

# COVID-19: Neuroimaging Features of a Pandemic

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## ABSTRACT

**BACKGROUND AND PURPOSE:** The ongoing Coronavirus Disease 2019 (COVID-19) pandemic is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is occasionally associated with manifold diseases of the central nervous system (CNS). We sought to present the neuroimaging features of such CNS involvement. In addition, we sought to identify typical neuroimaging patterns that could indicate possible COVID-19-associated neurological manifestations.

**METHODS:** In this systematic literature review, typical neuroimaging features of cerebrovascular diseases and inflammatory processes associated with COVID-19 were analyzed. Reports presenting individual patient data were included in further quantitative analysis with descriptive statistics.

**RESULTS:** We identified 115 studies reporting a total of 954 COVID-19 patients with associated neurological manifestations and neuroimaging alterations. A total of 95 (82.6%) of the identified studies were single case reports or case series, whereas 660 (69.2%) of the reported cases included individual information and were thus included in descriptive statistical analysis. Ischemia with neuroimaging patterns of large vessel occlusion event was revealed in 59.9% of ischemic stroke patients, whereas 69.2% of patients with intracerebral hemorrhage exhibited bleeding in a location that was not associated with hypertension. Callosal and/or juxtacortical location was identified in 58.7% of cerebral microbleed positive images. Features of hemorrhagic necrotizing encephalitis were detected in 28.8% of patients with meningo-/encephalitis.

**CONCLUSIONS:** Manifold CNS involvement is increasingly reported in COVID-19 patients. Typical and atypical neuroimaging features have been observed in some disease entities, so that familiarity with these imaging patterns appears reasonable and may assist clinicians in the differential diagnosis of COVID-19 CNS manifestations.

**Keywords:** COVID-19, CT, neuroimaging, MRI, SARS-CoV-2.

**Acceptance:** Received October 8, 2020, and in revised form November 20, 2020. Accepted for publication November 21, 2020.

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**Acknowledgements and Disclosure:** We would like to thank Professor Ralf Gold (Dean of the Medical Faculty of the Ruhr University of Bochum, and Director of the University Department of Neurology, St. Josef-Hospital Bochum) for his support in the implementation and completion of this review. All authors declare no conflicts-of-interest relevant to this work. The study was not industry sponsored and did not receive any funding.

Open access funding enabled and organized by Projekt DEAL.

<sup>#</sup>Georgios Tsivgoulis and Christos Krogias contributed equally to this work.

J Neuroimaging 2021;31:228-243.

DOI: 10.1111/jon.12819

## Introduction

About 9 months have passed since the outbreak of the Coronavirus Disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Being initially reported as a pure respiratory infection, COVID-19 is increasingly considered as a multi-organ disease, giving rise to cardiovascular, renal, gastrointestinal, hepatic, hematological, metabolic as well as neurological disorders.<sup>1-3</sup>

In this context, manifold neurological manifestations involving the central as well as the peripheral nervous system have been increasingly described.<sup>4,5</sup> In particular, diverse cerebrovascular diseases are frequently observed in association with SARS-CoV-2 infection.<sup>6</sup> Beyond, inflammatory and immune-mediated processes such as encephalitis, myelitis, and demyelination have been occasionally described in some cases, an observation, which might indicate a possible neurotropism of

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the virus.<sup>7</sup> However, apart from the direct involvement of the central nervous system (CNS), many of the observed neurological manifestations might be related to secondary parainfectious or postinfectious pathophysiological mechanisms, because immune-mediated vulnerability of the CNS is frequently being observed in association to several viral infections<sup>8</sup> as well as to prolonged critical hospitalization.<sup>9</sup> Worth emphasizing, CNS involvement was also reported in the prior two coronavirus epidemics in the past, severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic in 2002-2003 and 2012, respectively.<sup>10,11</sup>

Although the prevalence of neurological involvement among COVID-19 patients is relatively low considering the number of people infected from SARS-CoV-2, the absolute number has exponentially increased due to the ongoing pandemic. As many of the neurological symptoms and signs are nonspecific, for example, confusion, agitation, headache, generalized muscle weakness, delirium, and disorders of consciousness, it is a challenging task for the clinician to differentiate between direct involvement of the nervous system and neurologic manifestations of systematic causes such as metabolic derangement and hypoxia.

In view of the former considerations, neuroimaging examinations have increased in order to assist in the differential diagnosis of different neurological manifestations of COVID-19. The most common indications for neuroimaging appear to be associated with altered mental status, syncope/fall, and focal neurologic deficits.<sup>12</sup> On the other hand, to avoid the additional risk of exposing other patients or healthcare providers to the virus, not all the COVID-19 patients with neurological symptoms have undergone neuroimaging studies. In particular, the American College of Radiology (ACR) and Centers for Disease Control and Prevention (CDC) agreed on postponing imaging studies that would not have an impact on physicians decision-making.<sup>13</sup> Nonetheless, a range of interesting and helpful brain and spinal cord MRI and CT findings have been described across the globe, necessitating careful review of these data. In this systematic review, we aimed to provide an overview of the currently described neuroimaging features of CNS diseases that have been associated with COVID-19. In addition, special emphasis was given to identify possible neuroimaging patterns that may raise the suspicion of COVID-19-associated neurological manifestations.

## Methods

This systematic review adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA)<sup>14</sup> and was compliant with the Meta-analysis of Observational Studies in Epidemiology (MOOSE)<sup>15</sup> recommendations. We searched the literature utilizing two different databases (PubMed and Scopus) and applied the following search strategy: “(“coronavirus” OR “SARS-CoV” OR “COVID-19” OR “SARS-CoV-2”) AND (“neurologic” OR “brain” OR “Central Nervous System” OR “Cerebral” OR “stroke” OR “encephalitis” OR “myelitis”) AND (“neuroimaging” OR “computed tomography” OR “CT” OR “magnetic resonance” OR “imaging”).” We screened the references of relevant studies and searched for preprints to ensure that we did not miss important published results by our database search.

All different forms of published scientific articles and studies were abstracted. Last literature search was conducted by two independent authors (TL and CK) on August 7, 2020. All of the studies included in our review concern confirmed, and not probable or possible, COVID-19 case definitions according to the WHO COVID-19 case definitions.<sup>16</sup>

Original contributions including case reports and case series, which presented CT and/or MRI findings of COVID-19 patients with CNS involvement, were included. Review articles, letters to the editor, and other correspondence not containing original data were excluded from further analysis.

