Characteristics of Patients with SARS-CoV-2 Positive Cerebrospinal Fluid: A Systematic Review

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Abstract

Background: The coronavirus disease 2019 (COVID-19) has been shown to affect several systems, notably the respiratory system. However, there has been considerable evidence implicating the nervous system in COVID-19 infection. This study aims to investigate the clinical characteristics of patients whose cerebrospinal fluid (CSF) tested positive for SARS-CoV-2.

Methods: A comprehensive search of PubMed, EMBASE, Scopus, WHO Coronavirus database, bioRxiv, medRxiv, and Web of Science databases was carried out in August 2020. Original studies involving patients who tested positive for SARS-COV-2 in their CSF were included. Key search terms encompassed all variations of "COVID-19" AND "Cerebrospinal Fluid".

Results: A total of 525 studies were identified. 56 full-text articles were assessed, of which 14 were included. In total, 14 patients tested positive for SARS-CoV-2 in their CSF. 21.4% (3/14) of patients had negative nasopharyngeal (NP) swabs despite a positive CSF sample. 14.2% (2/14) of patients who initially had positive NP swabs developed neurological deterioration after a supposed recovery as indicated by their negative NP swabs, but their CSF still tested positive for SARS-CoV-2. Common symptoms were headache (42.8%; 6/14), fever (35.6%; 5/14), vomiting (28.6%; 4/14), cough (28.6; 4/14), visual disturbances (28.6%; 4/14), diarrhea (21.4%; 3/14), and seizures (21.4%; 3/14). Four patients (28.6%) were admitted to ICU, one (7.14%) was admitted to a rehabilitation facility, and two (14.3%) died.

Conclusions: Physicians should be familiar with the presenting neurological features of COVID-19, and be aware that they can occur despite a negative NP swab. The results of this study are intended to aid in the development of informed guidelines to diagnose and treat COVID-19 patients with neurological manifestations.

1. Background

Coronavirus Disease 2019 (COVID-19) is a novel infectious disease capable of causing mild to severe illness, typically respiratory, in both humans and animals. It belongs to a wider family of viruses known as *Coronaviridae*, and is a new strain among six others commonly known to cause disease in humans. The virus responsible for COVID-19, referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), resides primarily in the respiratory tract and causes symptoms such as cough, sore throat, and nasal congestion. However, it has recently been shown to have neuroinvasive potential.[1]

Infected patients globally have been reported to have headaches, paresthesia, anosmia, ageusia, neuralgia, and dizziness. [2]

Additionally, several single case reports and cohort studies have reported rare cases of meningoencephalitis, seizures, and immune-mediated neurological diseases.[3]

Dealing with a pandemic of this magnitude requires rapid and effective diagnostic tools to help combat the disease as early as possible. The diagnostic tool most widely implemented globally is the reverse transcriptase polymerase chain reaction (RT-PCR)[4]. It is a real time diagnostic test used to detect SARS-CoV-2, and subsequently diagnose COVID-19. An amplification of a nucleic acid segment followed by the use of probes to identify regions on the virus's nucleocapsid gene, helps clinicians diagnose potential carriers of the virus.

SARS-CoV-2 RT-PCR is typically conducted on a Nasopharyngeal (NP) swab, however, it can also be conducted on a cerebrospinal fluid (CSF) sample. The latter requires a Lumbar Puncture (LP). This procedure involves patients lying on their side with their knees bent to their chest, to open up the intervertebral space. The physician will then disinfect the skin and insert a thin spinal needle between L3-4 to obtain 6-15ml of CSF. lower back pain may be felt alongside localized bruising and bleeding.[5] [6] [7]

This systematic review aims to compile and synthesize the results from original studies that report on patients who tested positive for SARS-CoV-2 via their CSF sample. Our study investigates the unique clinical manifestations and characteristics of this patient cohort, along with relevant outcomes, disease progression and management. In order to better understand this novel disease, it is critical to address and study the impact the virus has on the CNS and its clinical course. Furthermore, we hope our findings will help identify when to consider PCR CSF tests despite a negative NP swab test(8).

The clinical importance of this study lies in establishing evidence of CNS involvement in the pathogenesis of COVID-19, which inturn can assist in the development of new guidelines to diagnose and treat COVID-19 patients with neurological involvement.

