A Comprehensive Systematic Review of CSF analysis that defines Neurological Manifestations of COVID-19

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Systematic Review

Keywords: COVID-19, SARS-CoV-2, Oligoclonal bands, CSF Protein, CSF cell count

Posted Date: October 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-96718/v1

Abstract

Background: Here we performed a systematic review of literature of CSF findings associated with neurological complications in coronavirus disease-2019 (COVID-19) to establish a pattern and understand the significance of CSF analysis which can possibly be useful in deciding prognosis and exploring therapeutic options in the future.

Methods: We screened all articles resulting from a search of PubMed, Google Scholar and Scopus, using the keywords “SARS-CoV-2 in cerebrospinal fluid”, “SARS-CoV-2 and CNS Complication”.

Results: We performed CSF analysis results in total of 113 patients from 67 papers. There were 7 patients out of 113 patients (6.2 %) were fatal and 35 patients (31 %) were considered severe and rest non-severe. Elevated cell counts (>5 cells/μL) were found in 43% (3/7) of the fatal cases, 25.7% (9/35) of the severe cases and 29.4% (15/51) of non-severe cases. The average CSF protein of 110.0 mg/dl found in fatal, and in 85.4mg/dl in non-fatal cases. Whereas, average CSF protein levels were 78 mg/dl in severe and 103 mg/dl in non-severe cases. In addition, 76.5% (13/17) of the patients with CNS complications and 74.1% (40/54) of the patients with a PNS manifestation showed elevated protein levels.

Conclusion: The most common finding of CSF analysis in the setting of neurological manifestations in Covid-19 is noted to be elevated CSF protein with occasionally elevated, predominantly lymphocytic cell count. Interestingly, CSF protein is noted to be majorly elevated in all spectrums of severity of neurological illness including CNS and PNS complications. This may be indicative of only one common pathophysiological mechanism of neurological illness. In future, A combination of SARS-CoV-2 CSF RT-PCR, CSF IgM testing, and CNS targeting antibodies should be further studied to understand pathophysiology of neurological complications in Covid-19.

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic continues to present with clinical challenges worldwide. Since the beginning of the pandemic, Neurological manifestations have been described and can be seen in more than half of patients with COVID-19 [1-3].

The spectrum of neurologic complications ranges from meningitis/encephalitis, encephalopathy, stroke and peripheral nervous system in the form of GBS [4-14] .The severity of the disease varies depending on the virus nervous tissue tropism. In contrast, a positive nasal swab test for the virus has not been correlated with the presence or absence of the virus in the CSF in patients with neurologic manifestations. Therefore, CSF analysis should be considered in patients with confirmed COVID-19 in order to further understand the virus pathology [4, 10, 15, 16].

Thus far, it is not clear, if the mechanism is due to direct viral invasion into the central nervous system (CNS) or due to inflammatory cytokine release induced by the virus, leading to a cascade of immune cells within the CNS [1, 17-20].

Other coronaviruses that have been studied demonstrated a combination of invasion of the CNS, damaging neurons, leading to a cascade of inflammatory cycle [18, 21, 22]. SARS-CoV-1 in mice showed expression of human ACE2 which was also found in human brain autopsies of patients infected [18] .The same receptor has been found in SARS-CoV-2 cells, that is specifically found in neurons which emphasizes the possible invasion of the CNS [19].

Elevated CSF protein, lactate or WBCs with a negative COVID-19 PCR indicate inflammatory changes seen in autoimmune encephalitis [10]. The high frequency of anti-neuronal and anti-glial antibodies is remarkable. However, larger cohorts are needed to establish the understanding about these connections.

CSF analysis can be of utmost importance in patients with confirmed COVID-19 in order to further understand the virus pathology and to rule out other infectious or inflammatory pathology. We performed a literature review of CSF analysis in COVID 19 patients with neurological manifestations to understand if there is a common pattern of CSF findings. We tried to elucidate if there is a difference in pattern of CSF findings when looking at CNS versus PNS manifestations. We also analyzed if CSF findings can be helpful to prognosticate patients with neurological complications. Lastly, we try to explore if the CSF findings can be helpful in guiding treatment of patients with COVID-19 and neurological complications.

