SYSTEMATIC REVIEW

Submission date: 14/03/2021
Revision date: 24/03/2021
Acceptance date: 04/04/2021

New-onset Seizures Associated with COVID-19: A Systematic Review

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Abstract

Introduction

COVID-19 is an example of a newly emerging, infectious disease with pandemic potential. Although there are numerous studies on this disease, the main focus now is on relating COVID-19 with possible long-term sequelae, as well as neurological manifestations. The aim of this study is to investigate the relationship between SARS-CoV-2 infection and the development of new-onset seizures, that is, in patients who had not been previously diagnosed with epilepsy.

Methods

A systematic search of articles and preprints was performed in three databases (MedLine, Scopus and Web of Science) between February 24 and March 7, 2021. The MeSH terms and keywords used in the search were: ("SARS-CoV-2" OR "COVID-19") AND ("Seizures" OR "Status Epilepticus" OR "Electroencephalography" OR "EEG") NOT ("Epilepsy").

Results

Twenty-one studies were included 21 studies in the systematic review after screening. It was estimated that approximately 2.9 % of COVID-19 patients with neurological symptoms developed new-onset seizures and about 0.67% of the total number of COVID-19 patients developed new-onset seizures. The most common coexisting symptoms among these patients were fever, vomiting, cough and malaise. Antiepileptic treatment was key to the improvement of the health status of patients who developed new-onset seizures.

Conclusion

With the limited data available, it is currently impossible to establish a direct association between SARS-CoV-2 infection and the development of new-onset seizures. The pathophysiologic mechanism causing the seizures cannot yet be determined either. However, it can be concluded that generally, these seizures are successfully reverted with antiepileptic treatment and patients usually respond favorably.

Keywords: COVID-19, SARS-CoV-2, neurological sequelae, seizures, status epilepticus.

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1. Introduction

Infectious diseases are a global problem, especially due to the emergence of new potentially dangerous infectious agents (1). The betacoronavirus genus is an example of a family of emerging diseases with pandemic potential (2): severe acute respiratory syndrome (SARS-CoV) in 2002, Middle East respiratory syndrome (MERS-CoV) in 2012 (3,4), and the first SARS-CoV-2 cases in 2019 (5,6). SARS-CoV-2 was declared a pandemic by the World Health Organization on March 11, 2020.

Articles analyzing the clinical features of the first SARS-CoV-2 outbreak reported a high incidence of rather nonspecific symptoms such as fever, cough, respiratory distress or diarrhea (7-9), with no mention of neurological manifestations. Neurological manifestations were first evaluated by Mao et al. 2020(10), where they were estimated to appear in 36% of COVID-19 patients. The most common symptoms found were dizziness, headache, loss of taste and loss of smell. The first case of seizures associated with COVID-19 was also reported in this study. However, most later reviews reported diver-

se neurological alterations (headache, dizziness or altered level of consciousness), with a much lower prevalence compared to respiratory complications (11,12). For this reason, neurological manifestations were reported later.

Regarding pathophysiology, the neuroinvasive pathway of SARS-CoV-2 is uncertain. Mainly, two hypothetical pathways have been suggested: neural dissemination (Figures 1 and 2) through the olfactory nerve and the cribriform plate, a pathway previously demonstrated for MERS-CoV and SARS-CoV in animals (13,14) and humans (15-17); and hematogenous dissemination (Figure 3) through cerebral circulation (18). Considering these possible pathways, neural invasion of SARS-CoV-2 may occur in a similar manner and be related to neurological symptoms (11).

Although there is an increasing number of articles on long-term, neurological sequelae in patients with COVID-19, there is still not much evidence on this regard and more studies are still needed to estimate them. Therefore, we performed a systematic review of the current literature on the topic, focusing on a very specific neurological manifestation: new-onset seizures. The reported cases of seizures caused by COVID-19 are few and the incidence is low. Still, they should not be dismissed, since they have an effective treatment and early detection could be of great clinical importance (19).

Therefore, the aim of this systematic review is to study the relationship between SARS-CoV-2infection and the development of new-onset seizures in patients who had not been previously diagnosed with epilepsy. The possible etiology of this manifestation, its outcome and potential associated comorbidities are also investigated.