SARS-CoV-2 can either infiltrate the peripheral nervous system (PNS) and migrate to the CNS or directly infect the CNS.(9) There are three postulated mechanisms of transmission of the SARS-CoV-2 virus via the PNS: the transcribial route, axonal transport and trans-synaptic transfer, and hematogenous and/or lymphatic route.(10) Transcribial route involves a primary olfactory infection followed by infiltration into the subarachnoid space via the cribriform plates.(9, 11) The axonal transport and trans-synaptic transfer hypothesis suggests that an initial infection of peripheral nerve terminals results in a migration of the virus, up the nervous system, to the trigeminal, olfactory, and/or vagus nerve.(9, 11) It is important to note that both the gastrointestinal and the respiratory branches of the vagus nerve are susceptible to the infection.(12–14) An infection of the CNS may occur via direct contact of the SARS-CoV-2 virus with the brain microvascular endothelial cells. This in-turn leads to abluminal virus release into the CNS parenchyma. Lastly, compromised tight junctions at the blood brain barrier or virally infected leukocytes may gain access to the CNS via endocytosis.(14, 15)

2. Methods

2.1. Eligibility

We included original studies (Case reports, case studies, cohort studies, cross sectional studies, randomised control trials, letters to the editor reporting original findings) that investigated the clinical course, outcomes, prognosis, management and characteristics of patients who tested positive for SARS-COV-2 in their CSF using RT-PCR test. Exclusion criteria included Non-English articles, animal studies, and non-original articles (e.g. editorials and commentaries).

2.2. Search Strategy

We conducted our search in PubMed NCBI, Excerpta Medica dataBASE, Scopus, WHO COVID-19 Global literature on coronavirus disease database, Biorxiv and Medrxiv, and Web of Science on August 24th, 2020 using the following search terms: (("Cerebrospinal fluid"[Mesh]) OR ("CSF" OR "Cerebrospinal fluid" OR "Cerebral spinal fluid" OR "Cerebro-spinal fluid" OR "Lumbar puncture" OR "Spinal tap")) AND ("coronavirus"[MeSH] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "covid 2019"[All Fields] OR "SARS2"[All Fields] OR "SARS-CoV-2"[All Fields] OR "SARS-CoV-19" [All Fields] OR "severe acute respiratory syndrome coronavirus 2" [supplementary concept] OR "coronavirus infection"[All Fields] OR "severe acute respiratory pneumonia outbreak"[All Fields] OR "novel cov"[All Fields] OR "2019ncov"[All Fields] OR "sars cov2"[All Fields] OR "cov22"[All Fields] OR "ncov"[All Fields] OR "covid-19"[All Fields] OR "covid19"[All Fields] OR "coronaviridae"[All Fields] OR "corona virus"[All Fields]). The selection criteria was limited to papers published from December 2019 until August 2020 and papers written in English.

2.3 Study selection

After deduplication of the titles, two reviewers independently screened all the titles and abstracts of the papers according to the predefined inclusion and exclusion criteria. Next, full texts of potentially eligible studies were retrieved and reviewed

independently by two authors. A third author resolved any disagreement. Reviews that included patients who tested positive for SARS-CoV-2 in their CSFwere cross checked to identify any studies that matched our eligibility criteria.

2.4 Data Extraction

Data was extracted via a dual approach by two independent reviewers, and inserted into a standardized review sheet. Data collected includes study characteristics (study title, authors, date of publication, publication type, study site, number of subjects), population characteristics, clinical findings, radiological findings, management and final outcome. A third author resolved any disagreement.

2.5 Risk of bias in individual studies

Two authors assessed the quality of the selected articles utilizing the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. Quality assessment of case reports was carried out using Joanna Briggs Institute (JBI) critical appraisal checklist for case reports.

3. Results

3.1. Study selection

An initial search of seven databases yielded a total of 525 publications. 56 full-text articles were included and assessed for eligibility post abstract screening for relevance and deduplication, of which 14 were qualitatively analyzed. After the application of the inclusion/exclusion criteria they were narrowed down to 14. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram explaining the steps of identification, screening, inclusion and exclusion is presented in Fig. 1.

