

# The Incidence of SARS-COV-2 Manifestations in the Central Nervous System: A Rapid Review and Meta-Analysis

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## Research article

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# Abstract

**Background:** Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 and presents itself mainly as a respiratory tract infection. However, reports of associated central nervous system (CNS) manifestations are increasing.

**Methods:** We conducted this rapid review to determine the frequency of CNS manifestations of COVID-19 (CNS symptoms, acute cerebrovascular disease, and infectious/inflammatory CNS diseases) and to summarize the current evidence for direct invasion of the CNS by SARS-CoV-2. An information specialist searched Ovid MEDLINE, the CDC: COVID-19 Research Articles Downloadable and WHO COVID-19 Databases, CENTRAL, and Epistemonikos.org on May 13, 2020. Two reviewers screened abstracts and potentially relevant full-text publications independently. The data extraction, assessment of risk of bias, and certainty of evidence using GRADE was done by one reviewer and double-checked by another. If possible and reasonable, a meta-analysis was carried out.

**Results:** We identified 13 relevant studies (four cohort studies, nine case studies) with a total of 866 COVID-19 patients. In a Chinese cohort, dizziness (16.8%; 36 of 214) and headache (13.1%; 28 of 214) were the most common CNS symptoms reported. A meta-analysis of four cohort studies including 851 COVID-19 patients showed an incidence of 3.3% (95% CI: 2.2–4.9) for ischemic stroke (follow-up: one to five weeks). In 13 of 15 encephalitis case studies, PCR testing of the cerebrospinal fluid did not detect any virus components.

**Conclusion:** CNS manifestations occur frequently in patients with COVID-19. It is important to integrate neurologists into the multiprofessional COVID-19 treatment team to detect neurological complications early and to treat them correctly.

## 1. Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2) [1]. The time between the first case of illness (December 31, 2019, Hubei Province, China) and the declaration of a pandemic by the World Health Organization (WHO, March 11, 2020) was rather short [2]. Clinically, COVID-19 presents itself mainly as a respiratory tract infection with fever, fatigue, and dry cough and with infiltrates on chest X-ray [3]. Pneumonia and the subsequent development of acute respiratory distress syndrome are the most common severe manifestations of the disease [3]. As the number of infected people increased, more differentiated data on the symptoms emerged. More and more studies have been published on neurological manifestations such as the loss of the sense of smell and taste and also on serious complications such as encephalitis or stroke [4–6]. A yet unanswered question is whether the virus has a direct effect on the central nervous system (CNS), or whether these neurological manifestations should be considered parainfectious. The neuroinvasive potential of SARS-CoV-2 is still under debate. Proposed mechanisms for CNS invasion are hematogenous spread via an impaired blood–brain barrier, neuronal retrograde, or transcribrial routes [7, 8].

Neurological damage to the CNS was observed in earlier epidemics of diseases such as Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS), which were also triggered by coronaviruses [9, 10]. In SARS, the pathogen could be detected by a polymerase chain reaction (PCR) in the

cerebrospinal fluid (CSF) and brain tissue [11–15]. To determine the frequency of CNS complications and to investigate whether the virus infection affects the brain tissue directly, we conducted a rapid review. As manifestations of the CNS underlie different pathomechanisms, we phrased the following key questions (KQs) as:

### **KQ1**

What is the incidence of central nervous symptoms in patients infected with SARS-CoV-2?

### **KQ2**

What is the incidence of acute cerebrovascular disease in patients infected with SARS-CoV-2?

### **KQ3**

Does SARS-CoV-2 cause infectious/inflammatory diseases of the CNS?

#### **KQ3.1**

Does the virus enter the CNS or should neurological manifestations be considered parainfectious?

## **2. Methods**

We adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) throughout this manuscript [16].

Compared with the methods of a systematic review, the review team applied the following methodological shortcuts for this rapid review:

- no searches of grey literature;
- no dual independent data extraction;
- no dual independent risk of bias assessment and rating of the certainty of evidence.

### **2.1 Literature search**

An experienced information specialist conducted a systematic search of the literature published from January 1, 2019 to April 15, 2020 in Ovid MEDLINE, the CDC: COVID-19 Research Articles Downloadable Database, the WHO COVID-19 Database, CENTRAL (Cochrane Library/Wiley), and Epistemonikos.org. On May 13, 2020, the information specialist performed an updated search. The search strategies were modified based on the findings of the initial searches, and the results were deduplicated with those of the first search. We also conducted similar article searches in PubMed based on the first 100 linked references for each seed article. Seed articles were potentially eligible studies identified during the preliminary searches or in the first round of databases searches. The additional file provides the detailed search strategies [see Additional file 1]. Furthermore, the review authors screened the reference lists of the included studies to identify relevant citations that were not detected by searches of electronic databases.

## 2.2 Eligibility criteria

We included studies concerning central nervous symptoms (e.g., dizziness, headache, etc.), encephalopathy, acute cerebrovascular disease, and infectious (e.g., encephalitis, meningitis) or inflammatory CNS diseases in confirmed COVID-19 patients older than 18 years. Studies with suspected but not confirmed cases of COVID-19 and including children and patients with primary neurological diseases or taking additional immunosuppressive drugs (e.g., for multiple sclerosis) were excluded. Only articles in English and German were considered. After a quick presearch, we prespecified a best-evidence approach for the literature screening. For KQ1 and KQ2, case studies were excluded because observational studies were already available. Due to the lack of data on infectious/inflammatory CNS disorders in COVID-19 cases, there were no restrictions regarding the specific study design for KQ3 and KQ3.1. However, case reports without SARS-CoV-2 PCR testing of the CSF were excluded.

## 2.3 Screening process

Two researchers independently screened all titles and abstracts of both searches based on the predefined inclusion and exclusion criteria. Included abstracts were retrieved as full-text publications and independently screened by two reviewers. In cases of disagreements about eligibility, the two reviewers reached consensus by discussion. The team screened the literature using Covidence Systematic Review software ([www.covidence.org](http://www.covidence.org)).