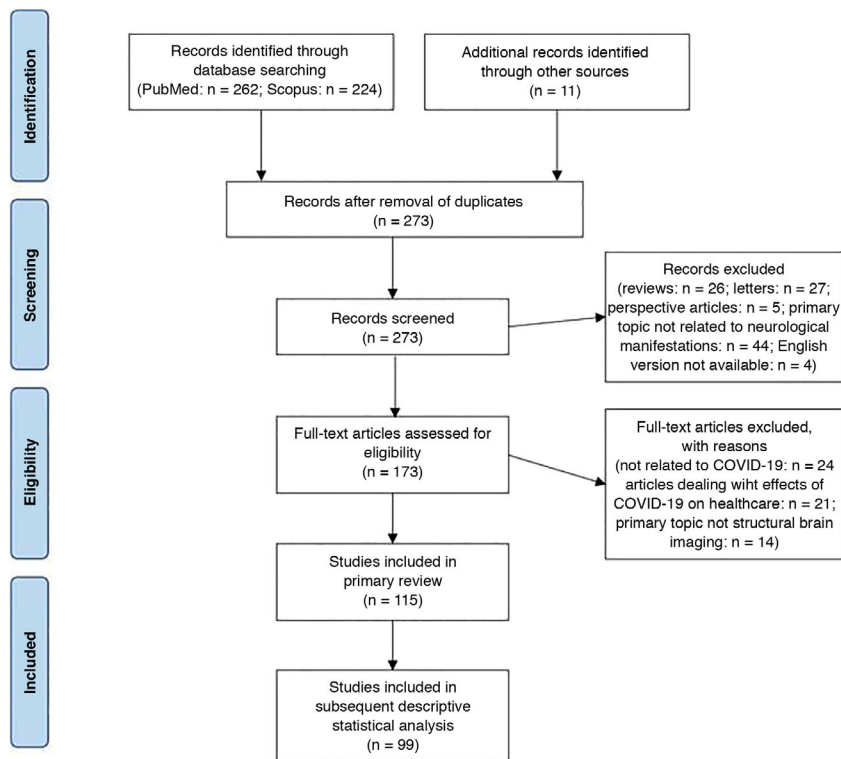
Data were extracted by three independent authors (TL, JM, and JCJ) with the use of standardized columns contained information about the authors, title, journal, date of publication, disease category, region, design (ie, case report of cohort study), number of COVID-19 patients with documented CNS involvement, age, sex, neuroimaging modality, and described neuroimaging findings. Disease category was defined as follows: 1 = ischemic stroke, 2 = hemorrhagic stroke, 3 = cerebral microbleeds, 4 = cerebral and sinus thrombosis (CVST), 5 = Posterior Reversible Encephalopathy Syndrome (PRES), 6 = other cerebrovascular manifestations (eg. cervical artery dissection), 7 = meningo-/encephalitis, 8 = demyelination/leukoencephalopathy, 9 = myelitis, and 10 = cranial nerve involvement. After reviewing all the included studies, three authors (TL, GT, and CK) reached consensus about the emerging common neuroimaging features in each disease category, which were frequently reported in COVID-19 patients. Subsequently, two further columns were added to the standardized form, which included (1) information about the number of patients with reported individual findings and (2) the number of patients exhibiting the suggested typical neuroimaging feature. Descriptive statistical analysis was based on the patient numbers given in these two columns, as proportion of patients exhibiting the suggested typical neuroimaging feature was determined. Examples of neuroimaging findings of COVID-19 patients are presented for most of the discussed neurological disease entities.

## Results

The initial literature search resulted in a list of 497 total records. The removal of duplicates yielded 273 articles. After a manual screening of these articles based on their titles or abstracts, a total of 115 studies reporting neuroimaging findings on a total of 954 COVID-19 patients met the inclusion criteria for this systematic review (Fig 1); 73 studies were single case reports, 22 were presented as case series, 19 were conducted as retrospective observational or cross-sectional studies, and one article represents a prospective cohort study. Sample sizes ranged from 1 to 242 patients per study.

A total of 48 studies were conducted in North America (USA = 47; Canada = 1), two in South America (Brazil), eight studies in East Asia (China = 5, Taiwan = 1, Japan = 1, Singapore = 1), 13 in West Asia (Iran = 6, United Arab Emirates = 2, Turkey = 2, Qatar = 1, Kuwait = 1, Israel = 1), and 44 studies were conducted in Europe (France = 14, Italy = 11, Spain = 6, UK = 6, Germany = 3, Sweden = 2, Netherlands = 2, Switzerland = 1).

Out of the 115 original studies included in this review, 99 articles further met the criteria of reporting individual data. Thus, the data of 660 (69.2%) patients with individual information



**Fig 1.** “Preferred Reporting Items for Systematic Reviews and Meta-Analyses”—flow diagram of the study. *n* = number.

were considered for subsequent descriptive statistical analysis (Table 1).

## Cerebrovascular Diseases

### Ischemic Stroke

In a large retrospective cohort study of a total of 3,218 COVID-19 confirmed patients, acute ischemic lesions were the most common neuroimaging finding in the subgroup of 454 COVID-19 patients with neurological symptoms (ie, stroke syndromes) who underwent neuroimaging. Acute stroke findings accounted for 92.5% of patients with positive neuroimaging studies and were present in .9-1.1% of the total number of hospitalized patients infected with SARS-CoV-2.<sup>17,18</sup> In this context, Large Vessel Occlusion (LVO) was reported to be the most common presentation of acute ischemic stroke accounting for 21.6-72.5% of the total acute ischemic strokes, with a 14.9% of the patients revealing multiple LVOs and only 7.5-8.7% showing lacunar strokes.<sup>19-25</sup> Overall, the whole spectrum of known ischemic stroke etiologic subtypes according to TOAST criteria was reported in several studies, showing also increased incidence of hemorrhagic transformation<sup>6,26</sup> and worse outcomes with a mortality rate of up to 45%.<sup>6,27</sup> Most of the patients were suffering from cardiovascular risk factors and were older than 60 years old (mean age: 63.4 ± 13.1 years). However, LVO strokes were also reported in younger patients without any known cardiovascular risk factor.<sup>19,20,28</sup> Interestingly, infarction of the splenium of the corpus callosum, an oftentimes very rare condition, was observed occasionally in some COVID-19 patients undergoing neuroimaging.<sup>29</sup> Noteworthy, a certain proportion of stroke cases were tested positive for antiphospholipid antibodies such as lupus anticoagulant (41.7%), anticardiolipin

antibodies (20% IgM and 42.9% IgA), and anti-β2-glycoprotein I antibodies (10% IgM, 38.5% IgG, and 42.9% IgA).<sup>6</sup>

An exemplary case with a typical neuroimaging pattern (LVO stroke with hemorrhagic transformation) for ischemic stroke in COVID-19 patients is depicted in Figure 2.

Our systematic review revealed a total of 45 studies reporting imaging features of a total of 483 COVID-19 patients suffering from acute ischemic stroke (AIS).<sup>12,18,21-24,30-67</sup> A total of 26 studies were presented as single case reports or as case series.<sup>30-55</sup> The remaining 19 studies were conducted as retrospective studies reporting on neuroimaging findings of AIS patients.<sup>12,18,21-24,56-66</sup> Sample sizes ranged from 1 to 116 patients. The median of reported mean age was 64.5 years (interquartile range [IQR] = 56-72 years; range = 43.5-81 years). The sex of 303 patients was specified, 195 (64.4%) of them being males.

A total of 24 studies were conducted in the United States, one in Brazil, three in China, one in Iran, and 16 in Europe (France = 9, Spain = 3, Italy = 2, Sweden = 1, and Netherlands = 1).

From the total of these 45 reports, 38 studies reported individual patient data, with 397 (82.2%) of the 483 AIS patients being considered for additional descriptive statistical analysis. Of these, 238 (59.9%) revealed the typical finding of LVO stroke.