3.2. Study characteristics

Of the 14 articles included in this study, nine were case reports(15–23), three were retrospective studies(24–26), one was a letter to the editor reporting original data of a patient(27), and one follow up letter to the editor of the same latter patient(28),. All were published in 2020. The studies were conducted worldwide, including France, USA, Spain, Brazil, Japan, Turkey, Sweden, UAE, France, Germany and Iran (Table 1). From the 14 eligible studies identified, the total sample size was 733. Out of these, only 14 patients tested positive for SARS-CoV-2 in their CSF samples. As the scope of this review is to investigate only patients who tested positive for SARS-CoV-2 in their CSF according to the eligibility criteria, we only described these 14 patients

Table 1
Characteristics of included studies.

Study	Authors	Country	Research Design	Sample Size	Number of CSF-Positive Cases	Gender	Age
1	Grégory Destras, et al.	France	Retrospective Cohort Study	555	2	N/A	Adults
2	Y. H. Huang, et al.	USA	Case Report	1	1	F	40
3	J. Cebrián, et al.	Spain	Case Report	1	1	F	74
4	Renan Barros Domingues, et al.	Brazil	Case Report	1	1	F	42
5	T. Moriguchi, et al.	Japan	Case Report	1	1	M	24
6	N. Fadakar, et al.	Iran	Case Report	1	1	M	47
7	G. Demirci Otluoglu, et al.	Turkey	Case Report	1	1	M	48
8	J. Helms, et al.	French	Cohort Study	140	1	N/A	N/A
9	Elham Rostami, et al.	Sweden	Case Report	1	1	F	55
10	M. Al-olama, et al.	UAE	Case Report	1	1	M	36
11	M. Mardani, et al.	Iran	Case Report	1	1	F	64
12	S. Kremer, et al.	France	Retrospective Cohort	28	1	N/A	N/A
13	T. H. Westhoff, et al.	Germany	Case Report	1	1	M	69

CSF = Cerebrospinal fluid; N/A = Not Available; M = male; F = Female

Clinical Course and Diagnosis

In 21.4% (3/14) of cases, nasopharyngeal (NP) swabs initially tested negative despite a positive CSF sample(15, 17, 18). 14.2% (2/14) of positive cases as per NP swab tested negative after supposed recovery, but progressed to neurological deterioration and positive CSF tests(20, 22). 10/14 patients had both positive nasopharyngeal sample and CSF sample(16, 19–25, 28) (in two of these cases CSF was not tested initially, but was found to be positive at post-mortem), however samples were not always positive on the first test; 3/14 cases demonstrated a positive nasopharyngeal test but an initially negative CSF test(20, 22, 28). Table 2 summarises the clinical and diagnostic findings.

Table 2
Summary of presentation and clinical course of all cases testing positive for SARS-CoV-2 in CSF samples.

Study	Author	NP Result	Positive CSF Result	General Signs	Neural Signs & Symptoms	Respiratory Symptoms
1	Grégory Destras, et al.	Positive	2/555	N/A	N/A	N/A
2	Y. H. Huang, et al.	Positive	1	Fever; Lethargy	Headache; Seizures; Photophobia; Impaired consciousness; Neck stiffness	None
3	J. Cebrián, et al.	Positive	1	Myalgia; Nausea;Vomiting	Headache; Photophobia; Visual disturbance (blurred binocular vision); Incoherent speech	None
4	Renan Barros Domingues, et al.	Negative	1	Diarrhoea	Paresthesia and hypoesthesia of the left upper limb; Left hemithorax and hemiface	Common cold; Nasal obstruction
5	T. Moriguchi, et al.	Negative	1	Fever; Fatigue	Headache; Seizures (transient generalised); Impaired consciousness	Sore throat
6	N. Fadakar, et al.	Positive	1	Myalgia; Fatigue	Headache; Visual disturbances (saccade eye movements, optokinetic and end gaze rotational nystagmus); Gait disturbances; Vertigo	Cough
7	G. Demirci Otluoglu, et al.	N/A	1	Myalgia; Fatigue	Headache; Neck stiffness; Anosmia	Cough
8	J. Helms, et al.	Positive	1/140	N/A	N/A	Acute respiratory distress syndrome
9	Elham Rostami, et al.	Positive	1	Fever; Myalgia	Impaired brain stem reflexes	None
10	M. Al-olama, et al.	Positive	1	Fever; Myalgia, Diarrhoea; Vomiting	Headache; Impaired consciousness	Cough; Pharyngitis
11	M. Mardani, et al.	Positive	1	Generalised weakness	Impaired consciousness	Acute progressive dyspnoea
12	S. Kremer, et al.	N/A	1/28	N/A	N/A	N/A
13	T. H. Westhoff, et al.	Positive	1	Fever; Diarrhoea	Seizures (convulsive); Left-sided neglect	Cough

N/A = Not Available; CSF = Cerebrospinal Fluid.

