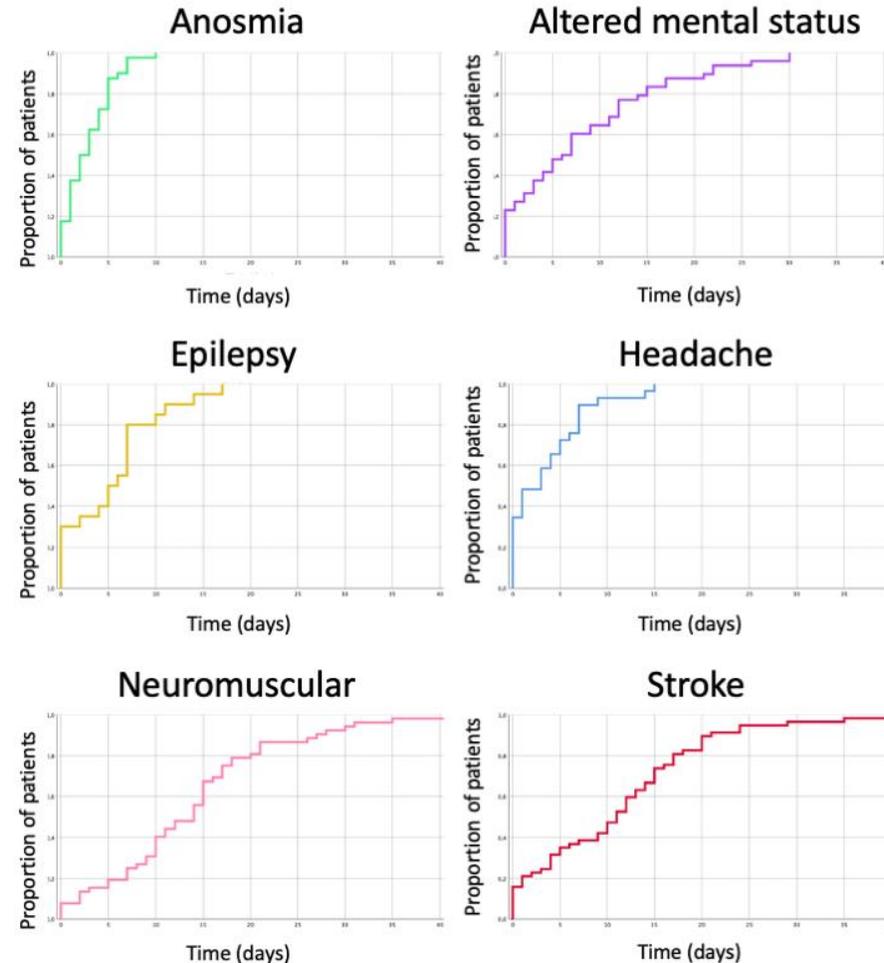
- 49 year-old female.
- No vasculr risk factors, including smoke.
- Regular physical activity.
- 25 days after COVID-19, which had a mild course (no pneumonia, no need of hospitalization) left MCA stroke.
- Delayed diagnosis due to ED collapse / lack of PPE.
- Complete work-up of stroke in a young patient: unremarkable.



3. Neurological manifestations are diverse in nature but also in timing^{1, 2}



Days between the symptom onset and the neurological manifestation

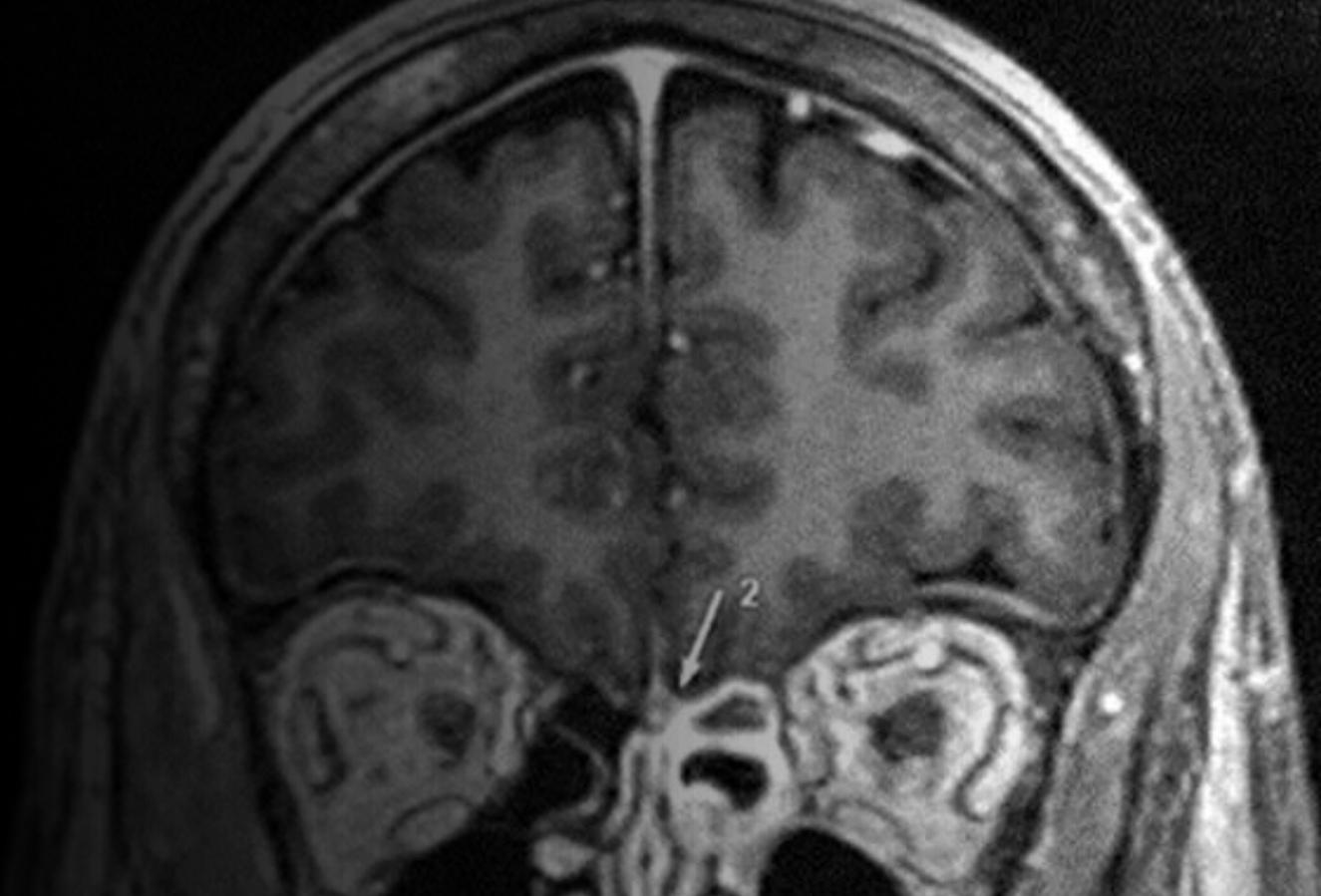


Proportion of patients who present each neurological manifestation

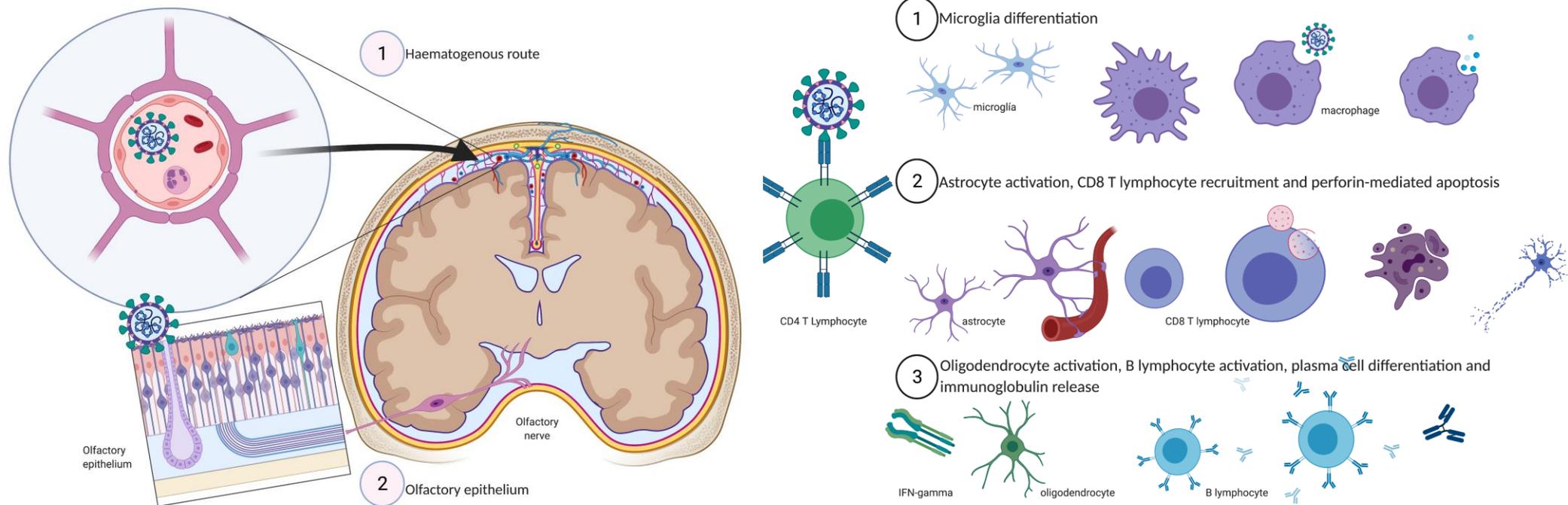
1. García-Azorín D; Spanish neuroCOVID registry group. Neurological presentations of COVID-19: Findings from the Spanish Society of Neurology neuroCOVID-19 registry. J Neurol Sci. 2021 Apr 15;423:117283.
2. García-Azorín D. Neurological symptoms in Covid-19 patients in the emergency department. Brain Behav. 2021 Apr;11(4):e02058.