### Hemorrhagic Stroke

A number of cases of intracerebral hemorrhage (ICH) were reported in patients with COVID-19. It has been speculated that SARS-CoV-2 enters cells via the angiotensin-converting-enzyme (ACE)-2 receptor and may cause dysregulation and fluctuations in cerebral blood pressure levels, resulting to an increased risk of hypertensive primary ICH.<sup>68</sup> It has been

Table 1. Synopsis of Neuroimaging Features and Characteristics of Studies Reporting on COVID-19 Patients with Associated CNS Manifestations

Neurological Manifestation	References	Study Type	Origin	Patients	Typical Neuroimaging Features	Typical Neuroimaging Feature with Possible Predominance in COVID-19 Patients	Prevalence of Typical Feature
Ischemic stroke	12,18,21-24,30-67	Total $n = 45$ Single case reports: $n = 17$ Case series: $n = 9$ Retrospective studies: $n = 19$	USA = 24 France = 9 China, Spain = 3 Italy = 2 Brazil, Iran, Sweden, Netherlands = 1	$n = 483$ Mean age, $y$ ; median (IQR): 64.5 (56-72) Male sex = 64.4% (195/303)	<ul style="list-style-type: none"> <li>-All types of ischemic stroke observed</li> <li>-Predominantly territorial strokes due to large vessel occlusion (IVO)</li> <li>- Rarely callosal ischemia and/or infarction of the splenium</li> </ul>	- IVO stroke, optionally with hemorrhagic transformation	59.9%(238/397)
Hemorrhagic stroke	12,18,21,22,26,48,56,57,59,65,70-76	Total $n = 18$ Single case reports: $n = 3$ Case series: $n = 6$ Retrospective studies: $n = 8$ Prospective studies: $n = 1$	USA = 8 Italy, Spain = 2 Canada, France, Sweden, Iran, Germany, UK = 1	$n = 135$ Mean age, $y$ ; median (IQR): 60.8 (57-66) Male sex = 67.0% (73/109)	<ul style="list-style-type: none"> <li>-All types of intracranial bleedings observed, hemorrhage (ICH), subarachnoidal hemorrhage, and subdural hematomas.</li> <li>-Non-hypertension-associated pattern of ICH even though most of the identified cases suffered from arterial hypertension</li> <li>-- Sometimes multifocal hemorrhages</li> </ul>	- Intraparenchymal ICH in non-hypertension-associated locations (cortical, cortical-subcortical, lobar);	69.2%(45/65)
Microbleeds	56,60,64,65,79,81,82	Total $n = 7$ Single case reports: $n = 1$ Case series: $n = 1$ Retrospective studies: $n = 4$ Prospective studies: $n = 1$	France = 3 USA, Qatar, Switzerland, Sweden = 1	$n = 135$ Mean age, $y$ ; median (IQR): 62.5 (61-68) Male sex = 80.5% (66/82)	<ul style="list-style-type: none"> <li>bullet-Microbleeds in deep as well as in atypical locations like corpus callosum and juxtacortical white matter</li> <li>- Often in association with diffuse confluent T2 hyperintensities</li> </ul>	- Callosal and juxtacortical location	58.7%(61/104)
Cerebral venous and sinus thrombosis (CVST)	60,84-87,89,90	Total $n = 7$ Single case reports: $n = 5$ Case series: $n = 1$ Retrospective studies: $n = 1$	USA, France = 2 Iran, UK, Italy = 1	$n = 9$ Mean age, $y$ ; Median (IQR): 44.3 (21-65) Male sex = 55.6% (5/9)	<ul style="list-style-type: none"> <li>-- Sigmoid and transverse sinus thrombosis, and also cases with involvement of the deep cerebral venous system</li> </ul>	- Currently no indication of a special neuroimaging feature in patients with COVID-19 - However, CVST rarely with concurrent pulmonary thrombosis reported	n/a

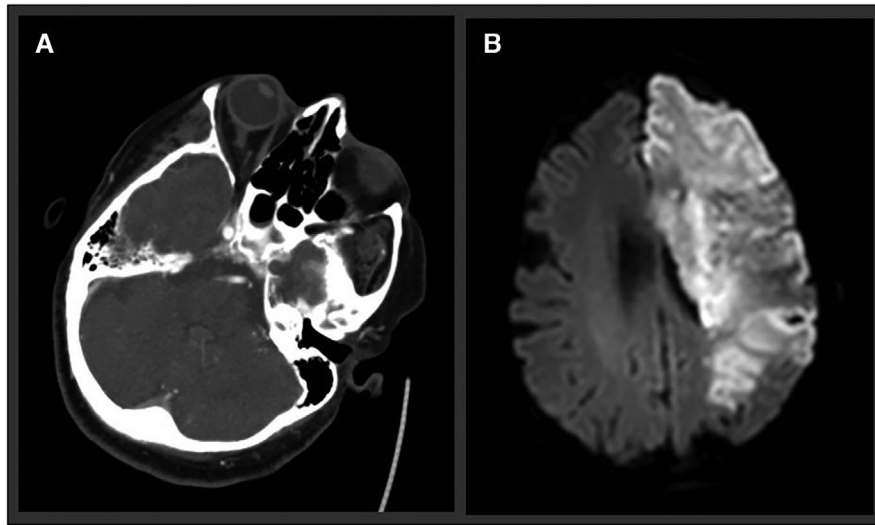
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Neurological Manifestation	References	Study Type	Origin	Patients	Typical Neuroimaging Features	Typical Neuroimaging Feature with Possible Predominance in COVID-19 Patients	Prevalence of Typical Feature
Posterior reversible encephalopathy syndrome (PRES)	60,95,97,98	Total $n = 4$ Single case reports: $n = 1$ Case series: $n = 2$ Retrospective studies: $n = 1$	USA = 2 France, Italy = 1	$n = 9$ Mean age, $y$ ; Median (IQR): 62.5 (56-69) Male sex = 44.4% (4/9)	<ul style="list-style-type: none"> <li>- Vasogenic edema, predominantly located in parieto-occipital regions</li> <li>- Rarely association petechial hemorrhages and hemorrhagic transformation of PRES lesions</li> </ul>	- Currently no indication of a special neuroimaging feature in patients with COVID-19	$n/a$
Meningo-encephalitis	18,24,61,64,101-106,108-119,129	Total $n = 21$ Single case reports: $n = 13$ Case series: $n = 3$ Retrospective studies: $n = 4$	France, UK = 4 USA = 4 Japan = 2 China, Sweden, Germany, UAE, Italy, Turkey = 1	$n = 65$ Mean age, $y$ ; Median (IQR): 59 (39-61) Male sex = 67.7% (21/31)	<ul style="list-style-type: none"> <li>- Restricted diffusion and FLAIR hyperintensities in mesial temporal lobe and hippocampus</li> <li>- Splenium T2w signal changes</li> <li>- (bilateral) temporal lobe and thalamus FLAIR hyperintensities with evidence of hemorrhage in SWI and postcontrast ring enhancement compatible with acute hemorrhagic necrotizing encephalopathy</li> </ul>	- Features of hemorrhagic necrotizing encephalopathy (FLAIR hyperintensities in temporal lobe and/or thalamus with evidence of hemorrhage in SWI and post contrast ring enhancement)	28.8%(15/52)
Demyelination/leukoencephalopathy	24,56,60,65,80,113,118-125	Total $n = 14$ Single case reports: $n = 8$ Case series: $n = 1$ Retrospective studies: $n = 5$	USA, France = 4 Italy = 2 Germany, Sweden, Turkey, Iran = 1	$n = 78$ Mean age, $y$ ; Median (IQR): 60.8 (57-66) Male sex = 67.3% (70/104)	<ul style="list-style-type: none"> <li>- Diffuse leukoencephalopathy with (symmetric) and confluent T2 hyperintensities across the subcortical white matter, mostly without restriction of diffusion or contrast enhancement.</li> <li>- Asymmetrical periventricular and callosal white matter hyperintensities and bilateral Globus pallidum lesions with restricted diffusion sparing the infratentorial regions</li> </ul>	- Currently no indication of a special neuroimaging feature in patients with COVID-19	$n/a$

