Int. j. adv. multidisc. res. stud. 2024; 4(6):1190-1191

Received: 02-12-2024
Accepted: 12-12-2024

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Commentary

The Clustering of Long-COVID Patients Requires a Host of Prerequisites to be Met

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DOI: https://doi.org/10.62225/2583049X.2024.4.6.3578
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We read with interest the article by Kemajou *et al*. on a study which investigated what clusters of symptoms and signs can be extracted in patients with multisystemic long-COVID syndrome and which correlated these results with a previously developed clinical classification in order to adapt treatment strategies for patients to the specific needs of these subgroups [1]. After applying a two-stage multidimensional exploratory analysis on a retrospective cohort of 206 patients with long-term COVID, which included a factorial analysis of mixed (demographic, clinical, biological) data and a hierarchical clustering post-component analysis, three clinical subtypes of long-term COVID patients were extracted - those with long, persistent and post-viral long-term COVID syndrome [1]. The biological data did not provide sufficient differentiation between the clusters, suggesting that the classification of patients with long-term COVID should be based on their clinical presentation [1]. The study is interesting, but some points should be discussed.

The first point is that no distinction was made between the symptoms included in the analysis which had appeared during the acute SARS-CoV-2 infection and persisted for more than 3 months without transient resolution, and those (either new or previous symptoms) which only developed after the acute symptoms had subsided and appeared after a certain latency period [1]. This point is crucial, as new symptoms may be due to causes other than SARS-CoV-2 infection, and it is therefore difficult to establish a causal link between the acute infection and these new symptoms. A causal link is possible of course, but may depend on the latency period between the resolution of the acute infection and the appearance of the new symptoms. And be less likely if this latency period is longer than three months, for example.

The second point is that the results of the cluster analysis strongly depend on nature and number of symptoms included in the analysis. This in turn will have depended on the care with which the patients were examined and the decision to attribute symptoms to long-COVID and or to other intercurrent diseases.

The third point is that the number of female and male patients included in the analysis was not equal. Since women may complain of different symptoms than men, it would have been important to ensure that the group sizes were equal between men and women. The fact that 76% of the patients included were female could bias the results. This should be addressed in the statistical analysis.

The fourth point is that the total number of patients included was small [1]. It is therefore recommended that this analysis be repeated in the form of a multicenter analysis with much larger cohorts.

The fifth point is that the cohort analyzed is a retrospective cohort [1]. Therefore, it needs to be made transparent how many of the included patients were found to have data missing and to what extent this influenced the results. A further disadvantage to retrospective data is that new data can no longer be added.

The sixth point is that symptoms may also depend on the particular strain of SARS-CoV-2 that caused the long COVID. It is known from acute SARS-CoV-2 infections that symptoms strongly depend on the virus strain, as shown in previous studies [2, 3]. Differences in the number and type of symptoms may be due to differences in virulence or vaccination protection [2].

The seventh point is that patients with probable SARS-CoV-2 infection were included in the study [1]. Since probable COVID-19 infection can be false positive, these patients should have been excluded from the analysis.

The eighth point refers to the statement that clinical subgroups of long-term COVID appear to be associated with different pathophysiological mechanisms or genetic predisposition. This statement is speculative and needs to be substantiated by appropriate studies.

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. Before using sophisticated statistical tools to form subgroups of patients with long COVID, various methodological requirements need to be met.

Keywords: Post-COVID, Long-COVID, SARS-CoV-2 Infection, Cluster Analysis, Clinical Presentation

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