Why are
neurological
symptoms so
diverse?



4. Neurological symptoms can be caused by the virus, the immune response or by organ dysfunction¹⁻³



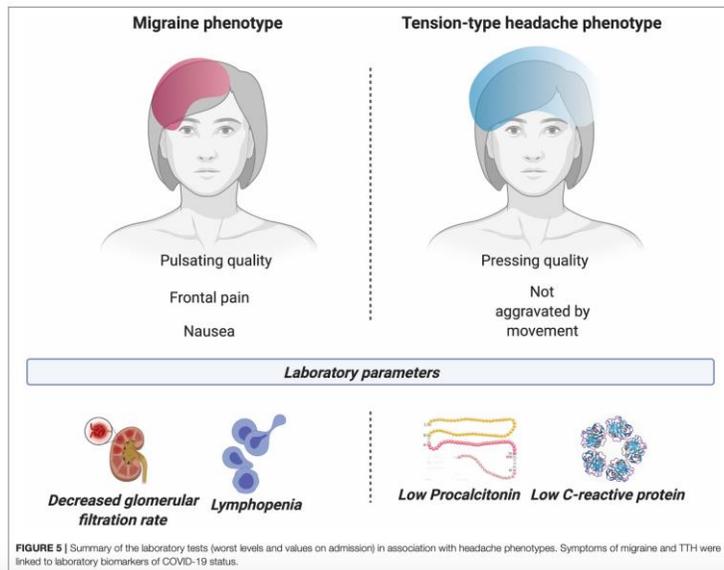
1. Finsterer J. Putative mechanisms explaining neuro-COVID. J Neuroimmunol. 2020 Dec 2;350:577453.

2. Newcombe VFJ; Cambridge NeuroCovid Imaging Collaborators. Neuroanatomical substrates of generalized brain dysfunction in COVID-19. Intensive Care Med. 2021 Jan;47(1):116-118.

3. 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.

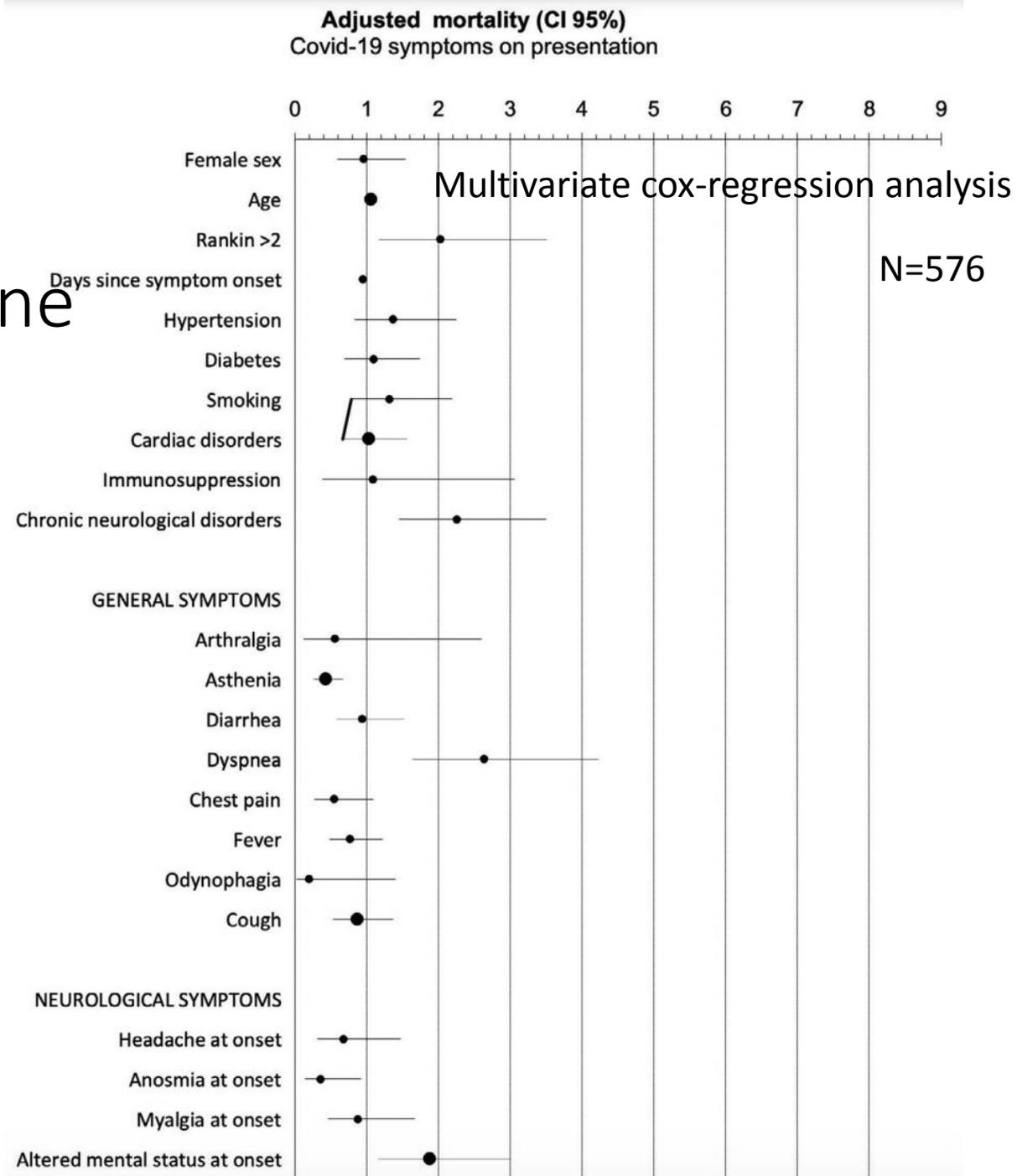
5. Some manifestations (headache, anosmia) may reflect a more efficient immune response

