

## REPLY:



We thank Morelli et al for their interest in our article and their feedback.

We think it is important to remember that coronavirus disease 2019 (COVID-19) was first recognized in December 2019, only 6 months ago.<sup>1</sup> Therefore, there will be inherent limitations to the size, scope, and implications of any research that can occur in such a truncated period.

In addition, as we acknowledge in our article, the patient described in our case report died on hospital day 3, before the completion of a complete laboratory work-up; furthermore, no postmortem examination was performed.<sup>2</sup> So, we agree with Morelli et al that it will require larger studies of more prolonged duration to draw definitive causal relationships between COVID-19 and various disease states, including acute cerebrovascular disease.

Until such studies occur, we would refer Morelli et al to the early-but-substantial medical literature that indicates a strong association between COVID-19 and cerebrovascular disease. This includes a retrospective study of 214 patients with COVID-19 in China, which revealed a 5.7% incidence of stroke in severely affected patients.<sup>3</sup> In a case series of 64 patients with severe COVID-19, three of 13 patients who underwent brain MRIs demonstrated evidence of ischemic stroke.<sup>4</sup> Researchers in New York City recently published a case series of 5 young patients (less than 50 years-old) with COVID-19 who presented with large-vessel stroke during a 2-week period; this represented an almost 7-fold increase in the frequency of large-vessel stroke seen in patients in this age group.<sup>5</sup> Because severely affected patients with COVID-19 are often intubated and sedated, the presence of stroke can be overlooked, and the current estimates of the incidence of stroke may, therefore, be spuriously low.<sup>6</sup> Additionally, Umapathi et al<sup>7</sup> reported an association between large-vessel stroke and the somewhat similar 2004 Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-1) outbreak. Combined with the growing literature on coagulopathy in severely affected patients with COVID-19, we think that dismissing this information as anecdotal belies reasonable evidence for a causative association between COVID-19 and cerebrovascular disease.<sup>8-10</sup>

Like Morelli et al, we also subscribe to the principle of Occam's razor. The patient described in our case report had tested positive for SARS-CoV-2 sixteen days before admission. Initially, he had a relatively benign course with mild respiratory symptoms and myalgia, and he had no preceding neurologic deficits. Several hours before admission, however, he developed, nearly simultaneously, stroke symptoms and respiratory distress, which ultimately led to CT-confirmed acute respiratory distress syndrome (ARDS) and hemodynamic instability. We do not think the synchronous timing of these disparate symptoms is coincidental. Rather, the delayed

onset of both respiratory and neurologic symptoms in COVID-19 is suggestive of a maladaptive immune response, including cytokine storm syndrome, resulting in not only ARDS but also abnormalities in the clotting cascade and endothelial inflammation.<sup>11,12</sup> Therefore, ascribing this patient's stroke to COVID-19 is entirely consistent with Occam's razor—to do otherwise risks invoking the Hickam dictum, which is the assignment of multiple different and independent diagnoses to explain a variety of signs and symptoms.<sup>13</sup>

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