Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correlation does not mean causation: Proofs of COVID-19 associated strokes!

Dear Editor

We thank Dr. Finsterer and Colleagues for the very interesting comments about our case series report on stroke in COVID-19 critically ill patients, and we respectfully consider their suggestions to strengthen the findings of our study.[1]

In this light, we would like to point out that hypercoagulable state after SARS-CoV-2 infection lasts for weeks or even months. In this regard, Ming Tu and Colleagues described an increased risk for acute ischemic stroke in asymptomatic COVID-19 patients after 130 days from a SARS-CoV-2 positive test.[2]

Zarifkar and Colleagues reported stroke events after COVID-19 infection at longer time than Ming and Colleagues, and at 12 months after infection relative risk to develop AIS was found to be 2.7 [95 % CI:2.3–3.2].[3]

Another important question raised by Finsterer and Colleagues was about arterial hypertension as the main risk factor for AIS in patient-2. Anyhow, we cannot definitively state that arterial hypertension was the only cause, but as frequently seen in medicine, patients develop illness when an acute triggering event fits on a substrate predisposed to develop disease.

Regarding patient with SAH (patient-5), we highlight that patient had no history of arterial hypertension, trauma or embolization. In this way, we exclude these events as the cause of bleeding.

The authors raise another important point and we thank for giving us the opportunity to clarify this issue regarding MRI. We recognize the importance of multimodal MRI to explore the brain of COVID-19 patients; however, we have to remember that all our patients were admitted to ICU in critical conditions during the pandemic peak, in a period with limited resources, and with entire hospital buildings converted to the treatment of COVID-19 patients.[4] From a practical point of view, it was very difficult at that time to perform MRI exam on a critically ill patient if we consider the restrictions to limit viral spread.

In addition, as reported by neuroradiologist expert group consensus concerning neuroimaging in patients with COVID – 19, a CT venogram (CTV) is indicated if there is a suspicion of cerebral venous thrombosis (CVT), either clinically or on non-enhanced CT.[5]

Regarding patient-5, he had no lung involvement at ED and SAH diagnosis, but he developed severe C-ARDS 6 days after ICU admission. However, the presence of PE at ED admission reinforces the potential relationship between COVID infection and hypercoagulability state.

Patient-4 presented a high ICH score (3) carrying high predicted mortality (72 % according ICH score). Rapid clinical worsening with GCS that decreased from 15 to 11, high ICH score, a fast progression to low cerebral blood flow according to TCCD led to a common multidisciplinary decision not to operate him. No anticoagulation (contraindicated due to the severe bleeding) nor ECMO was administered to the patient.

Post-mortem examination concluded that patient died due to severe intracranial hemorrhage and diffuse alveolar damage, both caused by SARS-CoV-2 infection.

In order to reply to Finsterer and Colleagues, we would like to add that PE was diagnosed in patient-3 with perfusion CT scan.

Patient-2 was treated with intravenous thrombolysis followed by mechanical thrombectomy.

COVID-19 patients received steroids according to WHO guidelines for the treatment of symptomatic lung disease.[6] In addition, unless contraindicated, he received enoxaparin at least 4000 UI bid, and the level of anticoagulation was monitored with antifactor Xa levels.

The medication taken by patient-2 for chronic arterial hypertension was valsartan 160 mg once a day. Other chronic medications are already listed in the main paper.

We add reference limits for laboratory tests included in the paper as it follows: WBC (4.00–11.00 $\times$ 10^3/μL), Ly (1.00–4.00 $\times$ 10^3/μL), PLT (150–400 $\times$ 10^3/μL), CRP (0.00–5.00) mg/L, IL-6 (<7 pg/mL), aPTT ratio (0.83–1.17), INR (0.80–1.20), D-dimer (0–500 FEU ng/mL).

We would like to share the idea that neurological manifestations of COVID-19 in critically ill patients have been largely described.[7]

Overall, we agree with Finsterer and Colleagues that causal relationship between SARS-CoV-2 infection and cerebrovascular events requires a plausible pathophysiological explanation and a temporal link. According to Vogrig et al. who reported a revised COVID associated stroke (CAS) case definition considering also the timing of onset of stroke after COVID-19 symptoms, we want to outline that all our cases fulfilled both major and at least one minor criteria of this classification making all our cases possible COVID associated CASs.[8]

In conclusion, we would like to remember that in the introduction we stated that the pictorial review presents five case reports describing the different possible manifestations of stroke in critically ill patients infected with SARS-CoV2.

We hope that Our Colleagues will agree with us that association does not imply causation, and at the moment further studies are required to respond whether inflammation and hypercoagulable state are guilty or innocent like Oedipus in the following:

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"*Oedipus is neither guilty nor innocent, but a victim of Fate, that is, of the immutable destiny, to which men and gods cannot oppose. Man can only limit himself to knowing him, through soothsayers*"

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Declaration of Competing Interest

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