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

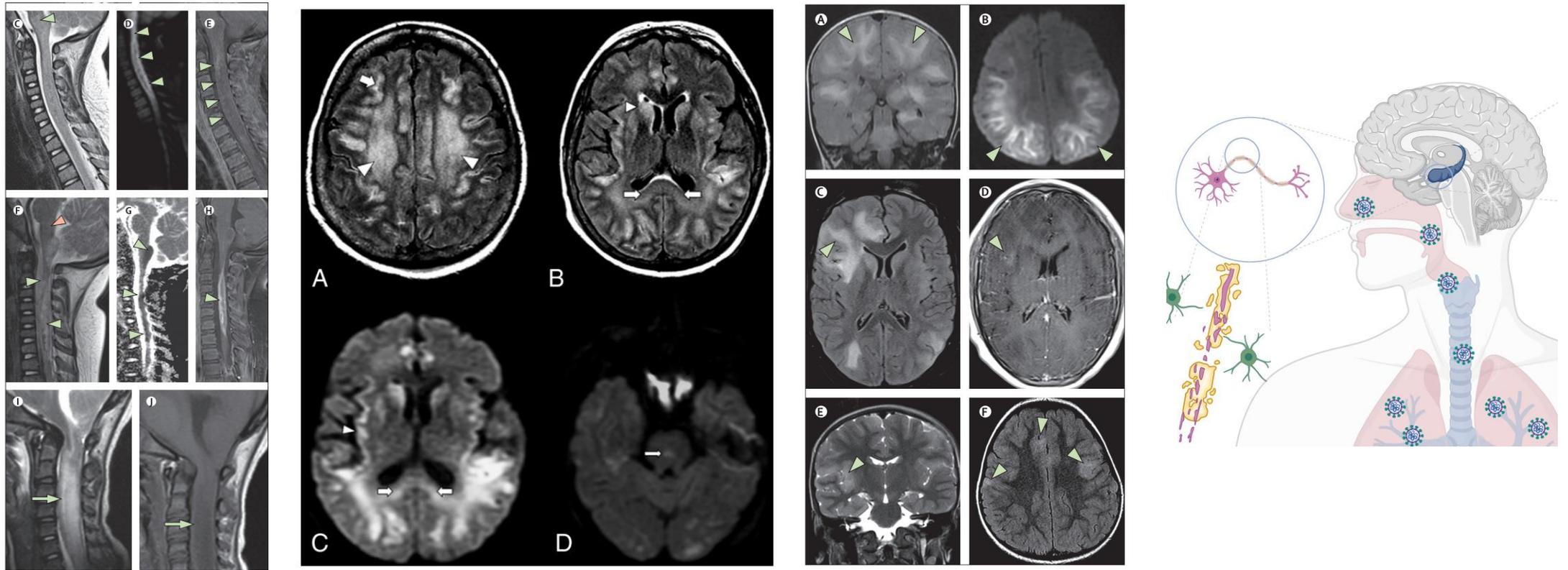


1. García-Azorín D. Neurological symptoms in Covid-19 patients in the emergency department. Brain Behav. 2021 Apr;11(4):e02058.

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



6. But the immune response may cause also neurological complications (e.g., Guillain-Barré, myelitis, encephalitis)



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.

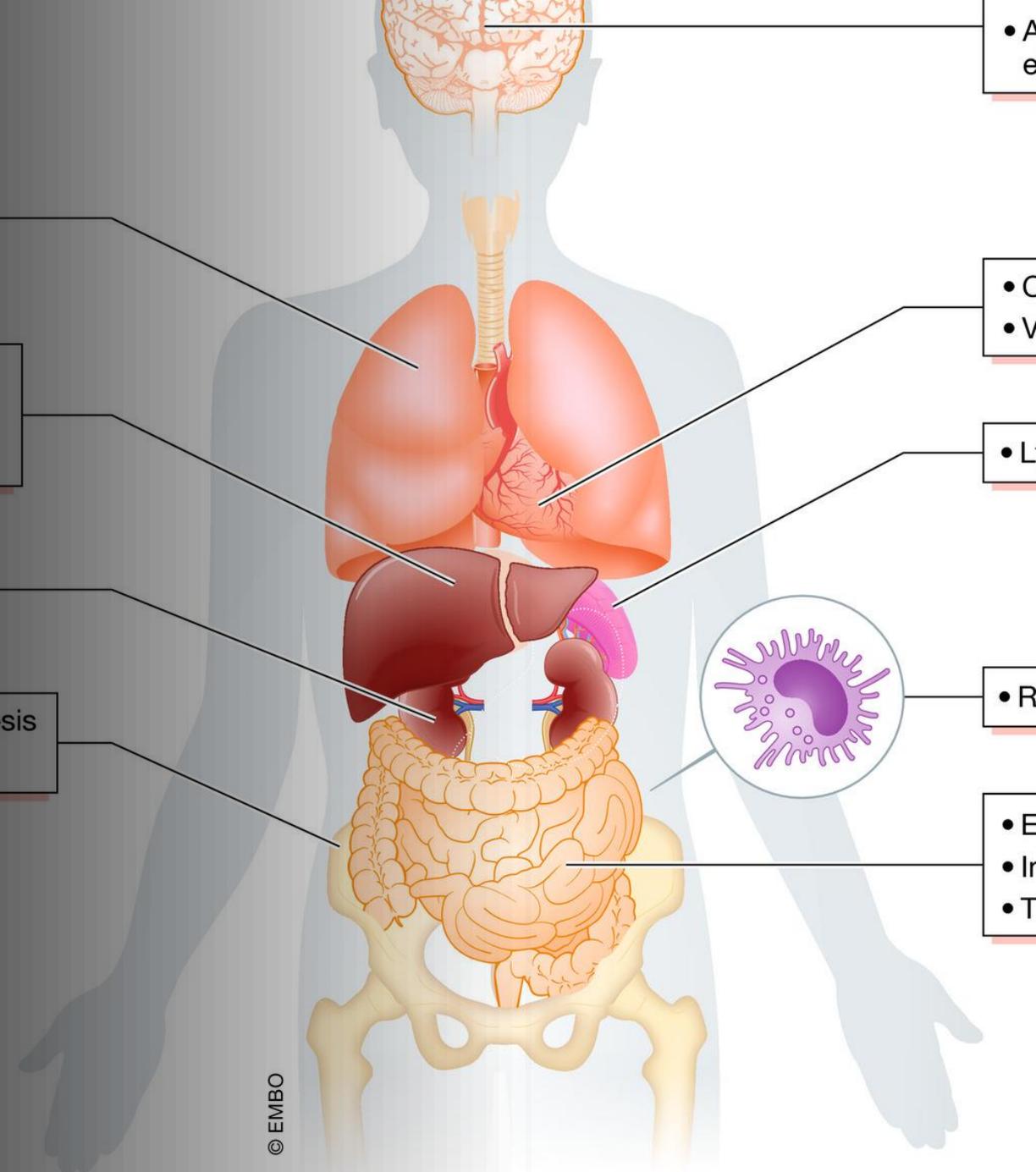
Which symptoms can be considered as non-infectious?

- ARDS
- Endothelial leakage

- Liver dysfunction
- Hypoalbuminemia
- Impaired detoxification

- Acute kidney injury

- Emergency hematopoiesis
- Thrombocytopenia



Case #3:

- 76 year-old male, with prior history of hypertension, diabetes, chronic emphysema, chronic kidney failure, insomnia and depression.
- Current treatment: Furosemide 40 mg/24h, metformin 850 mg/8h, enalapril 2,5 mg/24h, lorazepam 1 mg/24h, venlafaxin 75 mg/24h.
- Day 1: Fever, cough, anosmia, headache
- Day 3: + Dyspnea, pleuritic chest pain
- Day 6: + somnolence, altered mental status
- Day 8: decreased level of consciousness

Case 3:

