Author Response 1

Reviewer: 1
The narrative review by Pelaia et al. focuses on the pathological mechanisms and potential therapeutic targets in the setting of the COVID-19 cytokine storm.
1. The abstract should be a summary of the salient features of the manuscript. It should be a concise summary of the main concepts discussed in the paper. The readers should be able to get the main information about the manuscript in the abstract itself. The abstract needs to be re-written.

The abstract has been completely rewritten according to this comment.

2. The manuscript should be edited for scientific writing, which aims at providing an equally rigorous amount of information with brevity. Unnecessary jargon, which does not add to the presentation of the point of view, needs to be avoided.

The revised manuscript has been edited according to this comment, thus being now characterized by a more concise scientific style, which avoids redundancy.

3. The manuscript should include subheadings within the domain of pathogenic mechanisms of cytokine storm in COVID-19. Some suggestions would go like
Mechanism of cytokine storm
Lymphopenia and lymphocytes exhaustion- A consequence of Impaired Adaptive immunity
Hypercytokinemia in COVID-19
IL-6 plays a central role in the COVID-19 Cytokine storm (An extra figure to illustrate this point would be needed)
Role of other cytokines in the COVID-19 Cytokine storm
Diagnosis of Cytokine storm
With in the domain of therapeutic implications, some subheadings can go like ‘ IL-6 inhibitors’
JAK inhibitors Steroids
Hydroxychloroquine, azithromycin

The revised manuscript has been organized according to these comments, thus being subdivided on the basis of the above subheadings.

4. Comment regarding Line 41-49, Page 3. The dysregulation and impairment in adaptive immunity spur the cytokine storm. However, the damage is likely mediated by both adaptive and innate immunity, as is evident from numerous elevated cytokines in severe COVID-19.

The revised manuscript has been changed according to this comment.

5. The introduction on Page 3 starts with non-specific general comments. I suggest to wrap it in a few lines and delve into the topic of cytokine storm with salient facts before the reader loses interest. A suggestion to start with would look like
‘ Cytokine storm, or historically labeled as secondary HLH, is a complication most commonly encountered in viral infections. Influenza, EBV, CMV, and the most recent COVID-19 have been implicated in the triggering of the cytokine storm. The cytokine storm may provide the possible mechanism on why certain sub-populations are more likely to die of COVID-19 than others'. Please provide appropriate references.

The revised manuscript has been changed according to this comment, and appropriate references have been provided.

6. Line 57-60, Page 3, Line 1-6, Page 4. The references enlisted are not related to COVID-19, and they do not provide a beyond doubt proof that the senescence of the immune system is the risk factor for COVID-19. While it may well be true, we would need experimental studies to prove that. It may be written as
'Besides the comorbidities involved, the senescence of the immune system plays a role in the worst outcomes observed in the elderly.'

The revised manuscript has been changed according to this comment.

7. Line 17-25. The point has already been discussed above. Suggest avoiding redundancy.

The revised manuscript has been changed according to this comment, thus avoiding redundancy.

8. Line 25-33 is out of context. The jump from the senescence of the immune system to targeting the cytokine storm for therapeutics is out of context.

The revised manuscript has been changed according to this comment.

9. Line 30-38 Page 6, the reference needs to be provided.

The reference has been provided in the revised manuscript.

10. Line 3, Page 7, reference 3 is a letter to the editor. Please avoid using secondary evidence to support a basic idea. It is preferable to credit the original experimental studies to illustrate a point. Please make sure of this on all the other references.

The manuscript has been changed according to this comment, and the revised text has been checked in order to provide appropriate references.

11. Line 34-58 The IL 1 beta is discussed as a stimulator of neutrophil function. Then the manuscript talks about IL-6, and then it talks about IL-8, GM-CSF, andIP10.
The organization of the manuscripts describing the cytokines is disorganized. Suggest that start with important interleukins such as IL-6 (supporting with a figure that needs to be added) and then talk about other important interleukins in a group fashion. Interleukins with similar functions need to be clumped together. If there is any unique function related to the cytokine that should be mentioned separately. The manuscript lacks the bigger picture of how all the interleukins connect the dots. Describing them one by one does not help develop a bigger picture.

The revised manuscript has been reorganized according to this comment and to the above suggested subheadings.

12 Line 16-17, Page 18. It should be written as Critically-ill or critically ill. Please proof-read the manuscript for grammatical errors.

The manuscript has been changed according to this comment, and the revised text has been carefully checked in order to detect and eventually correct grammatical errors.

13 Line 14-20 summarizes the cytokine events. Although it does mention the salient features in the cytokine storm, it lacks the stepwise organizational approach of summarizing it.

The manuscript has been changed according to this comment, and the revised text has been reorganized according to a more rational, stepwise approach.

14. Before the therapeutic implications are discussed, the article should address how to diagnose cytokine storm as a clinician. To fulfill the criteria, the H score has been devised, which uses ferritin value of greater than 2000 by which time many patients have already died. Based on the studies done on COVID-19, the authors should provide a fair idea when a clinician should be comfortably able to diagnose cytokine storm clinically and think about using therapeutic interventions.

The manuscript has been changed according to this comment, and the revised text now includes a new paragraph regarding the diagnosis of cytokine storm.

15. Page 11, Page 12 Therapeutic implications of cytokine storm: The article starts with medications such as favipiravir, lopinavir-ritonavir, which is out of context. They work through a separate mechanism as antivirals and have little to do with cytokine storm. Regarding hydroxychloroquine, the piece that mentions the role of cytokines should be kept.

The manuscript has been revised according to this comment, thus deleting antiviral drugs.

16. Start with the commonly used drugs. Tocilizumab is most commonly used; after that can talk about JAK inhibitors and steroids. Discuss the pros and cons of tocilizumab why it may or may not work in a clinical setting. The high viral load which drives the cytokine storm would be unsuppressed by the use of tocilizumab is the fear of the scientific community.

The manuscript has been changed on the basis of this comment, and the revised text has been reorganized accordingly.

17. Line 50-58, Page 14 Provide numbers on how anakinra helped in survival in septic patients. Please provide the right context, on how anakinra was used in which category of septic patients (bacterial or viral).

The manuscript has been changed according to this comment, and the revised text now includes the above mentioned numbers and the context referring to the typology of septic patients undergoing evaluation.

18. Line 12-14, Page 15, needs to be reworded.

These lines have been reworded in the revised manuscript.

18. Line 20-28, 33-42 Page 15. Observational studies on steroids with no control should not be used to provide any conclusion and should be clearly stated in the review.

The revised manuscript has been changed according to this comment.

19. Page 15, 16 Conclusion does not provide any insight into the cytokine storm or therapeutic implications.

The revised manuscript has been changed according to this comment; therefore, conclusion has been completely rewritten.

Reviewer: 2

Comments to the Author
This work describes in an adequate way the cytokine storm after Sars-CoV-2 infection that leads to COVID-19. In addition, it concludes with the possible available treatments that are being used already to combat other viral diseases and could be tested for COVID-19 as well.
The paper can be published after minor revisions and rewriting of the conclusions section in an appropriate way that discuss the main findings of the work. Also, please replace the term COVID-19 with the term SARS-CoV-2 when you discuss about the virus and not the disease.

In the revised manuscript, conclusion has been completely rewritten according to this comment. Moreover, the term COVID-19 has been replaced by the term SARS-CoV-2 every time the virus and not the disease is discussed.

Therefore, on behalf of all the authors who contributed to revise the manuscript and approved the final version, I would like to thank the Editor and the Reviewers for having carefully edited and reviewed our paper, thus suggesting those changes which have significantly improved its overall quality.