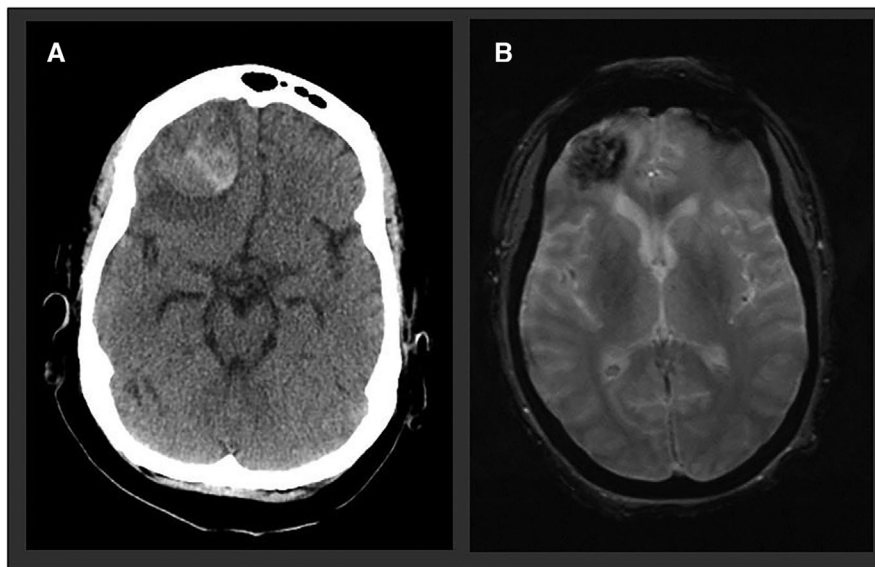
Table 1. Continued

Neurological Manifestation	References	Study Type	Origin	Patients	Typical Neuroimaging Features	Typical Neuroimaging Feature with Possible Predominance in COVID-19 Patients	Prevalence of Typical Feature
Myelitis	119,128-131	Total $n = 5$ Single case reports: $n = 5$	USA, Germany, Spain, UK, UAE $= 1$	$n = 5$ Mean age, $y$ ; Median (IQR): 60 (32-69) Male sex = 80.5% (66/82)	<ul style="list-style-type: none"> <li>- Isolated or multifocal hyperintense lesions of cervical and/or thoracic cord on STIR or T2w MRI images</li> <li>- Occasionally with tissue edema showing enlargement of spinal cord caliber</li> <li>- Usually without contrast enhancement, rarely evidence of restricted diffusion on DWI</li> </ul>	- Currently no indication of a special neuroimaging feature in patients with COVID-19	n/a
Olfactory system involvement	65,136,138	Total $n = 3$ Single case reports: $n = 2$ Retrospective studies: $n = 1$	Italy, Taiwan, Sweden = 1	$n = 9$ Mean age, $y$ ; Median (IQR): 23 (21-25) Male sex = 50.0% (1/2)	<ul style="list-style-type: none"> <li>- Bilateral olfactory bulb FLAIR signal hyperintensities and edema</li> <li>- Signal abnormalities in cortical areas associated with the olfaction (eg, posterior gyrus rectus)</li> </ul>	- Currently no indication of a special neuroimaging feature in patients with COVID-19 - However, due to the neurotropism with high prevalence of hyposmia (34-68% of the patients), alterations of olfactory system should be indicative for SARS-CoV-2-infection	n/a

$n$  = number;  $y$  = year; n/a = not applicable; IQR = interquartile range; STR1 = Short-T1 Inversion Recovery; DWI = diffusion weighted imaging; SWI = susceptibility-weighted imaging; FLAIR = fluid-attenuated inversion recovery; T2w = T2 weighted.



**Fig 2.** (A) CT angiography demonstrates left internal carotid artery occlusion (large vessel occlusion stroke) in a 79-year-old female patient. (B) Despite thrombolysis in cerebral infarction scale 2b recanalization, complete infarction of the left media and anterior cerebral artery was visible on follow-up diffusion-weighted imaging sequence.



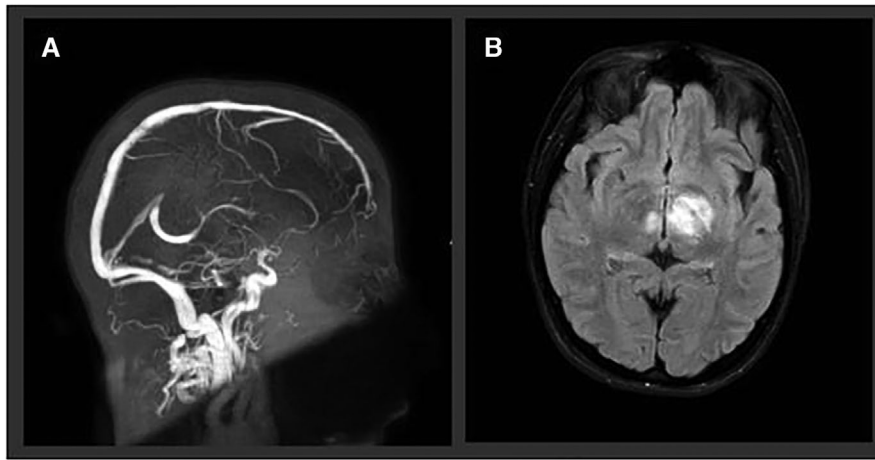
**Fig 3.** Atypical ICH in a 57-year-old woman with prolonged encephalopathy and hypoxic respiratory failure. Polymerase chain reaction for SARS-CoV-2 was positive in the nasopharyngeal swab. (A) Brain CT performed in the acute setting revealed a right frontal lobe hemorrhage with perifocal edema. (B) T2\* image demonstrating the right frontal lobar intracerebral hemorrhage.

estimated that 17% of the total strokes in SARS-CoV-2-infected patients are hemorrhagic.<sup>25</sup> However, many of the reported ICHs were located in a nontypical location for hypertensive hemorrhage such as lobar and/or cortical locations (*loco atypico*). Interestingly, in a British retrospective study of cases with COVID-19 associated ICH, Bengner et al report relatively young ages of affected patients (mean age = 52.2 years, range = 41-64 years), with predominantly lobar location in the anterior circulation, even though most of the identified cases suffered from arterial hypertension.<sup>69</sup> According to Kvernland et al, 89.5% of the patients with hemorrhagic stroke were on anticoagulation.<sup>70</sup> In this context, an underlying COVID-19-induced endotheliopathy is discussed, complicating anticoagulation decision, as clinicians have to balance risk of thrombosis with risk of ICH.

One exemplary case with a large hypertensive ICH in a COVID-19 patient is depicted in Figure 3.

Our review documented a total of 18 studies reporting about imaging features of 135 COVID-19 patients with ICH.<sup>12,18,21,22,26,48,56,57,59,65,71-77</sup> Eight studies were presented as single case reports or as case series.<sup>48,59,71-75,77</sup> Another eight studies were conducted as retrospective studies reporting on neuroimaging findings of ICH patients.<sup>12,18,21,22,26,57,65,76</sup> Sample sizes of these 18 studies ranged from 1 to 33 patients. Median of reported mean age was 60.8 years (IQR = 56.9-66.2 years; range = 30-74 years). The sex of 109 patients was specified, 73 (67.0%) of them being males.

Nine studies were conducted in North America (USA = 8; Canada = 1), one in Iran, and seven in Europe (Spain = 2, Italy = 2, France = 1, Germany = 1; Sweden = 1, UK = 1).



