Review of: "Proposal to Explain the Cause of Long COVID Based on the Concept of Host Factor Variants"

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Potential competing interests: No potential competing interests to declare.

The aim of this manuscript is to investigate the association of cellular variants, MHC polymorphism, and the role of APCs in the cause of long COVID, focusing on the roles of Tc and Th cells in relation to viral persistence in APCs.

This manuscript shows rich content, providing deep insight for some works: the study is within the journal's scope, and I found it to be well-written, providing sufficient information. Even if the manuscript provides an organic overview, with a densely organized structure and based on well-synthetized evidence, there are some suggestions necessary to make the article complete and fully readable. For these reasons, the manuscript requires major changes.

Please find below an enumerated list of comments on my review of the manuscript:

MINOR POINTS:

Please use the past simple in the abstract section.

Please, if possible, provide a list of the abbreviations mentioned in this manuscript.

MAJOR POINTS:

INTRODUCTION:

Coronavirus disease 2019 (COVID-19) is a global health threat, commonly spread through respiratory droplets and aerosol transmission. The causative agent of COVID-19, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an enveloped positive single-stranded RNA virus, whose infection may affect the lungs primarily, leading to respiratory failure, but simultaneously involves several organs, from kidneys to the heart, blood vessels, liver, pancreas, and immune system, with multiple extra-pulmonary consequences (see, for reference: https://doi.org/10.3390/pathogens11080867). This is the major concern of this manuscript: the manuscript may benefit from providing, in this introductory section, a concise and complete background about the most important genetic, molecular, and also clinical features of SARS-CoV-2 infection.

Cellular molecules and viral receptors/co-receptors are associated with viral infections for viral attachment and penetration into the target cells. MHC molecules play a role in inducing an adaptive immune response that increases the efficiency of virus clearance, and their polymorphism could also explain how the virus generally persists as a chronic infection in both animals and humans (see, for reference: Arora J, Pierini F, McLaren PJ, Carrington M, Fellay J, Lenz TL. HLA

Heterozygote Advantage against HIV-1 Is Driven by Quantitative and Qualitative Differences in HLA Allele-Specific Peptide Presentation. Mol Biol Evol. 2020;37(3):639-50).

The main topic is interesting and certainly of great clinical impact. As regards the originality and strengths of this manuscript, this is a significant contribution to the ongoing research on this topic, as it extends the research field on the association of cellular variants, MHC polymorphism, and the role of APCs in the cause of long COVID, focusing on the roles of Tc and Th cells in relation to viral persistence in APCs. Overall, the contents are rich, and the authors also give their deep insight for some works.

The conclusion of this manuscript is perfectly in line with the main purpose of the paper: the authors have designed and conducted the study properly. As regards the conclusions, they are well-written and present an adequate balance between the description of previous findings and the results presented by the authors.

Finally, this manuscript also shows a basic structure, properly divided, and looks very informative on this topic. Furthermore, figures and tables are complete, organized in an organic manner, and easy to read.

In conclusion, this manuscript is densely presented and well organized, based on well-synthesized evidence. The authors were lucid in their style of writing, making it easy to read and understand the message portrayed in the manuscript. Besides, the methodological design was appropriately implemented within the study. However, many of the topics are very concisely covered. This manuscript provided a comprehensive analysis of current knowledge in this field. Moreover, this research has futuristic importance and could be potential for future research. However, major concerns with this manuscript are in the introductory section: for these reasons, I have major comments for this section, for improvement before acceptance for publication. The article is accurate and provides relevant information on the topic, and I have some major points to make that may help to improve the quality of the current manuscript and maximize its scientific impact. I would accept this manuscript if the comments are addressed properly.