Symptoms

Most commonly reported symptoms included: Headache (6/14)(15–17, 19, 21, 28), fever (5/14)(17, 20, 21, 23, 28), vomiting (4/14)(16, 21), cough (4/14)(15, 19, 21, 23), visual disturbances (4/14)(16, 19, 23, 28), diarrhea (3/14)(18, 21,

23), and seizure (3/14)(17, 23, 28)(Table.2). In two of the studies, the patients' COVID status was identified as severe(25, 26) and in one of these cases the patient was noted to be suffering from acute respiratory distress syndrome(25). Neurological symptoms were cited as the reason CSF test was carried out in 6/14 of the studies(16–18, 20, 22, 28).

Lab findings

Studies of the positive patients' CSF samples (Table 3) revealed leukocytosis in 2/14 patients(17, 22), elevated protein in 3/14(22, 23, 28), hypoglycorrhachia in 1/14(22), and an elevated RBC in 1/14 samples(28). D-dimers were elevated in 3/14 blood samples(16, 21, 22).

Table 3
Blood and cerebrospinal fluid lab findings of cases with SARS-CoV-2 positive CSF samples.

Study	Author	Laboratory Findings						
		CSF Sample				Blood Sample		
		RBC	WBC	Protein	Glu	WCC	Glu	CRP
1	Grégory Destras, et al.	Data could not be extracted						
2	Y. H. Huang, et al.	↑	N/A	↑	*	↑ (100% lymphocytes)	*	N/A
3	J. Cebrián, et al.	N/A	N/A	N/A	N/A	↑	N/A	↔
4	Renan Barros Domingues, et al.	N/A	↔	↔	↔	N/A	N/A	↔
5	T. Moriguchi, et al.	↔ None	↑ (10MN**, 2PMN***)	N/A	N/A	↑ (Neutrophil Predominant)	N/A	↑
6	N. Fadakar, et al.	N/A	N/A	N/A	N/A	↔ (32% lymphocytes)	N/A	↔
7	G. Demirci Otluoglu, et al.	N/A	↔	↔	↑	↔ (24.4% lymphocytes, 62.8% Neutrophils)	↑ 105mmol/L****	↔
8	J. Helms, et al.	Data could not be extracted.						
9	Elham Rostami, et al.	N/A	N/A	N/A	N/A	↔ / ↑	N/A	↔/ ↑
10	M. Al-olama, et al.	N/A	N/A	N/A	N/A	↑	↑	↔
11	M. Mardani, et al.	N/A	↑ (90% polymorph)	↑	↓	↑ Polymorphs > lymphocytes	↑	N/A
12	S. Kremer, et al.	Data could not be extracted.						
13	T. H. Westhoff, et al.	N/A	↔ (100% lymphocytes)	↑	↔	↓ Lymphopenia	N/A	↑

*Units Not Reported, **Polymorphonuclear, ***Mononuclear. ****Non-fasting blood glucose

RBC = Red blood cells; WBC = White blood cells; Glu = Glucose; WCC = White cell count; CRP = C-reactive protein; N/A = Not available; ↑= elevated levels; ↓= decreased levels; ↔= normal levels

Radiological findings

Radiological findings (CXR, chest CT, systemic CT, Brain MRI and head CT) were reported for 11/14 patients. However, we could NOT extract the data from one cohort study(26). Radiological findings were normal in 2/14 patients(18, 28). The most common findings on brain MRI FLAIR were hyperintense regions in different areas of the brain (6/14)(15, 17, 19–21, 23), and the commonest finding on chest CT was ground glass opacities in the lungs (5/14)(15, 17, 20, 22) (23)(Table 4).