2. Methods

A systematic review of the literature on COVID-19 and its neurological sequelae was performed. Special focus is placed on seizures in patients who had not been previously diagnosed with epilepsy. The PRISMA statement for reporting systematic reviews was followed as a guideline to develop this review (20).

2.1. Search strategy

A systematic search of articles and preprints was conducted in three databases (MedLine, Scopus and Web of Science) between February 24 and March 7, 2021. The MeSH terms and keywords used when searching for articles on seizures as a sequela of COVID-19were: ("SARS-CoV-2" OR "COVID-19") AND ("Seizures" OR "Status Epilepticus" OR "Electroencephalography" OR "EEG") NOT ("Epilepsy").

2.2. Data management

The articles found after searching the databases were imported to Zotero (a free reference manager). After eliminating duplicates, the title and abstract of the remaining articles were read, eliminating those that were not related to the topic. The articles that were not relevant to the topic, those that did not mention seizures in patients with COVID-19 and those that only focused on neurological sequelae in general were also dismissed. Once the articles were screened, the reading process began to select the definitive articles for this systematic review. The selection criteria were the following:

1. Original studies, cohort studies, case and control studies or case series published in English that provided information about patients not diagnosed with epilepsy who developed seizures in the context of COVID-19.
2. Articles that provided sufficient information about patients, neurological symptoms (especially seizures), tests performed (imaging and laboratory tests), treatments and patients' progress.
3. Articles where the patients had tested positive for SARS-CoV-2 by any diagnostic method (PCR, serological tests or antigen test).

The exclusion criteria were:

1. Systematic or narrative reviews, meta-analyses or letters to the editor.
2. Studies that did not provide enough information about patients or studies where the information provided was not relevant for this review.

The choice of including or excluding the remaining articles was made by two of the three authors to avoid selection, performance or attrition bias. Once the choice had been made, the results were shared and any discrepancies were solved through dialogue. The selected articles were screened for other references that could provide original information about the topic of the study that may have been accidentally overlooked during the systematic search. The inclusion and exclusion criteria were applied to the relevant references. Figure 4 (PRISMA flowchart) summarizes the process described above.

Lastly, two of the authors performed a bias assessment of all the observational studies included in the review using a modified version of the Newcastle-Ottawa Scale (NOS)to determine the quality of the studies. Discrepancies between the authors were solved through dialogue. As the NOS is not suitable for assessing case-control studies, these

were excluded from the assessment because, according to the level of evidence of the JAMA network, these are the most biased (21).

3. Results

Of the 790 records identified, 21 studies were included in this systematic review, following the procedure described above. The selected articles are summarized in Tables 1, 2 and 3. Table 2 includes the values obtained on the modified NOS (22). The values were classified as unsatisfactory (0-3 points), satisfactory (4-5 points), good (6-7 points) and very good (8-9 points). Following these criteria, four articles were rated as satisfactory, three as good and one as very good. The detailed assessment of bias for each article according to the modified NOS can be found in the appendix (Table 1).

Table 1 summarizes the information obtained (23-35). Some of the most common symptoms among are fever, cough, vomiting and malaise. Most studies show that patients present comorbidities, although we found some exceptions. For example, in a study by Farsano et al. (26), a patient without previous history developed a seizure with clonic movements of the right arm. In another study by Suhail Hussain (31), a patient with hardly any symptoms experienced four episodes of generalized clonic-tonic seizures. Regarding the treatment, the efficacy of antiepileptic drugs is noteworthy. With the exception of four studies where patients worsened or even died (28, 30), studies showed that patients stopped having seizures and their health status improved until they were eventually discharged.

Tables 2 and 3 summarize the cohort observational studies (36-42). Thanks to the sample size, it was possible to estimate the frequency of new-onset seizures in COVID-19 patients by mathematical analysis. Thus, it was estimated that approximately 2.9% of patients with neurological symptoms derived from COVID-19 will develop new-onset seizures. The total proportion of COVID-19 patients that will develop new-onset seizures was also estimated, as shown in Table 3. It was estimated that 0.67% of COVID-19 patients will suffer from new-onset seizures. Table 2 explains the mathematical analysis performed.

