

Xue-Jiao Wang
Science Editor
World Journal of Gastroenterology

Re: Manuscript ID: 37864 – “Review Article: Update on current and emergent data on Hepatopulmonary Syndrome”

Athens, 8 February 2018

Dear Dr Xue-Jiao Wang,

Thank you for considering our manuscript for publication in *World Journal of Gastroenterology*. We also thank the reviewers for their thoughtful comments, which have been extremely helpful for the final improvement of our manuscript. Please find below the changes that we have made to our initial submission in response to the reviewers’ recommendations.

Reviewer # 1

Point 1. My only suggestion is to check carefully for spelling or grammar mistakes to make the manuscript perfectly readable.

Thank you for this recommendation. We carefully revised the manuscript and corrected spelling and grammar mistakes extensively. We also replaced some words or phrases with more appropriate terms and rephrased some sentences so that the text reads now much better. The changes are highlighted in the updated version of our manuscript.

i.e.

..obvious reason of for pulmonary disease..

.. leading to a wide range in prevalence of HPS of HPS prevalence rates.

..Gravitational pulmonary blood flow redistribution leads ~~too~~ to overperfusion of these lower lung zones..

... may act as a ~~vasodilator~~ vasodilator in HPS patients.

.. The role of specific chemokines, ~~like~~ such as the circulating chemokine...

.. It is the result of the decrease in partial pressure of arterial oxygen ~~decreases by~~ of 5% or more or ~~by~~ of 4 mmHg from supine to upright position..

Reviewer # 2

Point 1. In this regard, a more critical view of studies involving a very reduced number of patients might provide a more realistic vision. Although mention to these data is relevant it is also truth that there is not strong statistical evidence to support any conclusion.

Thank you for this comment. We totally agree. We had already mentioned in the original version this limitation regarding diagnosis, therapy etc. In the manuscript we underline the need for further studies with large cohorts and standardized protocols for a more efficient assessment of the several aspects off hepatopulmonary syndrome. Furthermore, in response to your comment and in order to provide a clear message, we rephrased the final paragraph of treatment section, where many studies with small samples were cited.

~~The aforementioned data underline for one more time the complexity of the pathogenetic pathways that contribute in the development of HPS in liver cirrhosis. , so that a global approach is required in order to achieve beneficial therapeutic outcomes. Clearly, their poor outcomes as well as the small number of patients enrolled, make the aforementioned studies insufficient to suggest effective therapeutic options for the management of HPS.~~

However, these data underline the complexity of pathogenetic interactions in HPS and outline potential areas of interest and future research.

Point 2. References must be carefully revised. The publication year is missing in some cases (65, 69, 74, 75...)

Thank you again for this comment. The references were revised carefully and corrected according to the journal's reference style recommendations. The publication year was added in the following references: 45, 65, 69, 74, 75, 112.

We hope that the above mentioned changes satisfactorily address the reviewers' comments and that our revised manuscript will now be approved for publication in your journal.

Sincerely,

Evangelos Cholongitas, MD, MSc, PhD