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Prospective Studies are needed to Record the Type, Severity, Frequency, and Outcome of Neurological COVID Complications

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LETTER TO THE EDITOR

We read with interest Lu *et al*'s article about a retrospective, cross-sectional study on the neurological complications of SARS-CoV-2 infections in 436 patients from three Chinese centers collected between 12th December 2022 and 12th January 2023 [Lu, L. *et al*., 2024]. Forty-four patients had a new-onset COVID-related neurological disease upon admission and 55 of them experienced worsening of a previously diagnosed neurological disease [Lu, L. *et al*., 2024]. The incidence of encephalitis and encephalopathy as well as mortality were higher compared to the same period a year earlier [Lu, L. *et al*., 2024]. The outcome did not differ between those who received COVID-specific treatment and those who did not [Lu, L. *et al*., 2024]. The study is impressive, but several points require discussion.

The major limitation of the study is its retrospective design [Lu, L. *et al*., 2024]. A retrospective design has the disadvantage, that data are missing, the correctness of the data cannot be checked, missing data cannot be supplemented, and desirable new data can no longer be generated. We should know how many of the included patient data were missing and how missing data were handled.

A second limitation is that the term "encephalopathy" has not been defined. Do the authors mean epilepsy, central nervous system abnormalities when there is no structural lesion on imaging, or do they mean confusion. Encephalopathy is a vague and not defined term that should not be used in the scientific literature unless clearly defined.

A third limitation is that the vaccination status of the included patients was not reported. Since the observational period lasted from 12th December 2022 to 12th January 2023, it can be assumed that several of the patients included had received vaccinations against SARS-CoV-2. Knowing how many have been vaccinated and how many have not is important because the response to acute SARS-CoV-2 infection and therefore the frequency and severity of neurological complications may differ between vaccinated and unvaccinated people.

A fourth limitation is that COVID-19 was diagnosed not only by PCR but also by antigen tests. Antigen tests are known to have lower sensitivity than PCR tests and an increased number of false negative results compared to PCR tests. Therefore, antigen tests should only be used as screening tests, but the diagnosis must be confirmed by PCR.

A fifth limitation is that the latencies between the onset of COVID-19 and the onset of the new neurological disease were not included in the analysis. Knowing this latency is crucial in order to assess whether a causal connection existed or not.

A sixth limitation is that it was not specified whether encephalitis meant immune encephalitis or infectious encephalitis. Since treatment and outcome can vary significantly between the two, this should be reported.

Fourteen patients without specific neurological manifestations were included according to table 2. These patients should be excluded from the analysis.

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Neurological complications due to SARS-CoV-2 infection should be assessed through an international, prospective, multicentre study using the same protocol in all patients.

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