Rapid Reviews COVID-19

Review 3: "Cytotoxic lymphocytes are dysregulated in multisystem inflammatory syndrome in children"

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RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

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Review:

Beckman et al. describe a transcriptional signature of MIS-C able to highlight some concordance with Kawasaki disease but not other autoimmune diseases and to link its pathogenesis to genes involved in downregulation of exhausted CD8+T cells and CD56dimCD57+ Nk cells.

This intriguing approach could potentially shed light on the characteristics of SARs-CoV2 infection and MIS-C pathogenesis. Unfortunately, the cohort consists of immunocompromised COVID-19 patients and does not permit to establish any strong conclusions.

I will address a few key evaluation questions in my review:

· Does the manuscript confirm previous work or refute the current understanding? Do the findings contribute to broader research understandings? Can the evidence and arguments presented support advancement of COVID-19 understanding within society?

The degree of novelty can be considered here but is not the main driver of this indicator.

The work is in line with the emerging literature on the pathogenesis characteristics of MIS-C which although sharing some similarities with other inflammatory condition is basically different in terms of proteomic/cellular profile, genetic signatures, etc.

· How well does the manuscript position the work within the current literature/understanding? Does the manuscript cite current literature and discuss limitations? Is it steeped in reality with the potential to impact the implementation of policy and programs? Would you recommend this manuscript for publishing?

Authors do not clearly describe the serious limitations of their work. Labs methods are robust but the cohort composition has serious bias. I would suggest to enlarge the COVID-19 cohort. On the other hand

comparison of enrolled MIS-C and KD DEGs from publicly available whole blood transcriptomic data are trustworthy. Authors should consider to write the paper focusing only on these data.

· Is there clarity regarding the recommended actions that result from the findings? Is the work clearly and accurately presented. That is, is it well-structured and well-written, with an ability to speak to key audiences?

Given the complexity of biological themes treated the paper is not easy to read.

· Do authors pay attention to ethics, diversity, and inclusion? Have the authors adequately discussed ethical concerns? When appropriate, have they been inclusive and taken into account equity, rights, and diversity?

There are no ethical concerns.

Should this preprint be published?

I would not recommend the manuscript for publication in RR:C19 Journal unless there are major revisions.

The main limitation of such works resides in COVID-19 cohort characteristics. Considering that 6 out of 7 patients were chronically immunocompromised, their transcriptomic profile is plausibly altered and this has ineluctable consequences on the results of the paper. The cohort should be enlarged in order to consider children with SARS-Cov2 infection without comorbidities.

The recruitment of age matched HCs was impractical for ethical reasons and the authors took age in account for variation in gene expression. The same cannot be said for immunocompromised patients. As a consequence of these all the claims deriving from the comparison of MIS-C and COVID19 are not reliable.

The pediatric COVID-19 signature is not reliable because the therapy influences the patho-physiolocal cell activity and the transcriptomic profile.

Authors should focus only on MIS-C and other inflammatory status.

Although “DE analyses permit the broad detection of genes and pathways associated with disease states”, the inconsistency of comparison between MIS-C and immunocompromised COVID-19 patients does not permit the establishment of any strong conclusion.