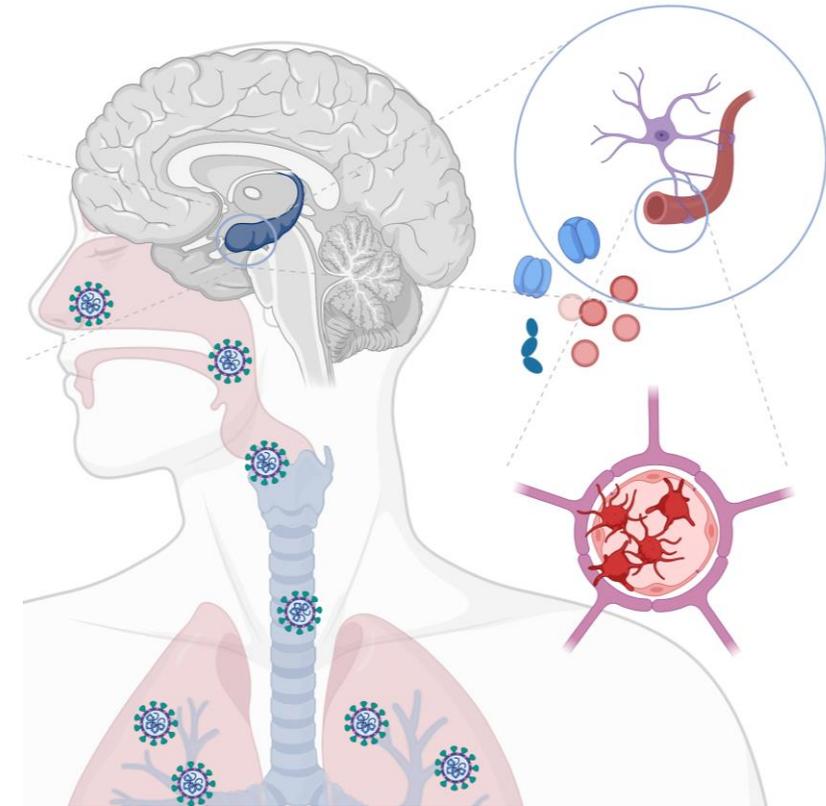
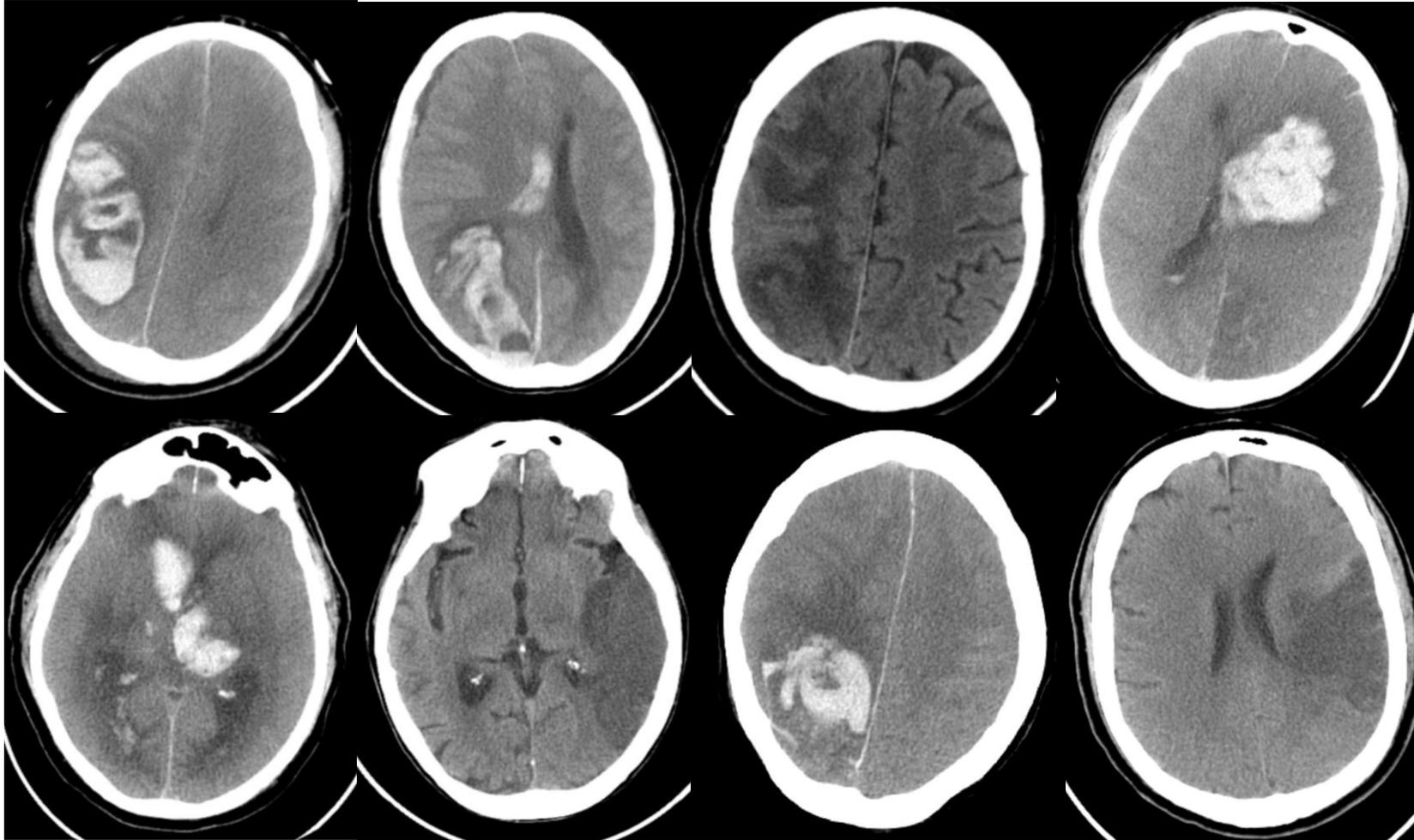
- Laboratory work-up:
 - Erythrocyte sedimentation rate: 90 mm/hour
 - C-reactive protein: 160 mg/L (normal range 0-5)
 - D-dimer: 2400 ng/mL
 - Creatinine 3.5 (Glomerular filtration rate: 27 mL/min)
 - Alanine aminotransferase: 98 Units per liter
 - Aspartate aminotransferase: 95 Units per liter
 - Arterial gasometry:
 - pO₂: 55 mmHg
 - pCO₂: 75 mmHg

Would you suspect a COVID-19 encephalitis?

7. While other manifestations (e.g., encephalopathy, seizures) can be associated with multiple organ failure and poor prognosis

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

8. And other manifestations (e.g., stroke) are related with the pro-thrombotic state



A healthcare worker wearing a white protective suit, hairnet, face mask, and blue gloves is administering a vaccine to a patient. The worker is focused on the task, and the patient is lying down. The background shows other healthcare workers in similar attire, suggesting a vaccination site or clinic. The overall scene is brightly lit, and the focus is on the healthcare worker's hands and the patient's shoulder.

How can we
treat/prevent
COVID?

9. The treatment is in most cases symptomatic and non-specific

- No neuro-specific RCT so far
- Solidarity and Discovery studies had **negative** results^{1, 2}
- Interferon beta 1-a: Positive results in small studies and surrogate variables, not confirmed in larger studies³⁻⁵

RCT: Randomized controlled trials

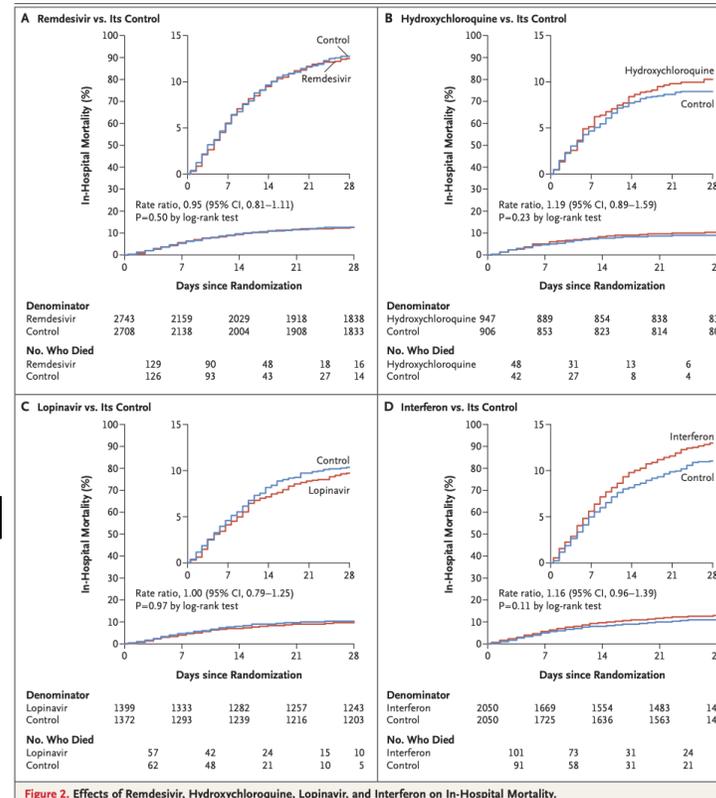
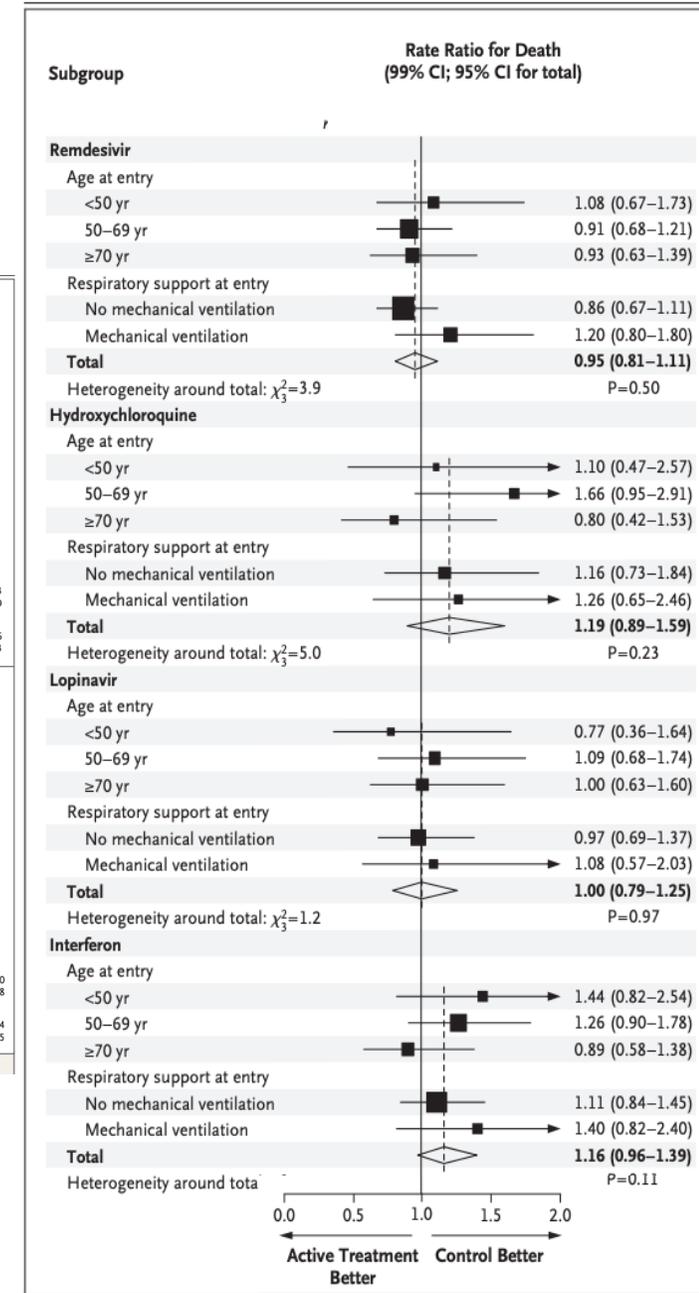


Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

1. WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med.* 2021 Feb 11;384(6):497-511.
2. DisCoVeRy study group. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect.* 2021 May 26;S1198-743X(21)00259-7.
3. Davoudi-Monfared E. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother.* 2020 Aug 20;64(9):e01061-20.
4. Inhaled Interferon Beta COVID-19 Study Group. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med.* 2021 Feb;9(2):196-206.
5. Alavi Darazam I. Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. *Sci Rep.* 2021 Apr 13;11(1):8059.



10. 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)

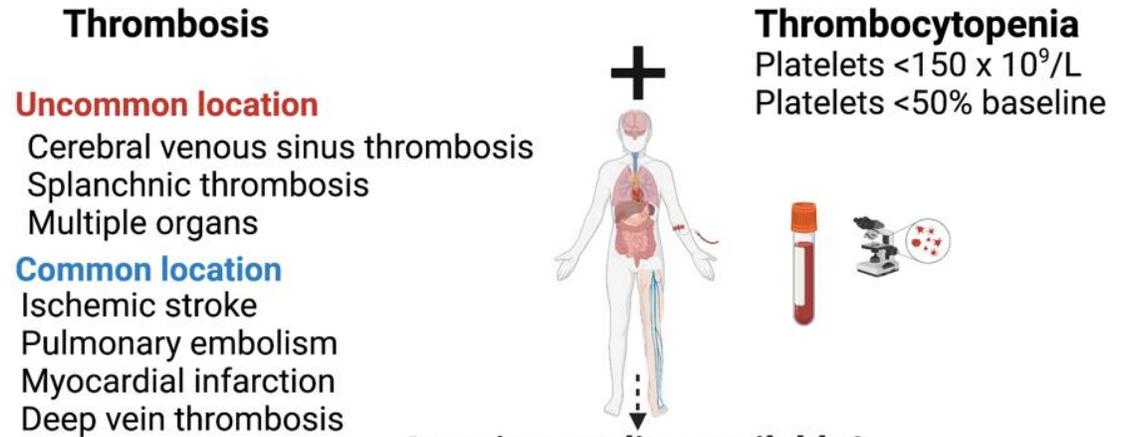
2. European Medicines Agency. Pharmacovigilance Risk Assessment Committee meeting 5-8 July 2021.

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.

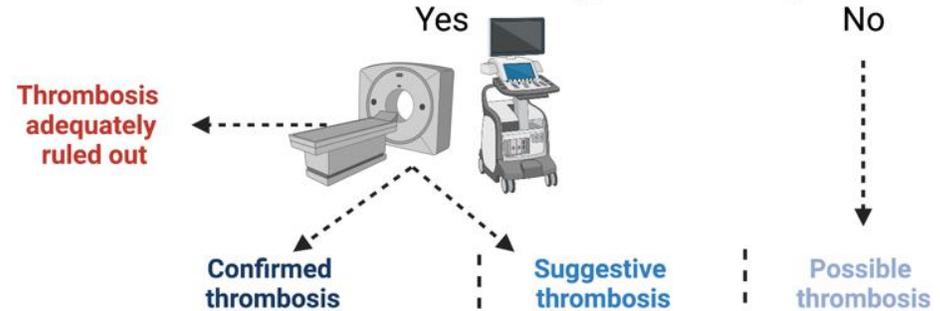
4. Koh JS. Neurology of COVID-19 in Singapore. *J Neurol Sci.* 2020 Nov 15;418:117118. doi: 10.1016/j.jns.2020.117118. Epub 2020 Sep 3. Erratum in: *J Neurol Sci.* 2021 May 15;424:117406. PMID: 32977228; PMCID: PMC7470792.

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.

WHO classification of TTS is based on the degree of certainty



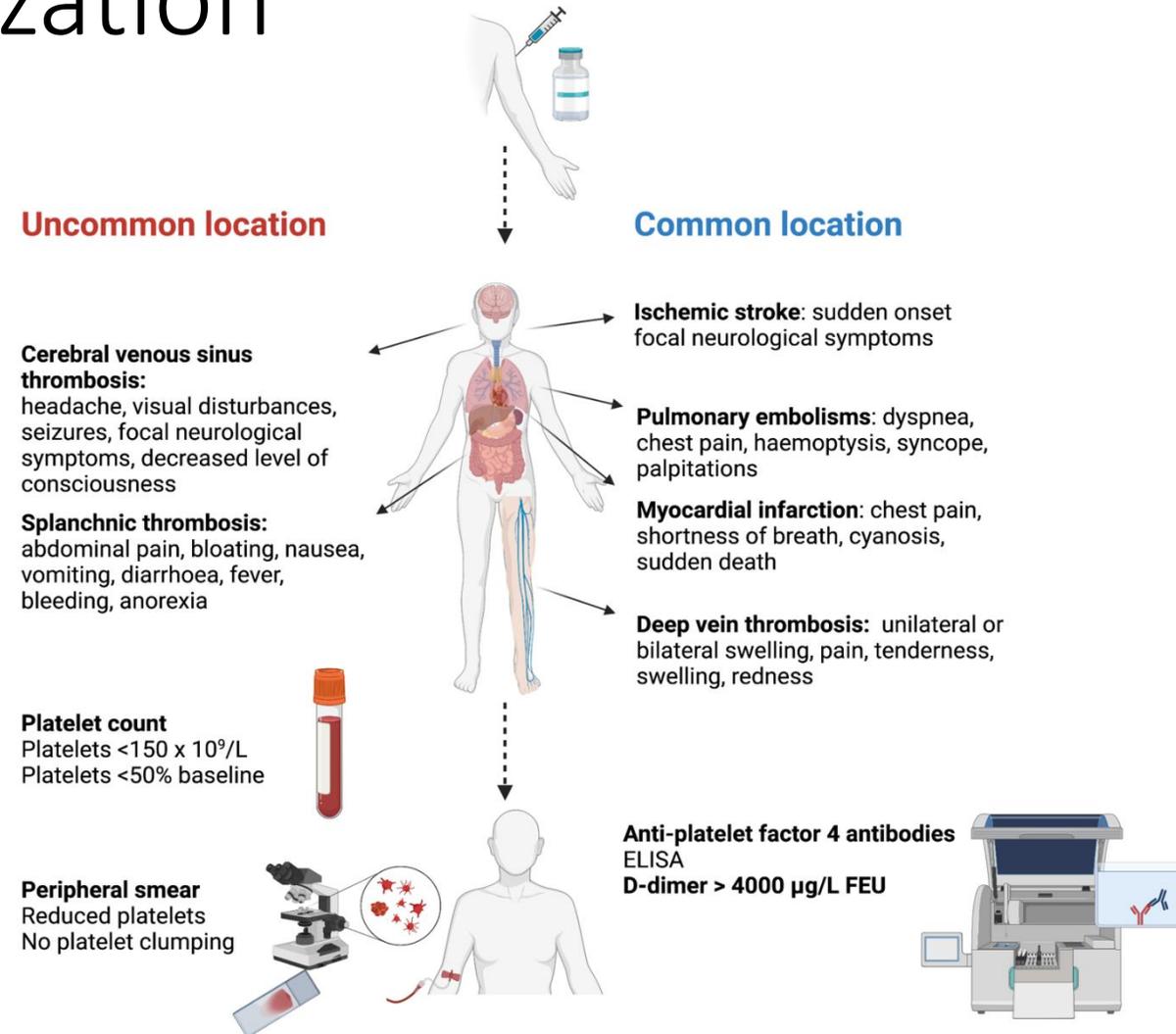
Imaging studies available?