2. Methods

2.1 Study Design:

We conducted a thorough literature review in August 2020 using the terms “SARS-CoV-2 in cerebrospinal fluid”, “SARS-CoV-2 and CNS Complication”. We searched PubMed, Google Scholar and Scopus databases for identifying case series and case reports published between December 01, 2019 to September 15, 2020 (Figure 1), whereas, review articles and consensus statements were excluded from the analysis. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) for the display of inclusions and exclusions [23]. Based on our search criteria, we found the following number of articles from PubMed (n=126), Google Scholar (n=3646) and Scopus (n=110). Amongst all, 236 were identified as duplicates. Finally, we screened 1076 articles for title and abstracts, and reviewed full-text literatures in accordance with our study objective after removing 2570 articles which were either missing clinical information, CSF data or did not meet our study objective. We included 67 articles for review for observational analysis (Figure 1).

2.2 Inclusion criteria:

The inclusion criteria for the published studies included: 1) Patient age ≥ 18 years; 2) COVID-19 diagnosis confirmed by RT-PCR nasopharyngeal or serum antibody test; 3) CSF study findings in COVID-19.

2.3 Exclusion criteria:

The exclusion criteria for the studies include: 1) Patient age < 18 years; 2) Duplicate articles which involved repetition of cases 3) Articles in languages other than English; 4) Studies that had no available individual patient's data; 5) Editorials

2.4. Quality assessment:

The critical appraisal checklist for case reports provided by the Joanna Briggs Institute (JBI) was used to perform assessment of overall quality of case series and case reports [24].

2.5 Data acquisition:

From the selected articles, we extracted the following data for our analysis: study type, date of publication, age, gender, clinical presentation of COVID-19, diagnostic tests for SARS-CoV-2 infection including RT-PCR nasopharyngeal and serum antibodies, CSF markers including cell count, lymphocytes percentage, protein, IL-6, severity of COVID-19 (based on IDSA/ATS criteria) [25].

2.6 Data Analysis

We performed demographic analysis including age, gender, severity of COVID-19 cases and fatality of the cases. Pooled descriptive analyses were conducted to assess differences in these markers among groups including severe vs non-severe, fatal vs non-fatal, CNS vs peripheral nervous system (PNS)

3. Results

A total of 67 articles describing 113 patients were examined. There were 57 males and 29 females; sex was not reported for 26 patients. The mean age for the patients were 57.0 (SD=14.3). The baseline characteristics for the patients are given in Table 1. Serum COVID test was reported for all patients except 8 and was positive for all, except 1. CSF RT-PCR was reported for 78 patients and was positive for only 12 patients. One unique patient with a negative CSF-RT PCR and negative Nasopharyngeal RT-PCR showed positive IgM and IgG CSF COVID-19 antibodies. Aside from this, 2 other patients also showed positive IgG antibodies against COVID-19 in their CSF. Following inflammatory markers for CSF were considered: CSF-cell count, CSF- proteins and elevated CSF- lymphocytes percentage. Cell count >5 cells/μL and CSF proteins >45 mg/dl were considered elevated. We considered patients only with elevated cell count for analysis of lymphocytes percentage.

Based on the IDSA/ATS criteria of either requiring vasopressor for septic shock or mechanical ventilation, 35 patients were considered to have a severe COVID infection. In our observational study, there were 7 fatal cases. Elevated cell counts (>5 cells/μL) were found in 43% (3/7) of the fatal cases, 25.7% (9/35) of the severe cases and 29.4% (15/51) of non-severe cases. Of patients who had a CNS neurological symptom, 43.2% (19/44) had elevated cell count while 16.7% (9/54) patients with PNS symptoms had elevated cell counts. CSF protein was elevated in 100% (7/7) of the fatal cases with an average of 110 mg/dl, and in 65.0 % (52/80) in non-fatal cases with an average 85.4 mg/dl. CSF protein levels were elevated in 74.5% (38/51) patients with non-severe COVID-19 and 68.6% (24/35) of those with a severe

COVID-19 infection. In addition, 59.1% (26/44) of the patients with CNS complications and 77.8% (42/54) of the patients with a PNS manifestation showed elevated protein levels (refer Table 1).

