

Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the Global COVID-19 Stroke Registry

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Word count: 823

Tables/Figures: 0/1

Acknowledgements: None

Source of Funding: None

Disclosures: None

Keywords: COVID-19; SARS-CoV-2; coronavirus; acute stroke; severity

Supplemental Materials

- Supplementary methods
- Supplementary tables

Abstract

Recent case-series of small size implied a pathophysiological association between Coronavirus disease 2019 (COVID-19) and severe large-vessel acute ischemic stroke (AIS). Given that severe strokes are typically associated with poor prognosis and can be very efficiently treated with recanalization techniques, confirmation of this putative association is urgently warranted in a large representative patient cohort to alert stroke clinicians, and inform pre- and in-hospital acute stroke patient pathways. We pooled all consecutive patients hospitalized with laboratory-confirmed COVID-19 and AIS in 28 sites from 16 countries. To assess whether stroke severity and outcomes (assessed at discharge or at the latest assessment for those patients still hospitalized) in patients with AIS are different between COVID-19 and non-COVID-19 patients, we performed 1:1 propensity score matching analyses of our COVID-19 patients with non-COVID-19 patients registered in the ASTRAL Registry between 2003 and 2019. Between 27/01/2020 and 19/05/2020, 174 patients (median age 71.2 years; 37.9% females) with COVID-19 and AIS were hospitalized (median of 12 patients per site). The median NIHSS was 10 (IQR: 4-18). In the 1:1 matched sample of 336 COVID-19 and non-COVID-19 patients, the median NIHSS was higher in COVID-19 patients [10 (IQR:4-18) versus 6 (IQR:3-14), $p=0.03$; OR:1.69, 95%CI:1.08-2.65 for higher NIHSS score]. There were 48 (27.6%) deaths, of which 22 were attributed to COVID-19 and 26 to stroke. Among 96 survivors with available information about disability status, 49 (51%) had severe disability at discharge. In the propensity score matched population ($n=330$), COVID-19 patients had higher risk for severe disability (median mRS 4 (IQR:2-6) versus 2 (IQR:1-4), $p<0.001$) and death (OR:4.3, 95%CI:2.22-8.30) compared to non-COVID-19 patients. Our findings suggest that COVID-19 associated ischemic strokes are more severe with worse functional outcome and higher mortality than non-COVID-19 ischemic strokes.

Non-standard Abbreviations and Acronyms.

COVID-19: Coronavirus Disease 2019

NIHSS: National Institute of Health Stroke Scale

AIS: Acute Ischemic Stroke

mRS: Modified Rankin Scale Score

Coronavirus disease 2019 (COVID-19), a viral disease caused by the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), may predispose patients to arterial thrombotic complications mediated by inflammation, endothelial dysfunction, thrombin generation and platelet activation¹. Three recent case-series of small size implied a pathophysiological association between COVID-19 and severe large-vessel acute ischemic stroke (AIS)²⁻⁴. Given that severe strokes are typically associated with poor prognosis and can be very efficiently treated with recanalization techniques, confirmation of this putative association is urgently warranted in a large representative patient cohort to alert stroke clinicians, and inform pre- and in-hospital acute stroke patient pathways.

We pooled all consecutive patients hospitalized with laboratory-confirmed COVID-19 and AIS in 28 sites from 16 countries. We excluded patients who were infected after the onset of stroke. Nineteen (70.4%) sites were reference hospitals for COVID-19 patients. A prespecified form was used to register anonymized patient data. To assess whether stroke severity (estimated by the National Institute of Health Stroke Scale, NIHSS) and outcomes (assessed by the modified Rankin score, mRS, at discharge or at the latest assessment for those patients still hospitalized) in patients with AIS are different between COVID-19 and non-COVID-19 patients, we performed 1:1 propensity score matching analyses of our COVID-19 patients with non-COVID-19 patients registered in the Acute STroke Registry and Analysis of Lausanne (ASTRAL)⁵ between 2003 and 2019. For the propensity score matching analysis of stroke severity, patients were matched without replacement on a set of pre-specified covariates, including demographics (age, sex), stroke risk factors and comorbidities (hypertension, diabetes, atrial fibrillation, coronary artery disease, heart failure, cancer, previous stroke, smoking, obesity, dyslipidemia). For the propensity score matching analysis of outcomes, the type of intervention and main stroke symptoms (motor symptoms, sensory symptoms, dysarthria and aphasia) were additionally matched (further details on statistical methods are available in the supplementary material). The Global COVID-19 Stroke registry was approved by the Institutional Review Board of the co-ordinating site (Larissa University Hospital). Informed consent was waived as this was an observational study on anonymized data. Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the first author.

Between 27/01/2020 and 19/05/2020, 174 patients (median age 71.2 years; 37.9% females) with COVID-19 and AIS were hospitalized (median of 12 patients per site). There were 45 patients aged >80 years and 41 aged <64 years.

In 96% of the cases, COVID-19 was confirmed with PCR and in the others by serology. The most prevalent stroke risk factors and comorbidities were hypertension (68.4%), obesity (37.4%) and diabetes (31.03%). Previous stroke was reported in 20 (11.5%) patients. The median delay between

the initiation of COVID-19 symptoms and stroke onset was 7 days (interquartile range, IQR: 2-15). The most prevalent COVID symptoms were fever (55.2%), cough (53.5%) and dyspnoea (43.7%).

