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Letter to the Editor

Cognitive Functions of long-COVID Patients Depend Strongly on Whether or Not They had Cerebral Disease during the SARS-CoV-2 Infection

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We read with interest the article by Panagea *et al*. on a systematic review of 36 articles published between 2020 and 2023 on the nature and frequency of neurocognitive deficits in adult patients with long-term COVID disease [1]. The cognitive domains that are most impaired in long-term COVID patients include executive functions, memory, attention, and processing speed, while language has not been sufficiently studied to draw definitive conclusions [1]. It was concluded that cognitive impairment is common in long-term COVID patients, affecting quality of life and ability to live independently, and that early detection and accurate definition of the factors leading to cognitive impairment is necessary to develop targeted rehabilitation interventions [1]. The study is excellent, but some points should be discussed.

The first point is that the inclusion/exclusion criteria did not differentiate between patients with and without central nervous system (CNS) involvement during acute SARS-CoV-2 infection (SC2I) [1]. The distinction between these two groups is crucial, as organic CNS disorders during SC2I can strongly influence performance on neurocognitive tests. In particular, patients with immune or infectious meningitis/encephalitis, stroke, hemorrhage, acute disseminated encephalomyelitis (ADEM), acute hemorrhagic necrotizing encephalopathy (AHNE), acute necrotizing encephalopathy (ANE) acute necrotizing encephalitis (AHLE), posterior reversible encephalopathy syndrome (PRES), multiple sclerosis (MS), myelin oligodendrocyte glycoprotein-associated disorder (MOGAD), neuromyelitis optica spectrum disorder (NMOSD), which occur as a complication of SC2I, may score differently on all neurocognitive tests or batteries used. When distinguishing between these two groups, data from imaging, cerebrospinal fluid, and electroencephalography (EEG) should also be considered, as patients with structural, immunologic, or functional abnormalities may perform differently than patients without such abnormalities.

The second point refers to the inclusion criterion “latency between onset of SC2I and test date >12 weeks” [1]. The lack of an upper latency limit has the disadvantage that studies could have been included in which neurocognitive tests were performed several months or even years after the onset of SC2I. Therefore, it is conceivable that any neurocognitive deficits in these tests are not only due to SC2I, but to a CNS disorder that occurred long after recovery from SC2I. Were alternative causes of neurocognitive deficits considered in studies with a long latency period between the onset of SC2I and the test? What was the range of latencies between the onset of SC2I and testing?

The third point is that SARS-CoV-2 vaccination (SC2V) was not considered as a cause of neurocognitive deficits. Since SC2Vs can be complicated by neurological, especially CNS disorders [2], it would have been imperative to assess how many of the included patients received a dose of an SC2V after SC2I.

The fourth point refers to the exclusion criterion “motor and sensory impairments that could interfere with neuropsychological assessment” [1]. We should know which particular motor and sensory impairments the authors mean and which particular diagnoses they have excluded. For example, did they exclude patients with sensorimotor polyneuropathy?

The fifth point is that different studies have used different tests and test batteries to assess neurocognitive deficits in post-COVID patients [1]. As the test results and the overall diagnosis strongly depend on the tests used, the test results may differ considerably between the tests. Since the methods section does not mention whether only studies in which the same specific tests were used were included, we should know whether the test batteries in the 36 included studies were always the same or differed, and if they differed, how this affected the test results. Test scores may also be strongly influenced by interrater variability and test-retest reliability. Were these variables considered as factors that might influence test scores?

To summarize, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and support the message of the study.

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