Cell count in CSF analysis was reported in 97 patients. We only considered the lymphocyte percentage in patients who had a cell count of >5 cells/μL. The value was reported in 9 patients. Only 1 patient reported lymphocyte percentage of 10% whereas the rest of the 8 patients had lymphocyte percentage >80%. Out of these 8 patients, 6 had CNS manifestation, 1 had PNS manifestation and the manifestation was not reported in 1 patient. All except for 1 case was non-severe and none of the 8 cases where the outcome was reported was fatal.

The other CSF marker that we studied for the purpose of this study was IL-6 levels. This was reported in 5 patients. It was found to be elevated in 2/5 of the non-severe cases and 3/5 of the severe cases. Only 1 out of the 5 fatal cases showed elevated IL-6 levels and 3 out of the 5 non-fatal cases had this finding. None of the cases with PNS manifestation had elevated IL-6 in their CSF while all 5 cases reported of elevated IL-6 had CNS manifestation.

4. Discussion

Novel coronavirus has been associated with predominant respiratory symptoms which have proved to be fatal in nature. Several studies describing the neurological manifestation of the disease have also been published in the last year showing its potential to invade the peripheral nervous system as well as the central nervous system and manifest as isolated syndromes [9, 26]. Moriguchi et al reported a first case of meningitis associated with SARS-CoV-2. This case put forward the neuroinvasive nature of the SARS-CoV-2 since the RT-PCR test using the nasopharyngeal swab was negative but was detected in the CSF [4].

However, there is only limited data available that can help us point to a specific biomarker for the CNS manifestations of this virus. This might be due to risk of cross-infection from invasive procedure, risk of complications including bleeding as many patients are on anticoagulant therapy. The technique could be also technically challenging due to the severity of underlying illness of COVID-19 patients. However, CSF analysis can be a very useful indicator of neurological involvement. CSF analysis can be considered as a venue to look for biomarkers and inflammatory markers which may be of diagnostic or prognostic use.

Of the limited data present that includes CSF analysis as an investigation for patients with neurological manifestation, most CSF analyses showed no presence of SARS-CoV-2RNA [11, 26-28]. While there was a small fraction of case reports and studies that showed its presence in CSF RT-PCR[4, 5, 15, 21, 29-36] but either absent or not available in nasal swab RT-PCR [4, 15, 21, 29, 32]. Only a few studies showed the concurrent presence of the virus in nasal swabs as well as CSF RT PCR [5, 30, 31, 33-36].

During our analysis, we found four cases where CSF IGM was positive [17, 37],whereas Wang et al. reported a case where both IgG and IgM antibodies against COVID -19 were positive [17]. In addition, CSF IGG was positive for COVID-19 in 2 cases [5, 16].

Study done by Karima et al reported the presence of IgM in CSF analysis of these patients with elevated cell count and protein content in only one patient. They concluded that a negative CSF RT-PCR does not rule out CSF neuroinvasion by the virus in these patients and recommended CSF analysis in such patients [37].

Guilmot et al reported cases of limbic encephalitis and a patient with para infectious polyradiculitis. Six cases had equal numbers of oligoclonal bands in csf and serum whereas 1 patient had CSF specific antibody. One case had positive Anti-caspr2 positive in csf [38].

Franke et al reported the presence of several antibodies such as anti-neuronal antibodies, anti Yo antibodies, anti-myelin antibodies and anti NMDAR antibodies. The presence of these antibodies in the CSF hints to the multi organ involvement of those infected with the novel coronavirus and may prove to play a significant role in creating immunotherapeutic guidelines for these patients in the future [39].

In this systematic review we describe findings of CSF analysis in Covid-19 patients with neurological manifestations. Our analysis reveals that the most common CSF picture in COVID-19 infection is elevated protein with very occasionally mild lymphocyte predominant pleocytosis. Interestingly, based on our analysis, all fatal cases had elevations of CSF protein. However, elevated CSF protein was also noted in almost three quarters of patients with both severe and non-severe presentations. Similar findings were also noted in cell counts and one fourth of patients with both severe and non-severe presentation had elevation in cell count.