**Fig 4.** Two-dimensional time-of-flight MR venography (A) with atypical internal cerebral vein thrombosis in a 30-year-old female SARS-CoV-2-positive patient, presenting with severe headache, vomiting, and bilateral papilledema. Axial 2-dimensional fluid-attenuated inversion recovery revealed bilateral thalamic edema due to venous congestion in the same patient (B).

From the total of these 18 reports, 17 studies reported individual data of at least some of the included cases. Thus, data from 65 (48.1%) of the 135 ICH patients were considered for additional descriptive statistical analysis. Of these, 45 (69.2%) presented with the characteristic finding of an ICH in non-hypertension-associated locations (cortical, cortical-subcortical, lobar).

#### *Microbleeds*

There is accumulating evidence that a high proportion of COVID-19 patients may exhibit multiple cerebral microbleeds (CMB), mostly in atypical locations such as corpus callosum and juxtacortical white matter.<sup>78,79</sup> However, most of the reported cases were critically ill patients with Acute Respiratory Distress Syndrome and prolonged mechanical ventilation, raising concerns whether it could be a causal relationship of SARS-CoV-2 infection or incidental comorbidity of critical illness. In a large retrospective study, Radmanesh et al reported atypical CMB in 24% of COVID-19 ICU patients. The authors also report in addition to CMB diffuse confluent T2 hyperintensities in the supratentorial white matter with mildly restricted diffusion, sparing characteristically the deep gray matter and the cortex and indicating a probable relation to delayed posthypoxic leukoencephalopathy.<sup>80</sup>

Our systematic review revealed a total of seven studies reporting imaging features of a total of 135 COVID-19 patients with evidence of CMB.<sup>56,60,64,65,79,81,82</sup> Only one study was presented as a single case report, and one further as case series ( $n = 9$ ).<sup>79,81</sup> Most cases were reported in retrospective cross-sectional studies ( $n = 4$ )<sup>60,64,65,82</sup> as well as in the only prospective cohort study.<sup>56</sup> Sample sizes ranged from 1 to 39 patients. The median of reported mean ages was 62.5 years (range = 61-67.7 years). Sex was specified in 82 patients, and 80.5% (66) of those were males.

One study was conducted in the United States, one in Qatar, and five studies were conducted in Europe (France = 3, Sweden = 1, and Switzerland = 1). All of these studies reported individual data of at least some of the included cases. Thus, data from 104 (77.0%) of the 135 CMB patients were considered for additional descriptive statistical analysis. Of these, 61 (58.7%)

revealed the suggested typical finding of microbleed in callosal and/or juxtacortical location.

#### *Cerebral Venous Sinus Thrombosis*

CVST represents another occasionally observed cerebrovascular complication of SARS-CoV-2, constituting also a possible etiological association with the underlying coronavirus infection. Shahjouei et al reported in their multinational study a CVST prevalence of 4% among all cerebrovascular events.<sup>25</sup> The few case reports<sup>83-86</sup> and one case series<sup>87</sup> published to date in literature report CVST consistently in critically ill COVID-19 patients. In most of these patients, CVST was accompanied with hemorrhagic venous infarction and the outcome in five (55.6%) of these nine cases was fatal. As in non-COVID cases, sigmoid and transverse sinuses were predominantly affected, so that no unusual pattern of CVST has been observed. Notable, in some cases, concomitant cerebral arterial and venous thrombosis<sup>88</sup> or CVST with concurrent pulmonary arterial or venous thrombosis has been described.<sup>84</sup>

An exemplary case of CVST in a COVID-19 patient is depicted in Figure 4.

Our review revealed a total of seven studies reporting imaging features of a total of 9 COVID-19 patients suffering from CVST.<sup>60,84-87,89,90</sup> Five studies were presented as single case reports,<sup>83-86,88</sup> one as case series ( $n = 3$ ),<sup>90</sup> and one patient was the only CVST patient reported in a retrospective cross-sectional study.<sup>60</sup> The mean age of these nine reported patients was 44.3 years (range = 21-65 years). Five (55.6%) of the patients were male. Two studies were conducted in the United States, one in Iran, and five studies were conducted in Europe (France = 2, UK = 1, Italy = 1). All of these seven reports provided individual data, which were considered for further descriptive statistical analysis. However, as the involvement of deep and superficial veins and sinuses was equally described, no typical pattern of COVID-associated CVST could be identified.

#### *Posterior Reversible Encephalopathy Syndrome*

PRES is a neurological entity that is characterized by vasogenic edema, most frequently in the parieto-occipital regions,



usually as a result of hypertensive emergencies or a direct effect of cytokines in the endothelium and subsequent disruption of it.<sup>91,92</sup> Interestingly, several COVID-19 cases with PRES have been diagnosed and reported during the pandemic. In a case series of PRES in two COVID-19 patients from Massachusetts, Kishfy et al describe a typical pattern of signal hyperintensities in fluid-attenuated inversion recovery (FLAIR) images in occipital, posterior temporal lobes and the cerebellar hemispheres.<sup>93</sup> Diffusion-weighted imaging abnormalities in occipital lobes and the splenium of corpus callosum indicative of the cytotoxic component of the edema were observed in one of the case reports.<sup>94</sup> Furthermore, there were three described cases of hemorrhagic transformation of the PRES-associated lesions with petechial hemorrhages at the SWI images or CT imaging.<sup>95</sup> Notably, the first postmortem MRI study of COVID-19 nonsurvivors supported the association of PRES-like vasogenic lesions in at least four (21%) of the 19 patients of the study.<sup>96</sup> Interestingly, PRES in association with reversible cerebral vasoconstriction syndrome (RCVS) was reported in only one case.<sup>97</sup>

Our systematic review revealed a total of four studies reporting about imaging features of a total of nine COVID-19 patients with documented PRES.<sup>60,95,97,98</sup> Three studies were presented as case report/series ( $n = 1-4$ )<sup>95,97,98</sup> and two further patients were identified in a retrospective cross-sectional study.<sup>60</sup> The median of reported mean age of the patients was 62.5 years (range = 56-69 years). At least four (44.4%) of the patients were male. Two studies were conducted in the United States, the others in France and Italy. Eight of these nine cases were eligible for further descriptive statistical analysis as they included patient-level data. However, as PRES pattern did not differ from reported PRES pattern in non-COVID patients, no typical feature of COVID-associated PRES could be identified.

### *Other Cerebrovascular Manifestations*

One case with bilateral and one with unilateral vertebral artery dissection were reported in two SARS-CoV-2-positive female patients with a history of migraine.<sup>99,100</sup> The latter was also found to suffer from bilateral high frontal convexity subarachnoid hemorrhage (cSAH) on CT and evidence of RCVS in the anterior and middle cerebral circulation. Whether the endothelial dysfunction caused by the SARS-CoV-2 led to the vertebral artery dissection and subsequently to RCVS caused the cSAH, or the underlying history of migraine was the crucial etiological factor with the coronavirus infection being incidental, remains speculative. Possibly, the cSAH could have caused secondary vasospasm. Two more cases of vertebral and internal carotid artery dissection have been reported from Hernandez-Fernandez et al,<sup>21</sup> both having evident intimal flaps in CT and MRI, with the latter causing secondary ischemic event after occlusion of the insular branch of the unilateral middle cerebral artery.

