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Research Article

Neuroimaging Features of COVID-19: Retrospective Northern Italy Multicenter Study and a Scoping Review of Prevalence of COVID-19 Associated Acute Cerebrovascular Diseases

Giorgianni A[1], D'Amore F[1]*, Vinacci G[2], Agosti E[3], Politi LS[4], De Vito A[5], Polistena A[5], Valvassori L[5], Trentadue M[6], Nicoli L[6], Sozzi C[6], Balbi S[3], Mercuri A[1], Terrana AV[1], Triulzi F[7], Casale S[8], Nuzzi NP[4], Asteggiano F[4], Genovese V[9], Lafe E[9], Bianchini E[10], Bernasconi P[11], Colli-Tibaldi E[12], Longhi L[13], Bandiera F[14] and Baruzzi F[1]

[1]Department of Neuroradiology, Di Circolo e Fondazione Macchi Hospital, Varese, Italy

[2]Division of Radiology, University of Insubria, Varese, Italy

[3]Division of Neurosurgery, Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy

[4]Neuroradiology Division, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy

[5]UO Neuroradiology, San Gerardo Hospital, ASST Monza, Monza, Italy

[6]SC Neuroradiology, Carlo Poma Hospital, Mantova, Italy

[7]University of Milan and Neuroradiology Unit IRCCS Ca Granda Foundation, Maggiore Policlinico Hospital, Milan, Italy

[8]Neuroradiology Unit, IRCCS Ca Granda Foundation, Maggiore Policlinico Hospital, Milan, Italy

[9]U.O.C Radiology and Neuroradiology Diagnostic and Interventional, Policlinic IRCCS "San Matteo", Pavia, Italy

[10]U.O.C Radiology, Civile Di Legnano Hospital, ASST Ovest Milanese, Legnano, Italy

[11]U.O.C Radiology, Circolo di Busto Arsizio Hospital, ASST Valle Olona, Busto Arsizio, Italy

[12]Department of Radiology, Maggiore Hospital, Civico Hospital Codogno, ASST Lodi, Italy

[13]U.O.C Radiology, S. Anna Como Hospital, ASST Lariana, Como, Italy

[14]U.O. Radiology, S. Antonio Abate Hospital, ASST Valle Olona, Gallarate, Italy

***Corresponding Author:** D'Amore F, Department of Neuroradiology, Di Circolo e Fondazione Macchi Hospital, Viale Luigi Borri, Varese, Italy.

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Abstract

Background: The primary aim of this study was to provide additional data of neuroimaging features of coronavirus disease 2019 (COVID-19) in a large-scale population admitted in several northern Italy institutions. The secondary aim was to analyze acute cerebrovascular disease (CVD) prevalence in COVID-19.

Methods: A database of confirmed COVID-19 hospitalized patients who developed acute neurological symptoms and underwent any neuroimaging was retrospectively gathered from twelve institutions based in Lombardy from February 21st to July 10th. To assess the prevalence of CVD we conducted a scoping review following the PRISMA extension guidelines for scoping reviews. We searched PubMed/Medline, SCOPUS and EMBASE databases for peer-reviewed in-press or published studies from December to January 2021 reporting CVD in COVID-19 patients.

Results: Out of 89 COVID-19 patients who were referred to neuroimaging, 80 (90%) showed CVD, in particular 65 had acute ischemic strokes (AIS), 8 had intracerebral hemorrhages, 2 subarachnoid hemorrhages (SAH) and 3 showed clinical and imaging findings in keeping with posterior reversible encephalopathy syndrome (PRES); 6 patients (7%) showed clinical and imaging findings highly suggestive of encephalitis; 3 patients (3%) showed demyelinating diseases: 1 case of MS progression, 1 case of newly diagnosed MS and 1 case of acute disseminated encephalomyelitis (ADEM); 2 cases (2%) acuity of chronic subdural hematoma (cSDH). In addiction two patients with CVD developed cauda Poly radiculitis and tetra paresis.