Table 4
Radiological findings of cases with SARS-CoV-2 positive CSF samples.

Study	Authors	Chest findings	Brain MRI	Head CT
1	Grégory Destras, et al.	N/A	N/A	N/A
2	Y. H. Huang, et al.	Unremarkable.	N/A	Unremarkable.
3	J. Cebrián, et al.	Unremarkable.	Right parietal cortical-subcortical restricted diffusion	Unremarkable.
4	Renan Barros Domingues, et al.	Unremarkable.	Unremarkable.	Unremarkable.
5	T. Moriguchi, et al.	Ground glass opacities	Hyperintense lesions in the right mesial temporal lobe and hippocampus; Slight hippocampal atrophy.	Unremarkable.
6	N. Fadakar, et al.	N/A	Bilateral cerebellar hemispheres and vermis hyperintensities; Edema; Cortical-meningeal enhancement of cerebellum	N/A
7	G. Demirci Otluoglu, et al.	Ground glass opacities; Consolidation	Hyperintense lesions in the posterior medial cortical surface of the temporal lobe; Hyperintense lesions in the upper cervical spinal cord.	Unremarkable.
8	J. Helms, et al.	N/A	N/A	N/A
9	Elham Rostami, et al.	Ground Glass opacities/ consolidations.	1st Brain MRI: Acute necrotizing encephalitis. 2nd Brain MRI: Partial regression of the changes in the brainstem and medial temporal lobes; More pronounced hyperintensities in central thalami and subinsular regions.	Symmetrical hypodensities in the thalami; Low attenuation areas in the thalami and midbrain.
10	M. Al-olama, et al.	Unremarkable	Right frontal intracerebral hematoma; Subarachnoid hemorrhage in the ipsilateral sylvian fissure and frontal and temporal lobes; Acute subdural hematoma; Edema causing midline shift.	Hyperintensities in the bilateral supratentorial leptomeningeal area; Chronic right subdural hematoma; Re-reabsorbing intracerebral hematoma; Perilesional brain edema causing midline shift.
11	M. Mardani, et al.	Bilateral Pleural effusion; Collapse consolidation of basal segments; Patchy ground-glass opacities	N/A	N/A
12	S. Kremer, et al.	Data could not be extracted		

Study	Authors	Chest findings	Brain MRI	Head CT
13	T. H. Westhoff, et al.	Ground-glass opacities; Consolidation	Linear meningeal hyperintensities; White matter edema	N/A

EEG findings

EEG findings were reported in two studies(20, 28), two of which noted a similar generalised slowing of waves with no epileptic activity(20, 28). One of these patients was noted to have a previous seizure(28).

Management and Treatment

The management of 4 patients was not discussed in their respective studies(18, 24–26), while the management for the remaining patients varied. Invasive intervention was required in two patients: Surgery was performed on 1/14 patients to remove the chronic subdural haematoma(21) and endotracheal intubation and mechanical ventilation was required on another patient with impaired consciousness(17). The mainstay initial management in 4/14 patients was acyclovir(15, 20, 22, 28)/This was however discontinued in one patient following negative herpes simplex virus results(28). Levetiracetam was given in 3/14 patients(15, 23, 28) and hydroxychloroquine was administered to 5/14 patients(15, 16, 22, 23, 28). Table.5 shows the management and outcomes of the 14 SARS-CoV-2 CSF positive patients.

Table 5
The management and outcomes of SARS-CoV-2 CSF positive patients.