## **Inflammatory Processes**

### *Meningo-/Encephalitis*

In reported COVID cases with additional encephalitis, the MRI abnormalities were considerably diverse and ranged from restricted diffusion and FLAIR hyperintensity in mesial temporal lobe and hippocampus in a patient presenting with seizures and neck stiffness<sup>101</sup> to mild encephalitis with a reversible splen-

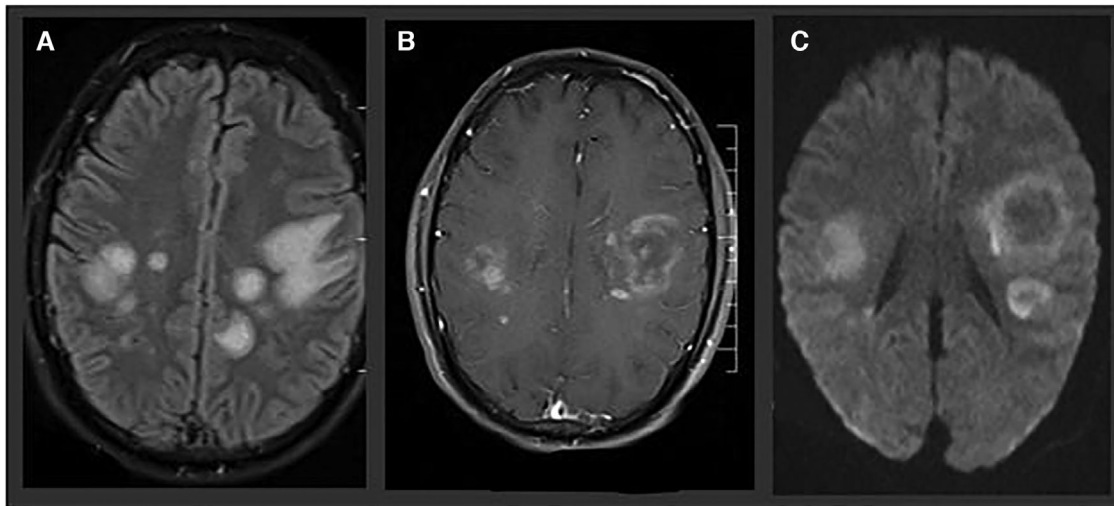
ial callosal lesion.<sup>102</sup> Splenium T2-weighted signal changes and restricted diffusion were seen also in SARS-CoV-2-infected children.<sup>103</sup> Many patients affected by COVID-19 were reported with acute hemorrhagic necrotizing encephalopathy, a rare but typical CNS complication of viral respiratory infection. A case reported by Poyiadji et al demonstrated bilateral temporal lobe and thalamus FLAIR hyperintensities with evidence of hemorrhage in SWI images and postcontrast ring enhancement of the lesions,<sup>104</sup> whereas another patient was characterized mainly from progressive pons edema accompanied with bilateral T2 hyperintensities with intrinsic hemorrhage in the subcortical perirolandic spaces. This second patient had a history of aplastic anemia in her medical history.<sup>105</sup> Increased FLAIR signal intensity in subsular regions, medial temporal lobes, hippocampi, cerebral peduncles, thalami, and brainstem; restriction of water diffusion in the same regions indicating cytotoxic edema; and faint contrast enhancement—seen predominantly in the subsular regions bilaterally—were also documented from other authors. SWI images showed evidence of petechial hemorrhages in thalami and external capsule. There was a substantial improvement of the above-mentioned findings in the follow-up MRI a week later.<sup>106</sup> Moreover, cortical involvement characterized by signal abnormalities in FLAIR images, cortical diffusion restriction, and sporadically leptomeningeal enhancement in postcontrast FLAIR could be a sign of infectious or autoimmune neurological manifestation of SARS-CoV-2 as reported by Kandemirli et al.<sup>107</sup> Notwithstanding, hypoxic injury, postictal phase, or even hypoglycemia should also be considered in the interpretation of these findings as the authors mentioned. An exemplary case of encephalitis in COVID-19 patients is depicted in Figure 5.

Our review revealed a total of 21 studies reporting imaging features for a total of 65 COVID-19 patients with evidence of meningo-/encephalitis.<sup>18,24,61,64,101-106,108-119</sup> Thirteen studies were presented as single case report<sup>101,102,104-106,108-114</sup> and three as case series ( $n = 2-4$ ).<sup>103,115,116</sup> The other cases were identified in four retrospective cross-sectional studies.<sup>18,24,61,64</sup> Sample sizes ranged from 1 to 22 patients. The median of reported mean age was 59 years (IQR = 39.5-61 years; range = 12-75 years). Sex was specified in 31 patients; 21 (67.7%) of the 31 patients were males.

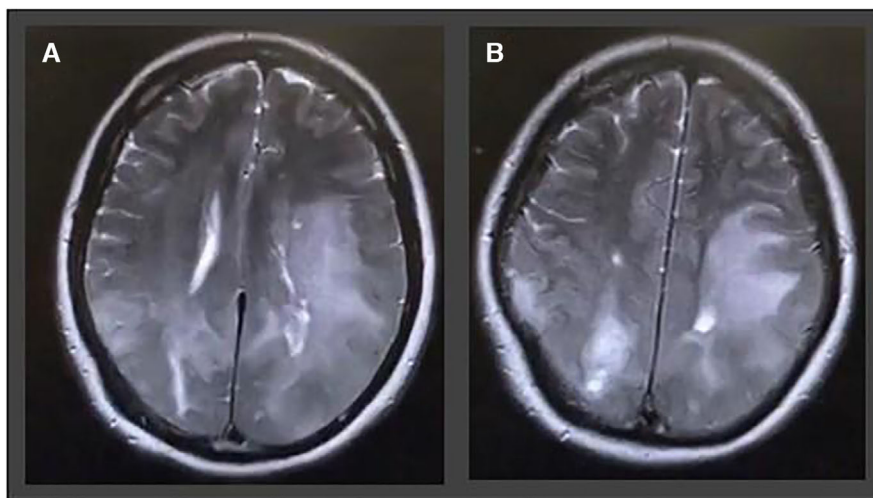
Four studies were conducted in the United States, three in East Asia (Japan = 2; China = 1), two in West Asia (Turkey = 1; United Arab Emirates = 1), and 12 studies were conducted in Europe (France = 4, UK = 4, Italy = 1; Sweden = 1, Germany = 1). All of these 21 studies reported individual data of at least some of the included cases. Thus, data from 52 (80.0%) of the 65 patients were considered for additional descriptive statistical analysis. Of these, 15 (28.8%) revealed the suggested typical finding of acute hemorrhagic necrotizing encephalitis.

### *Demyelination/Leukoencephalopathy*

The first reported demyelinating event in a 59-year-old COVID-19 female patient supported by neuroimaging findings depicted periventricular confluent FLAIR hyperintensities adjacent to temporal, occipital, and frontal horns and across the spinal cord without the restriction of diffusion or contrast enhancement.<sup>120</sup> Following that, Radmanesh et al reported 10 cases of SARS-CoV-2-positive and prolonged intubated patients that demonstrated diffuse leukoencephalopathy with



**Fig 5.** Acute necrotizing hemorrhagic encephalopathy in a 32-year-old man presenting with speech impairment, disorientation, and epileptic seizures. MRIs show predominantly subcortical fluid-attenuated inversion recovery hyperintensities (A), with ring enhancement in T1-weighted sequence (B) and ring-shaped diffusion-restriction (C).