## 2.4 Quality assessment

The review team assessed the risk of bias of the observational studies using an adapted version of the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool [17]. A single reviewer rated the risk of bias for each relevant outcome of each study; a second reviewer checked the ratings. As there is no validated risk of bias checklist for case studies available, the review team checked whether SARS-CoV-2 PCR tests were carried out twice to reduce the risk of a false positive result.

To assess the certainty of the body of evidence for all the outcomes of interest, we applied the approach by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [18]. A single review author applied GRADE, and a second review author verified all judgments. GRADE uses four categories to classify the certainty of evidence. A high certainty of evidence means that we were very confident the estimated effect lies close to the true effect; a moderate certainty assumes it is likely to be close; with a low certainty rating, the true effect might substantially differ from the true effect; and a very low certainty means that we had no confidence in the effect estimate.

## 2.5 Data extraction

One reviewer extracted data from the included studies into standardized tables; a second reviewer checked the data extraction for completeness and correctness. We extracted the following data: report characteristics (year, authors), study design, setting, participant characteristics (age, preexisting medical conditions, main symptoms,) and results.

## 2.6 Synthesis

We synthesized the results both narratively and in tabular form. If three or more studies were similar with respect to outcomes and populations and provided data for quantitative analyses, we conducted meta-analyses. Therefore, we conducted a test of heterogeneity ( $I^2$  statistic, Cochran's q-test) and applied the DerSimonian and Laird method for random-effects models. A sensitivity analysis was performed by excluding high risk of bias studies. We planned to assess publication bias using funnel plots, Egger's regression intercept, and Kendall's S statistic. All statistical analyses were conducted using Comprehensive Meta-Analysis (CMA), version 2.2.050 ([www.meta-analysis.com](http://www.meta-analysis.com)).

### 3. Results

The PRISMA flow diagram in Fig. 1 provides an overview of the study selection process. Our searches identified 13 relevant studies published in 15 articles [6, 19–31]. Of these, four were cohort studies, two case series, and seven case reports.

The cohort studies were retrospective observational studies and were performed in France [19], Italy [21], the Netherlands [20], and Wuhan, China [6, 22]. All four retrospective observational studies including 851 individuals described acute cerebrovascular disease related to COVID-19 [6, 19–22]. Two retrospective observational studies including 279 COVID-19 patients described central nervous symptoms relating to COVID-19 [6, 19, 22]. One of the four studies presented the data of 221 hospitalized COVID-19 patients admitted to hospital in Wuhan [6, 22]. The data of these 221 patients were analyzed at two different time-points: the first publication presented the data of 214 patients and focused on neurological symptoms [22]. In the preprint of the second analysis, seven patients were added, the observation period was extended by ten days, and additional data concerning cerebrovascular disease was released [6]. One French study was published in a "Letter to the Editor" and provided only limited data [19]. The baseline characteristics of the observational studies and the case studies are shown in Tables 1 and 2, respectively.

Table 1  
Characteristics, main results, and risk of bias of the observational studies

	Lodigiani 2020 <sup>21</sup>	Mao L 2020 <sup>22</sup> Li Y 2020 <sup>6</sup>	Klok 2020 <sup>20</sup>	Helms J 2020 <sup>19</sup>
KQ	KQ2	KQ1, KQ2	KQ2	KQ1, KQ2
Study design	retrospective observational study	retrospective observational study with two dates of evaluation	retrospective observational study	retrospective observational study
Number of patients (severe cases)	N = 388 (61)	N = 221 (94)	N = 184 (184)	N = 58 (58)
Setting	University hospital in Milan (Italy), admission: February 13 to April 4, 2020	Union Hospital, Wuhan (China), admission: January 16 to February 29, 2020	Dutch ICUs, admission: March 7 to April 5, 2020	ICUs in Strasbourg (France), admission: March 3 to April 3, 2020
Mean age (years; SD)	66 (55–75) <sup>1</sup>	53.3 (± 15.9)	64 (± 12)	63 <sup>1</sup>
Sex (female n, %)	124 (32%)	90 (40.7%)	45 (24.5%)	NA
Medical history (n, %)				
Hypertension	183 (47.2%)	31 (14%)	NA	NA
Diabetes	88 (22.7%)	31 (14%)	NA	NA
Cardio-cerebrovascular disease	74 (19.1%) <sup>2</sup>	17 (7.7)	NA	NA
Neurologic disorders	NA	NA	NA	7 (12.1%)
Malignancy	25 (6.4%)	14 (6.3%)	5 (2.7%) <sup>3</sup>	NA
<sup>1</sup> median age: years, quartile 1 – quartile 3), <sup>2</sup> prior stroke n = 20 of 388, coronary artery disease n = 54 of 388, <sup>3</sup> active cancer				
Abbreviations: ICU: intensive care unit; KQ: key question; NA: not available; SD: standard deviation				