Study	Authors	Antivirals	Antibiotics	Antiepileptics	Other Medications	Outcomes
1	Grégory Destras, et al.	N/A	N/A	N/A	N/A	Death (2)
2	Y. H. Huang, et al.	Acyclovir	Ceftriaxone/Vancomycin	Levetiracetam	HCQ	Full Recovery
3	J. Cebrián, et al.	Lopinavir/ Ritonavir	Ceftriaxone	none	Pain drugs; Fluid replacement; Oxygen therapy; HCQ; Acetaminophen; Dexketoprofen; Acetylsalicylic acid	Discharged
4	Renan Barros Domingues, et al.	N/A	N/A	N/A	N/A	Full recovery
5	T. Moriguchi, et al.	Aciclovir; Favipiravir	Ceftriaxone; Vancomycin	Levetiraceta	Endotracheal intubation + Mechanical ventilation; Steroids	ICU
6	N. Fadakar, et al.	Lopinavir; Ritonavir	none	none	none	Discharged
7	G. Demirci Otluoglu, et al.	Favipiravir; Acyclovir	Piperacillin/Tazobactam	Levetiracetam	HCQ; Steroids	Stable under treatment
8	J. Helms, et al.	N/A	N/A	N/A	N/A	ICU
9	Elham Rostami, et al.	Acyclovir	none	none	IVIG; Immunotherapy with plasma exchange	Discharged; Rehabilitation
10	M. Al-olama, et al.		none	none	Burr hole	ICU
11	M. Mardani, et al.	Lopinavir/ Ritonavir; Acyclovir	Ceftriaxone; Clindamycin; Meropenem; Vancomycin; Ampicillin	none	HCQ; Steroids; Folinic acid; Fluorouracil; Irinotecan	N/A
12	S. Kremer, et al.	N/A	N/A	N/A	N/A	N/A

N/A = Not available; HCQ = Hydroxychloroquine; IVIG = intravenous immunoglobulin G; ICU = Intensive Care Unit.

Study	Authors	Antivirals	Antibiotics	Antiepileptics	Other Medications	Outcomes
13	T. H. Westhoff, et al.	none	none	Levetiracetam	Steroids; Insulin; Oxygen supply; Tacrolimus; HCQ	ICU → full recovery
N/A = Not available; HCQ = Hydroxychloroquine; IVIG = intravenous immunoglobulin G; ICU = Intensive Care Unit.						

Clinical Outcomes

The outcomes at the end of the study periods varied in these 14 SARS-CoV-2 CSF positive patients (Table 5). 2/14 deaths(24) and 4/14 ICU admissions(17, 21, 25) were reported overall. Symptoms improved in 1/14 cases who remained admitted(15), while 6/14 cases were discharged/recovered(16, 18–20, 23, 28), and 1/14 was transferred to a rehabilitation centre(20). Outcomes were not stated for two of the 14 patients(22, 26).

3.5 Risk of bias across studies

Bias assessment is documented in Appendix 1.

4. Discussion

The implications of COVID-19 on extra-respiratory systems and the disease's diverse manifestations have gathered a lot of attention from specialists across the spectrum. The nervous system has been no exception, with neurological manifestations of the disease ranging from a characteristic loss of smell and taste to less frequently reported severe neuroinflammatory disorders.(2) In fact, according to a case series of 214 patients in Wuhan, China, neurologic symptoms may be as common as 36.4% generally, and up to 45.5% of those with severe infection.(29) Beyond its role in pathogenesis and disease progression however, the presence of the SARS-CoV-2 virus in the nervous system, specifically in the brain tissue or CSF, is associated with important diagnostic considerations as well. In this study, we systematically reviewed all reports of RT-PCR positive SARS-CoV-2 CSF samples in the literature since the start of the outbreak in December. A mixed-methods exploratory approach was adopted for data analysis, making observations and investigating any preliminary patterns and theories that can be extracted from the sporadic cases reported.

To begin with, the majority of included studies reported being case reports (10/14) may indicate that SARS-CoV-2 identification in the CSF is not a common phenomenon. However, CSF tests would not be commonly conducted nor indicated in COVID-19 patients unless serious neurological manifestations of unknown causes are manifest, requiring a routine CSF sample. Thus, it would be reasonable to believe that a larger number of COVID-19 patients may have had a viral presence in their CSF that is unknown, or that is not reported in the literature. Interestingly, the earliest papers reporting SARS-CoV-2 positive CSF samples are dated May 2020, around 5 to 6 months after the outbreak. This may indicate the progressive development of COVID-19's clinical picture as a self-limiting respiratory illness, to a systemic disease of varying manifestations. Additionally, the 14 studies included are reported from 10 different countries, indicating an international phenomenon rather than being region or ethnicity-specific.