**Fig 6.** A 54-year-old man with no previous medical history admitted with headache, disorientation, nausea, vomiting, and blurred vision. T2-weighted images show pronounced acute disseminated encephalomyelitis like leukoencephalopathy in the parietal and frontal lobes involving u-fibers as well as cortical areas on both sides.

symmetric and confluent T2 hyperintensities across the subcortical white matter, with equal or more limited restricted diffusion, sparing the deep gray matter structures as well as the juxtacortical white matter and the infratentorial regions in most cases.<sup>80</sup> These findings were interpreted by the authors as possible demyelination, probably in the context of delayed posthypoxic leukoencephalopathy. A more diverse imaging presentation of suspected demyelination in a patient tested positive to SARS-CoV-2 was described by Brun et al.<sup>121</sup> Asymmetrical periventricular and callosal white matter hyperintensities and bilateral Globus pallidum lesions with restricted diffusion sparing the infratentorial regions might be a typical manifestation of an acute disseminated encephalomyelitis (ADEM), whereas punctiform white matter lesions may be associated with a concurrent small-vessel vasculitis as a combined secondary immune-mediated phenomenon. Interestingly, contrast enhancement was observed only in a follow-up MRI a few days later. Considering possible postinfectious ADEM, two

more case reports were published, concerning two middle-aged women critically and noncritically ill with asymmetrical FLAIR hyperintensities in subcortical white and gray matter structures, mildly restricted diffusion, and gadolinium enhancement. Both cases manifested neurological symptoms more than 10 days after the initiation of the SARS-CoV-2-related symptoms, supporting the hypothesis of a postinfectious immune-mediated pathogenesis.<sup>122</sup>

An exemplary case of ADEM in a COVID-19 patient is depicted in Figure 6.

Our review revealed a total of 14 studies reporting imaging features of a total of 78 COVID-19 patients analyzing the distribution of demyelination/leukoencephalopathy.<sup>24,56,60,65,80,113,118,120-126</sup> Eight studies were presented as a single case report and one as case series ( $n = 11$ ).<sup>80,117-123</sup> The other cases were identified in five retrospective cross-sectional studies.<sup>24,56,60,65,80</sup> Sample sizes ranged from 1 to 17 patients. The median of reported mean age was 54 years (IQR = 52-62.5

years; range = 21-64 years). Sex was specified in 29 patients; a total of 16 (55.2%) out of the 29 patients were males.

Four studies were conducted in the United States, two in West Asia (Turkey = 1; Iran = 1), and eight studies were conducted in Europe (France = 4, Italy = 2; Sweden = 1, Germany = 1). All of these 14 studies reported detailed individual data of at least some of the included cases. However, as manifold patterns of demyelination and leukoencephalopathy were described, no typical pattern of COVID-associated CVST could be identified.

### *Myelitis*

Various patterns of acute or chronic myelitis have been causally linked to several viruses such as HSV-1 or HSV-2, West Nile Virus, Cytomegalovirus, Epstein-Barr virus, Varicella zoster virus, etc.<sup>127</sup> The main pathophysiological pathway is usually immune- or autoimmune-mediated processes triggered by the viral agent, with the neurotropic and/or cytolytic behavior of some pathogens, being far more infrequent. Overall, there were four published case reports of COVID-19-associated myelitis, with only 3 patients having received an MRI of the spinal cord. Early (after 2 days)<sup>128</sup> and late (after 7-8 days)<sup>129</sup> development of neurological signs and symptoms after the first manifestation of the respiratory symptoms due to SARS-CoV-2 infection were described. Isolated or multifocal hyperintense lesions on STIR or T2-weighted MRI images were detected in the cervical and thoracic cord. Some lesions were accompanied with tissue edema showing enlargement of spinal cord caliber. None of the patients demonstrated pathological gadolinium enhancement, whereas evidence of restricted diffusion on diffusion-weighted imaging and apparent diffusion coefficient sequences supported the presence of cytotoxic edema.

Our review revealed a total of five single case reports studies reporting about imaging features of a total of five COVID-19 patients with documented myelitis.<sup>119,128-131</sup> The median age of these patients was 60 years (range = 32-69 years). At least two (40%) of the patients were male. The study group of these single case reports is from United States, United Arab Emirates, the United Kingdom, Spain, and Germany, respectively. Evaluating the pattern of these five patients, neuroimaging features did not differ from reported myelitis pattern in non-COVID patients, thus, no typical feature of COVID-associated myelitis could be identified.

### **Olfactory Pathway and Cranial Nerve Involvement**

Anosmia/hyposmia is considered to be one of the principal symptoms of SARS-CoV-2 infection accounting for 33.9-68.0% of the total cases.<sup>132</sup> The olfactory dysfunction in COVID-19 patients can be quantified and objectively assessed.<sup>133</sup> Nasal epithelial injury is the leading proposed mechanism causing anosmia as manifestation. However, some MRI studies indicated bilateral olfactory bulb FLAIR signal hyperintensities and edema as well as signal abnormalities in cortical areas associated with the olfaction (eg, posterior gyrus rectus).<sup>134-136</sup> These findings underpin the initial hypothesis regarding the neurotropism of SARS-CoV-2, as CNS involvement could happen not only hematogenously in critically ill patients with viremia, but also via the nasal epithelium and the olfactory nerve.<sup>137</sup> In addition, olfactory bulb atrophy has been reported in COVID-19 patients with persistent anosmia.<sup>131</sup>

Our systematic review revealed a total of three studies reporting about imaging features of a total of nine COVID-19 patients with alterations in the olfactory bulb and tracts. Two studies were presented as single case reports, and 7 patients were reported in a retrospective study.<sup>65,136,138</sup> The case reports were related to young patients (one 21-year-old male and one 25-year-old female).

Apart from the involvement of the olfactory nerve, some case reports have demonstrated alteration of the ophthalmokinetic nerves in the context of a presumptive Miller-Fisher syndrome and facial nerve involvement. Contrast enhancement and T2 signal abnormalities were the hallmarks in the neuroimaging studies in such cases.<sup>4,139</sup>

Our review revealed a total of seven studies reporting about imaging features of a total of 26 COVID-19 patients with neuroimaging alterations of other cranial nerves than the olfactory bulb and tracts.<sup>65,139-144</sup> Six studies were presented as single case reports,<sup>137-142</sup> whereas 20 cases were identified in one retrospective cohort study from Sweden.<sup>65</sup> The case report studies were conducted in the United States ( $n = 4$ ) as well as in Brazil and in Singapore ( $n = 1$ , respectively). The median age of the six patients presented in the case reports was 34 years (range = 21-69), all (100%) of them being males. Mainly ophthalmokinetic nerves like trochlear and abducens were involved in these cases revealing to corresponding nerve palsies. Rarely, facial nerve palsy has been reported in two COVID-19 patients, one in association with Miller-Fisher-Syndrome.

### **Discussion**

Since the beginning of the COVID-19 pandemic, various clinical neurological manifestations with manifold neuroimaging features have been described in patients with SARS-Cov-2 infection. In our systematic review, we summarized for a total of nine disease entities with documented neuroimaging characteristics of the pandemic. Additionally, we sought to analyze possible typical neuroimaging patterns that could indicate a COVID-19-associated manifestation. In four of the nine disease entities, we could identify the following typical neuroimaging features: (a) pattern of LVO infarction, frequently with hemorrhagic transformation in ischemic stroke; (b) ICH in non-hypertension-associated locations (lobar and/or cortical) in hemorrhagic stroke; (c) callosal and juxtacortical location in patients with CMB; and (d) hemorrhagic necrotizing encephalopathy in patients with meningo-/encephalitis.