4. Discussion

This systematic review estimated that less than one in ten patients with COVID-19 and neurological symptoms developed seizures, and that out of every 10,000 COVID-19 patients, 67 developed new-onset seizures. These data indicate that although neurological alterations are common among COVID-19 patients (43), this is not the case with seizures. In fact, paradoxically, these cases represent a relatively low proportion (between 1% and 26%) in contrast to other neurological manifestations (36, 38).

Patients that develop new-onset seizures associated with COVID-19 usually share a great number of comorbidities and suffer from severe COVID-19 symptoms. However, despite the severity, most seizures revert successfully with antiepileptic drug treatment (44). In addition, as shown by Hepburn et al., 2020 (33), patients with clinical signs of seizures or unexplained encephalopathy can benefit from electroencephalographic monitoring in addition to empiric antiepileptic treatment.

There are different hypotheses for the appearance of these seizures. On one hand, they might be associated with the pathophysiologic characteristics of severe cases of COVID-19. These cases present hypoxic encephalopathy, cardiovascular events and hypercytokinemia, which might be responsible for triggering these seizures (45). On the other hand, seizures might be caused by invasion of the nervous system by the virus, as suggested in different studies in which was detected in the CSF of COVID-19 patients that subsequently developed encephalitis (46). Lastly, the appearance of seizures in COVID-19 patients might be nothing but a mere coincidence and a matter of chance. This is not surprising considering the extremely low ratio of reported COVID-19 cases with seizures and the total amount of reported COVID-19 cases (47).

Regarding the strengths of this study, it is important to point out the adherence to the PRISMA system when elaborating this review. The exhaustive and comprehensive search carried out, the meticulous interpretation of all the studies included, as well as the assessment of potential bias are also worth highlighting. Moreover, the quality of the studies was determined using the NOS. Regarding the limitations of this study, it is possible that the search equation used and the use of only three databases and may have led to relevant studies being overlooked. The short follow-up time of observational studies may be another possible limitation of this study.

5. Conclusion

Although little is known about the sequelae of COVID-19, this review presents different perspectives and estimates on the incidence rates of new-onset seizures in COVID-19 patients. About 2.9% of COVID-19 patients with neurological symptoms developed new-onset seizures and about 0.67% of the total number of COVID-19 patients developed new-onset seizures. However, with the limited data available, it is currently impossible to establish a

direct association between SARS-CoV-2 infection and the development of new-onset seizures. The pathophysiologic mechanism behind the seizures cannot yet be established, but it can be concluded that antiepileptic drug treatment can successfully revert the seizures and that patients usually make good progress.

Statements

Acknowledgements

The authors of this paper would like to thank the involvement of the coordinating and teaching staff of the "Producción y traducción de artículos científicos biomédicos (III ed.)" and the "Traducción inversa de artículos científicos biomédicos (español-inglés)" courses, as well as the English translation team.

Conflicts of interest

The authors of this paper declare no conflicts of interest.

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FIGURES

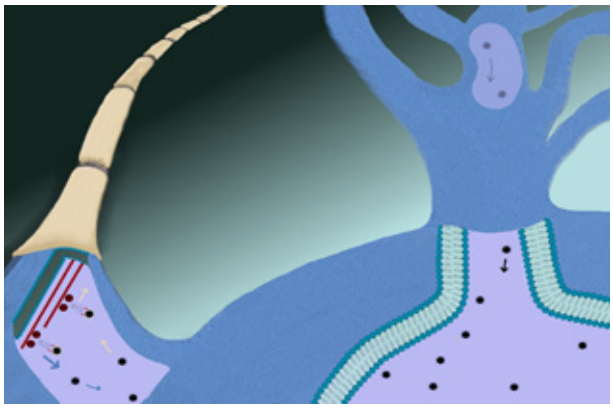

Figure 1. Simplified representation of the axonal transport machinery. On the left, a neuron is depicted with cuts in the soma membrane in some parts of the axonal growth cone. This represents the hypothetical axonal transport of the virus.