In our scoping review out of 3275 studies, 24 satisfied the inclusion criteria: in a pooled total population of 136198 patients, the pooled prevalence of CVD was 0.9%. In particular 0.8% of AIS and 0.1% of ICH and 0.003% of PRES.

Conclusion: Our study shows a high prevalence of CVD among patients who developed acute neurological symptoms, which is in line with papers reporting data comparable to ours. The heterogeneity of clinical reports, however, constitutes a limitation when comparing our findings with those of the clinical papers. Nonetheless, CVD could be a frightening association with COVID-19, particularly in critically ill patients. Healthcare policymakers and clinicians should be prepared to a likely increase in workload and to rearrange the strategy of healthcare delivery.

Keywords: COVID-19; SARS-CoV-2; Neuroimaging

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; CVD: Cerebrovascular Disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; DSA: Digital Subtraction Angiography; PRES: Posterior Reversible Encephalopathy Syndrome; AIS: Acute Ischemic Stroke; ICH: Intracranial Hemorrhages; SAH: Subarachnoid Hemorrhages; SDH: Chronic Subdural Hematomas; MS: Multiple Sclerosis; ADEM: Acute Disseminated Encephalomyelitis; GBS: Guillain-Barré syndrome; GCS: Glasgow Coma Scale; CNS: Central Nervous System

Background

SARS-CoV-2 and its variants are still dramatically imposing a burden to healthcare worldwide [1]. In early 2020 Italy became the second world epicenter after China [1]. A growing body of evidences is unveiling a multi-organ involvement [2] related to SARS-CoV-2, rather than the sole respiratory and gastrointestinal systems manifestations as initially thought. Central and peripheral nervous system involvement most commonly manifests as anosmia, ageusia and impaired consciousness [3,4], however acute cerebrovascular diseases (CVD), hereinafter referred as ischemic/hemorrhagic stroke and PRES (posterior reversible encephalopathy syndrome), seem to have a high share among other etiologies of acute neurological impairment. As of today few large scale studies on neurological manifestations in COVID-19 and their imaging findings have been published [5-8], thus the vast majority of current literature consists of case series or single case reports and focus on a single neurological manifestation [5,10-15].

Aim of the Study

The aims of this study were to collect further data on neuroimaging features of COVID-19 patients and to estimate the prevalence of cerebrovascular disease in SARS-CoV-2 infection using, respectively, a multicenter retrospective study design and a scoping review of the literature.

Materials and Methods

Multicenter retrospective study

Study design

We retrospectively collected imaging and clinical data from eleven major Lombard institutions: *BLINDED* in the time frame between February to July, including hospitalized patients with: 1) symptoms of SARS-CoV-2 infection and positive rRT-PCR at hospitalization (i.e. at the neuroradiological examination); 2) concurrent or subsequent abnormal neurological examination; 3) receiving neuroimaging scans of the brain and/or spine. Ethical approval for this study was waived by the ethics committee of the Di Circolo e Fondazione Macchi Hospital, ASST Settelaghi, Varese, Italy because the emergency setting and the retrospective nature of the study.

Data collection

Demographic data, comorbidities, neurological findings were retrieved from electronic medical records for each patient by each participating institution (Table 1).

Image acquisition and analysis

All imaging scans were performed using standard of care protocols. Head computed tomography (CT) with or without contrast scans was employed as the first imaging modality. Brain and spine magnetic resonance imaging (MRI) with or without contrast were acquired either on 1.5T or 3T scanners. Digital subtraction angiography (DSA) was performed on neuroangiography suites with the aim to perform endovascular thrombectomy. Scans were initially read by neuroradiologists at their own Institution and then reviewed by coauthors by each Institutions.

