Neuroimaging features of COVID-19: retrospective Northern Italy multicenter study and a scoping review of prevalence of COVID-19 associated acute cerebrovascular diseases

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Keywords COVID-19 – Coronavirus - Neuroimaging – Neurological – Cerebrovascular disease

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
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 90 COVID-19 patients who were referred to neuroimaging, 78 (87%) 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); 1 patient (1%) with Guillain Barré syndrome. In addiction two patients with CVD developed cauda polyradiculitis and tetraparesis.

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.

**Conclusions** 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.
Background

Since the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, [1] worldwide SARS-CoV-2 infections are still dramatically increasing with over 90 million total cases and roughly 2 million deaths on January 13, 2021 [2]. USA has been suffering the highest number of infections and deaths, closely followed by India and Brazil [2]. On February 21, the first Italian COVID-19 case was diagnosed in the northern region of Lombardy. From there the infection rapidly spread in the whole country, which became the second world epicenter of COVID-19 outbreak, after China [2]. Currently Europe is facing a second wave of the pandemics. In Italy a total of 2.3 million infections and almost 80.000 deaths have been reported so far [2]. A growing body of evidences is unveiling the multi-organ involvement [3] by SARS-CoV-2 rather than the sole respiratory and gastrointestinal systems manifestations as initially thought. In particular the nervous system involvement most commonly manifests as anosmia, ageusia and impaired consciousness [4-7], however acute cerebrovascular diseases (CVD), hereinafter comprising 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 [9, 16, 18, 23–28], thus the vast majority of current literature consists of case series or single case reports and focus on a single neurological manifestation [8-22]. 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.

Material 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; 2) concurrent or subsequent acute neurological symptoms; 3) receiving neuroimaging scans of the brain and/or spine.

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

Table 1

| Demographic data       | Total subset n=90 |
|------------------------|-------------------|
| 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 n=90 11% |
|--------|---------------|
| Ischemic stroke | 5/85 8% |
| ICH      | 3/8 38%      |
| SAH      | 0/2 0        |
| PRES     | 0/3 0        |
| Acute on chronic SDH | 0/2 0 |
| Encephalitis | 2/8 33% |
| Demyelinating diseases | 0/4 0 |

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. 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 (Fig. 1).

Fig 1

Of these, 90 (36%) patients (55% male predominance, mean age 69) showed acute neuroimaging findings. Eighty-eight (98%) patients underwent brain CT, 41 (46%) head and neck CT angiography (CTA), 32 (36%) brain MRI, 5 (6%) spinal MRI, 12 (13%) had DSA (Table 2).
Table 2

| Neuroimaging findings | Head CT | Head and Neck CTA | Brain MRI | Spine MRI | DSA |
|-----------------------|---------|------------------|-----------|-----------|-----|
| Ischemic stroke       | 65/65 (100%) | 35/65 (54%) | 19/65 (29%) | - | 12/65 (13%) |
| ICH                   | 8/8 (100%) | 3/8 (37%) | 3/8 (37%) | 1/8 (12%) | - |
| SAH                   | 2/2 (100%) | 0/2 (0%) | 0/2 (0%) | 1/2 (50%) | - |
| PRES                  | 3/3 (100%) | 2/3 (67%) | 3/3 (100%) | - | - |
| a/c SDH               | 2/2 (100%) | - | - | - | - |
| Encephalitis          | 6/6 (100%) | 1/6 (17%) | 5/6 (83%) | - | - |

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%).

Table 3

| Neuroimaging findings | Notes |
|-----------------------|-------|
| Ischemic stroke       | 65% involved anterior circulation, 23% posterior circulation, 11% multifocal lesions, 1 venous stroke; 11% developed hemorrhagic transformation; 18% eligible 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 underlying vascular malformations; 1 patient developed transient flaccid tetraparesis. |
| PRES                  | 2 cases showed multiple hemorrhagic foci. |
| a/c SDH               | 100% non traumatic. |
| Encephalitis          | 100% involved the temporal lobes; 1 cerebellar peduncles involved, 1 meningeal enhancement |
| Demyelinating diseases | 1 MS exacerbation, 1 new onset MS, 1 ADEM, 1 GBS |

Among the 65 cases of acute ischemic stroke (AIS), 42 (65%) involved the anterior circulation (fig. 2), 15 (23%) posterior circulation, 7 (11%) were multifocal and 1 (2%) was a venous stroke (fig. 3).
Of all intracranial hemorrhages (ICH), 8 were intraparenchymal (fig 4), 2 non-aneurysmal and non-traumatic subarachnoid hemorrhages (SAH) and 2 acute on chronic subdural hematomas (SDH).
All 6 patients presenting with acute encephalopathy, showed temporal lobe lesions in keeping with encephalitis (Table 3). We also observed 4 (4%) 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, multifocal lesions and 1 case of Guillain–Barré Syndrome (GBS). Three patients had spinal involvement: the above described GBS, 1 patient with SAH that developed polyradiculitis and transient flaccid tetraparesis, and 1 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.