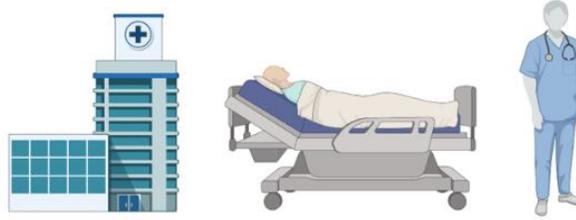
	Uncommon location	Common location		
Severe thrombocytopenia Platelets $<50 \times 10^9/L$	Confirmed TTS	Probable TTS	Possible TTS	Possible TTS
Mild-to-moderate thrombocytopenia Platelets $<150 \times 10^9/L$	Probable TTS	Possible TTS	Possible TTS	Possible TTS

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

Within 30 days following adenovirus vector-based immunization



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



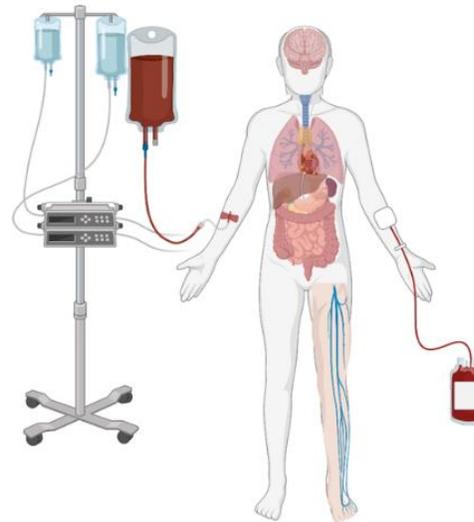
Administer non-heparin based anticoagulants

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



Consider IV Immunoglobulins

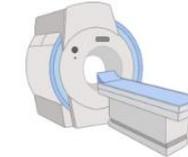
1 g/kg x 2 days or 0.4g/kg x 5 days



PCR test for COVID-19



Monitor platelet count



Complete examinations per patient



Report the case

11. Care of neurological patients was severely disrupted during the pandemic

Journal of Neurology

<https://doi.org/10.1007/s00415-021-10588-5>

REVIEW



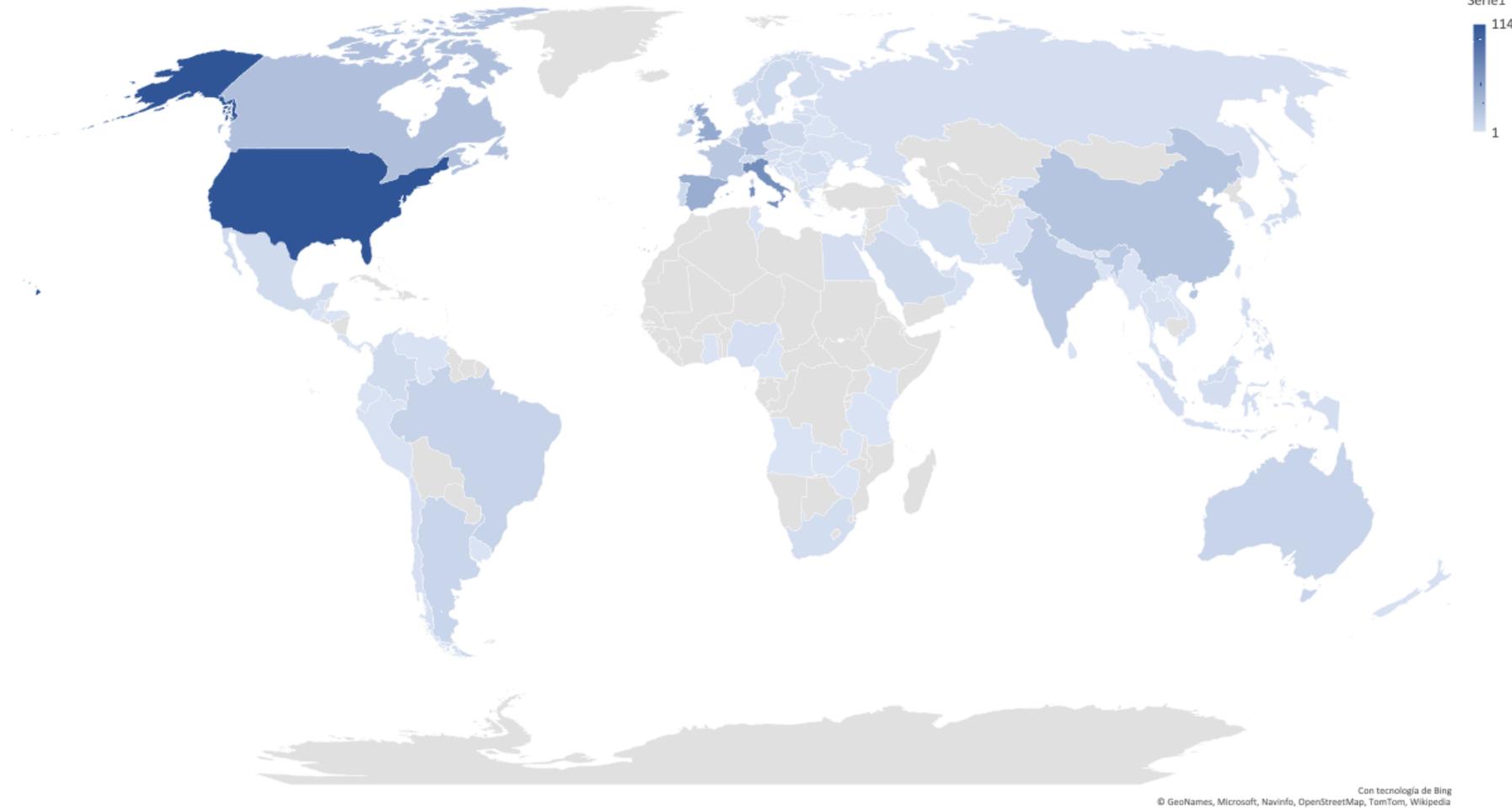
Disruptions of neurological services, its causes and mitigation strategies during COVID-19: a global review

David García-Azorín¹  · Katrin M. Seeher² · Charles R. Newton³  · Njideka U. Okubadejo⁴  · Andrea Pilotto⁵  · Deanna Saylor⁶  · Andrea Sylvia Winkler^{7,8}  · Chahnez Charfi Triki⁹  · Matilde Leonardi¹⁰ 

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Countries represented in the study



N=105 countries

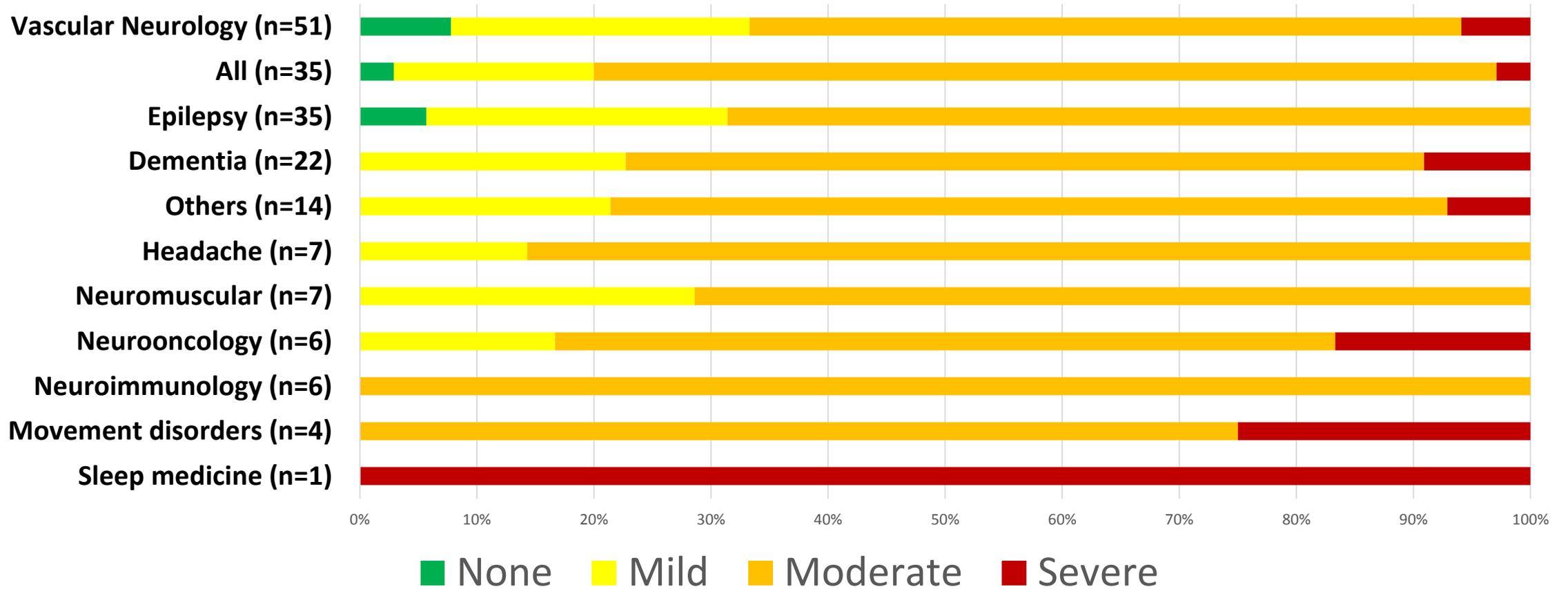
N=210,419 patients

Studies included in qualitative synthesis

(n=369)