Scoping review

The scoping review was carried out according to the Preferred Reporting Items for Systematic Reviews and Metanalyses extension for scoping reviews (PRISMA-ScR) guidelines. FD and GV conducted the scoping review. Eligibility criteria were: 1) peer-reviewed original research studies, editorials, review studies published or in-press, 2) population with confirmed diagnosis of COVID-19, 3) reported data on cerebrovascular diseases. Studies published in any language were considered eligible. Unpublished or ongoing studies and case reports were not included. Boolean logic was employed to search MEDLINE/Pubmed, SCOPUS and EMBASE databases from December 2019 to January 12, 2021 using the following terms: COVID-19 AND stroke, COVID-19 AND "hemorrhage*", COVID-19 AND "cereb*", COVID-19 AND cns, COVID-19 AND pres. Two authors independently searched and screened all results first by title and abstract to assess whether the studies fulfilled the inclusion criteria; included studies were further full text reviewed to retrieve data and pooled prevalence of CVD.

Results

Multicenter retrospective study

Out of a total of 7937 consecutive patients, 253 (3%) patients had an abnormal neurological examination and underwent neuroimaging (Figure 1). 164 (65%) patients, of which most frequent symptoms reported were headache, loss of consciousness, vertigo and dizziness, no acute neuroimaging findings were reported. The remaining 89 (36%) patients (55% male predominance, mean age 69) showed acute neuroimaging findings. Eighty-eight (99%) patients underwent head CT, 48 (54%) head and neck CT angiography (CTA), 33 (37%) head MRI, 5 (6%) spinal MRI, 12 (13%) had DSA (Table 2). Eighty patients (89%) had imaging findings of acute cerebrovascular diseases (Table 3), in particular, 65 patients suffered ischemic strokes, 12 patients had intracranial hemorrhages and 3 patients showed typical findings of posterior reversible encephalopathy syndrome (PRES), that was primarily hemorrhagic in 2 cases (66%). Among the 64 cases of acute ischemic stroke (AIS), 42 (65%) involved the anterior circulation (Figure 2), 15 (23%) posterior circulation, 7 (11%) were multifocal. 23 (35%) patients had a large artery occlusion (LAO), of which only 12 (52%) underwent endovascular treatment. A 61 female with hypertension had a venous stroke (Figure 3), a pooled prevalence of 2% between the CVD. Of all intracranial hemorrhages (ICH), 8 were intraparenchymal (Figure 4), 2 non-aneurysmal and non-traumatic subarachnoid hemorrhages (SAH) and 2 acute on chronic subdural hematomas (SDH). All hemorrhagic patients were evaluated with CTA that excluded the presence of vascular malformations. All 6 patients presenting with acute encephalopathy, showed temporal lobe lesions in keeping with encephalitis (Table 3). Of these patients all had cerebrospinal fluid (CSF) protein increased but SARS-CoV-2 DNA was not detected by RT-PCR. The EEG of those patients showed diffuse slow waves with a generalized delta activity.

Figure 1: Flowchart of the multicenter study.

We also observed 3 (3%) inflammatory demyelinating disorders, in particular 1 case of multiple sclerosis (MS) exacerbation, 1 case of newly diagnosed MS with supra-tentorial lesions, 1 case of acute disseminated encephalomyelitis (ADEM) with bilateral and multifocal lesions. Two patients had spinal involvement: a patient

Figure 2: Anterior circulation stroke. A 85 year-old woman with history of hypertension presenting with sudden onset of left hemiparesis. (A) CT without contrast shows an ill-defined cortical-subcortical hypoattenuating area in the right lateral posterior frontal lobe. (B) CTA VR reformat shows thrombotic occlusion of the (right) middle cerebral artery M2 segment. (C-D) b1000 and ADC map: the lesion shows restricted diffusion and (E) T2-FLAIR hyperintensity consistent with acute ischemia.

Figure 3: Dural sinus thrombosis and venous ischemia. A 61 year-old woman with history of hypertension presenting with altered consciousness and headache. CT without contrast shows hyperattenuating right transverse sinus (a) straight sinus, vein of Galen and internal cerebral veins (b) and focal mesial parietal ischemic changes (c). Venous CT angiography MIP reformats show filling defects at the level of the right transverse sinus and torcula Herophilii (d), jugular bulb and superior sagittal sinus (e) sinus and right internal cerebral vein (f). A somewhat generalized superficial venous engorgement is also noted.