Table 2  
Characteristics and main results of the case studies

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Bernard-Valnet et al. 2020 <sup>23</sup> case series (N = 2) KQ3, KQ3.1	Central University Hospital Vaudois (Switzerland) 2020	case 1: 64-year-old female medical history: no psychiatric diseases, other NA	case 1: <b>general symptoms:</b> mild asthenia, myalgia, cough <b>neurological symptoms:</b> psychotic symptoms, disorientated, tonic-clonic seizures	case 1: <b>MRI:</b> unremarkable CSF: exclusion of neurotropic viruses, antineuronal antibodies negative <b>EEG:</b> nonconvulsive focal status epilepticus (at admission) <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative
		case 2: 67-year-old female medical history: NA	<b>mechanical ventilation:</b> no <b>neurological examination:</b> no neck stiffness or focal signs, bilateral grasping, attention deficit, verbal and motor perseverations	<b>MRI:</b> unremarkable CSF <b>EEG:</b> NA <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative
			case 2: <b>general symptoms:</b> mild respiratory symptoms <b>neurological symptoms:</b> intensive wake-up headache <b>mechanical ventilation:</b> no <b>neurological examination:</b> disorientated, motor perseverations, bilateral grasping, aggressiveness, left hemianopia, sensory hemineglect; no neck stiffness	case 2: <b>MRI:</b> unremarkable CSF <b>EEG:</b> NA <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Chaumont et al. 2020 <sup>24</sup> case study KQ3, KQ3.1	University Hospital Guadeloupe (French Indies) 2020	69-year-old male medical history: none	<p><b>general symptoms:</b> headache, fever, myalgia cough, dyspnea, diarrhea</p> <p><b>neurological symptoms:</b> anosmia, ageusia, painful neck, confusion, walking disability</p> <p><b>mechanical ventilation:</b> no</p> <p><b>neurological examination:</b> altered consciousness (GCS of 14 at admission), neck stiffness, right-sided hemiparesis, swallowing disorders</p>	<p><b>MRI:</b> unremarkable</p> <p><b>CSF:</b> purely lymphocytic (37 × 10<sup>6</sup>/L), no red blood cells, increased protein 84 mg/dL, normal glucose level, exclusion of HSV, VZV, enterovirus</p> <p><b>EEG:</b> bilateral slowed activity without seizures</p> <p><b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 2x</p> <p>negative, CSF 2x negative, bronchoalveolar lavage 1x positive</p>

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Dogan et al. 2020 <sup>25</sup> case series (N = 6) KQ3, KQ3.1	ICU at Altunizade Acibadem Hospital, (Istanbul, Turkey) March–April 2020	mean age (y): 49.2 (± 13.9) sex (n, %): 1 female (16.7%) medical history (n, %): none:1 (16.7%) hypertension: 4 (66.7%) diabetes: 2 (33.4%) obesity: 1 (16.7%)	<b>symptoms:</b> NA <b>supplement of setting:</b> 29 COVID-19 patients developed severe ARDS, admitted to the ICU and either failed to regain consciousness after mechanical ventilation or developed agitated delirium. In 6 of these patients, CNS involvement was diagnosed.	<b>MRI:</b> 3x compatible with meningoencephalitis, 3x unremarkable <b>CSF:</b> high CSF protein levels without pleocytosis in all cases, exclusion of neurotropic viruses NA <b>EEG:</b> NA <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
<p>Hanna Huang et al. 2020<sup>27</sup></p> <p>Duong et al. 2020<sup>26</sup></p> <p>case study</p>	<p>Hospital Downtown Los Angeles (USA)</p> <p>April 2020</p>	<p>41-year-old female</p> <p>medical history: obesity, diabetes</p>	<p><b>general symptoms:</b></p> <p>headache, fever</p> <p><b>neurological symptoms:</b></p> <p>new-onset seizure</p> <p><b>mechanical ventilation:</b> no</p> <p><b>neurological examination:</b></p> <p>neck stiffness, photophobia, no focal signs, in the course of the disease: disorientation, hallucinations</p>	<p><b>MRI:</b> NA</p> <p><b>CSF:</b> 70 white cells with 100% lymphocyte. Red cells 65, protein 100, glucose 120 (serum glucose 200), exclusion of HSV</p> <p><b>EEG:</b> generalized slowing with no epileptic discharges</p> <p><b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x positive</p>
<p>KQ3, KQ3.1</p>				

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Moriguchi et al. 2020 <sup>28</sup> case study KQ3, KQ3.1	ICU of the University Hospital of Yamanashi (Japan) March 2020	24-year-old male medical history: NA	<b>general symptoms:</b> headache, fever, sore throat  <b>neurological symptoms:</b> consciousness impairment, generalized seizures,  <b>mechanical ventilation:</b> yes  <b>neurological examination:</b> neck stiffness, GCS of 6 at admission	<b>MRI:</b> right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus  <b>CSF:</b> clear, colorless, initial pressure higher than 320 mm H <sub>2</sub> O, cell count 12/μl, 10 mononuclear and 2 polymorph nuclear cells, no red blood cells, exclusion of HSV-1, VZV;  <b>EEG:</b> NA  <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 2x negative, CSF 2x positive
Pilotto et al. 2020 <sup>29</sup> case study KQ3, KQ3.1	Brescia Hospital (Italy) April 2020	60-year-old male medical history: none	<b>general symptoms:</b> fever, cough  <b>neurological symptoms:</b> consciousness impairment, irritability, confusion, cognitive fluctuations, asthenia  <b>mechanical ventilation:</b> no  <b>neurological examination:</b> severe akinetic syndrome associated to mutism, positive palmomental and glabella reflexes, moderate nuchal rigidity, no focal signs	<b>MRI:</b> unremarkable  <b>CT:</b> unremarkable  <b>CSF:</b> mild lymphocytic pleocytosis (18 μ/L), moderate increase of protein (69.6 mg/dL), exclusion of neurotropic viruses  <b>EEG:</b> generalized slowing with decreased reactivity to acoustic stimuli  <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Ye et al. 2020 <sup>30</sup> case study KQ3, KQ3.1	Wuhan Huoshenshan Hospital, (China)  February 2020	male, age NA  medical history: NA	<b>general symptoms:</b> fever, dyspnea, myalgia  <b>neurological symptoms:</b> confusion, consciousness impairment  <b>mechanical ventilation:</b> no          <b>neurological examination:</b> meningeal irritation signs          and extensor plantar response positive	<b>MRI:</b> NA  <b>CT:</b> unremarkable  <b>CSF:</b> pressure 220 mmHg, white blood cells, protein and glucose within normal limits, exclusion of neurotropic viruses NA       <b>EEG:</b> NA  <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal 1x positive, CSF 1x negative
Yin et al. 2020 <sup>31</sup> case study KQ3, KQ3.1	Wuhan (China)  February 2020	64-year-old male  medical history: no hypertension, no diabetes, no cardio- cerebrovascular disease	<b>general symptoms:</b> fever, cough  <b>neurological symptoms:</b> insomnia, muscle soreness, lethargy  <b>mechanical ventilation:</b> no  <b>neurological examination:</b> consciousness impairment, lower limbs: positive ankle clonus (left pronounced), left positive Babinski and Chaddock signs, slight neck stiffness, positive Brudzinski sign, positive leg raise test	<b>MRI:</b> NA  <b>CT:</b> unremarkable  <b>CSF:</b> colorless, clear, pressure 200 mmHg,  cell count: $1 \times 10^6/L$ ; protein 275.5 mg/L, glucose 3.14 mmol/L, exclusion of neurotropic viruses NA  <b>EEG:</b> NA  <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal repeatedly positive, CSF 1x negative

Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus

Study characteristics	Setting	Patient characteristics	Main symptoms	Test results
Zanin et al. 2020 <sup>33</sup> case study KQ3, KQ3.1	Brescia Hospital (Italy)  2020	54-year-old women  medical history: anterior communicating artery aneurysm treated surgically; other diseases NA	<b>general symptoms:</b> none  <b>neurological symptoms:</b> anosmia, ageusia, new-onset seizure  <b>mechanical ventilation:</b> yes  <b>neurological examination:</b> GCS of 12 without focal sensorimotor deficits; familiars reported no signs of both tongue biting and incontinence.	<b>MRI:</b> alterations of the periventricular white matter, hyperintense in T2WI, without restriction of diffusion or contrast enhancement, Similar lesions at the bulbo-medullary junction and in the cervical and dorsal spinal cord  <b>CT:</b> unremarkable  <b>CSF:</b> Chemical-physical examination was normal, no signs of multiple sclerosis, exclusion of neurotropic viruses  <b>EEG:</b> two seizures starting from right frontotemporal region and diffusing in homologous contralateral hemisphere  <b>SARS-CoV-2 PCR Test:</b> nasopharyngeal repeatedly positive, CSF 1x negative
Abbreviations: ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computer tomography; EEG: electroencephalography; GCS: glasgow coma scale; HSV: herpes simplex virus; ICU: intensive care unit; KQ: key question; MRI: magnetic resonance imaging; NA: not available; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome - coronavirus 2; VZV: varicella-zoster virus				

Two studies from China and Italy were classified as low risk of bias [6, 21, 22], while two studies from the Netherlands and France were rated as high risk of bias due to the insufficient description of relevant confounders [19, 20].

### 3.1 KQ1: Central nervous symptoms related to SARS-CoV-2

Two retrospective observational studies including 279 COVID-19 patients described central nervous symptoms relating to COVID-19 [6, 19, 32]. Both had a different focus: The retrospective study from Wuhan covered general neurological manifestations in the context of COVID-19 diseases and included 41.1% (88 of 214) [32] of cases with severe illness [32]. The French study by Helms et al. focused on unexplained encephalopathic symptoms in COVID-19 patients in intensive care units (ICUs) [19]. The age ranged from a mean age of 53 years in the Chinese study to a median age of 58 years in the French study.

In the Wuhan study, neurological signs and symptoms were observed in 36.4% (78 of 214) of patients during COVID-19 disease, and about 24.8% (53 of 214) had symptoms affecting the CNS [6]. Categories within the CNS-related symptoms were dizziness (16.8%; 36 of 214), headache (13.1%; 28 of 214), consciousness impairment (7.5%; 16 of 214), ataxia (0.5%; 1 of 214), and seizures (0.5%; 1 of 214). These CNS symptoms were more common in the severely ill group (30.7%; 27 of 88) than in the non-seriously ill group (20.6%: 26 of 126 people); in particular, this was the case for impairment of consciousness (14.8% vs. 2.4%,  $p < 0.001$ ). This category also differed from the others with respect to the time of onset: while the other CNS symptoms manifested early during the first two days of hospitalization, impairment of consciousness occurred on average after eight and nine days, respectively.

The study performed in France presented the data of 58 COVID-19 patients with acute respiratory distress syndrome (ARDS) [19]. However, the brevity of the publication allowed only a limited data collection. Overall, 22.4% (13 of 58) showed encephalopathy features that could not be otherwise explained, for example, by side effects of drug treatment. In addition, 67.2% (39 of 58) showed positive pyramidal trajectory signs, and of the 45 patients discharged at the time of publication, 33.3% (15 of 45) had dysexecutive syndrome.

Table 3 provides the main results, risk of bias, and certainty of evidence rating for central nervous symptoms relating to COVID-19.

Table 3  
Central nervous symptoms relating to COVID-19

Author, Year	Study design	Risk of bias	Population	Follow-up	Outcome	Incidence	Certainty of evidence
Helms et al. 2020 <sup>19</sup>	Retrospective observational study	high	Intensive Care Unit	NA	Unexplained encephalopathy features	22.4% (13 of 58)	⊕000 VERY LOW <sup>1,2</sup>
Mao et al. 2020 <sup>22</sup>	Retrospective observational study	low	Severe disease: 41.1% (88 of 214)	Up to 5 weeks	Any central nervous symptom	24.8% (53 of 214)	⊕000 VERY LOW <sup>1,2</sup>
					Dizziness	16.8% (36 of 214)	
					Headache	13.1% (28 of 214)	
					Consciousness impairment	7.5% (16 of 214)	
					Ataxia	0.5% (1 of 214)	
					Seizures	0.5% (1 of 214)	

<sup>1</sup> retrospective study design, <sup>2</sup> imprecision

### 3.2 KQ2: Acute cerebrovascular disease related to SARS-CoV-2

Four retrospective observational studies including 851 individuals reported on the incidence of acute cerebrovascular disease relating to COVID-19 [6, 19–22]. While three studies referred only to ischemic strokes [19–21], the Chinese study also included other acute cerebrovascular manifestations (cerebral hemorrhage, cerebral venous sinus thrombosis) [6, 22]. The largest study from Italy contained only 15.7% severe cases of COVID-19 (61 of 388) [21]; the other three studies included 42.5% (94 of 221) of severe cases [6, 22] or only considered patients with admission to an ICU for inclusion [19, 20].

