A stroke in severe acute respiratory syndrome coronavirus 2 infected is not necessarily a COVID-stroke

Dear Editor,

We read with interest the article by Kurian *et al*. on a retrospective study of five patients with bilateral embolic stroke and concomitant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring mechanical ventilation.[1] Atrial fibrillation (n = 2), hypercoagulability (n = 2), and disseminated intra-vasal coagulation (n = 1) were identified as the cause of stroke.[1] The stroke was treated with intravenous heparin (n = 4) or apixaban (n = 1).[1] The outcome was poor with death (n = 3), modified Rankin Scale (mRS) 4 (n = 1), and mRS 5 (n = 1).[1] The study is excellent, but a number of considerations are in order.

The first limitation is the retrospective design, which does not allow for repetition or new investigations and long-term follow-up.

The second limitation is that all five patients were diagnosed with stroke by cerebral computed tomography (CCT) but not by cerebral magnetic resonance imaging (MRI).[1] The native CCT has the disadvantage that the age of the stroke cannot be reliably assessed. Furthermore, a mismatch between penumbra and stroke core is not visible unless perfusion computed tomography (CT) is performed in addition. CCT also does not allow to assess which lesions were already present before the SARS-CoV-2 infection and which were not.

The third limitation is that several stroke mechanisms in addition to atrial fibrillation, disseminated intra-vasal coagulation (DIC), and hypercoagulability, were not considered and sufficiently excluded. These include venous sinus thrombosis (VST), cerebral vasculitis, endothelialitis, myocarditis, endocarditis, bilateral carotid or vertebral artery stenosis, and reversible cerebral vasoconstriction syndrome (RCVS). VST can only be ruled out with certainty by CT or magnetic resonance venography (CTV, MRV). VST can be complicated by bilateral ischemic stroke.[2] Cerebral vasculitis has been repeatedly reported as a complication of SARS-CoV-2 infections[3] and can be complicated by bilateral ischemic stroke. We should know if CTA or digital subtraction angiography suggested vasculitis and if any of the five patients had increased blood sedimentation rate, anti-nuclear antibodies, or anti-neutrophil cytoplasmic antibodies. SARS-CoV-2 related microvascular damage, manifesting as endothelialitis is a known phenomenon and can be held responsible for both arterial and venous thrombosis. Bilateral embolic stroke can also be due to myocarditis or endocarditis complicated by intraventricular or valvular thrombus formation with subsequent cardioembolism.[4] RCVS has only rarely been described as a complication of SARS-CoV-2 infection.[5] RCVS is characterized by multifocal spasms of the cerebral arteries, occasionally leading to unilateral or bi-lateral ischemic stroke. RCVS can be confirmed by repeat CTA showing dynamic vasculature or by the resolution of multiple stenoses on nimodipine.

The fourth limitation is that patients 3–5 were not autopsied.[1] Brain autopsy could help clarify the stroke mechanism, especially if atherothrombosis, embolism, VST, endocarditis, or myocarditis were present.

The fifth limitation is that CTA was only performed in two patients.[1] It therefore remains speculative whether the stroke in the three patients without CTA was really due to an embolism.

Regarding DIC in patient-1, we should know if this patient had the signs of sepsis. DIC is often associated with sepsis, so it is crucial to know whether the blood culture was positive for bacteraemia and whether or not pro-calcitonin was elevated in this patient. Sepsis must also be ruled out in the remaining patients, since multi-organ failure was described in all of them.

Intravenous heparin is an uncommon treatment for subacute stroke. We should be informed why patients 2–5 were treated with intravenous heparin and whether any of them developed an intracerebral bleeding on follow-up CCT. In this regard, we should be informed of the cause of death in patients 3–5. Did they die of cerebral, pulmonary, cardiac, or multiorgan causes?

Overall, the interesting study has limitations that challenge the results and their interpretation. Addressing these limitations could further strengthen and reinforce the statement of the study. Before attributing bilateral

ischemic stroke to acute SARS-CoV-2 infection, all alternative causes must be thoroughly ruled out. Both strokes and SARS-CoV-2 infections were widespread during the pandemic, and the co-occurrence of both simultaneously was very likely coincidental with no causal relationship.

Ethics approval
Was in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent to participate
Consent was obtained from the patient.

Consent for publication
Was obtained from the patient.

Availability of data
All the data are available from the corresponding author.

Author contribution
JF: Design, literature search, discussion, first draft, critical comments, final approval, SM: Literature search, discussion, critical comments, final approval.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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