Figure 4: Hemorrhagic stroke. A 79 year-old male with history of hypertension with loss of consciousness and coma. Upon admission CT without contrast (A and B) shows right frontal-parietal hematoma with massive intraventricular extension.

with SAH that developed polyradiculitis and transient flaccid tetraparesis, and a patient with a frontal hemorrhage that developed transient flaccid tetraparesis. The most frequent reported neurological symptoms were those related to acute stroke, followed by altered level of consciousness that was reported in 19 patients, of which, 16 had a Glasgow Coma Scale (GCS) score less than 7.

The highest mortality rate was related to ICH (38%) followed by the encephalitis subgroup (33%) (Table 1). Hypertension (36.6%), diabetes (17.9%) were the most frequent comorbidities, followed by previous or current history of malignancy (16.6%). The most relevant comorbidities, neurological findings are summarized in table 1. Prevalence data of our cohort are shown in table 4. CVD was the commonest finding in patients who underwent neuroimaging (32%, 80/253), followed by encephalitis (2.4%, 6/253). Among CVD, AIS occurred more frequently (26%, 65/253). In the total COVID-19 population, CVD prevalence was 1% (Table 4).

Demographic data	Total subset n = 89	
Mean age (SD)	69 ± 15	
Male	50	55%
Neurological findings		
Paresis	38	42.7%
Altered level of consciousness	19	21.1%
Aphasia	14	15.5%
Dysarthria	10	11.1%
Asthenia	8	8.9%
Seizures	6	6.7%
Visual field impairment	5	5.6%
Headache	4	4.4%
Drowsiness	1	1.1%
Tetraparesis	2	2.2%
Other	18	20.2%
Comorbidities and pre-existing conditions		
Hypertension	33	36.6%
Diabetes	16	17.9%
Malignancy	15	16.6%
Dyslipidemia	12	13.3%
AF	11	12.2%
Cardiovascular intervention	10	11.1%
CAD	9	10%
Previous stroke	8	8.9%
COPD	6	6.7%
CKD	6	6.7%
Obesity	5	5.6%
Other	31	34.4%
None	19	21.1%
Deaths		
Total	10/89	11%
Ischemic stroke	5/65	8%
ICH	3/8	38%
SAH	0/2	0
PRES	0/3	0
Acute on chronic SDH	0/2	0
Encephalitis	2/6	33%
Demyelinating diseases	0/3	0

Table 1: Demographic and clinical data.

AF = Atrial Fibrillation, CAD = Coronary Artery Disease, COPD = Chronic Obstructive Pulmonary Disease, CKD = Chronic Kidney Disease, ICH = Intracerebral Hemorrhage, SAH = Subarachnoid Hemorrhage, PRES = Posterior Reversible Encephalopathy Syndrome, SDH = Subdural Hematoma.

	Head CT	Head and Neck CTA	Brain MRI	Spine MRI	DSA
	88/89 (99%)	48/89 (54%)	33/89 (37%)	5/89 (6%)	12/89 (13%)
Ischemic stroke	65/65 (100%)	35/65 (54%)	19/65 (29%)	-	12/65 (18%)
ICH	8/8 (100%)	8/8 (100%)	3/8 (37%)	1/8 (12%)	-
SAH	2/2 (100%)	2/2 (100%)	-	1/2 (50%)	-
PRES	3/3 (100%)	2/3 (67%)	3/3 (100%)	-	-
Acute on chronic SDH	2/2 (100%)	-	-	-	-
Encephalitis	6/6 (100%)	1/6 (17%)	5/6 (83%)	-	-
Demyelinating diseases	2/3 (67%)	0/3 (0%)	3/3 (100%)	3/3 (100%)	-

Table 2: Neuroimaging studies.

ICH = Intracerebral Hemorrhage, SAH = Subarachnoid Hemorgrhage, PRES = Posterior Reversible Encephalopathy Syndrome, a/c SDH = Acute on Chronic Subdural Hemorrhage.