The Wuhan study was the only one of the included publications that provided the data of the total population and of the patients with an acute cerebrovascular event separately. Patients with an acute cerebrovascular event were significantly older (71.6 years [± 15.7] vs. 52.1 years [± 15.3],  $p < 0.05$ ) and had an increased incidence of severe COVID-19 disease (84.6% vs. 39.9%,  $p < 0.01$ ) [6]. COVID-19 patients with an acute cerebrovascular event had more preexisting conditions than those without an acute cerebrovascular event, in particular, arterial hypertension (69.2% vs. 22.1%,  $p < 0.001$ ), diabetes (46.2% vs. 12%,  $p = 0.004$ ), and cardiovascular disease (23.1% vs. 6.7%,  $p = 0.07$ ).

Table 4 provides the main results, risk of bias, and certainty of evidence rating for acute cerebrovascular events relating to SARS-CoV-2.

Table 4  
Acute cerebrovascular diseases relating to COVID-19

Outcome	Author, Year	Number of studies	Study design	Risk of bias	Population	Follow-up	Event-Rate	Certainty of evidence
Acute ischemic stroke	Lodigiani et al. 2020 <sup>21</sup>	2	Retrospective study	low	Severe disease: 15.7% (61 of 388)	Median 10 days	2.3% (9 of 388)	⊕⊕OO LOW <sup>1</sup> .
	Li et al. 2020 <sup>6</sup>				Severe disease: 42.5% (94 of 221)			
	Klok et al. 2020 <sup>20</sup>	2	Retrospective study	high	Severe disease: 100% (184 of 184)	Median 14 days	2.7% (5 of 184)	
	Helms et al. 2020				Severe disease 100% (58 of 58)			
Cerebral venous sinus thrombosis	Li et al. 2020 <sup>6</sup>	1	Retrospective study	low	Severe disease 42.5% (94 of 221)	Up to 5 weeks	0.5% (1 of 221)	⊕OOO VERY LOW <sup>1,2</sup>
Cerebral hemorrhage	Li et al. 2020 <sup>6</sup>	1	Retrospective study	low	Severe disease 42.5% (94 of 221)	Up to 5 weeks	0.5% (1 of 221)	⊕OOO VERY LOW <sup>1,2</sup>

<sup>1</sup> retrospective study design, <sup>2</sup> optimal information size not met

### 3.2.1. Ischemic strokes relating to SARS-CoV-2

We performed a meta-analysis of four observational studies that included the data of 851 patients with COVID-19 to assess the incidence of ischemic strokes (Fig. 2). The overall incidence of ischemic strokes in COVID-19 patients was 3.3% (95% CI: 2.2–4.9; follow-up range one to five weeks after hospital admission). A sensitivity analysis was conducted by excluding high risk of bias studies and showed no major changes in the incidence of ischemic strokes (3.4%; 95% CI: 1.16–7.2; follow-up range one to five weeks after hospital admission). However, it should be noted that the sensitivity analyses resulted in the loss of half the studies. Due to the small number of studies, an assessment of publication bias was not carried out.

Among the studies with a low risk of bias, in the study population with more severe cases of COVID-19, a higher patient proportion suffered an ischemic stroke than in the study population with less severe cases (5.0% vs. 2.3%) [6, 21].

The Italian study reported that in six of nine cases, ischemic stroke was the primary reason for admission to the hospital. The Wuhan study measured a different period: the mean time from the onset of COVID-19 symptoms

to acute ischemic stroke was 10.8 days. In the remaining studies, the ischemic strokes were diagnosed at the ICU. While the Dutch study did not mention whether the patients showed any focal neurological signs, in the French study, brain imaging was performed due to unexplained encephalopathy symptoms in patients without any focal neurological deficits [19].

Only the Wuhan study provided data concerning the etiology of the ischemic strokes: five of the eleven ischemic strokes were classified as macroangiopathic, three as microangiopathic, and three as cardioembolic in terms of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification[6].

### **3.2.2. Other acute cerebrovascular diseases**

The Chinese study also included other acute cerebrovascular manifestations [6]. Of the 221 reported patients, one had a sinus vein thrombosis (0.5%), and one had a cerebral hemorrhage (0.5%). Both patients were defined as severe cases, and the cerebrovascular event occurred after more than nine days.

## **3.3 KQ3: Infectious/inflammatory CNS disease relating to SARS-CoV-2; KQ3.1: Neuroinvasion of SARS-COV-2**

No case of an infectious/inflammatory CNS disease associated with SARS-CoV-2 was described in the cohort studies. That is why for KQ3 we also included case studies and case series. In nine articles, the data of 15 individuals was presented [5, 23–25, 27–31, 33]. The main symptoms and diagnostic results (neurological examination, brain imaging, CSF, electroencephalography, PCR tests) are included in Table 2. In two COVID-19 patients, the CSF was positive for SARS-CoV-2 in the PCR test [26–28]. One of these was a case of meningoencephalitis associated with COVID-19 and took place in Japan [28]. A 24-year-old man was admitted to the hospital because of generalized seizures and loss of consciousness. He already had shown symptoms of a general infection several days before. Neck stiffness was detected. The MRI supported the assumption of a meningoencephalitis. The nasopharyngeal swab tested negative for SARS-CoV-2 and the CSF sample positive. Both tests repeatedly led to the same results.

General symptoms of an infection, such as headache and fever, and a new-onset seizure (not described whether generalized or focal) were also present in the case of a 41-year-old female in the USA [26, 27]. Neck stiffness and photophobia were documented at the emergency department. In the course of the disease, she developed disorientation accompanied by hallucinations. In this case, both the nasopharyngeal swab and the CSF tested positive for SARS-CoV-2. A repetition of the tests was not stated.

