

ANSWERING REVIEWERS:

Dear editor,

I would like to thank to editors and reviewers for the cautiously analysis of the manuscript. I believe that the comment made by reviewer have enabled an improvement in manuscript.

Please, find below a response point-by-point to reviewer.

Sincerely,

Anderson Brito-Azevedo.

RESPONSE POINT-BY-POINT:

REVIEWER COMMENTS:

Nonselective beta blockers (NSBB) have been associated with a reduced survival in patients with RA probably due to an increased incidence of PICD, suggesting a potential unfavorable mechanism linked with the worsening of central hemodynamics. However, these data were in contrast with those reported by several studies, in which NSBB were associated with lower rate of liver decompensation, higher transplant-free survival, and a reduced risk of developing spontaneous bacterial peritonitis. The deleterious effect in patients with refractory ascites in a few studies led to a U-turn in clinical practice, with some in the hepatology community withdrawing their usage in patients with advanced cirrhosis. This also led to the “window hypothesis” suggesting there may be only be a finite time frame when NSBBs have a beneficial effect in portal hypertension. In the present review the authors revised the state of the art of this subject. However, it lacks recent studies about this topic such as: Ferrarese A, Tikhonoff V, Casiglia E, Angeli P, Fasolato S, Faggian D, Zanetto A, Germani G, Russo FP, Burra P, Senzolo M. Hemodynamic Evaluation of Nonselective β -

Blockers in Patients with Cirrhosis and Refractory Ascites. *Gastroenterol Res Pract.* 2018 May 9;2018:4098210, and recent reviews: Rajoriya N, Tripathi D. Non-selective beta-blockers in cirrhosis: Current concepts and controversies. *World J Pharmacol.* Mar 9, 2016; 5(1): 15-31; Garcia-Tsao G. Beta blockers in cirrhosis: The window re-opens. *J Hepatol.* 2016 Mar;64(3):532-4. I suggest including them and making the table updated.

RESPONSE:

Thank you for the valuable analysis and suggestions. I agree with your analysis about NSBB in advanced cirrhosis. Regarding to the inclusion of references suggested, I included the study performed by Ferrarese et al about incidence of PICD. It was a very valuable suggestion since it contrasts to another PICD study included in “window hypothesis”, with an opposite conclusion. I chose not to include the reference in table, since the table presented assembled only studies included in “window hypothesis” article, by Krag et al. However, the Ferrarese et al study was included in text underlined in main manuscript, as reference number 15.