Neuroimaging findings	Notes
Ischemic stroke	65% involved anterior circulation, 23% posterior circulation, 11% multifocal lesions, 1 venous stroke; 11% developed hemorrhagic transformation; 18% elegible for endovascular treatment.
ICH	50% supra and infratentorial, 50% supratentorial, 12.5% basal nuclei; 1 patient developed transient flaccid tetraparesis.
SAH	100% non traumatic and without vascular malfomations; 1 patient developed transient flaccid tetraparesis.
PRES	2 cases showed multiple hemorrhagic foci.
Acute on chronic SDH	100% non traumatic.
Encephalitis	100% involved the temporal lobes; 1 cerebellar peduncles involved, 1 menigenal enhancement
Demyelinating diseases	1 MS exacerbation, 1 new onset MS, 1 ADEM

Table 3: Neuroimaging findings.

ICH = Intracerebral Hemorrhage, SAH = Subarachnoid Hemorrhage, PRES = Posterior Reversible Encephalopathy Syndrome, a/c SDH = Acute on Chronic Subdural Hemorrhage, MS = Multiple Sclerosis, ADEM = Acute Disseminated Encephalomyelitis, GBS = Guillain-Barré Syndrome.

Scoping review

Titles and abstracts of 1643 studies were reviewed after excluding n = 1632 duplicates out of a total 3275 records: 726 studies met the inclusion criteria (Figure 5) and were full text screened. Of these, 24 studies [3,7,8,16-36] showed appropriate data to derive prevalence: thirteen retrospective multicentric studies, and eleven retrospective single center studies (Table 5), from the North America, Europe, Asia and Oceania. A total population of 136198 COVID-19 patients was included (60.2% of males, mean age 64.8).

	Cases (n = 89)	Mean age (Range)	Male	COVID-19 (n = 7937)	COVID-19 with neurological symptoms (n = 253)		
CVD	80	71 (21-90)	59%	1.01%	31.6%	7937	253
AIS	65	72 (47-88)	65%	0.82%	25.7%	7937	253
ICH	8	60 (21-84)	50%	0.10%	3.2%	7937	253
SAH	2	84 (78-90)	100%	0.03%	0.8%	7937	253
PRES	3	70 (63-84)	100%	0.04%	1.2%	7937	253
acSDH	2	67 (49-85)	50%	0.03%	0.8%	7937	253
Encephalitis	6	69 (40-90)	83%	0.08%	2.4%	7937	253
Demyelinating diseases	3	43 (9-65)	67%	0.04%	1.2%	7937	253
Total	89	69 (9-90)	55%	1.12%	35.2%	7937	253

Table 4: Diseases prevalence and demographic data in the study cohort.

CVD = Cerebrovascular Disease, AIS = Acute Ischemic Stroke, ICH = Intracerebral Hemorrhage, SAH = Subarachnoid Hemorrhage, PRES = Posterior Reversible Encephalopathy Syndrome, a/c SDH = Acute on Chronic Subdural Hemorrhage.

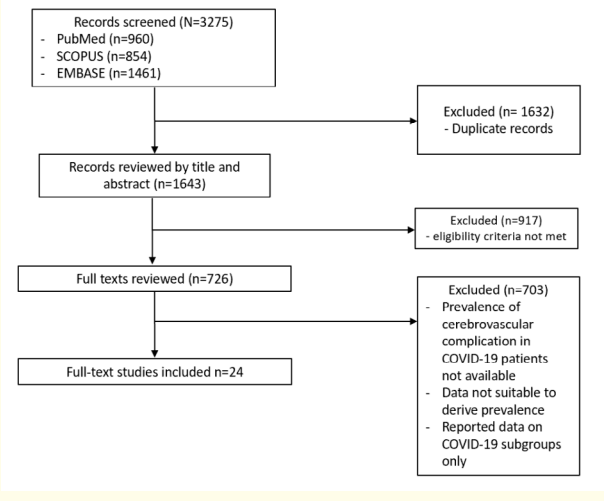

Figure 5: PRISMA-ScR Extension flow diagram.

