

All Factors Influencing the Outcome of SARS-CoV-2 Infected Patients in the ICU Must Be Considered before Final Conclusions are Drawn

Josef Finsterer

MD, PhD, Neurology Dpt., Neurology & Neurophysiology Center, Vienna, Austria, Orcid: 0000-0003-2839-7305

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LETTER TO THE EDITOR

We were interested to read the article by Chang *et al.* on a retrospective study of the outcome of 231 patients with critical infection with the alpha variant (n=72) or the omicron variant (n=159) of the SARS-CoV-2 virus requiring intensive care unit (ICU) admission [Chang, C. J. *et al.*, 2024]. In multivariate analysis, the omicron-dominated period was not identified as an independent factor associated with increased 28-day mortality [Chang, C. J. *et al.*, 2024]. In propensity score matching, COVID-19 patients in alpha and omicron-dominated periods also had comparable 28-day mortality [Chang, C. J. *et al.*, 2024]. Independent factors associated with 28-day mortality were lower PaO₂/FiO₂ ratio, septic shock and non-administration of remdesivir [Chang, C. J. *et al.*, 2024]. It was concluded that although the Omicron variant had higher severity, it was not independently associated with higher 28-day mortality [Chang, C. J. *et al.*, 2024]. The study is elegant, but some ambiguities should be clarified.

The first point is that the outcome of a SARS-CoV-2 infection strongly depends on the severity of the disease [Priya, S. *et al.*, 2021]. This refers not only to lung involvement, but also to whether organs other than the lungs were affected by the infection. Of particular interest is how many of the included patients had central nervous system (CNS) involvement in the SARS-CoV-2 infection. Since SARS-CoV-2 infection can be complicated not only by ischemic stroke but also by a number of CNS disorders that strongly influence the outcome of the infection [Gao, Y. *et al.*, 2021], it is imperative to report how many of the patients had cerebral hemorrhage, venous sinus thrombosis, immune or infectious meningitis/encephalitis, acute disseminated encephalomyelitis (ADEM), acute hemorrhagic necrotizing encephalopathy (AHNE), AHLE, ANE, PRES, cerebral vasculitis or reversible cerebral vasoconstriction syndrome. As the majority of patients included were sedated

and intubated, it may have been difficult to diagnose these CNS disorders. Therefore, it is recommended that SARS-CoV-2 infected patients undergo a prospective neurological examination in the ICU to avoid overlooking silent or subclinical neurological complications of the infection.

The second point is that the included patients were only screened for some specific comorbidities, as indicated in Table 1 [Chang, C. J. *et al.*, 2024]. However, there are many other comorbidities that may influence the outcome of SARS-CoV-2 infection. These other comorbidities include genetic disorders, endocrine disorders, immunologic disorders, and cerebral disorders other than stroke. Unless all of these comorbidities are considered and excluded as factors influencing the outcome of infection, the reported results are not reliable. For example, immunological diseases are known to strongly influence the course and outcome of SARS-CoV-2 infection [Tan, E. H. *et al.*, 2021].

The third point is that the outcome of SARS-CoV-2 infections may also depend on whether an infected patient has been previously vaccinated or not [Hrycek, E. *et al.*, 2024]. Since only one patient in the alpha variant group but 106 patients in the omicron variant group were vaccinated at the time of admission to the ICU, a comparison of the results between these two groups is not reliable.

The fourth point is that the current medication that the included patients were regularly taking before admission to the ICU was not reported [Chang, C. J. *et al.*, 2024]. Since several medications can strongly influence the course and outcome of a SARS-CoV-2 infection [Larrosa-García, M. *et al.*, 2024], it would have been imperative to include the current medication in the assessment. Patients with polypharmacy prior to admission are most likely to have worse outcomes than patients who were either taking no medication or only one or a few medications [Chang, C. J. *et al.*, 2024].

The fifth point is that it was not stated whether all patients admitted during the alpha-variant or the omicron-variant period were actually tested for the presence of the alpha- or omicron-variant. If this was not the case, the comparison between the two groups may not be reliable, as some patients from one group may in fact belong to the other group and vice versa.

In summary, before final conclusions can be drawn about the factors that influence the outcome of a SARS-CoV-2 infection, all influencing factors must be included in the assessment.

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