In both cases, the CSF results were not sufficiently presented to allow a more precise interpretation regarding an impairment of the blood–brain barrier. As for neurotropic viruses, only the herpes simplex virus and the varicella zoster virus were excluded. Additionally, in the second case, cerebral imaging was entirely missing.

In the other seven case studies and series with 13 individuals, the PCR tests for SARS-CoV-2 in the CSF samples were negative [23–25, 29–31, 33]. In total, only two studies repeated the PCR tests on the CSF samples [24, 28].

CSF testing was also carried out in the previously mentioned study of Helms et al., in which seven patients with unexplained encephalopathy symptoms were lumbar punctured. In none of these patients could SARS-CoV-2 be detected by PCR tests [19]. However, whether cerebral imaging indicated an inflammatory process or the results of the liquor samples were released in detail to prove if there is any hint of SARS-CoV-2.

Notable is a case report of Xiang et al. that described consciousness impairment in a 56-year-old male COVID-19 patient [5]. The CSF of the patient was also positive for SARS-CoV-2 in the PCR test, but this was not included in this review due to the publication language (Chinese).

## 4. Discussion

Initially, neurological manifestations were not the focus of attention in the scientific discourse of SARS-CoV-2. In the meantime, an increasing number of articles on the neurological manifestations of SARS-CoV-2 have been published, even first reviews that summarize these data [34–36]. While previously published reviews covered a wide range of neurological symptoms and included case reports for all outcomes, we focused on CNS disorders and prespecified a best-evidence approach. Although ours is a rapid review, it has methodological advantages such as a discriminated literature search, a risk of bias and GRADE assessment, and the inclusion of a quantitative analysis (regarding acute ischemic stroke). We consider these steps necessary to assess the available evidence.

Our meta-analysis of four cohort studies including a total of 851 patients with COVID-19 infections showed that 3.3% (95% CI: 2.2–4.9; follow-up range one to five weeks) suffered from an ischemic stroke. The Wuhan study was the only one of the included publications that provided the data of the total population and of the stroke patients separately [6]. A comparison of these results with an epidemiological study of patients with ischemic stroke in China (n = 19,604, median age 65 years) is limited due to the low number of cases in the Wuhan COVID-19 study. However, in the Wuhan COVID-19 study, previous cardio-cerebrovascular diseases were known in fewer patients with an acute cerebrovascular event (23.1% vs. 42.7% [atrial fibrillation and previous stroke or TIA]), and diabetes was two times more frequent than in the epidemiological study (46.2% vs. 20.7) [6, 37]. The percentage of patients with previous arterial hypertension was similar in both studies. In regard to age, a case series of five COVID-19 ischemic stroke patients with a lower age (ranged between 33 and 49 years) remains outstanding [38].

In comparison to our meta-analysis, Yaghi et al. described a lower rate of ischemic strokes in patients with COVID-19 infections in New York City with a follow-up of up to four weeks [39]. Referring to 3,556 hospitalized COVID-19 patients, the researchers reported 32 patients with COVID-19 that suffered from an ischemic stroke. That indicates an incidence of ischemic stroke in COVID-19 patients of 0.9%. However, they did not specify where they derived the number of 3,556 COVID-19 patients and did not state the characteristics of the total population. Furthermore, not all of the 3,556 COVID-19 patients were tested for SARS-CoV-2 with a PCR test. The fact that stroke patients without respiratory symptoms of COVID-19 may have been wrongly excluded should not be underestimated. Particularly, as we know, patients with severe cases of COVID-19 have fewer typical symptoms, such as dry cough and fever, than patients with mild cases of COVID-19. [22] In regard to the data provided, it is not possible to draw conclusions about the stroke incidence and, therefore, we decided against a post-hoc inclusion of this study. In contrast, in the two larger studies included in our meta-analysis, COVID-19 was laboratory proven in all patients, and the baseline characteristics of the population were described in detail [6, 21].

In the past, respiratory infections in general were repeatedly associated with an increased incidence of ischemic stroke [40–43]. In 2018, Blackburn et al. presented their results of a time-series analysis of English hospital admissions for stroke and myocardial infarction [40]. They reported that respiratory viruses except

parainfluenza were significantly associated with ischemic stroke admission in the elderly ( $\geq 75$  years). In particular, influenza was widely discussed in the scientific discourse because an influenza vaccination is available and may possibly lead to a risk reduction [44]. However, the evidence is limited due to the lack of randomized controlled studies. A high concentration of C-reactive protein (CRP) was also discussed as a marker of elevated risk of ischemic stroke [45]. In the Wuhan study, the mean CRP concentration in patients with cerebrovascular events was significantly higher than in those without (51.1 mg/dl vs. 12.1 mg/dl) [6]. Nevertheless, the relevance of CRP to ischemic cerebrovascular disease remains unclear. Associations with ischemic stroke depend significantly on conventional risk factors and other laboratory signs of inflammation [45]. Of course, treatment teams must also consider laboratory signs and the general risks of hypercoagulability. Further, confounding atrial fibrillation must be taken into account because previous studies showed that new-onset atrial fibrillation occurs more frequently in the context of sepsis [46, 47]. The presence of atrial fibrillation was not explicitly stated in any of the included studies of our meta-analysis.

Genetically related coronaviruses caused SARS and MERS pandemics. During these past pandemics, virus-related neurological symptoms and acute cerebrovascular disease were rather a marginal issue. [48] The latter had been associated with the intravenous administration of immunoglobulins. Umapathi et al. reported five patients with large artery cerebral infarctions among 206 SARS patients in Singapore. Three of the five patients received intravenous immunoglobulins. The proportion of critically ill cases was 23.3%; further information on the age and comorbidities of the study population was not reported [49]. In comparison, the proportion of severe cases in the two larger COVID-19 studies was 42.7% and 17.3%, respectively [6, 21].

