

24th June 2023

Professor Hua-Dong Wang, MD, PhD,
Editor-in-chief,
World Journal of Critical Care Medicine.

Sub: Submission of revised article addressing reviewers' comments

Dear Prof. Hua-Dong Wang,

Thank you for the opportunity to revise and resubmit the article titled, *"Delayed inflammatory pulmonary syndrome – a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection?"* for consideration by the World Journal of Critical Care Medicine, and for the detailed review that we received.

The comments raised by the queries have helped us focus on areas which needed further clarification and enriched the message that we sought to convey through this submission. Attached is an updated copy of the manuscript, with the changes from the previous version highlighted in red. The point-wise response to the reviewers' queries have been attached as a separate file, titled, "Response to reviewer queries". The tables and figures remain unchanged.

Thank you for your time and consideration of our article.

With regards,

Dr John Victor Peter,
Senior Professor,
Department of Critical Care Medicine,
Christian Medical College,
Vellore, India.

Response to reviewer's comments

Number	Comment	Response
Reviewer 1 comments	It was pleasure to read this well written article. The objective is clear and grammar is also okay. However, there are few minor points, which should be addressed prior to publications In the page 4, authors have mentioned "This presentation does not fit in to the definition of Multisystem Inflammatory Syndrome Adults". This sentence seems unclear. Please consider rephrasing Conclusion seems very short and less information. Consider it rephrasing.	1. Thank you for your positive comments on our submission and for the opportunity to clarify the queries raised. We have rephrased the statement mentioned here and expanded upon it, as follows, "This presentation does not fit in to the definition of Multisystem Inflammatory Syndrome Adults, owing to the predominance of pulmonary symptoms and the notable absence of cardiac, gastrointestinal, and mucocutaneous manifestations". 2. We have also expanded the conclusion section in the abstract as well the main body of the text as follows: a. Abstract conclusion: "This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation appears to contrast the well described Multisystem Inflammatory Syndrome – Adults (MIS-A) by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like c-reactive protein, interleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection." b. Main conclusion: "Delayed inflammatory pulmonary syndrome is a serious and life-threatening complication of long COVID, occurring commonly in the fourth week of illness and characterised by a predominance of pulmonary hyperinflammation in the absence of secondary infections or fluid overload or extrapulmonary organ system involvement. This entity can be considered in the differential diagnoses

		in a patient with delayed deterioration in pulmonary function, after a period of initial improvement. The diagnosis is supported by raised inflammatory markers. Treatment with immunomodulation (systemic glucocorticoids or intravenous immunoglobulin) can be considered and a good response expected.”
Reviewer 2 comments:	Is the word pathognomic on page 11, line 11, wrong as pathognomonic? The article is well written with concept and definitely about delayed respiratory deterioration in critically ill COVID-19 for physicians and there is good answer as to how to deal with this situation. The article points out that delayed respiratory deterioration in critically ill COVID-19 do not fit in to the definition of Multisystem Inflammatory Syndrome Adults, I feel the article needs to be supplemented and revised. The article said that respiratory failure is not explained by left atrial hypertension or cardiac failure, and I suggest the paper should have the results of laboratory such as left atrial pressure, ventricular ejection fraction and natriuretic peptide.	1. Thank you for the opportunity to refine our work and clarify the points raised. We have replaced the word, ‘pathognomic’, with ‘pathognomonic’ in the section mentioned. 2. We have reviewed our hospital records and have added the following statement to the ‘results’ section to clarify that every effort was taken to rule out a cardiac cause for respiratory deterioration: “All five patients underwent point of care echocardiography for assessment of left ventricular function. There was no evidence of left ventricular dysfunction; in addition, 3 of the 5 patients in whom an NT pro-BNP was done had values of 449, 132 and 146 pg/mL (reference range: up to 125 pg/mL).”