

## RESUMEN

La pandemia causada por el COVID-19 ha supuesto un gran cambio, especialmente en relación a la salud. El COVID-19 es una enfermedad que presenta una variedad de síntomas causados por el síndrome respiratorio agudo severo (SARS-CoV-2) (Kumar, Kumar y Gupta, 2020). Los síntomas más comunes son fiebre, tos, falta de respiración y fallo respiratorio (Fotuhi, Mian, Meysami y Raji, 2020). Sin embargo, COVID-19 puede a veces producir problemas neurológicos, como la encefalopatía. Esta enfermedad es una disfunción cerebral, que típicamente manifiesta delirio, otros problemas mentales, de personalidad y comportamentales debido a la condición fisiológica conocida, desorientación, somnolencia y estupor entre 4 días antes y 2 semanas después del diagnóstico de COVID-19 (Taquet, Geddes, Husain, Luciano y Harrison, 2021).

Buscamos artículos que nos ayudasen a obtener información relacionada con la siguiente pregunta: ¿Cuál es la prevalencia de desarrollar encefalopatía secundaria al COVID-19? Para ello, aplicamos criterios de inclusión y exclusión y buscamos “COVID-19 AND encephalopathy AND cohort study” en SCOPUS el 27 de Mayo. Dichos criterios son que los artículos debían estar publicados a partir de 2020, estar escritos en español e inglés, ser estudios de cohorte y los participantes tener mínimo 18 años.

Los 5 artículos han sido seleccionados por PRISMA. Todos ellos contaban con participantes hospitalizados y/o no hospitalizados, con y sin encefalopatía. Los resultados son diversos, pero todos ellos muestran más casos de encefalopatía cuanto más severa es la infección por COVID-19, mostrando mayor prevalencia en los pacientes en UTI (69,6-84,3%). La prevalencia en cuanto a todos los pacientes con COVID-19 está entorno al 0,5%, 1,48% y 3%, mientras que la de los pacientes hospitalizados es aproximadamente del 10,55% y 13,4%. Los pacientes con encefalopatía muestran diferentes comorbilidades que pueden actuar como factores de riesgo y además muestran diferentes características que pueden ser debidos a la encefalopatía. Además, los resultados de EEG (88% / 61,9%) y RM (72% / 27,12%) no han sido concluyentes. Trascurridos 3 meses de la infección, los síntomas de encefalopatía siguen presentes (24%).

*Palabras clave:* COVID-19, encefalopatía, SARS-CoV-2, complicaciones neurológicas, prevalencia, bienestar, salud.

## ABSTRACT

The pandemic caused by COVID-19 has supposed a big change, especially in health-related issues. COVID-19 is a disease that present a variety of symptoms caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Kumar, Kumar and Gupta, 2020). The most common symptoms are fever, cough, shortness of breath and respiratory failure (Fotuhi, Mian, Meysami and Raji, 2020). Nevertheless, COVID-19 can sometimes produce neurological issues, such as encephalopathy. This disease is a brain dysfunction, which typically manifests with delirium, other mental, personality and behavioral disorders due to known physiological condition, disorientation, somnolence and stupor between 4 days before and 2 weeks after COVID-19 diagnosis (Taquet, Geddes, Husain, Luciano and Harrison, 2021).

We looked for articles that helped us get information related to the following question: What is the prevalence of developing encephalopathy secondary to COVID-19? To achieve this goal, we applied inclusion and exclusion criteria and searched for “COVID-19 AND encephalopathy AND cohort study” in SCOPUS on 27<sup>th</sup> May. This criteria was that the articles had to be published since 2020, to be written in Spanish and English, cohort studies and the participants be at least 18 years old.