The main stroke symptoms were motor (67.8%), dysarthria (46%) and sensory (42%). The median NIHSS was 10 (IQR: 4-18). In the 1:1 matched sample of 336 COVID-19 and non-COVID-19 patients, the median NIHSS was higher in COVID-19 patients [10 (IQR:4-18) versus 6 (IQR:3-14), $p=0.03$; OR:1.69, 95%CI:1.08-2.65 for higher NIHSS score] (Figure 1/upper panel).

The vascular territory most frequently affected was the middle cerebral artery (in 93 out of 163 patients with available information). In the matched database ($n=366$), 132 of 168 COVID-19 patients had a complete diagnostic work up towards stroke etiology. Among those 132 patients, 30 (22.7%) and 10 (7.6%) had a large-artery or a lacunar stroke, respectively. In the non-COVID-19 matched cohort, we recorded 22 (13.1%) patients with large-artery atherosclerosis and 17 (10.2%) with lacunar stroke. Overall, we did not find a difference in the prevalence of large-artery and lacunar stroke between the two populations (non-parametric chi-squared test $p=0.082$).

In the overall population of the COVID-19 patients, alteplase was administered in 34 (19.7%) of patients and endovascular thrombectomy was performed in 21 (12.1%) patients (33 and 20 among the COVID-19 patients who were included in the matched analysis, respectively). The outcomes per intervention in the matched cohort of stroke patients with and without COVID-19 are presented in the supplemental material. Any haemorrhagic transformation of the infarct was diagnosed in 22 patients, of whom 5 had been treated with intravenous alteplase. Malignant brain oedema was present in 4 (5.1%) patients and 3 of these patients were treated with hemicraniectomy.

Among 112 patients who had pulmonary imaging with chest CT, 89.3% had lung opacities. Twenty-seven patients (15.5%) were intubated, 40 (23%) were transferred to an intensive care unit and 110 (63.2%) were discharged from the hospital. There were 48 (27.6%) deaths, of which 22 were attributed to COVID-19 and 26 to stroke. Among 96 survivors with available information about disability status, 49 (51%) had severe disability at discharge. In the propensity score matched population ($n=330$), COVID-19 patients had higher risk for severe disability (median mRS 4 (IQR:2-6) versus 2 (IQR:1-4), $p<0.001$) and death (OR:4.3, 95%CI:2.22-8.30) compared to non-COVID-19 patients (Figure 1/lower panel).

The strengths of this analysis are the large patient cohort, the multicentre international design, the inclusion of all consecutive known COVID-19 AIS patients treated in each site, and the propensity score matching comparison with a non-COVID-19 AIS cohort. A limitation of the study is that the propensity score match cohort was from a single site; however, as described in the supplemental

material, our sensitivity analysis for potential hidden bias in the matched database confirmed the robustness of the main findings. Even if this extra, unobserved indicator (i.e. site of recruitment) could affect the odds of a patient's conditional classification to the case or control group by up to 130% and in parallel was totally unrelated to all of the variables taken into consideration (demographic characteristics, risk factors, comorbidities, stroke symptoms and treatment), still our results of increased mortality and disability in COVID-19 patients would not substantially change.

There are several potential explanations for the relation between COVID-19 associated ischemic strokes and increased stroke severity, which may co-exist. It was proposed that viral infections may cause a direct vasculopathic effect (endotheliopathy) or potentiate the pro-thrombotic milieu via several mechanisms including immune-mediated platelet activation, dehydration and infection-induced cardiac arrhythmias⁶. It is unclear whether the finding of increased severity in COVID-19 associated ischemic strokes applies to all ischemic stroke types or is mainly driven by an increase in large-vessel occlusion strokes, as implied by recent findings². Finally, it may be possible that the stay-at-home recommendations/orders and the general fear of the hospital during the COVID-19 pandemic may have prevented acute stroke patients with smaller deficits from presenting to the hospital, although a recent study reported that the decrease in the number of patients evaluated for stroke in a commercial neuroimaging database was seen across stroke severity subgroups⁷.

The increased stroke severity at admission in COVID-19 associated stroke patients compared to the non-COVID-19 cohort may explain the worse outcomes. The broad multi-system complications of COVID-19 including acute respiratory distress syndrome, cardiac arrhythmias, acute cardiac injury, shock, pulmonary embolism, cytokine release syndrome and secondary infection⁸, probably contribute further to the worse outcomes including higher mortality in these patients.

Our findings suggest that COVID-19 associated ischemic strokes are more severe with worse functional outcome and higher mortality than non-COVID-19 ischemic strokes. The association between COVID-19 and severe stroke highlights the urgent need for studies aiming to uncover the underlying mechanisms and is relevant for prehospital stroke awareness and in-hospital acute stroke pathways during the current and future pandemics, since severe strokes have typically poor prognosis and can potentially be treated with recanalization techniques.

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Figure 1: Histogram and Kernel Density Estimates of the NIHSS score (upper panel) and modified Rankin Scale scores (lower panel) in matched populations of COVID-19 patients from the Global COVID-19 Stroke Registry and non-COVID-19 patients from the ASTRAL registry.