Table 4

| CVD       | Cases (n=90) | Mean age (Range) | Male | COVID-19 (n=7937) | COVID-19 with neurological symptoms (n=253) |
|-----------|--------------|------------------|------|-------------------|-------------------------------------------|
|           |              |                  |      |                   |                                           |
| AIS       | 65           | 72 (47-88)       | 65%  | 0.82%             | 25.7%                                     |
| ICH       | 8            | 60 (21-84)       | 50%  | 0.10%             | 3.2%                                      |
| SAH       | 2            | 84 (78-90)       | 100% | 0.03%             | 0.8%                                      |
| PRES      | 3            | 70 (63-84)       | 100% | 0.04%             | 1.2%                                      |
| a/c SDH   | 2            | 67 (49-85)       | 50%  | 0.03%             | 0.8%                                      |
| Encephalitis | 6          | 69 (40-90)       | 83%  | 0.08%             | 2.4%                                      |
| Demyelinating diseases | 4 | 43 (9-65) | 50% | 0.05% | 1.6% |
| Total     | 90           | 69 (9-90)        | 55%  | 1.13%             | 35.6%                                     |

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).

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 (Fig. 5) and were full text screened.
A total population of 136198 COVID-19 patients was included (60.2% of males, mean age 64.8). Pooled prevalence of CVD was 0.9% (range 0.1 – 5.7%), and ischemic stroke was the most common
manifestation (1047/1222, 86%). The prevalence of CVD in the cohort of 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 [29, 33, 34, 38, 40-43, 47, 49, 50].

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 [51] which results in endothelial damage. [51-52]. 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 [53]. In addition, the endothelial ruptures in cerebral capillaries, due to the inflammatory process, can contribute to the pathophysiology of SARS-CoV-2 brain damage [51]. Ischemic stroke, cerebral venous thrombosis included, could be related both to the development of endotheliitis and hypercoagulability status. In this regard, Spiezia et al. [54] described a severe hypercoagulability status related to the inflammatory response and Zhang et al. [55] found the presence of antiphospholipid antibodies in few patients. In addition, SARS-CoV-2 infection can lead to cardiovascular complications including incident atrial fibrillation [56-58], 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 [38]. In addition, acute viral infections may increase the risk of ischemic stroke as noted by some authors [59]. 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 [60]. It is suggested that Coronavirus infections, and other respiratory infections, is an independent risk factor for acute cerebrovascular disease [61].

We had severe PRES cases, some of which were primarily hemorrhagic. The occurrence of PRES in COVID-19 has been reported by some [14, 21, 62-65] and, notably, a number cases were complicated by intracranial hemorrhages [21, 62, 64, 65]. This evidence may support that endothelium
inflammation and the resulting abnormal vasoconstriction has a role in the pathophysiology of PRES in COVID-19 patients [66]. Many studies have shown that COVID-19 effects on CNS and peripheral nervous system most often become apparent [4–7, 67] 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 [38]. Furthermore Merkler et al. found that initial plasma D-dimer levels were higher in COVID-19 ischemic stroke versus patients with influenza [38]. 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% [68], 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 [51, 69, 70]. Only few case reports recently described the association of COVID-19 with demyelinating diseases [71]. However a clear causative correlation between SARS-CoV-2 and the new onset or exacerbation of demyelinating diseases is yet to be determined [72]. 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 [73, 74]. 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.

Conclusions

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**

Ethics approval and consent to participate

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.

All methods were carried out in accordance with ethical committee guidelines and regulations.

Consent for publication

Written informed consent was obtained from all subjects before the study

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable

Funding

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.

Authors’ contributions

GA, DAF, VG, AE, PLS, DVA, PA, VL, TM, NL, SC, BS, MA, TAV, TF, CS, NNP, AF, GV, LE, BE, BP, C-TE, LL, BF and BF collected patients data. DAF, VG, AE and GA analyzed and interpreted the patient data. DAF and VG wrote the manuscript. DAF, VG, GA and LP review the manuscript. All authors read and approved the final manuscript

Acknowledgements

Not applicable.

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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.

Table 2

Neuroimaging studies
ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage, PRES = posterior reversible
encephalopathy syndrome, a/c SDH = acute on chronic subdural hemorrhage

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

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.

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

Figure 1
Flowchart of the multicenter study.
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 Herophili (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.

Figure 5
PRISMA-ScR Extension flow diagram.