The 5 articles were selected through PRISMA. All of them were about hospitalized and non-hospitalized participants, with and without encephalopathy. The results are diverse, but all of them show more encephalopathy cases in more severe COVID-19 infection, showing the higher prevalence in ITU patients (69,6-84,3%). Prevalence of all COVID-19 patients is around 0,5%, 1,48% y 3%, while the hospitalized patients' one is approximately 10,55% and 13,4%. Encephalopathy patients show different comorbidities that could act as risk factors, and also present different characteristics that could appear due to encephalopathy. Besides, results from EEG (88% / 61,9%) and RM (72% / 27,12%) are not conclusive. After 3 months from COVID-19 infection, encephalopathy symptoms are still present (24%).

*Keywords:* COVID-19, encephalopathy, SARS-CoV-2, neurological complications, prevalence, wellbeing, health.

## INTRODUCTION

The pandemic caused by COVID-19 has supposed a big change regarding to everyone's lives, especially in health-related issues. COVID-19 is a disease that presents a variety of symptoms caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Kumar, Kumar and Gupta, 2020). The most common symptoms are fever, cough, shortness of breath and respiratory failure (Fotuhi, Mian, Meysami and Raji, 2020). Nevertheless, COVID-19 can sometimes produce neurological issues, such as anosmia, stroke and encephalopathy. Encephalopathy is defined as a brain dysfunction, which typically manifests with delirium, other mental, personality and behavioral disorders due to known physiological condition, disorientation, somnolence and stupor between 4 days before and 2 weeks after COVID-19 diagnosis (Taquet, Geddes, Husain, Luciano and Harrison, 2021).

## OBJECTIVE

What is the prevalence of developing encephalopathy secondary to COVID-19?

## METHODS

### Search strategy

The literature was extracted from SCOPUS. This search involved the concepts "COVID-19", "encephalopathy" and "cohort study". Multiple data bases were excluded for not reviewing medical topics related to encephalopathy and only cohort studies were selected. Query:

COVID-19 AND encephalopathy AND cohort study

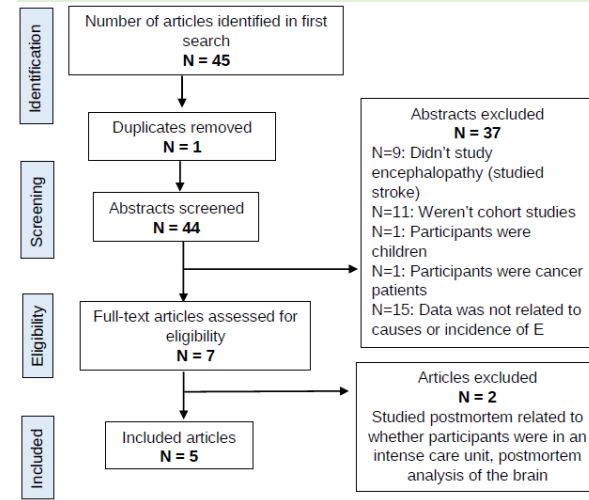
### Inclusion and exclusion criteria

- Published > 2020
- Spanish & English
- Cohort studies
- > 18 years old

### Methodological Quality Assessment

Article	Selection				Comparability			Outcome		
	1	2	3	4	1	2	3	1	2	3
Taquet, M. et al. (2021)	A	A	A	A	A	A	A	A	A	B
Lambreccq, V. et al. (2021)	A	A	A	A	B	A	A	A	A	A
Helms, J. et al. (2020)	B	A	A	A	B	A	A	A	A	A
Portela, S. et al. (2020)	A	A	A	A	A	A	A	A	A	A
Rass, V. et al. (2021)	A	A	A	A	A	A	A	A	A	A

- Representativeness of the exposed cohort
  - Selection of the non-exposed cohort
  - Ascertainment of exposure
  - Demonstration that the outcome of interest wasn't present at the start of the study
- Comparability of cohort on the basis of the design
  - Assessment of outcome
  - Follow-up was long enough for outcomes to occur
  - Adequacy of follow-ups cohorts