In SARS and MERS, there have also been isolated case reports of associated infectious/inflammatory brain diseases, of which only two showed positive PCR results in CSF analyses [12, 15, 50]. In addition, in SARS, the virus was detected in the brain tissue of an affected patient [14] and of autopsied patients [11, 13]. The current pandemic involves several isolated cases of infectious/inflammatory brain diseases associated with SARS-CoV-2, however, only two cases in which the virus was detected in the patient's CSF [26–28]. It is generally accepted that a positive PCR result in the CSF is an indication of direct viral infection of the brain. However, one must bear in mind that during COVID-19, a marked systemic inflammatory response syndrome (SIRS) has been described [51]. In this context, the proinflammatory cytokine storm is likely to lead to an increased permeability of the blood–brain barrier [52]. The receptor by which SARS-Cov-2 enters its host cell is the angiotensin-converting enzyme 2 (ACE2) receptor. Immunohistochemistry for the ACE2 receptor in CNS tissue, though with limited description, failed to show neuronal or glial positivity but did confirm it in the brain vasculature [8]. Hence, viral replication in the brain's microvasculature in parallel with an open blood–brain barrier could explain the CSF detection of virus particles despite the absence of neuronal/glial cell invasion. An additional receptor binding the spike protein of SARS-Cov-2 has been possibly recognized in CD147 through an in vitro experiment, and CD147 is widely present in the CNS [53]. However, taken together with the paucity of reports on meningoencephalitis associated with COVID-19, direct CNS infection seems to be rare or confined to very special patient/virus constellations during SARS-Cov-2.

In both reported cases referenced in the current review, the CSF results were not presented sufficiently to allow a more precise interpretation regarding an impairment of the blood–brain barrier, and the results of important diagnostic tests were missing (e.g., brain imaging, exclusion of further neurotropic viruses, intrathecal synthesis of antibodies) [26–28]. At least, the following must be considered: CSF tests for SARS-CoV-2 were rarely

reported, and the test accuracy of the various test kits was not specified. It is to be expected that a possible positive result can also be a false positive. That is why the data extraction of case reports included whether the CSF PCR tests were repeated. Overall, in only two case studies were the PCR tests on the CSF samples repeated [24, 28], and in one the results were SARS-CoV-2-positive twice [28].

Overall, our results support the assumptions of other reviews. Considering the results in context with those of previously published studies, the following implications can be outlined: The treatment team for patients with an infection of SARS-CoV-2, particularly with severe disease progression, should be aware of the development of neurological signs and symptoms. The integration of neurologists into the multiprofessional COVID-19 treatment team can help detect neurological complications early. Introducing a suitable risk assessment concerning hypercoagulability in severe COVID-19 cases may be particularly important, following a recent meta-analysis that revealed that acute cerebrovascular disease in COVID-19 patients was associated with an increased poor composite outcome and mortality [54].

Furthermore, in the pandemic situation, even if the symptoms are exclusively neurological, a SARS-CoV-2 infection should be considered, and patients should be tested accordingly.

Obviously, more clinical studies are needed to improve the current evidence of the neurological CNS manifestations of SARS-CoV-2. In our search we also identified ongoing studies, which can provide more detailed information, for example, on the prevalence of acute encephalopathy in severely ill COVID-19 patients or on the long-term cognitive deficits in COVID-19 patients with acute neurological symptoms [55, 56].

## 5. Limitations Of The Review

Due to the urgency of the COVID-19 pandemic, we conducted a rapid review and abbreviated certain methodological steps of the review process. Specifically, we applied a single risk of bias assessment, data extraction, and certainty of evidence rating, with a second person checking for plausibility and correctness.

There was a limitation in regard to language; full texts only in German and English were included. This concerned only two case studies. It has been proved in previous studies that the exclusion of non-English publications from systematic reviews had a minimal effect on the overall conclusions[57]. We are confident that none of these limitations changed the overall conclusions of this review.

However, the evidence of a review is only as solid as the underlying primary studies. Due to the low number of studies, we conducted a quantitative analysis for only one outcome (ischemic stroke). The study of Li et al. was a preprint and the manuscript was not peer-reviewed[6]. For infectious/inflammatory CNS disease associated with SARS-CoV-2, we referred to case studies, as this outcome was not described in any cohort study. Nevertheless, our numbers, especially those of the cerebrovascular events, can be used as a first orientation.

## 6. Conclusion

Central nervous complications occur frequently in patients with COVID-19 and are most likely of parainfectious origin. It is important to integrate neurologists into the multiprofessional COVID-19 treatment team in order to detect neurological complications early and to treat them correctly.

## 8. List Of Abbreviations

ACE2 receptor: angiotensin-converting enzyme 2 receptor

CNS: central nervous system

COVID-19: Coronavirus disease 2019

CSF: cerebrospinal fluid

CT: computer tomography

EEG: electroencephalography

GCS: glasgow coma scale

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HSV: herpes simplex virus

ICU: intensive care unit

KQ: key question

MERS: Middle East Respiratory Syndrome

MRI: magnetic resonance imaging

NA: not available;

PCR: polymerase chain reaction

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

SARS: Severe Acute Respiratory Syndrome

SARS-CoV-2: Severe Acute Respiratory Syndrome - Coronavirus 2

SD: standard deviation

SIRS: systemic inflammatory response syndrome

VZV: varicella-zoster virus

## 10. Declarations

### 10.1 Ethics approval and consent to participate

Not applicable

## 10.2 Consent for publication

Not applicable

## 10.3 Availability of data and materials

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

## 10.4 Competing interests

The authors declare that they have no competing interests.

## 10.5 Funding

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## 10.6 Authors' contributions

V.M. devised the protocol for the review and coordinated the reviewing process of abstracts and full-text articles. I.K. conducted the literature search. V.M. and A.G. conducted the screening of articles, extracted the data and performed the statistical analysis. V.M., A.G., G.G. and P.L. wrote the manuscript. All authors have read and approved the manuscript. V.M. is responsible for the integrity of the work as a whole.