Pooled prevalence of CVD was 0.9% (range 0.1 - 5.7%), and ischemic stroke patients with neurological symptoms (n = 11146) was 11%, based on twelve of the total nine studies since in the remainder that cohort was not specified [8,19,20,24,26-29,31,33,35,36].

Discussion

In this study we showed neurological and imaging findings in consecutive COVID-19 patients admitted in eleven centers in Lombardy region, which was the first in Europe to bear the burden of the outbreak of COVID-19 epidemic. Acute CVD had the highest prevalence among the COVID-19 related acute neurological diseases. The association between acute cerebrovascular events and SARS-CoV-2 infection has been reported in several studies, with ischemic events outnumbering the primarily hemorrhagic. This evidence has been ascribed to the neurotrophic and neuroinvasive tendency of SARS-CoV-2, specifically, to its interaction with ACE-2 host receptors expressed on neurons and nervous system endothelial cells membranes [37] which results in endothelial damage [37]. Once it reaches the central nervous system (CNS), SARS-CoV-2 can determine the activation of self-reinforcing inflammatory response through a 'cytokine storm', causing irreversible neuronal damage [38]. In addition, the endothelial ruptures in cerebral capillaries, due to the inflammatory process, can contribute to the pathophysiology of SARS-CoV-2 brain damage [37]. Ischemic stroke, cerebral venous thrombosis included, could be related both to the development of endotheliitis and hypercoagulability status. In this regard, Spiezia., *et al.* [39] described a severe hypercoagulability status related to the inflammatory response and Zhang., *et al.* [40] found the presence of antiphospholipid antibodies in few patients. In addition, SARS-CoV-2 infection can lead to cardiovascular complications including incident atrial fibrillation [41], which in turn is a risk factor of to cardio-embolic cerebral infarction. In our cohort, the majority of CVD occurred in older patients (mean age: 71 year old) with typical risk factors for CVD, in accordance to other reports [24]. In addition, acute viral infections may increase the risk

(2) Dogra., *et al*. [18]	Mahammedi., *et al*. [17]	Jain., *et al*. [16]	Giorgianni., *et al*. [7]	(1) Lodigiani., *et al*. [8]	Mao., *et al*. [3]	**Authors**	
23-May	21-May	19-May	15-May	23-Apr	10-Apr	**Date of Publication**	
Retrospective multi-centric	Retrospective multi-centric	Retrospective single center	Retrospective single center	Retrospective single center	Retrospective multi-centric	**Study design**	
USA, New York	Italy, Brescia, Novara, Sassari	USA, New York	Italy, Varese	Italy, Milan	China, Wuhan	**Country**	
3824	725	3218	1000	388	214	**Population of COVID-19**	
62**	69**	64***	71***	66	52.7	**Age***	
(37-83)**	15**	(2weeks-105 year)***	(21-88)***	(55-75)	15.5		
79%**	64%**	60.7%***	46%***	68%	41%	**Male**	
755 (19.7%)	108(14.9%)	454 (14.1%)	26 (2.6%)	Not specified	78 (36.4%)	**Cohort of COVID-19 with neurological symptoms**	
_	34 (4.6%)	26 (0.8%)	4 (0.4%)	9 (2.4%)	5 (2.3%)	AIS	**CVD in COVID-19**
33 (0.9%)	6 (0.8%)	9 (0.2%)	5 (0.5%)	_	1 (0.5%)	ICH	
_	1 (0.1%)	-	_	_	_	PRES	
_	31.5%	5.7%	15.4%	_	6.4%	AIS	**CVD in COVID-19 with neurological symptoms**
4.4%	5.5%	1.9%	19.2%	_	1.3%	ICH	
_	0.9%	-	_	_	_	PRES	
ICH only				thromboembolic complications		**Notes**	