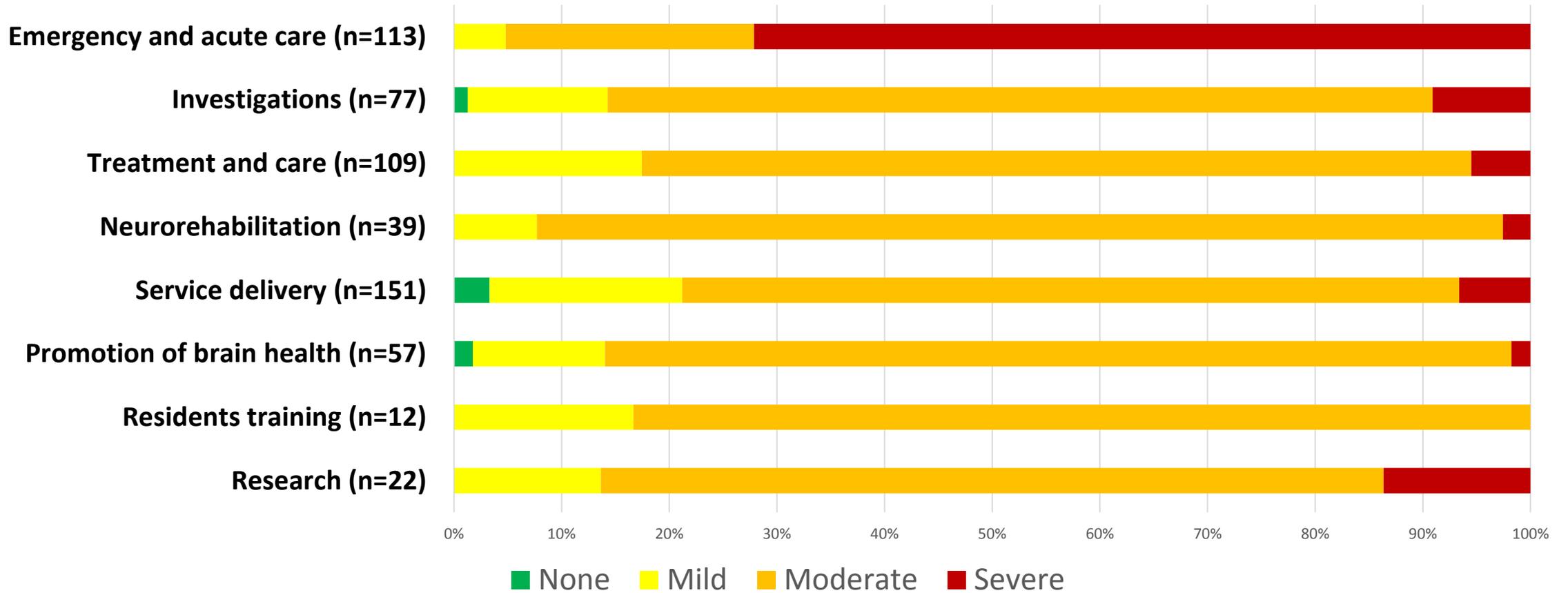
Degree of disruption per subspecialty

N refers to the number of studies addressing each subspecialty



Which were the most affected areas and the causes for the disruption?





Reason of the disruption	Number of studies (%)
Travel restrictions hindering access to the health facilities for patients	196 (81.7%)
Closure of services or consultations as per health authority directive	157 (65.4%)
Decrease in outpatient volume due to patients not presenting	135 (56.2%)
Decreased volume of patients due to cancellation of elective care	109 (45.4%)
Inpatient services and or hospital beds not available	52 (21.7%)
Clinical staff deployed to provide COVID-19 clinical management or emergency support	40 (16.7%)
Unavailability or stock out of essential medicines, medical diagnostics or other health products at health facilities	40 (16.7%)
Insufficient PPE available for health care providers to provide services	22 (9.2%)
Insufficient staff to provide services	11 (4.6%)

Ok, no much literature from Africa, but what do we know?