In the 14 positive cases reported, there were no noticeable similarities in age. This is in-line with other reports of neuro-associated presentations, with Guilian Barre syndrome patients for instance having a mean age of 63 years, but ranging from 23 to 77.(29) This is essential to keep in mind, as COVID-19 patients who are not yet diagnosed may present with more imminent neurological symptoms rather than respiratory illnesses, which may especially be the case with younger, healthier individuals. Most interestingly, however, and perhaps in line with the previous point, we did not identify comorbidities to be commonly present, only reported in 4/14 CSF-positive patients. This again re-emphasizes that

otherwise healthy individuals may present with neurological symptoms and viral CSF infiltration in the absence of co-morbidities in the setting of COVID-19.

Patients where CSF samples were tested for SARS-CoV-2 reported a range of symptoms, with respiratory distress not always being reported. Headache and fever were most commonly reported. Vomiting, coughing, and visual disturbances were also commonly reported, before progressing to more severe/intense neurological symptoms. Compared to a meta-analysis of COVID-19 cohorts, there is a higher prevalence of headache, vomiting, and visual disturbances in patients who met our inclusion criteria(30). This may indicate a unique presentation of patients with CSF-positive neurologic involvement in COVID-19, which could help signal an alarm for clinicians. Since three of the patients did not initially present with respiratory illnesses, despite the positive CSF samples(16, 20, 28), it would be important for healthcare professionals to ensure that COVID-19 is at the top of the differential diagnosis list regardless of the presence of typical symptoms or a typical presentation.

In terms of further findings upon investigation, high levels of inflammatory markers and lymphocytes were commonly reported in CSF samples of COVID-19 positive patients. Additionally, brain radiological findings (MRI and CT) were often reported in patients, clearly indicating pathology, which was not necessarily the case with chest radiographic images. Again, this highlights the need to keep a COVID-19 diagnosis as a top differential in such a pandemic situation as we learn more about the disease, regardless of the presenting symptoms or typical diagnostic features.

The findings of this review raise a number of arguments. First, testing negative in NP samples appears to not imply full body eradication of the virus. This might raise the assumption that patients can still be infectious despite testing negative in their NP swab. On the contrary, it is also possible that the virus stays in the nervous system longer than it stays in the respiratory system. This phenomena may be attributed to the virus taking longer time to shed from the nervous system in comparison to the respiratory system. Secondly, a positive CSF sample can be due to increased virus load over time, prolonged SARS-CoV-2 shedding from damaged nerve cells, or even a false positive result. Regardless, it is clear that those patients with positive CSF samples had severe neurological manifestations, which can indicate that the virus was still viable when LP was performed. Hence, cases of COVID-19, with CNS implications, can utilize RT-PCR of SARS-CoV-2 in the CSF as a detection modality. Third, we had patients who tested positive for the virus in their CSF sample, but negative in their NP swab. A potential explanation to this may be in the virus's ability to infect RBC's and cross the blood-brain barrier to gain access to the CNS. Furthermore, since the CNS is more immune-privileged than other areas of the body, the SARS-CoV-2 virus may be able to remain persistent there despite not being detected in the nasopharynx. Fourthly, initial normal CSF cell counts and negative PCR samples are not sufficient to rule out CNS engagement, as there were three patients who initially tested negative for the virus in their CSF before testing positive later in disease progression(20, 22, 28). Lastly, physicians should not overlook neurological involvement in COVID-19 patients.

The aim of this review is to aid clinicians in understanding and identifying possible COVID-19 cases who might test positive using CSF samples, while their NP swabs may or may not be negative.

5. Conclusions And Limitations

This review describes the unique characteristics of patients who tested positive for SARS-CoV-2 in their CSF sample, regardless of the test outcome of the NP sample. Nevertheless, there is not enough data in the literature for guideline formation, especially given the fact that COVID-19 is a novel virus and an emergent crisis. Hence, more evidence is needed to improve our understanding regarding using LP CSF samples to diagnose COVID-19 in patients that present with neurological symptoms.

List Of Abbreviations

coronavirus disease 2019 (COVID-19)

cerebrospinal fluid (CSF)

nasopharyngeal (NP)

reverse transcriptase polymerase chain reaction (RT-PCR)

Lumbar Puncture (LP)

peripheral nervous system (PNS)

National Institutes of Health (NIH)

Joanna Briggs Institute (JBI)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Declarations

Ethics Approval and Consent to Participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files

Competing interests

The authors declare no conflicts of interest.