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(1) Altschul., *et al.* [26]	Rothstein., *et al.* [25]	(1) Merkler., *et al.* [24]	Nalleballe., *et al.* [23]	Li., *et al.* [22]	Pons-Esconda [21]	(1) Cantador., *et al.* [20]	(1) Yaghi., *et al.*. [19]
26-Jul	20-Jul	2-Jul	17-Jun	12-Jun	11-Jun	9-Jun	26-May
Retrospective single center	Retrospective multicentric	Retrospective multicentric	Retrospective multicentric	Retrospective single center	Retrospective single center	Retrospective single center	Retrospective multicentric
USA, New York	USA, Philadelphia	USA, New York	Global clinical research platform	China, Huazhong	Spain, Barcellona	Spain, Madrid	USA, New York
5227	844	1916	40469	219	2249	1419	3556
67**	59	69**	not specified	75.7**	74***	76**	62.5**
15.5**	18	(66-78)**	not specified	10.8**	(50.2-90)***	7**	17**
60%**	48%	58%**	45%	56%**	61%***	77%**	72%**
Not specified	209 (24.8%)	Not specified	9086 (22.5%)	83 (37.8%)	103 (4.6%)	Not specified	Not specified
-	20 (2.4%)	31 (1.6%)	406 (1%)	10 (4.6%)	13 (0.6%)	8 (0.5%)	32 (0.9%)
16 (0.3%)	8 (0.9%)	_	-	1 (0.5%)	7 (0.3%)	_	_
-	-	_	-	_	-	_	_
-	9.6%	_	4.5%	12%	12.6%	_	_
-	3.8%	_	-	1.2%	6.8%	_	_
-	-	_	-	_	-	_	_
ICH only		ischemic only				ischemic only	ischemic only

Citation: D'Amore F., *et al.* "Neuroimaging Features of COVID-19: Retrospective Northern Italy Multicenter Study and a Scoping Review of Prevalence of COVID-19 Associated Acute Cerebrovascular Diseases". *Acta Scientific Neurology* 4.7 (2021): 84-96.

Sabayan., *et al.* [35]	Rifino., *et al.* [34]	Siegler., *et al.* [33]	Xiong., *et al.* 32	Romero-Sanchez., *et al.* [31]	Iltaf., *et al.* [30]	Shahjouei., *et al.* [29]	Katz., *et al.* [28]	Requena., *et al.* [27]
6-Nov	07-Oct	30-Sep	15-Sep	25-Aug	18-Aug	17-Aug	6-Aug	5-Aug
Retrospective multicentric	Retrospective single center	Retrospective multicentric	Retrospective multicentric	Retrospective multicentric	Retrospective single center	Retrospective multicentric	Retrospective multicentric	Retrospective single center
Iran	Italy, Bergamo	USA, Spain, Egypt, Romania	China, Wuhan, Chongqing, Sichuan	Spain, Albacete	Pakistan, Karachi	USA, Brazil, Greece, Italy, Finland, Turkey, Lebanon, Iran, India, New Zealand	USA, New York	Spain, Barcellona
18407	1760	14483	917	841	350	17799	10596	2050
65**	64.9***	not specified	48.7	66.4	49.5	66 **	67.9**	66.5 **
(38-93)**	14.0***	not specified	17.1	14.96	17.4	15**	(25-94)**	15.2**
79%**	66%***	not specified	55%	56.2%	70%	58%**	55.8%**	56%**
Not specified	137 (7.8%)	Not specified	39 (4.3%)	Not specified	68 (19.4%)	Not specified	Not specified	Not specified
14 (0.1%)	37 (2.1%)	156 (1.1%)	10 (1.1%)	11 (1.3%)	2 (0.6%)	123 (0.7%)	72 (0.7%)	18 (0.9%)
-	11 (0.6%)	28 (0.2%)	-	3 (0.4%)	-	25 (0.1%)	14 (0.1%)	4 (0.2%)
-	-	-	-	-	-	-	-	3 (0.1%)
-	27%	-	25.6%	-	3.9%	-	-	-
-	8%	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-
					ischemic only			

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*** referring to population with neurological symptoms	** refferring to CVD population	* mean age (standard deviation or range)	(2) study cohort of intracranial hemorrage	(1) study cohort of ischemic strokes								
						range:						
						11146 (8.2%)	60.2%	–	64.8	136198		
						Not specified	54%	(52-74)	62	3727	USA, Hartford	Retrospective single center
						6 (0.2%)	-	-	-	-	-	11-Jan 2021
						n: 1222 (0.9%, 0.1 - 5.7%)						
						0.1 - 4.6%	0.1 - 0.9%	–				
						1047 (0.8%)	171 (0.1%)	4 (0.003%)	9.4%	1.5%	0.03%	
												(2) Lee., *et al*. [36]

Table 5: Prevalence and demographic data of cerebrovascular diseases in COVID-19 patients.

