

## Peer Review File

Article information: <http://dx.doi.org/10.21037/jxym-20-105>

Comment 1: In the third paragraph of Mechanism of Cardiovascular Injury, it is mentioned that cytokine release syndrome (CRS) may cause myocardial injury. We have already known that severe infections may cause cytokine release syndrome (CRS), What is the difference?

Reply 1: Though some have used the term COVID-19 related cytokine release syndrome, the sepsis like “cytokine storm” in COVID-19 is different from typical cases of CRS after chimeric antigen receptor T-cell (CAR-T) therapy in that the levels of cytokines such as IFN-gamma is lower in COVID-19 patients. Severe COVID-19 also differs from CRS in that IL-6 receptor blocking with Tocilizumab does not seem to work given the recently published trial result.

Comment 2. In the fourth paragraph of The Mechanism of Cardiovascular injury, it is mentioned that COVID-19 patients have a high incidence of thrombosis. What do you think is the reason for thromboembolism? Is there an autoimmune mechanism in addition to vascular endothelial injury and dysfunction?

Reply 2: Immune response also have an important role in endothelial activation and dysfunction and have an important role in cause thrombosis. We have added information on the inflammatory response causing hypercoagulability and updated the mechanisms of endothelial injury. Thank you so much for the suggestion.

Comment 3: The discussion regarding the various aspects of the cardiovascular impact of COVID-19 is limited. The article referred to “focal myocarditis has been reported on autopsies in SARS patients”; however, there is lack of detailed coverage of the incidence, management of myocarditis in COVID-19. The issue of myocarditis is important, and needs to be fully explained and delineated; while myocarditis is an important complication to consider, it is not one of the most common manifestations in COVID-19.

Reply 3: Thanks for the comment. The true incidence of myocarditis in COVID-19 is unknown but based on the limited number of reported cases, we agree that myocarditis should be relatively rare. We have updated this in our manuscript. With the low number of reported cases, little evidence exists to guide us on the management. And because it is so rare, it may not deserve much discussion.

Comment 4: The authors refer to ACE2 has a cellular receptor; strictly, it is not correct to refer to ACE2 as a receptor; SARS-CoV-2 uses membrane-bound form of ACE2 for entry into host cells; however, ACE2 is found in many other cellular types.

Reply 4: For the human body, the ACE2 is not a receptor. But in the process of receptor-mediated viral entry into cells, ACE2 is correctly described as the cell entry receptor for SARS-CoV-2. This is used in many articles in this field and we believe this use is appropriate. However, we have added more explanation on what is ACE2 and its physiologic function to illustrate the possible contribution of ACE2 downregulation to organ injuries.

Comment 5: There are many ongoing studies regarding medication therapies in COVID-19, including those related to hydroxychloroquine, remdesivir, etc. There are many types of vaccines under development as well. The current discussion about medication therapies in COVID-19 is very limited.

Reply 5: We have added discussion about recently published trials on dexamethasone and tocilizumab and added the cardiac safety profile of remdesivir and tocilizumab. Thanks for the comment.

Comment 6: A Kawasaki-like disease has also been reported in COVID-19 in children. This is important, and needs to be reported.

Reply 6: We have already included report of multisystem inflammatory syndrome but we updated our manuscript to mention it's a Kawasaki-like disease. Due to recent reports of such cases in adults, we have updated our manuscript to reflect that too.

Comment 7: Only one figure is presented for this article. This does not fully cover the complexities of the cardiovascular manifestations of COVID-19.

Reply 7: We have updated our figure to reflect the more complicated mechanisms of cardiovascular injury and added therapeutic points and added another diagram further explaining the mechanisms.

Comment 8: Language: Abstract – dysregulate immune response should be changed to dysregulation of the immune response

Reply 8: Thanks for the corrections. Our apologies for the grammar error.

Comment 9: Abbreviations: the first time an abbreviation is used, it should be spelt out fully, e.g. Acute Respiratory Distress Syndrome (ARDS)

Reply 9: We have updated our manuscript to make sure abbreviations are spelt out the first time used.