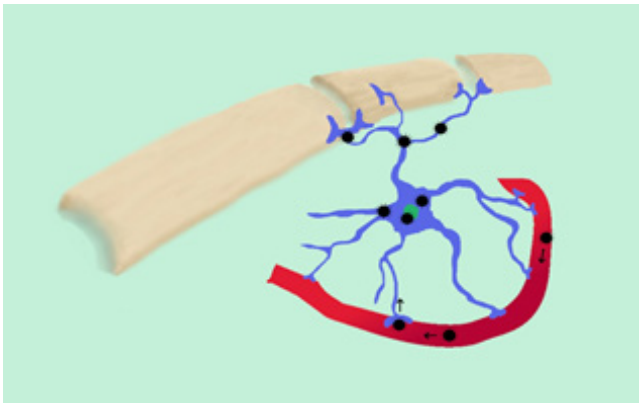

Figure 2. Neural dissemination. Presynaptic exocytosis and postsynaptic endocytosis of the virus are depicted.

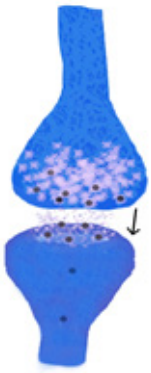

Figure 3. Presence of coronavirus in astrocytes. Representation of an infected astrocyte and hematogenous dissemination.

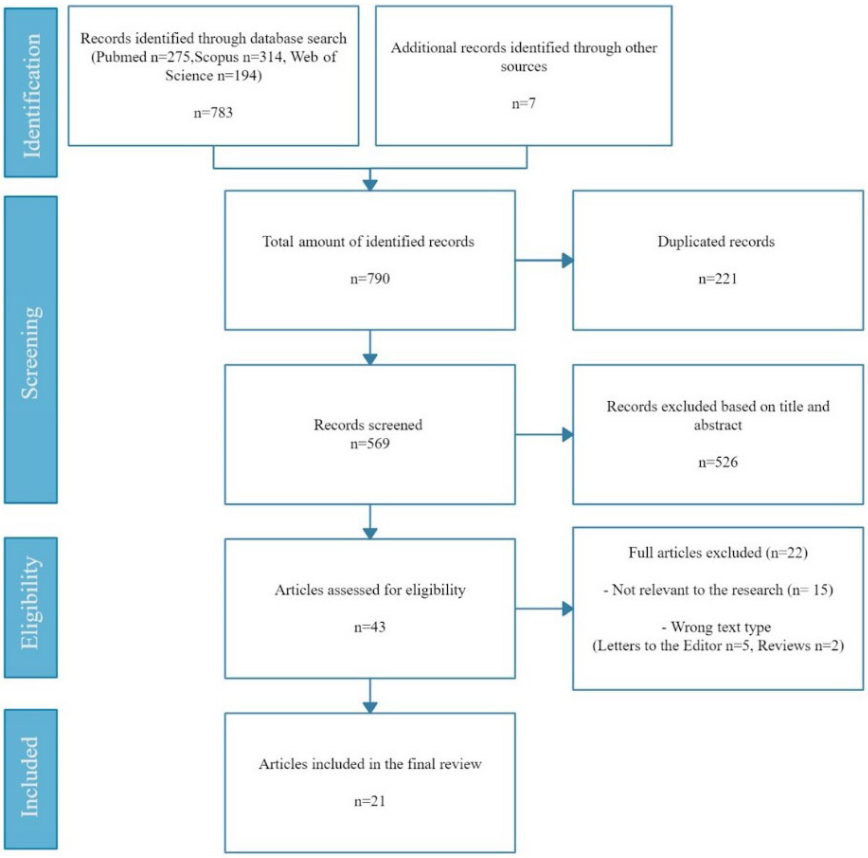

Figure 4. Flowchart following PRISMA guidelines (20).

