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Letter to the Editor

COVID-19 can be Multisymptomatic and Multisystemic, which Implies a Dynamic Development and Regression of Symptoms

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Letter to the Editor

We were interested to read the article by Wang *et al*. on a retrospective cohort study of the characteristics and evolution of symptoms in 486 patients with subclinical or mildly manifesting SARS-CoV-2 infection (SC2I) [1]. It concluded that SC2I with the Omicron variant causes an accumulation of symptoms, most of which resolve within 7-10 days, and that omicron SC2I symptoms are associated with a prolonged duration of illness and prolonged shedding of the virus [1]. The study is convincing, but some points should be discussed.

The first problem is the retrospective design of the study [1]. Retrospective designs have the disadvantage that some data may be missing, the accuracy of the data cannot be easily verified, desired missing or new data cannot be added and references to specific studies are often not traceable. We should therefore know how many patients had to be excluded due to missing data, how many were included despite missing data and to what extent this influenced the results. Were all examinations the same for all included patients? Were the doctors who performed the examinations the same?

The second problem is the discrepancy between the aim of the study to describe the characteristics and development of symptoms and the inclusion of asymptomatic cases [1]. Patients without symptoms cannot be followed for symptoms and should therefore be excluded from the analysis as they cannot contribute to the aims of the study and contradict the intention of the study.

The third point is that it was not taken into account that SC2I can also present with extrapulmonary manifestations at the onset of infection [2]. Knowing this is crucial as these extrapulmonary symptoms may develop later with the progression of the disease classic respiratory symptoms. Extrapulmonary symptoms can easily be overlooked or misinterpreted as they are not usually associated with SC2I. Among the extrapulmonary symptoms, those related to cardiac or cerebral involvement must be given special consideration, as they can significantly determine the outcome and prognosis of the disease. Therefore, it must be made transparent in how many patients COVID-19 did not start in the lungs but in other organs and these extrapulmonary symptoms should be included in the analysis.

The fourth point is that almost a quarter of the included patients had headaches, but the causes of the headaches were not specified [1]. It is not mentioned whether the headache was further investigated by neurologic examination, including clinical neurologic examination, imaging studies, electrophysiologic studies, blood and cerebrospinal fluid studies, and biochemical studies.

The fifth point is that pediatric patients and adults were mixed [1]. Since the spectrum of symptoms may vary between these two groups [3], it is recommended to either exclude pediatric patients from the analysis or to analyze and compare the two age groups separately.

The sixth point is that only one third of the patients in the symptomatic group were female [1]. As the symptoms of SC2I can differ greatly between genders [4], it is conceivable that the results are misleading due to this gender bias.

The seventh point is that it is not reported why the patients had to be hospitalized, although none of the included patients had moderate or severe COVID-19 infection [1].

A final point is that it was only assumed that all included patients were infected with the Omicron variant, but no specific tests were performed to support this assumption. As symptoms can vary by strain, some of the results could be misleading.

Overall, this interesting study has significant limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and support the message of the study. COVID-19 is usually

multisymptomatic and multisystemic, implying a dynamic change in symptoms with progression and regression of the infection.

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