AIS = Acute Ischemic Stroke, ICH = Intracranial Hemorrhage, PRES = Posterior Reversible Encephalopathy Syndrome.

of ischemic stroke as noted by some authors [42]. It could therefore be speculated that SARS-Cov2 could possibly play a role as a precipitating factor in the development of CVD through diverse mechanisms. CVD has also been reported in other Coronavirus infections, as in MERS and SARS, even if most of the paper published were case series [43]. It is suggested that Coronavirus infections, and other respiratory infections, is an independent risk factor for acute cerebrovascular disease [42].

We had severe PRES cases, some of which were primarily hemorrhagic. The occurrence of PRES in COVID-19 has been reported by some [12,14] and, notably, a number cases were complicated by intracranial hemorrhages [14]. This evidence may support that endothelium inflammation and the resulting abnormal vasoconstriction has a role in the pathophysiology of PRES in COVID-19 patients [44]. Many studies have shown that COVID-19 effects on CNS and peripheral nervous system most often become apparent [3,4] as anosmia, ageusia, impaired consciousness, dizziness and headache, on the other hand, acute CVD syndromes are less frequent but bear potentially permanent CNS dysfunction hence worse prognosis. Notably, compared to influenza virus, COVID-19 patients have higher prevalence of AIS, highlighting how COVID-19 may be a risk factor for AIS [24]. Furthermore Merkler., *et al*. found that initial plasma D-dimer levels were higher in COVID-19 ischemic stroke versus patients with influenza [24]. The prevalence of acute CVD in COVID-19 population was 1.0% and on COVID-19 with neurological symptoms was 36%, the highest among other neurological syndromes, which is comparable to the results in the pooled population from the scoping review (1% vs 0.9%). Compared to the Italian population, where the most recent prevalence data of CVD in the general population is 6.5% [45], according to our results, CVD was lower in COVID-19 patients. This could be due to the clinical setting, i.e. intensive care unit patients with multiorgan failure and to the difficulty to obtain a complete neurological examination (intubated patients) which may have led to an underestimation of the true prevalence.

Central nervous system damage associated with SARS-CoV-2 invasive potential may underly the development of encephalitis and myelitis. This evidence confirms the neurotrophic and neuroinvasive tendency of SARS-CoV-2 ACE-2 host receptor mediated expressed on brain and spinal cord neurons [37,46,47]. Only few case reports recently described the association of COVID-19 with demyelinating diseases [48]. However a clear causative correlation between SARS-CoV-2 and the new onset or exacerbation of demyelinating diseases is yet to be determined. It has been speculated that SARS-CoV-2 may activate lymphocytes and induce an inflammatory response leading to exacerbation or new onset of demyelinating disorders [49].

Although our study has one of the largest populations of COVID-19 patients with neurological manifestations and positive neuroimaging, further data and larger samples could widen further the multifaceted nervous system involvement in COVID-19. Our scoping review is limited by the heterogeneity of study designs of the included works, their retrospective nature, fragmentary data reported and relatively small samples.

Conclusion

Our multicenter retrospective observational data confirm the high variability of neuroimaging features of COVID-19, additionally, CVD has the highest prevalence among other acute neurological manifestations in our cohort as well as in the current literature. This evidence demands awareness among clinician and healthcare policy maker to hone the daily practice and healthcare delivery strategy towards a more efficient response to the pandemic.

Declaration

KARDIA SRL sustained the submission fee, but KARDIA SRL had no role in the design of the study, neither in the collection, analysis, and interpretation of data nor in writing of the manuscript.

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