Since the elevated protein is noted in all spectrum of neurological manifestations including fatal, it cannot be necessarily postulated that it can be a marker of prognosis. However, the similarity of CSF picture indicates that there might be only one common neuro-inflammatory pathophysiology responsible for the neurological manifestations of COVID-19 specially when the CSF findings are similar between CNS and PNS manifestations. Due to limited therapeutic options in COVID-19, CSF markers and protein levels could be used as a future guiding marker for treatment initiation with higher dose of steroids or another immunotherapy.

A recent study of 5 patients with persistent encephalopathy showed significant improvement with high dose steroids but their CSF findings did not show elevated protein or cell count [40].

The trends noted in our observational study suggest that presence of SARS-CoV-2 in the CSF is highly variable and may depend on the turnover of the virus and the level of neuroinvasion. CSF IgM testing has shown variable results and cannot be relied upon as the sole marker for SARS-CoV-2 presence.

Our study suffers from the limitation that CSF analysis can be highly variable due to different timing of lumbar puncture from timing of infection or positive serum test. This is also a systematic review of all case reports and case review studies hence there is difference in demographics data, treatment methods and management protocols of patients from different studies.

5. Conclusion

More severe and fatal cases with neurological complications were associated with elevated protein as compared to non-severe and nonfatal cases, which can be a marker for CNS involvement. A combination of SARS-CoV-2 CSF RT-PCR, CSF IgM testing, and specific CNS targeting antibodies can be used together to guide diagnosis and prognosis. More studies including RCTs are needed to note the trend of the above-mentioned markers that may serve as biomarkers for diagnosis as well as prognostication of the neurological manifestations of SARS-CoV-2.

Abbreviations

Novel Coronavirus, nCov; Coronavirus infectious disease-2019, COVID-19; Middle East Respiratory Syndrome, MERS; Severe Acute Respiratory Distress Syndrome coronavirus 2, SARS-CoV-2; Cerebrospinal fluid, CSF; CNS, Central Nervous System; PNS, Peripheral Nervous System; NFL, Neurofilament Light Chain; RT-PCR, Reverse Transcription Polymerase Chain Reaction; GBS, Guillain-Barre Syndrome; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Data was extracted from the articles published in PUBMED, Google Scholar, Scopus. This will be provided on request.

Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Table 1: Demographic characteristics of 113 patients for CSF observational study on COVID-19 associated neurological complications*

	CSF high protein**	CSF normal protein	CSF Elevated cell count ***	CSF normal cell count
Age(year)mean±SD	56.9±15.0	57.3±12.6	54.6±17.9	58.0±12.6
Gender (%)				
Female	21 (33.9)	8 (33.3)	10 (41.7)	19 (30.7)
Male	41 (66.1)	16 (66.7)	14 (58.3)	43 (69.4)
COVID-19 Severity				
Non-Severe	38 (74.5)	13 (25.5)	15 (29.4)	36 (70.6)
Severe	24 (68.6)	11 (31.4)	9 (25.7)	26 (74.3)
Fatality				
Non-fatal	52 (65.0)	28 (35.0)	23 (28.7)	57 (71.3)
Fatal	7 (100.0)	0 (0.0)	3 (42.9)	4 (57.1)
Outcome				
CNS Manifestation[a]	26 (59.1)	18 (40.9)	19 (43.2)	25 (56.8)
PNS Manifestation[b]	42 (77.8)	12 (22.2)	9 (16.7)	45 (83.3)

* Severity was not reported in 27 cases, fatality was not reported in 26 cases, CNS status or PNS status was not reported in 15 cases

** Cerebrospinal fluid

** Cerebrospinal fluid cell count

a Central nervous system

b Peripheral nervous system

Table 2: CSF Findings of COVID-19 and related Neurological manifestation (for published case report and case series)