Author, date and reference	Type of study	(n)	Confirmation SARS-CoV-2	Symptoms	Comorbidities	New-onset seizures	Drug therapy	Outcome
Wendy Chen et al., 2020 (23)	Case series	5	Positive on nasopharyngeal swab	Case 1: diarrhea for one week Case 2: progressive shortness of breath, myalgia, diarrhea, chest and abdominal pain for one week Case 3: shortness of breath and myalgia Case 4: not mentioned Case 5: generalize weakness, fever, nausea and vomiting	Case 1: dialysis Case 2: hypertension Case 3: no history Case 4: diabetes, pulmonary hypertension, heart and kidney transplant Case 5: hypertension, diabetes, kidney failure	Case 1: myoclonic movements Case 2: status epilepticus detected in EEG Case 3: generalized seizure episode Case 4: seizure-like movements Case 5: not mentioned	Case 1: levetiracetam and phenytoin Case 2: levetiracetam Case 3: levetiracetam Case 4: levetiracetam Case 5: not mentioned	Case 1: discharges decreased and mental state improved Case 2: progressive improvement of mental state and discharges Case 3: not mentioned Case 4: not mentioned Case 5: not mentioned
Muddasir Ashraf et al., 2020 (24)	Case series	3	Positive (RT-PCR)	Case 1: seizures Case 2: altered mental status Case 3: seizures	Case 1: dementia and seizures Case 2: hypertension, type 2 diabetes and dementia Case 3: heart attack, Crohn's disease, hyperlipidemia and dementia	Case 1: five generalized seizure episodes Case 2: generalized seizures Case 3: generalized seizures	Case 1: antiepileptic medication Case 2: levetiracetam (keppra) Case 3: levetiracetam	Case 1: clinical improvement Case 2: clinical improvement Case 3: progressive improvement
Riwaj Bhagat et al., 2020 (25)	Case report	1	Positive (RT-PCR)	Five-minute episode of loss of consciousness, headache, diaphoresis, palpitations and nausea	Paroxysmal atrial fibrillation, hypertension, hepatosteatosis, glucose-6-phosphate dehydrogenase deficiency	One minute long generalized convulsion followed by 15 minutes of confusion	Lorazepam, levetiracetam, heparin, amiodarone y diltiazem	Seizures ceased, no neurologic deficits
Antonio Fasano et al., 2020 (26)	Case report	1	Positive (RT-PCR)	Seizure, conjunctivitis, fever. Came back days later with high fever, cough and shortness of breath	No history	Seizure with clonic movements in the right arm and loss of consciousness	Lopinavir-ritonavir	Seizures ceased

(continued on next page)

Author, date and reference	Type of study	(n)	Confirmation SARS-CoV-2	Symptoms	Comorbidities	New-onset seizures	Drug therapy	Outcome
S. Haddad et al., 2020 (27)	Case report	1	Positive (RT-PCR)	Abdominal pain, fever, vomiting, confusion, dry cough	Well-controlled HIV	Tonic-clonic seizure on day 2 of admission	Hydroxychloroquine, azithromycin	Extubation on day six and clinical improve
Sandeep Sohal et al., 2020 (28)	Case report	1	Positive (RT-PCR)	Hypoglycemic episode	Hypertension, coronary stent, type 2 diabetes, hemodialysis	Long-lasting generalized tonic-clonic movements of upper and lowers extremities for 2-3 days on day 3 of admis	Hydroxychloroquine, azithromycin, levetiracetam	Died on day five
Sean T. Hwang et al., 2020 (29)	Case series	4	Positivenasopharyngeal swab	Case 1: fever, cough, vomiting and malaise Case 2: fever, cough, headache and iron deficiency anemia Case 3: headache, malaise, vomiting and cough Case 4: diarrhea, fever, malaise, cough and shortness of breath	Case 1: not mentioned Case 2: not mentioned Case 3: hypertension, kidney failure, type 2 diabetes Case 4: not mentioned	Case 1: three consecutive generalized tonic-clonic seizure episodes Case 2: two episodes of generalized tonic-clonic seizure Case 3: two episodes of generalized tonic-clonic seizure Case 4: status epilepticus	Case 1: acyclovir, ceftriaxone, hydroxychloroquine, tocilizumab, levetiracetam and lorazepam Case 2: heparin, acetazolamide, levetiracetam and enoxaparin Case 3: lorazepam, levetiracetam, labetalol Case 4: hydroxychloroquine, ceftriaxone, lorazepam and levetiracetam	Case 1: discharged on day 25 Case 2: clinical improvement Case 3: discharged on day 21 Case 4: discharged on day 49
Ava Hamidi et al., 2020 (30)	Case report	1	Positive (RT-PCR)	Progressive cough, fever and dyspnea on day five	Former opioid user	Generalized tonic-clonic seizure on day nine	Methadone, hydroxychloroquine, levetiracetam	Progressive mental deterioration, died on day 17
Suhail Hussain et al., 2020 (31)	Case report	1	Positive (RT-PCR) nasopharyngeal swab	No other symptoms (neither neurological nor respiratory). No fever	No comorbidities	Four generalized episodes of generalized clonic-tonic seizures	Levetiracetam 500 mg twice a day. Low-molecular-weight heparin subsequently changed by rivaroxaban15 mg twice daily for the first three weeks	He remained stable through the course of admission and was discharged to a quarantine center