Although nonspecific symptoms of encephalopathy such as dizziness, headache, and confusion are common in COVID-19 patients, cerebral neuroimaging evaluation is performed in less than 15% of the patients.<sup>18</sup> This raises a probable selection and reporting bias of underreporting cases with presumable neuroimaging findings but mild clinical symptoms, where a brain MRI or CT was considered unnecessary. Furthermore, as some of the aforementioned neuroimaging findings (eg, PRES-like lesions, microhemorrhages, and ischemic lesions) are also found in many other constellations such as sepsis-associated encephalopathy, carefully planned and more systematic studies are needed to clarify if observed imaging patterns are attributed to direct COVID-19 pathophysiology.<sup>166</sup>

The vast majority of the reported neuroimaging findings in the current COVID-19 literature represent cases of

cerebrovascular diseases because they are by far the leading cause of disability-adjusted life years among all neurological disorders<sup>145</sup> and the initial work-up of these entities always requires neuroimaging studies in the emergency setting. Noteworthy, due to this considerable incidence of SARS-CoV-2 infection between stroke patients, it has been proposed to incorporate chest CT into the emergency imaging protocol in order to reduce the probability of exposing all medical professionals.<sup>167</sup> The most common indications for neuroimaging appear to be associated with altered mental status and focal neurologic deficits, and this may introduce bias as the latter is often associated with stroke. An association between COVID-19 and several cerebrovascular events as well as other vascular complications has been repeatedly reported already from the beginning of the pandemic. The prevalence of reported ischemic and hemorrhagic stroke in COVID-19 patients ranges between .2% and 2.7%.<sup>6,10,21</sup> Several studies reported a higher mortality despite the lower baseline modified Rankin scale score.<sup>6,26,170</sup> Underlying hypercoagulable condition,<sup>146</sup> blood pressure dysregulation, hypoxia, viral neurotropism, endothelial dysfunction,<sup>147</sup> presence of antiphospholipid antibodies,<sup>148</sup> virus-associated myocardial injury,<sup>149</sup> immobilization, triggering of atrial fibrillation, and rupture of an unstable carotid plaque through infectious processes<sup>150</sup> are some of the proposed pathophysiological aspects increasing the risk of thromboembolic complications<sup>151</sup> and being indicated to play an important role in cerebrovascular complications during the pandemic. A plausible mechanism of blood clot formation including oxidative stress triggered by the viral-induced endothelial damage, formation of antiphospholipid antibody complexes (mainly with beta2-Glycoprotein), and subsequent platelet adhesion is proposed by Janardhan et al.<sup>168</sup> A high proportion of ischemic stroke cases is estimated to be caused by LVO. The prevalence of LVO in a noninfected population compromises only 24-39% of acute ischemic stroke.<sup>152,153</sup> In our subsequent descriptive analysis, we could identify this pattern in 60.00% of the reported COVID-19 patients. Even if we take into account the possible bias of underreporting of minor stroke cases, SARS-CoV-2 might be a risk factor for LVO stroke. It is worth noting that the prevalence of lacunar strokes in our review (8%) is consistent with the findings of Shahjouei et al multinational study (7.5%).<sup>25</sup>

Regarding hemorrhagic stroke in COVID-19 patients, the atypical lobar location of hypertension-related hemorrhages should be underscored. A plausible explanation, as indicated by Kvernland et al, might be the empiric therapeutic anticoagulation of most patients in the context of the hypercoagulable state caused by the COVID-19. Up to 89.5% of the patients positive to SARS-CoV-2 with ICH were under empiric anticoagulation.<sup>70</sup> As frequently reported in the literature, anticoagulant-related ICH occurs predominantly in a lobar and/or cortico-subcortical location.<sup>154,155</sup> In line with it, a greater prevalence of hemorrhagic transformation of ischemic strokes was reported in SARS-CoV-2-positive patients.<sup>6,26</sup> Considering the delay in the diagnosis<sup>156,157</sup> by isolation measures and the fact that a differential diagnosis based only on a CT is not always possible, some hemorrhagic transformations might have been misclassified as ICH.

Because of the relatively low total number of SARS-CoV-2-associated CVST cases in current literature reported so far, no safe conclusions can be withdrawn. We could not identify any

typical neuroimaging patterns in CVST cases. Similarly, PRES imaging characteristics in COVID-19 patients seem to not differ substantially from non-COVID-19 individuals. However, further investigation via larger observational studies is needed for these two neurological manifestations.

Apart from cerebrovascular events, there were many cases of inflammatory phenomena that became evident during the pandemic. A significant number of meningitis/encephalitis cases implied a possible neurotropism<sup>158</sup> of the virus or its ability to trigger secondary immune-mediated responses. However, the so far performed neuropathological and neurochemical studies have produced inconsistent results and the manifold alternative clinical explanations suggest that direct brain invasion of the virus is a possible but rare cause for the aforementioned pathology.<sup>169</sup> It is worth noting that many of the cases (in our limited analysis 28.8% of these patients) represented the rare neuroimaging feature of acute hemorrhagic necrotizing encephalitis. Interestingly, this finding has been previously reported as secondary to respiratory virus infections, mainly influenza virus and HHV-6. However, the exact etiology and pathogenesis of this disorder is purely defined, with some evidence indicating cytokine storm conditions, such as severe SAR-CoV-2 infection,<sup>159</sup> as a possible key factor.<sup>160</sup>

Animal, as well as human neuropathological, studies suggest a possible causality of SARS-CoV-2 and other coronaviruses and demyelinating events of the CNS.<sup>161-164</sup> On the other hand, hypoxic ischemic leukoencephalopathy in critically ill patients could also be a leading cause of demyelination in the subcortical white matter.<sup>165</sup> Overall, we could not identify any typical neuroimaging pattern regarding the demyelinating events and the myelitis cases in COVID-19 patients.

Olfactory nerve and olfactory pathway involvement have been assumed from the very early days of the pandemic, indicating a nonhematogenous virus entry in the human body. Indeed, some patients appear to have relevant MRI findings with, however, to date unknown clinical significance. Furthermore, other cranial nerves have been sporadically affected in the course of SARS-CoV-2 infection, demonstrating a probable predominant involvement of ophthalmokinetic nerves. However, these neuroimaging features appear seldomly, so that such a finding might represent itself a typical feature of SARS-CoV-2 infection.

In conclusion, having summarized the so far documented neuroimaging characteristics of the pandemic in our narrative review, we identified four typical neuroimaging patterns that might indicate a possible COVID-19 associated manifestation: (a) pattern of LVO infarction, frequently with hemorrhagic transformation in ischemic stroke; (b) ICH in non-hypertension-associated locations (lobar and/or cortical) in hemorrhagic stroke; (c) callosal and juxtacortical location in patients with CMB; and (d) hemorrhagic necrotizing encephalopathy in patients with meningo-/encephalitis. Familiarity with these imaging patterns appears reasonable because manifold CNS involvement is increasingly being reported in COVID-19 patients. However, because many of these patterns are also seen in many critical ill patients with alternative explanations such as multiple organ dysfunction syndrome and sepsis, further studies are needed to elucidate if these neuroimaging patterns are directly associated with COVID-19 or are confounding results in the context of critical illness. The classification according to imaging

findings and not according to etiopathogenetic criteria, together with the author-based consensus regarding the identification of typical neuroimaging patterns, represents a further limitation of our study. In view of the abundance of case reports and the lack of prospective etiopathogenetically oriented studies, this approach seems appropriate at the current time point of the pandemic. As evaluation at this early stage is likely to be influenced by different types of bias, further research on this topic is required to identify neuroimaging findings that are either sensitive or specific of COVID-19 CNS manifestations.

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