Author/Country All studies from year/year published 2020	No. of patients included in the study	Neurological manifestation CNS=1, PNS=2	CSF findings	Severity of COVID-19* (Non-severe=1, Severe=2)	Outcome (Non-fatal=1, fatal=2)
Toscano et al. Italy 2020	5	Patients 1 to 5 = 2	Patient 1 to 3: High protein, Albuminocytological dissociation Patient 4 to 5: Normal CSF findings	Patient 1=2 Patient 2=1 Patient 3=2 Patient 4=1 Patient 5=2	Patient 1=1 Patient 2=1 Patient 3=2 Patient 4=1 Patient 5=1
Paybast, Sepideh Iran 2020	3	Patients 1 to 3 = 2	Patient 1 to 3: High protein, Albuminocytological dissociation	Patient 1=N/A Patient 2=2 Patient 3=1	Patient 1=1 Patient 2=2 Patient 3=N/A
Agustina M. Lascano Switzerland 2020	3	Patients 1 to 3 = 2	Patient 1 and 3: High protein, Albuminocytological dissociation Patient 2: Normal CSF findings	Patient 1=1 Patient 2=1 Patient 3=2	Patient 1=1 Patient 2=1 Patient 3=1
Otávio de Melo Espíndola Brazil 2020	8	Patient 1=1 Patient 2=1 Patient 3=1 Patient 4=2 Patient 5=N/A Patient 6=N/A Patient 7=1	Patient 1=High Protein, Low Sugar, Cell=18 (100% Lymphocytes) Patient 2=Normal Patient 3=Normal Patient 4=Normal Patient 5=High Protein, Cells=3 (100% Lymphocytes)	Patient 1=1 Patient 2=1 Patient 3=2 Patient 4=1 Patient 5=1	Patient 1=1 Patient 2=1 Patient 3=2 Patient 4=1 Patient 5=1

		Patient 8=2	Patient 6= High Protein, Cells=3 (100% Lymphocytes) Patient 7=Normal Patient 8=Normal	Patient 6=2 Patient 7=1 Patient 8=1	Patient 6=2 Patient 7=1 Patient 8=1
Karima Benameur USA 2020	3	Patient 1 to 3=1	Patient 1= High opening pressure; High Protein; Low Sugar; Cells= 115; Lympho=10%, Macrophages= 39%, Neutro= 51%; IL-6,8,10: elevated; Anti-S1 IgM, Anti-E IgM Positive Patient 2= High opening pressure; IL-8, 10: elevated; Anti-S1 IgM Positive Patient 3= IL-8, 10: elevated; Anti-S1 IgM Positive	Patient 1=2 Patient 2=2 Patient 3=2	Patient 1=2 Patient 2=N/A Patient 3=N/A
Antoine Guilmot Belgium 2020	15	Patient 1=2 Patient 2=2 Patient 3=1 Patient 4=1 Patient 5=N/A Patient 6=N/A Patient 7=N/A Patient 8=N/A Patient 9=N/A Patient 10=N/A Patient 11=N/A	Patient 1= High Protein; Cells=101; Lympho=95%; anti-GD1b IgG Positive Patient 2=Normal Patient 3=elevated Qalb Patient 4=elevated Qalb Patient 5= High Protein; Cells=9; Lympho=100%; Anti-Caspr2, anti-GD1b IgG Positive Patient 6= High Protein; elevated Qalb Patient 7= Normal Patient 8= Normal Patient 9= elevated Qalb Patient 10= Normal Patient 11= Normal Patient 12= Normal	Patient 1=1 Patient 2=1 Patient 3=2 Patient 4=2 Patient 5=1 Patient 6=2 Patient 7=1 Patient 8=1 Patient 9=2 Patient 10=2	Patient 1=1 Patient 2=1 Patient 3=1 Patient 4=1 Patient 5=1 Patient 6=1 Patient 7=1 Patient 8=1 Patient 9=1 Patient 10=1