(continued on next page)

Author, date and reference	Type of study	(n)	Confirmation SARS-CoV-2	Symptoms	Comorbidities	New-onset seizures	Drug therapy	Outcome
Zohaib Khan et al., 2020 (32)	Case report	1	Positive nasopharyngeal swab	Altered mental status, pneumonia, fever and Guillain-Barre syndrome	Morbid obesity and gastroesophageal reflux	Fall from the bed followed by convulsive movements	Levetiracetam, lorazepam and phenytoin (seizures prevention). Antibiotics, aciclovir. Anticoagulation with heparin and apixaban	Hemodynamically stable, mental state gradually improved
Madihah Hepburn et al., 2020 (33)	Case series	2	Positive	Case 1: lower extremity pain, fever, encephalopathy Case 2: progressive dyspnea for 10 days, altered mental status, generalized weakness	Case 1: asthma, high blood pressure, chronic kidney disease, hyperlipidemia Case 2: EPOC, venous thromboembolic disease, chronic kidney disease	Case 1: three focal seizures for 30 seconds Case 2: frequent seizures detected in EEG	Case 1: vancomycin, piperacilina–tazobactam Case 2: unknown	Case 1: Discharged after 30 days in the ICU Case 2: After 20 days with life support in the ICU, the family opted for withdrawal
Takeshi Moriguchi et al., 2020 (34)	Case report	1	Positive in CSF	High fever, fatigue, headache, encephalitis and loss of consciousness	No comorbidities	Generalized new-onset seizures for a minute, stiff neck	Levetiracetam, favipiravir. Ceftriaxone, vancomycin, acyclovir and steroids	At day 15, the patient remains in ICU: bacterial pneumonia and impaired consciousness due to encephalitis associated with SARS-CoV-2
Asia Filatov et al., 2020 (35)	Case report	1	Positive (RT-PCR) nasopharyngeal swab	Encephalopathy, fever and cough. Headache, altered mental status	Atrial fibrillation, stroke, Parkinson''s disease, chronic obstructive pulmonary disease , recent cellulitis	The EEG showed bilateral slowing and focal slowing in the left temporal region with sharply countered waves	Unknown antiepileptic treatment. Vancomycin, meropenem, acyclovir, hydroxychloroquine, lopinavir, ritonavir and broad-spectrum antibiotics	The patient remains in the ICU, critically ill with poor prognosis

Table 1. Summary of the reviewed case reports or case or series with extensive individualized patient information.

Author, date and reference	Type of study	Participants (n)	Follow-up time	Patients with neurological disorders	Patients with new on-set seizures	NOS
Krishna Nalleballe et al., 2020 (36)	Cohorts	n=40,469	1 month	n=9086 (22.5%)	n=258 (2.8%)	8
Brandon L. Waters et al., 2021 (37)	Cohorts	n=79	4 months	n=6 (7.5%)	n=3 (3.7%)	4
Ling Mao et al., 2020 (10)	Cohorts	n=214	1 month	n=78 (36.5%)	n=1 (1.3%)	7
Carlos Manuel et al., 2020 (38)	Cohorts	n=841	1 month	n=483 (57.4%)	n=5 (1%)	5
Abdelkader Mahammedi et al., 2020 (39)	Cohorts	n=725	1 month	n=119 (16.4%)	n=10 (8.4%)	6
Stephane Kremer et al., 2020 (40)	Cohorts	n=190	1 month	n=190	n=4 (2.1%)	7
Pranusha Pinna et al., 2020 (41)	Cohorts	n=650	2 months	n=50 (7.7%)	n=13 (26%)	4
Sara Radmard et al., 2020 (42)	Cohorts	n=33	3 weeks	n=33	n=6 (18.2%)	4

Table 2. Summary of observational cohort studies that do not provide individualized patient information.