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## Figures

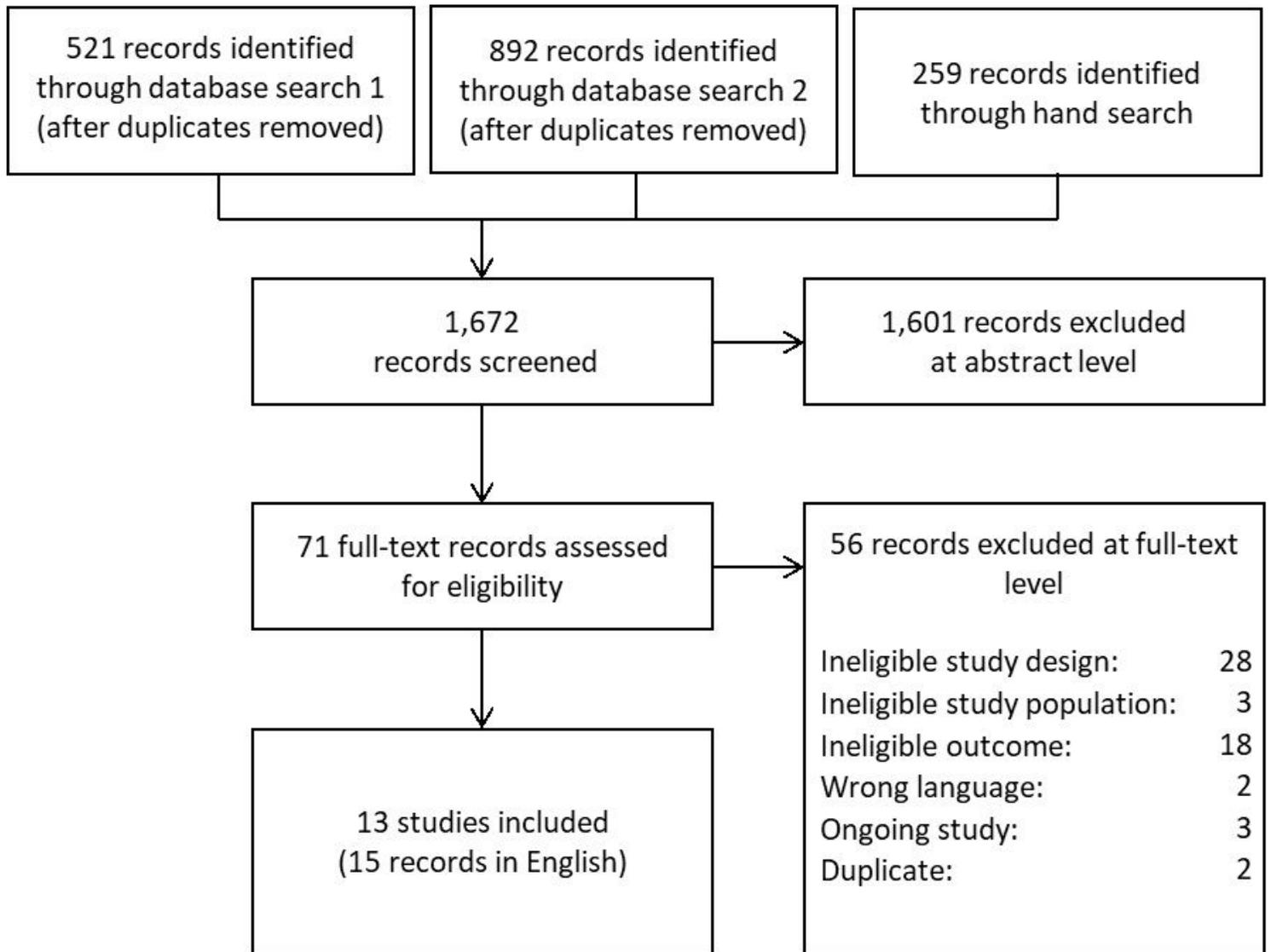
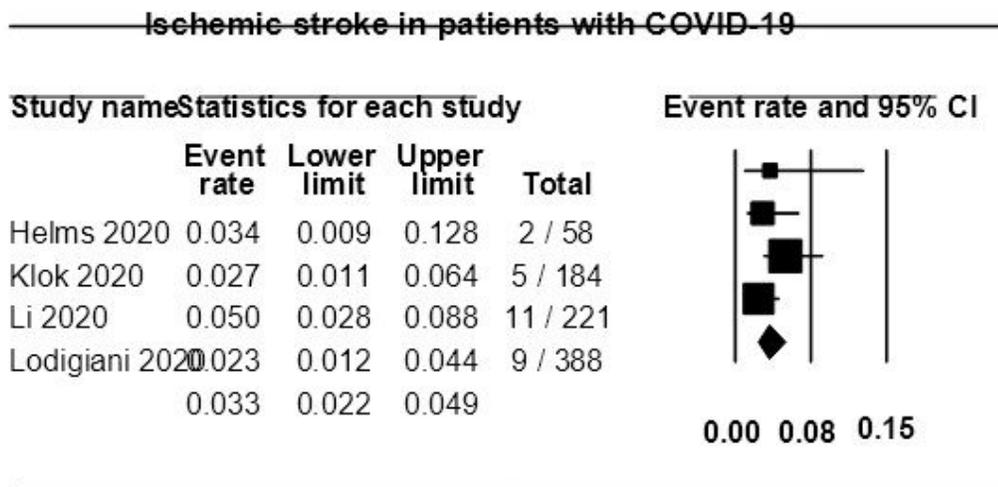


Figure 1

Figure 1



Random-Effects Meta-Analysis: I<sup>2</sup>: 8.2%; Tau: 0.12

## Figure 2

Figure 2

## Supplementary Files

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