## RESULTS

Articles	Study	N	Cohorts (n)	♂ %	Mean age	E after 2 weeks from infection	H or NH	Follow-up (months)	PCR (%)	Definition of E	Com	Prevalence	Results			
Taquet, M. et al. (2021)	RC	236379	-COVID-19 (236379) -Influenza (105579) -RTI (236038)	44	46	✓	H & NH	6	Antigen test or (+) RNA (40,9)	Presence (between 4 days before and after COVID-19 diagnosis) of: - Other and unspecified E - Delirium - Other mental disorders - Personality and behavioral disorders - Disorientation - Somnolence - Stupor	Obesity Hypertension Diabetes Tobacco	All COVID-19 patients: 2,36-3% Hospitalized COVID-19 Patients: 13.4% ITU Patients: 69.6%	Incidence of more neurological or psychiatric after 6 months: - COVID-19 → Influenza & RTI (higher in ICU patients). - More severe COVID-19 infections.	COVID-19 survivors: less visits during H.	E consequences: Cerebral infection, more probabilities of dementia	
Lambreccq, V. et al. (2021)	RC	644	-EEG (78) -RM (57)	73	61	✓	H	NR	PCR (+) (47,4)	- Neurological symptoms after COVID. - EEG confirmed diagnosis	Obesity Diabetes Tobacco Immune diseases	H: 10,55%	EEG: Pathological findings (88%) -Metabolic-toxic E. -E pattern: Frontal slow waves. -12% → E symptoms -30% → E pattern	RM: Pathological findings (72%). -15,78% → CORE... -8,77% → White-matter enhancing lesions.	-Movement impairment -Frontal syndrome -Brainstem impairment -Periodic discharges -White-matter enhancing lesions.	CORE:
Helms, J. et al. (2020)	RC	140	-H with delirium and/or ANE (118) -H with no delirium and/or NNE (22)	71,4	62	✓	HI	3	PCR (+) (100)	Delirium and/or abnormal neurological examination	Immune diseases Diabetes	ITU: 84,3%	EEG: Unspecific pathologies (61,9%). Slow bilateral activity (26,19%).	RM: (27,12%) White-matter enhancing lesions 28,57%	Neurological examination: No movement disorder 63,57%	84,3% → Delirium with a combination of acute attention, awareness, and cognition disturbances
Portela, S. et al. (2020)	PC	2750	-H with COVID-19 in COVID-19 wards (58) -H with COVID-19 in UCI (13)	70,4	69	✓	NH	3	PCR (+) (81,7)	Neurological complications coursed as E	Obesity Hypertension Diabetes	All COVID-19 patients: 0,5%	-Disorientation (69,2%) -Impaired consciousness -Confusion -Memory loss -Agitation	Risk factors: -Previous cognitive impairment -Metabolic imbalance	-Impaired consciousness -Hyperthermia -Myoclonus. -Hyperreflexia	Medicated E patients:
Rass, V. et al. (2021)	PC	135	-COVID-19 not H (32) -COVID-19 H (72) -COVID-19 in ICU (31)	61	56	✓	H & NH	3	PCR (+) (100)	Clinical E	Diabetes Hypertension Immunological deficiency	All COVID-19 patients: 1,48%	After 3 months of infection: Symptoms still present. 24% → Neurological disorders (before infection from COVID-19).	15% → New neurological disorders not present before COVID-19 (more frequent in ICU patients) → Mild E (2%).	After 3 months: abnormal reflex state and signs of positive frontal liberation (found in encephalopathy patients).	

