JIM Editorial

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Post-acute cognitive and mental health outcomes amongst COVID-19 survivors: early findings and a call for further investigation

Early in the course of the COVID-19 pandemic, concerns were raised about the potential for neuropsychiatric disturbances based on observations from prior coronavirus epidemics. Patients hospitalized for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) frequently experienced in-hospital delirium as well as depressed and labile mood, anxiety, sleep difficulties and memory impairment that spanned both the acute and post-acute phases of illness [1]. As the current pandemic has evolved, early reports of delirium and neurologic symptoms have heightened concern about potential longer-term neuropsychiatric sequelae amongst COVID-19 survivors [2].

Although we remain in the early stages of delineating the cognitive and mental health consequences of COVID-19, there are several proposed mechanisms underlying these associations [3]. COVID-19 is associated with a systemic inflammatory response that may contribute to delirium and neuronal cell death. The pro-thrombotic state associated with COVID-19 is further believed to contribute to neuropsychiatric outcomes via microvascular infarcts and haemorrhages as well as ischaemic stroke. Data suggest that the virus targets vascular and immune cells, possibly further exacerbating inflammation and blood–brain barrier dysfunction and contributing to neuronal cell death. There is also some evidence for direct neuroinvasion by SARS-CoV-2. Respiratory distress, hypoxia, prolonged mechanical ventilation, sedation and other factors may further compromise cognition. It is also well appreciated that survivors of critical illness experience increased rates of psychiatric distress including depression and post-traumatic stress disorder (PTSD) that can persist a year or more post-illness [4,5]. The severity of psychiatric distress is an independent predictor of long-term cognitive dysfunction in critical illness survivors, suggesting an additional pathway by which COVID-19 may contribute to and perpetuate neuropsychiatric morbidity [6].

The majority of currently available knowledge about neuropsychiatric symptoms associated with COVID-19 comes from studies of patients in the acute setting. Up to 65% of patients experience delirium during the ICU stay, and approximately 31% present with altered mental status [7, 8]. In the post-acute phase, the literature is largely limited to case reports and small case series, as well as data from cognitive screening instruments. There remains a lack of detailed, standardized neuropsychological evaluation of COVID-19 patients following hospitalization. Further, because subjective cognitive impairment does not necessarily correspond to objective deficits and can be associated with mood and sleep disturbances common in critical illness survivors, patient-reported outcome measures are an insufficient method of determining the prevalence and nature of cognitive impairment associated with COVID-19 in the post-acute phase. Existing data suggests that following hospitalization, COVID-19 survivors may most frequently demonstrate deficits in letter-cued verbal fluency and executive function [9, 10]. However, this body of research is in its early stages and further investigation is needed.

Mendez and colleagues present important evidence of post-acute cognitive deficits and co-occurring neuropsychiatric symptoms using cross-sectional data from 179 Spanish patients hospitalized for COVID-19 during spring 2020 [11]. Patients spanned the ages of 22 to 81 and were free of cognitive and psychiatric conditions prior to COVID-19. A detailed assessment of learning, memory, working memory, and verbal fluency was conducted via telephone at approximately two months after hospital discharge. Cognitive scores were classified as consistent with moderate or severe impairment as defined by performances ≥ 1 or ≥ 2 standard deviations below age-, sex- and education-adjusted norms, respectively. Hence, on any of the four cognitive tests, 16% of the sample would be expected to produce a moderately impaired score with only 2% being

expected to produce a score in the severely impaired range. Patients also completed standardized self-report questionnaires addressing symptoms of anxiety, depression, PTSD and quality of life (QOL) with previously established cut-offs defining casehood.

Providing some of the first and most comprehensive objective cognitive data to date, Menendez and colleagues found that 58.7% of COVID-19 survivors produced at least one score in the moderate range of impairment, with 18.4% scoring in the severely impaired range on at least one test. Moderate and severe impairment were most frequent on tests of learning (38% and 11%) and verbal fluency (35% and 8%) [11]. Rates of impairment on tests of memory and working memory did not exceed expectation (i.e., <16% or 2%). Psychiatric morbidity was also quite common, particularly in women, with 39% of COVID-19 survivors reporting clinically elevated symptoms of anxiety (30%), depression (27%) or PTSD (25%). Reductions in physical (41%) and mental (39%) QOL were frequently reported. From amongst an array of disease and patient characteristics, delirium and elevated psychiatric symptoms were associated with increased risk of cognitive impairment.

Although the excellent work of Mendez et al. [11] provides much needed insight into the short-term effects of COVID-19 on neurocognitive symptoms and quality of life, there are still many unchartered areas of investigation. All of the patients in their study were more severely ill COVID-19 patients who required hospitalization. Whether milder COVID-19 cases or even asymptomatic COVID-19 infection has significant impact on neurocognitive symptoms remains to be seen. The patients were a selective population as those with pre-existing dementia or cognitive dysfunction were excluded, and therefore, we do not know how more typical COVID-19 patients, who are likely to have pre-existing conditions, may fare from a neuropsychiatric perspective. Similarly, although the study included adults up to < 85 years, older adults were a smaller proportion of the overall study population, and therefore, the impact on the neurocognitive status of older COVID-19 survivors remains to be investigated. As data from the United States suggest that underrepresented minorities may be disproportionately impacted by the pandemic, future studies of cognitive and mental health outcomes are also needed in more diverse patient populations [12]. The current study was conducted early in the COVID-19 pandemic when mortality was higher, and therefore, there may be survival bias. The authors are applauded for taking the most comprehensive assessment of cognition to date. However, as one of the proposed mechanisms of COVID-19-related neuropsychiatric decline is ischaemic events, additional cognitive domains such as processing speed and a broader array of executive functions need to be assessed. Future work should also account for the now common finding that even healthy adults produce low cognitive scores and that they are more likely to do so as the number of tests in the battery increases [13]. Statistical methods can account for this and reduce the likelihood of false positive findings of impairment. The finding of Mendez and colleagues that psychiatric morbidity increased the likelihood of objective cognitive impairment also warrants further follow-up to disentangle the extent to which observed deficits in thinking skills represent the direct effects of COVID-19 versus the cognitive manifestation of psychiatric distress. In sum, the study by Mendez and colleagues [11] lays the foundation for much needed longitudinal studies aimed at understanding the nature and trajectory cognitive mental health symptoms following COVID-19 infection across patients of different demographic backgrounds and illness severities.

Conflict of interest statement

Neither author has any conflicts of interest connected to this paper.

Author contribution

Tracy Vannorsdall: Writing-original draft (equal); Writing-review & editing (equal). **Esther Oh:** Writing-original draft (equal); Writing-review & editing (equal).

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