

Dear Dr. Jia-Ping Yan,

Please find attached a revised version of our manuscript "Diabetes and COVID-19: Role of insulin resistance as a risk factor for COVID-19 severity". We are grateful to all the reviewers for their insightful comments and appreciate the time and effort in providing us with valuable feedback. We have considered most of the suggestions provided by the reviewers and incorporated the changes in the manuscript. We have also since collaborated with Dr Rupa Ahluwalia, diabetologist based at Norwich, United Kingdom to assist with further modifications, restructuring and general revision of the manuscript especially in line with the reviewers' comments.

Once again thank you for considering our manuscript for your journal and we certainly look forward to hearing from you.

Regards

Dr Charitha Gangadharan,  
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Kindly find the point-by point response to reviewers' comments and queries

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** My recommendation for this MS is a major revision. This is an interesting review manuscript, which illuminated insulin resistance as a possible pathogenesis underpinning the severity of symptoms in patients with COVID-19. The authors reviewed the literature to link the mechanisms (particularly inflammatory pathways leading to thromboembolism) of insulin resistance associated with COVID-19 severity. This review concluded insulin resistance likely contributes to the severe symptoms of COVID-19. However, there are some concerns listed below.

**Comment 1:** The authors should provide summary tables: 1) For the clinical and biochemical markers of insulin resistance for evaluating diabetes status in patients with COVID-19, 2) The mechanisms associated with insulin resistance, for instance, insulin and vascular inflammation, and the factors associated with portal circulation, RAS system and inflammation reflecting special emphasis in COVID-19.

**Response:** Thank you for the suggestion, we have revised the manuscript to emphasise on this point. However, there is a scarcity of information on the relationship between insulin resistance and COVID-19. The revised manuscript includes a table listing a few studies that assessed IR using surrogate markers and related it to the severity of COVID-19. An additional figure depicting the physiological pathways linking COVID-19 to underlying insulin resistance is included in the manuscript, along with potential clinical and biochemical markers.

**Comment 2:** A figure legend in Figure 1 is missing. Words in Figure 1 are also hard to read. Increase the fonts.

**Response:** Thank you for pointing out, the figure legend is included with increased font size

**Comment 3:** In the introduction section the author mentioned "Epidemiological data has revealed that the fatality rate is higher in older population with common comorbidities". Please elaborate on the common comorbidities manifested in the older population.

**Response:** Thank you for the suggestion, in the revised manuscript common comorbidities manifested in older population is elaborated

**Comment 4:** Check and use the name of "COVID-19" across the manuscript (e.g., COVID19, COIVD19).

**Response:** All errors are corrected with consistency maintained in the revised manuscript

**Comment 5:** Define the gene names and then use the abbreviations (e.g., IL-2, IL-7, IL-10, G-CSF, TNF, MCP1).

**Response:** All errors are corrected with gene names and abbreviations in the revised manuscript

**Comment 6:** There are several grammatical errors.

**Response:** Thank you for the suggestion. The manuscript is restructured with the help of a Diabetologist from England and is an author in the manuscript.

**Comment 7:** The title does not represent the model and conclusion:

**Response:** Thank you for the suggestion, the title is changed

Reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The authors showed an important and advanced topic relating diabetes and Covid-19.

**Comment 1:** The authors have to support their study by meta-analysis. One figure in the present version is not enough to explain the review concept.

**Response:** Additional figures and tables included to explain the review concept

**Comment 2:** The authors have to revise their manuscript for sentence structure and language grammar e.g., page 8 has a lot of language mistakes. In addition, the authors have to revise their references specially reference numbers 3, 4, 25 & 28.

**Response:** Manuscript is restructured with the help of a Diabetologist from England and is an author in the manuscript. The references are revised and corrected.

Reviewer #3:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

**Comment 1:** This is a well-written manuscript with an important topic. I would like to suggest you to elaborate in the end of the manuscript how to improve this line of research.

**Response:** A section on future perspectives is now included in the manuscript.

Reviewer #4:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:**

**Comment 1:** The effect and mechanism of COVID-19 influences the  $\beta$  - cell function and insulin resistance should be illustrated with pictures .The effects of covid-19 on the function of  $\beta$  - cells, including the direct effects, the specific mechanisms of blood supply reduction and the signal pathways which involved should be listed.

**Response:** Explained in the revised version of manuscript

**Comment 2:** At last, future research hotspots and directions should be described in detail

**Response:** A section on future perspectives is now included in the manuscript