Journal of Neurology

<https://doi.org/10.1007/s00415-021-10641-3>

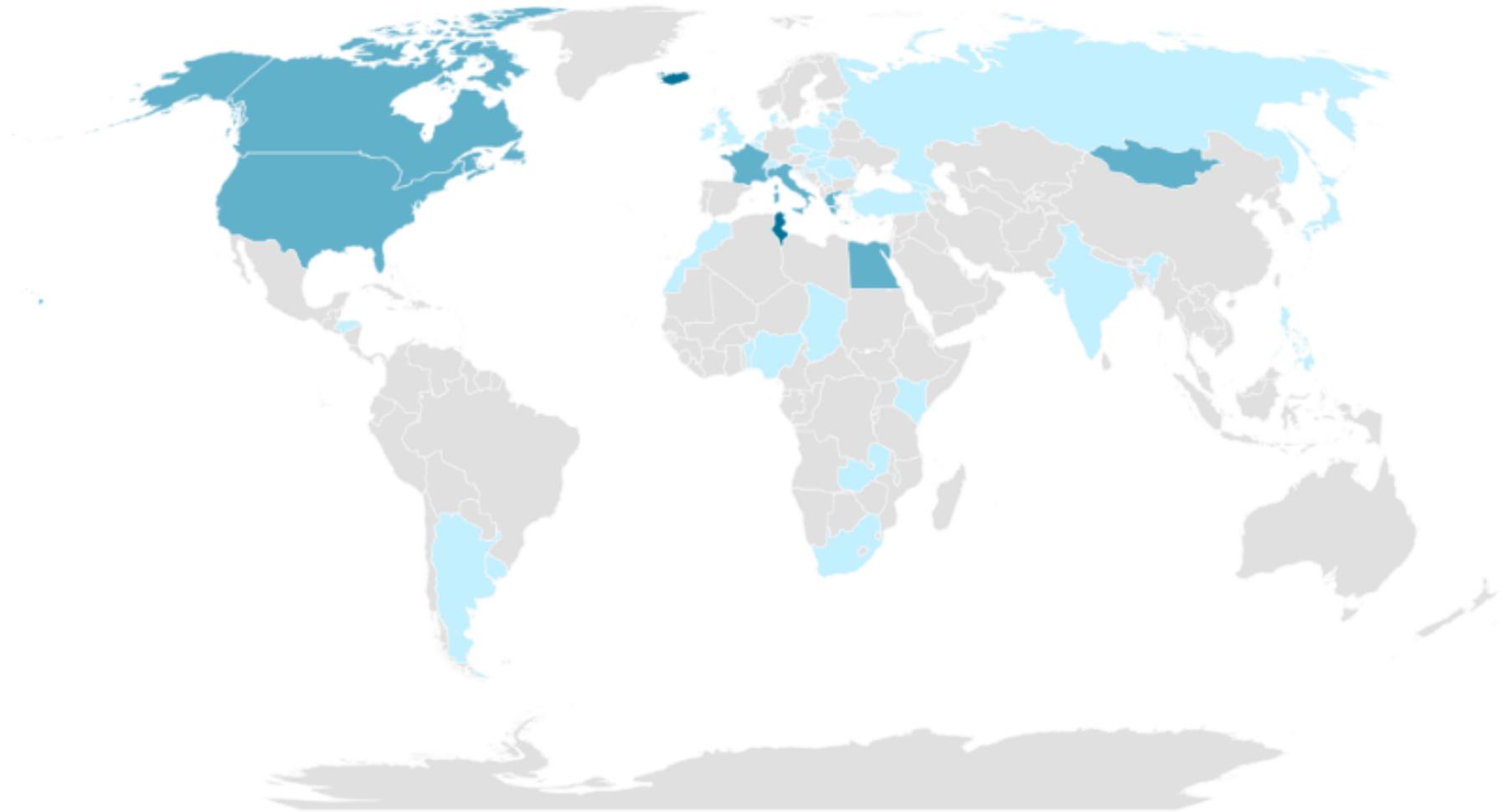
ORIGINAL COMMUNICATION



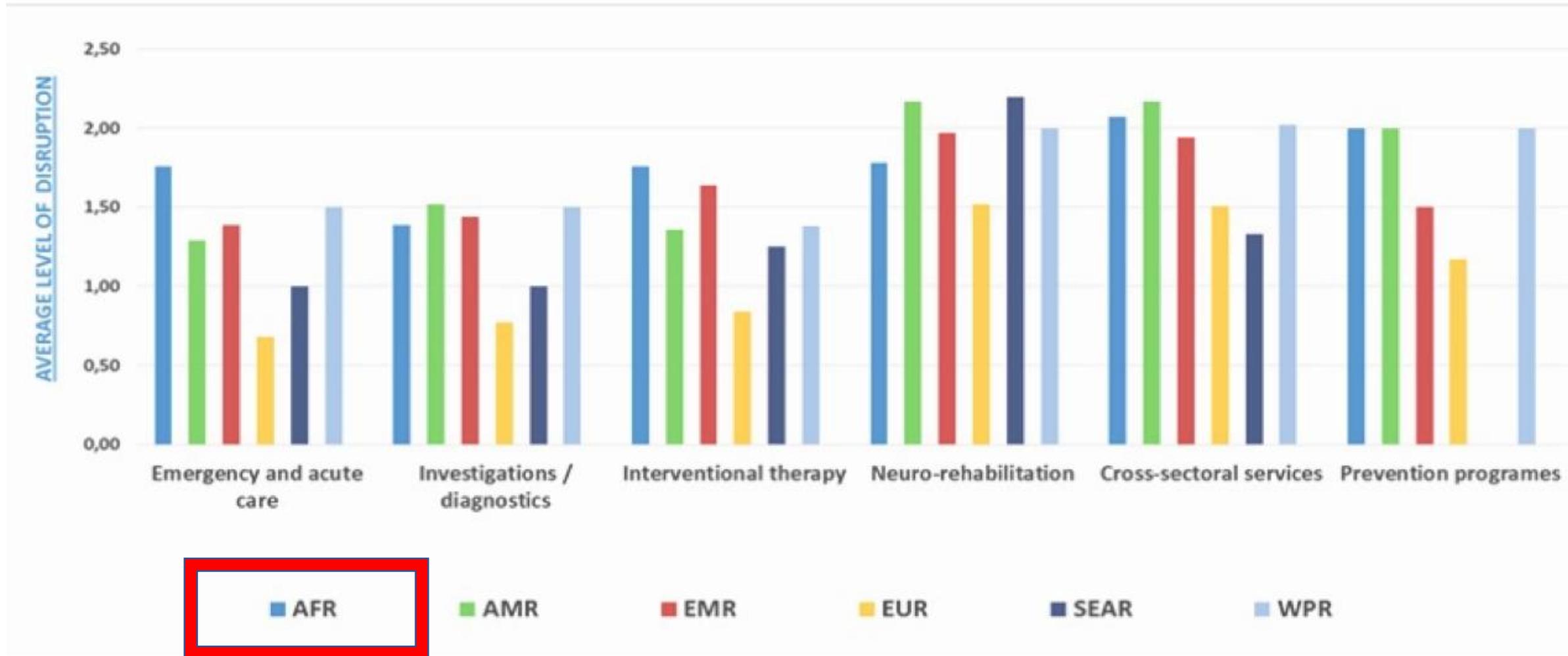
Global survey on disruption and mitigation of neurological services during COVID-19: the perspective of global international neurological patients and scientific associations

Chahnez Charfi Triki¹  · Matilde Leonardi²  · Salma Zouari Mallouli¹ · Martina Cacciatore² · Kimberly Coard Karlshoej³ · Francesca Giulia Magnani² · Charles R. Newton⁴  · Andrea Pilotto⁵  · Deanna Saylor⁶ · Erica Westenberg⁷  · Donna Walsh⁸  · Andrea Sylvia Winkler^{7,9} · Kiran T. Thakur¹⁰  · Njideka U. Okubadejo¹¹  · David Garcia-Azorin¹² 

- 43 countries participated to this survey
- Covering all the 6 WHO Regions and all income levels

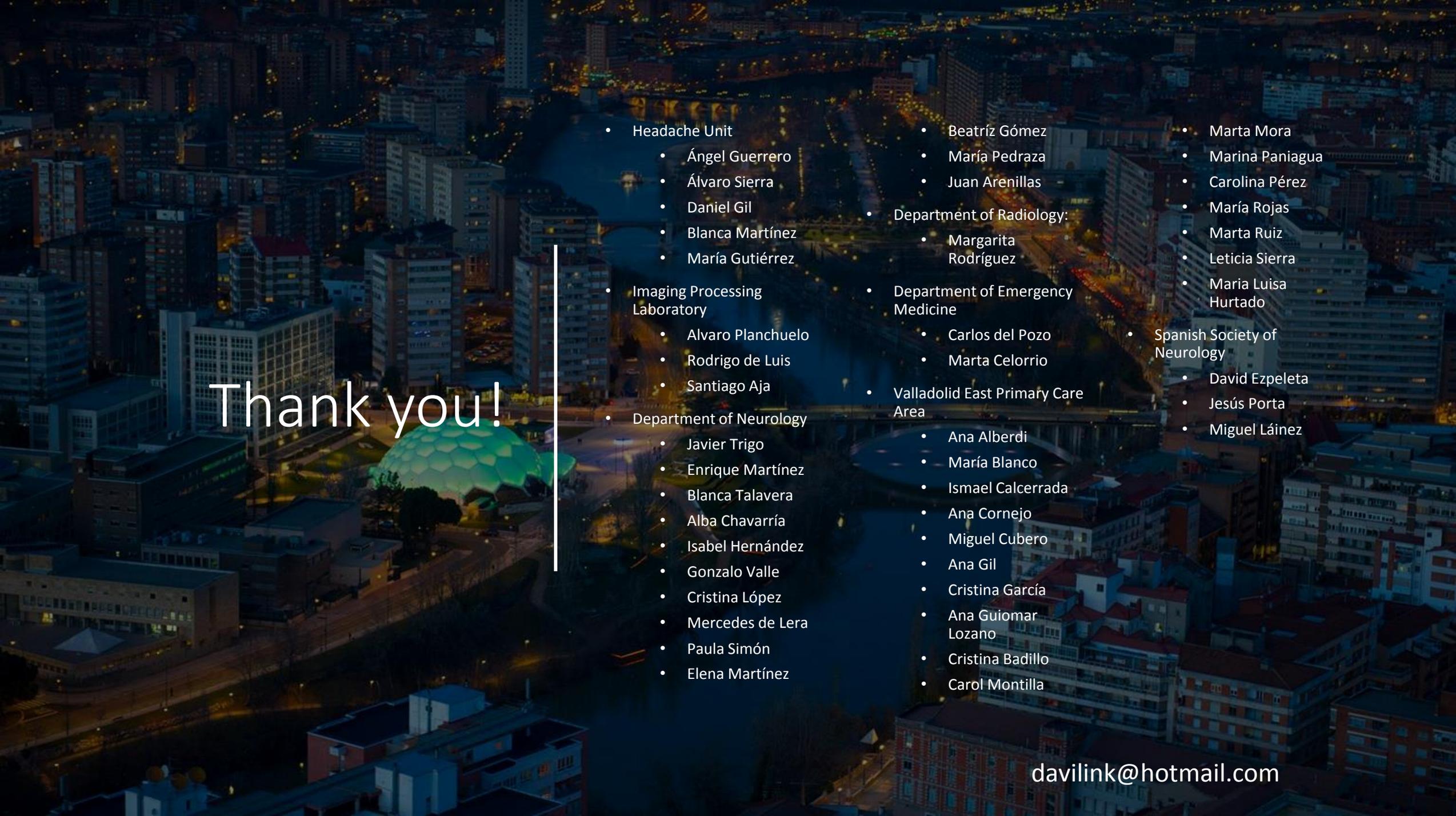


Disruption of services by WHO region



Take-home messages

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. Work-up of patients should consider metabolic, toxic, vascular, septic and nutritional causes
4. We have to work together to answer all the remaining questions



Thank you!

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