		Patient 12=N/A Patient 13=1 Patient 14=1 Patient 15=1	Patient 13= High Protein Patient 14= High Protein Patient 15= Normal	Patient 11=2 Patient 12=2 Patient 13=2 Patient 14=1 Patient 15=2	Patient 11=2 Patient 12=1 Patient 13=N/A Patient 14=N/A Patient 15=N/A
Christiana Franke, MD Germany 2020	11	Patient 1=1 Patient 2=1 Patient 3=2 Patient 4=N/A Patient 5=1 Patient 6=1 Patient 7=1 Patient 8=1 Patient 9=1 Patient 10=N/A Patient 11=1	Patient 1= High Protein; Cells=8; OCBs; High NfL; High lactate Patient 2= OCBs; High NfL; High lactate Patient 3= High lactate; OCBs Patient 4= High lactate; OCBs Patient 5= High Protein; Cells=117; High lactate; OCBs; High NfL Patient 6= High lactate Patient 7= High lactate Patient 8= High Protein; High lactate; OCBs; High NfL Patient 9= High Protein; High lactate Patient 10= High lactate Patient 11= High lactate	N/A	Patient 1 to 11=1
Duong L, Xu P, Liu A USA April 2020	1	1	Cells high 100% lymphocytes, Protein high, Glucose normal	1	1
Moriguchi T, Harii N, Goto J, et al Japan 2020	1	1	Cells high 90% mono.	2	1
Xiang P.	1	1	N/A	N/A	N/A

Et al China 2020					
Huang YH, Et al USA 2020	1	1	SARS Positive	N/A	1
Färber K Et al Germany 2020	1	1	SARS-CoV-2 positive	N/A	1
Kremer S France 2020	37 31 HAS LP	1	Only one positive for SARS-COV-2 21= HIGH PTN, CELLS,	N/A	N/A
Domingues RB BRAZIL 2020	1	2	SARS COV-2 POSITIVE Normal protein, cells and glucose	1	1
Westhoff TH, , et al Germany 2020	1	1	Cells normal, protein high normal glucose high oligoclonal IgG SARS-CoV-2 RNA positive	1	1
Mardani M Et al Iran 2020	1	1	Cells high 90% polymorphs, glucose low, High protein, Negative PCR	2	N/A
Fadakar N Et al Iran 2020	1	1	Cells high mainly lymphocytic High protein SARS-CoV-2 RNA positive	1	1
Helms J, Kremer S, France 2020	58	1	Cells high mainly lymphocytic High protein SARS-CoV-2 RNA positive	1	1
Cebrián J Et al spain 2020	1	1	OCB= 2 Positive High protein=1 Low albumin= 4 Negative SARS= 7	N/A	N/A

Cebrián J Et al spain 2020	1	1	Normal csf	1	1
Virhammar J Et al Sweden 2020	1	1	the cell normal, IgG high, protein normal negative autoantibodies negative PCR for HSV, VZV, and SARS-CoV-2	2	1
Khodamoradi Z, Iran 2020	1	1	Cells high, mononuclear 100% Protein normal Glucose normal COVID 19 positive	1	1
Yin R, Feng W, China 2020	1	1	Opening pressure high Cells high Protein high Glucose normal	1	1
Destras G, Bal A, Escuret France 2020	578	N/A	Only 2 COVID positive	N/A	N/A
Espíndola OM, Siqueira M Brazil 2020	8	Patient 1=1 Patient 2=1 Patient 3=1 Patient 4=1 Patient 5=2 Patient 6=2 Patient 7=1 Patient 8=1	Patient 1= Cells high, protein high Patient 2= normal Patient 3= normal Patient 4= normal Patient 5= normal Patient 6= Only protein high Patient 7= Normal Patient 8= Normal	N/A	N/A
Wang M, Li T, Qiao F China 2020	1	1	Cells no, protein high, IgM and IgG high PCR negative	1	1

Lu S, Wei N, Jiang J, et al. China 2020	1	1	Cells high Protein normal IgG POSITIVE PCR negative	1	1

CNS manifestation includes -stroke (ischemic, hemorrhagic, dural sinus venous thrombosis, meningoencephalitis, encephalitis, encephalopathy, seizure, ADEM, Acute hemorrhagic necrotizing, CNS vasculitis, transverse myelitis.

