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

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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, platelet activation and endothelial dysfunction[1](#_ENREF_1). Three recent case-series of small size implied a pathophysiological association between COVID-19 and severe large-vessel acute ischemic stroke (AIS)[2-4](#_ENREF_2). Given that severe strokes are typically associated with poor prognosis and can be very efficiently treated with recanalization techniques[5](#_ENREF_5), 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)[6](#_ENREF_6) 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 added for the matching process (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.

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 other 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] (Supplementary Table 3, Figure 1/upper panel).

The vascular territory most frequently affected was the middle cerebral artery (in 93 out of 163 patients with available information). There were 32 large-artery atherosclerotic strokes (18.5% among patients who had vascular imaging) and 10 lacunar strokes.

Alteplase was administered in 34 (19.7%) of patients and endovascular thrombectomy was performed in 21 (12.1%) patients. 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 patients were treated with hemicraniectomy. The COVID-19-targeted medication that patients received during hospitalization is summarized in the supplementary table 1.

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 the 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 (Supplementary Table 3, 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.

Our findings suggest that COVID-19 associated ischemic strokes are more likely to be more severe and have worse functional outcome and higher mortality than non-COVID-19. The association between COVID-19 and severe stroke highlights the urgent need for studies aiming to uncover the underlying mechanisms and are 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 rechniques.

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