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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Letter to the Editor

Reply to "Digging deeper on the neurophysiological assessment in COVID-19 patients" and "Myopathy in acute and long-term COVID-19"

We appreciate the comments provided to us in the Letters "Digging deeper on the neurophysiological assessment in COVID-19 patients" by Bocci et al. (2022), and "Myopathy in acute and long-term COVID-19" by Tankisi and Ochala (2022). We thank the editors for the opportunity to respond to the observations offered and to expand the discussion of our work (Hameed et al., 2021).

Neurological manifestations, involving both the central and peripheral nervous system, have been reported in patients with coronavirus disease 2019 (COVID-19) (Mao et al., 2020). Neuromuscular manifestations have increasingly been reported among COVID-19 patients, especially with severe illness. Since COVID-19 is a newly emerging infection, a lot of the early information about COVID-19-related neuromuscular manifestations came from case reports and small case series. Isolated reports of myopathy and acute neuropathy (i.e., Guillain-Barre syndrome) were initially reported (Tankisi et al., 2020; Ghosh et al., 2020; Sedaghat and Karimi, 2020). With time, larger case series were published (Cabañes-Martínez et al., 2020; Bax et al., 2021; Bocci et al., 2021; Frithiof et al., 2021).

We reported myopathic EMG changes in 39% of our cases, neuropathic changes in 6%, and mixed myopathic-neuropathic changes in 28%. A higher percentage of myopathy in COVID-19 patients has been reported by Cabañes-Martínez et al. (2020), while other studies have reported a higher incidence of neuropathy (Bax et al., 2021; Bocci et al., 2021; Frithiof et al., 2021). Subclinical myopathic changes have also been reported in COVID-19 patients in the absence of the clinical features of myopathy (Villa et al., 2021). We believe some of the reasons for this discrepancy are small sample sizes, patient selection, duration of hospitalization, different therapeutic regimens, and different electrodiagnostic techniques used. We included all COVID-19 inpatients that underwent electromyographic and nerve conduction studies (EMG/NCS) in our hospital irrespective of their disease severity, intensive care unit (ICU) admission, or need of mechanical ventilation, while some of the published studies only included COVID-19 ICU patients (Cabañes-Martínez et al., 2020; Bax et al., 2021; Bocci et al., 2021; Frithiof et al., 2021). We also included only those patients that were referred by the primary physician or consulting neurologists. Therefore, we may have missed some of the cases that were either having mild neuromuscular manifestations or were critically ill with multiple issues and did not undergo EMG/NCS. Further, different SARS-COV-2 variants in different parts of the world may also lead to different neuromuscular manifestations.

Rightly stated, some of our patients with myopathy had normal creatine phosphokinase (CPK) levels, especially those who did not require mechanical ventilation or ICU admission. Due to certain limitations, such as the lack of muscle biopsy ordered by the primary physician and unavailability of second-level electrophysiological tests, including the direct muscle stimulation (DMS) technique, we were unable to differentiate whether our patients developed myopathy secondary to the direct viral attack or had critical illness myopathy (CIM). Some of the patients would likely have CIM, but rightly said, we could not answer if COVID-19 associated CIM is different from CIM caused by other etiologies due to our study limitations. The myopathic EMG changes in our patients may also be due to other reasons, such as steroid use, which may present with normal CPK levels. We have also repetitively evaluated the NCS and EMG data for all of our patients and could not find any specific changes that are different in COVID-19 patients. Entering all the EMG/NCS data for all the patients in a table will be too cumbersome for the readers, however, if any specifics are required, we will be happy to collaborate and share the data.

Further, two patients in our study had long time intervals of 120 and 180 days, respectively, between COVID-19 infection and EMG/NCS testing. Both patients had multiple hospital admissions for worsening respiratory function post-COVID-19. At that time, we were no longer able to establish a causal relationship of their neuromuscular manifestations with COVID-19. It is, in fact, always difficult to establish a causal relationship in observational studies with small sample sizes with multiple risk factors. On the other hand, we cannot simply refute a causal relationship only on the basis of the delay since COVID-19 onset, as the long-term effects of COVID-19 on the nervous system are still largely elusive. If the respiratory systems may worsen as a long-term post-COVID-19 sequelae (Ojo et al., 2020), the same may occur with the nervous/neuromuscular system. Many COVID-19 patients presenting with non-specific symptoms of chronic myalgias and fatigue were reported to have myopathic changes on EMG (Agergaard et al., 2021), suggesting a possibility of a post-infectious pathophysiology.

At present, we can safely presume that the number of unanswered questions is greater than the answered ones for COVID-19-related neuromuscular manifestations. With time and large-scale studies, we may be able to unravel some of the present mysteries. Our paper is an effort to add another piece to the puzzle of COVID-19-related neuromuscular manifestations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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