Authors' contribution

MS conceived of the idea. MS, SIM, WK, LRM, and YA drafted one or more sections of the manuscript. MS, SIM, and GAJ reviewed and edited the manuscript. GAJ supervised the work. All authors contributed significantly to and approve of the final version of the manuscript.

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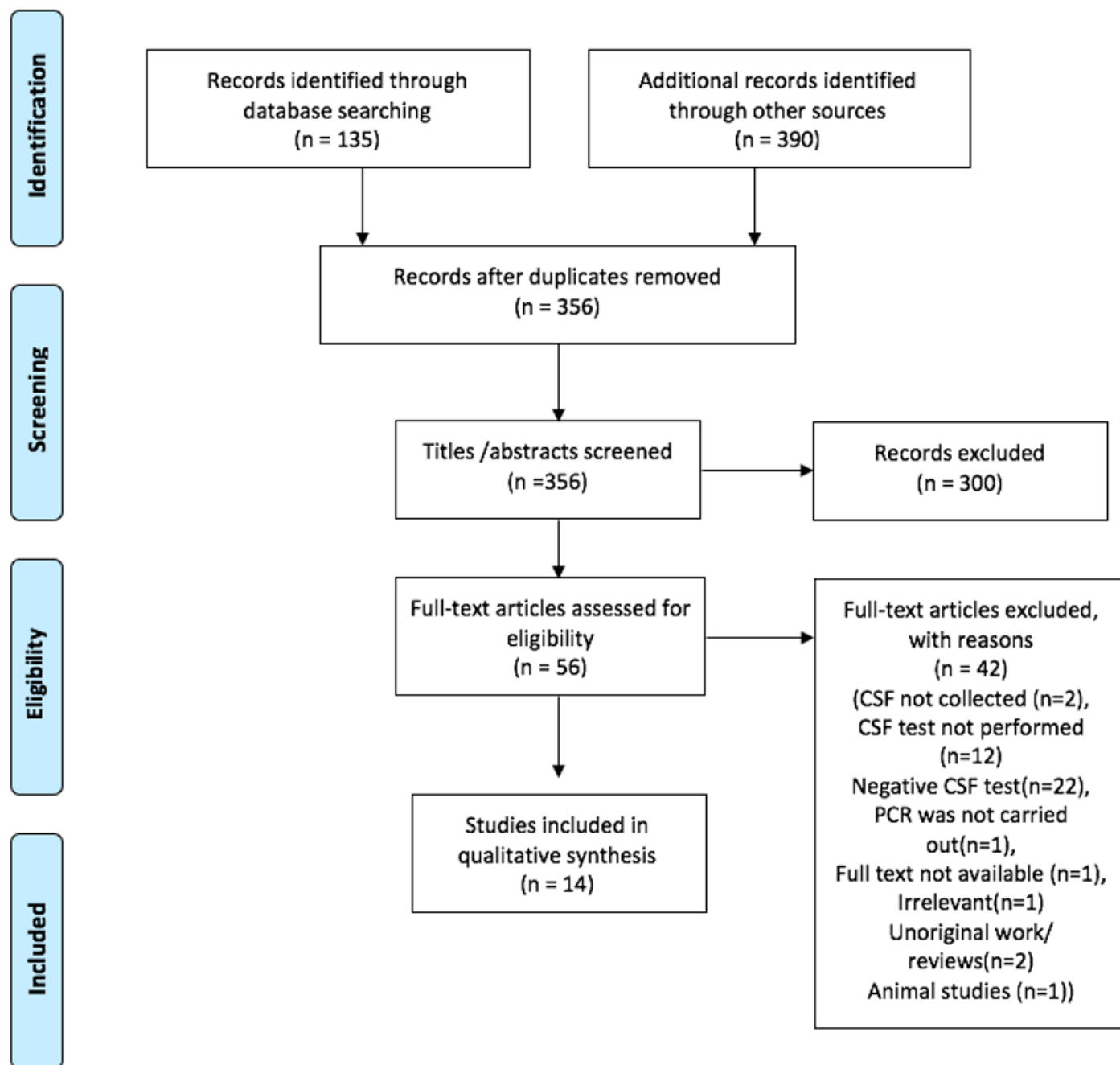
Figures

Figure 1

PRISMA flow diagram of literature search and selection.

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