Author, date and reference	Type of study	Participants (n)	Follow-up time	Patients with new-onset seizures
Krishna Nalleballe et al., 2020 (36)	Cohorts	n=40 469	1 month	n=258 (0.64%)
Ling Mao et al., 2020 (10)	Cohorts	n=214	1 month	n=1 (0.47%)
Carlos Manuel et al., 2020 (38)	Cohorts	n=841	1 month	n=5 (0.60%)
Abdelkader Mahammedi et al., 2020 (39)	Cohorts	n=725	1 month	n=10 (1.38%)
Pranusha Pinna et al., 2020 (41)	Cohorts	n=650	2 months	n=13 (2%)

Table 3. Total number of patients with COVID-19 and number of reported new-onset seizures.

Study	Selection				Comparability	Results			Score
	Representativeness of the exposed cohort/sample	Selection of unexposed cohort/ sample size	Determination of the infection	Demonstration that the outcome of interest was not present prior to infection	Comparability of cohorts on the basis of design or analysis of the subjects indifferent outcome groups	Assessment of the results	Was the follow-up long enough for sequalae to occur?	Adequacy of cohort follow-up/statistical analysis	
Krishna Nalleballe et al., 2020 (36)	1	1	1	1	1	1	1	1	8
Brandon L. Waters et al., 2021 (37)	0	0	1	1	0	1	0	1	4
Ling Mao et al., 2020 (10)	1	1	1	1	1	1	0	1	7
Carlos Manuel et al., 2020 (38)	1	0	1	1	0	1	1	0	5
Abdelkader Mahammedi et al., 2020 (39)	1	0	1	1	1	1	0	1	6
Stéphane Kremer et al., 2020 (40)	1	1	1	1	1	1	0	1	7
Pranusha Pinna et al., 2020 (41)	0	0	1	1	0	1	0	1	4
Sara Radmard et al., 2020 (42)	0	0	1	1	1	1	0	0	4

Appendix 1 - Table 1. Bias assessment using the modified Newcastle-Ottawa Scale (NOS).

FIRST RESULT - TABLE 2 (% of COVID-19 patients with neurological manifestations that develop new-onset seizures)		
Author, date and reference	Relative importance (total number of neurological manifestations)	(number of seizures/total number of neurological manifestations) × 100
Nalleballe et al., 2020 (36)	9086	2.8
Mao et al., 2020 (10)	78	1.3
Carlos Manuel et al., 2020 (38)	483	1
Mahammedi et al., 2020 (39)	119	8.4
Kremer et al., 2020 (40)	190	2.1
Pinna et al., 2020 (41)	50	26
Radmard et al., 2020 (42)	33	18.2
	% of COVID-19 patients with neurological manifestations that developed new-onset seizures:	
	WEIGHTED ARITHMETIC MEAN	**2.921047913**
Observations	Waters et al., 2021 is not included in this analysis since they do not report the total number of patients that developed neurological manifestations.	

SECOND RESULT - TABLE 3 (% of COVID-19 patients that developed new-onset seizures)		
Author, date and reference	Relative importance (total number of COVID-19 patients)	(number of seizures/ total number of COVID-19 patients) × 100
Nalleballe et al., 2020 (36)	40,469	0.64
Mao et al., 2020 (10)	214	0.47
Carlos Manuel et al., 2020 (38)	841	0.6
Mahammedi et al., 2020 (39)	725	1.38
Pinna et al., 2020 (41)	650	2
	% of COVID-19 patients with neurological manifestations that developed new-onset seizures:	
	WEIGHTED ARITHMETIC MEAN:	**0.6714804541**

Appendix - Table 2. Mathematical analysis carried out to obtain the results.