E → Encephalopathy // RC → Retrospective cohort // PC → Prospective observational cohort // H → hospitalized // NH → Not-Hospitalized // HI → Hospitalized Intubed // Com → Comorbidities // RTI → Respiratory tract infection // ICU → Intensive care unit // CSF → Líquido cefalorraquídeo // NR → Not reported // ANE → Abnormal Neurological Exam // NNE → Normal Neurological Exam // ITU → Intensive Therapy Unit // CORE → COVID-19 related encephalopathy

## DISCUSSION

All the articles reviewed in this study agree that the appearance of encephalopathy after COVID-19 infection is still unclear due to the lack of information and studies in this area. Nevertheless, there is one big idea: encephalopathy may occur as a result of physiological processes derived from the infection (such as the cytokine storm), not being a direct cause from COVID-19. However, it usually presents with frontal impairment and disorientation and consciousness alterations. There would be also risk factors that could contribute to the development of encephalopathy, such as previous cognitive impairment, metabolic imbalance and different medical comorbidities that notably influence health wellbeing. Attention given to those patients from the hospital is also a very important variable. Regarding to prevalence, it is noted in the articles that severity is very important. Generally, the incidence is low, but it is showed that the bigger the severity of COVID-19 infection is, the more encephalopathy cases appear, as showed in the results (0,5-3%, 10,55-13,4% and 69,6-84,3% for all COVID-19 patients, hospitalized ones and ICU ones respectively). The highest levels of patients with encephalopathy are found in ICU wards.

## REFERENCIAS BIBLIOGRÁFICAS

- Fotuhi, M., y Mian, A., Meysami, S. y Raji, C. (2020). Neurobiology of COVID-19. *Journal of Alzheimer's Disease*, (76), 3-19.
- Helms, J., Kremer, S., Merdji, H., Schneck, M., Severac, F., Clere-Jehl, R., Studer, A., Radosavljevic, M., Kummerlen, C., Monnier, A., Noulay, C., Fafi-Kremer, S., Castelain, V., Ohana, M., Anheim, M., Schneider, F. y Meziani, F. (2020). Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Critical Care*.
- Kumar, R. y Kumar, V. y Gupta, A. (2020). Encephalopathy in patients with COVID-19: A review. *Journal of Medical Virology*.
- Lambrecq, V., Hanin, A., Minoz-Musat, E., Chougar, L., Gassama, S., Delorme, C., Cousyn, L., Borden, A., Damiano, M., Frazzini, V., Huberfeld, G., Landgraf, F., Nguyen-Michel, V., Pichit, P., Sangare, A., Chavez, M., Morélot-Panzini, C., Morawiec, E., Raux, M., ... Navarro, V. (2021). Association of Clinical, Biological, and Brain Magnetic Resonance Imaging Findings With Electroencephalographic Findings for Patients With COVID-19. *JAMA Network Open*, 4(3), doi:10.1001/jamanetworkopen.2021.1489
- Portela-Sánchez, S., Sánchez-Soblechero, A., Melgarejo, P. J., Rodríguez, A., Velilla, G., Palacios-Mendoza, M. A., Cátedra, C., Amaya, L., Mas, M., Massot-Tarrús, A., De la Casa-Fages, B., Díaz-Otero, F., Catalina, I., García, J. M., Pérez-Sánchez, J. R., Muñoz-Blanco, J. L. y Grandas, F. (2020). Neurological complications of COVID-19 in hospitalized patients: The registry of a neurology department in the first wave of the pandemic. *European Journal of Neurology*, 1-9.
- Rass, V., Beer, R., Schiefecker, A. J., Kofler, M., Lindner, A., Mahlkecht, P., Heim, B., Limmert, V., Sahanic, S., Pizzini, A., Sonnweber, T., Tancevski, I., Scherfler, C., Zamarian, L., Bellmann-Weiler, R., Weiss, G., Djamshidian, A., Kiechl, S., Seppi, K., Loeffler-Ragg, J., Pfausler, B. y Helbok, R. (2021). Neurological outcome and quality of life 3 months after COVID-19: A prospective observational cohort study. *European Journal of Neurology*, 1-12.
- Taquet, M., Geddes, J., Husain, M., Luciano, S. y Harrison, P. (2021). 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*, (8), 416-427.