PNS manifestation includes-GBS, polyneuritis cranialis, facial nerve palsy

*Severity based on Infectious Diseases Society of America/ American Thoracic Society

(IDSA/ATS) guidelines

Legend: CNS, Central Nervous system, CSF; CSF, Cerebrospinal fluid; PNS, Peripheral Nervous System; GBS, Guillain-Barre Syndrome; ADEM, Acute disseminated Encephalomyelitis

Figures

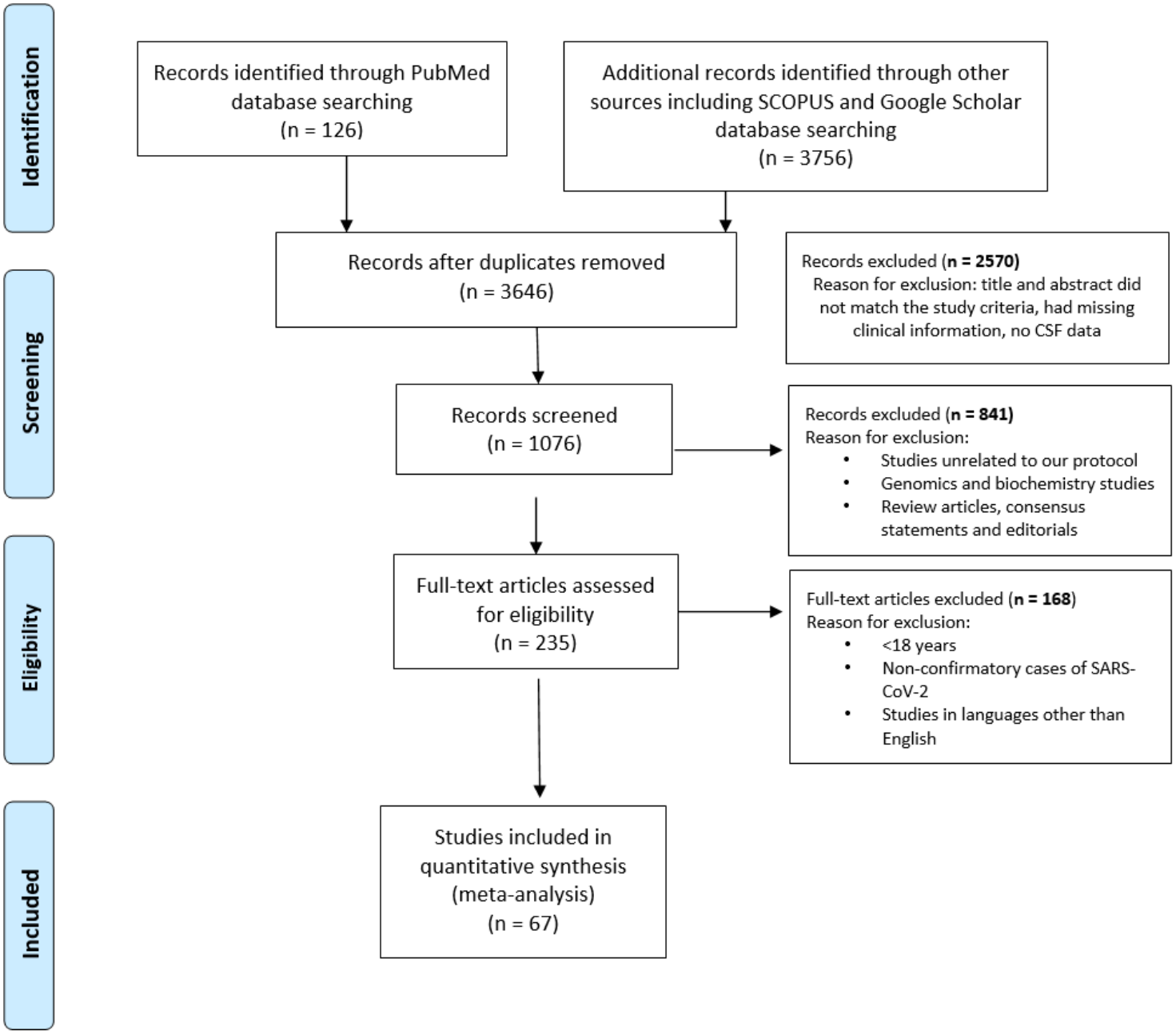

Figure 1

PRISMA Flow Diagram. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing criteria for article selection. n = number of articles