Reply to letter Ref: JHEPAT-D-16-00820 by Ustungad et al.

Non selective beta-blockers in ACLF (reply).

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We read with great interest the letter by Ustungad et al. The main issue they raise is about the mechanism underlying the beneficial effects of non-selective beta-blockers (NSBB) in the observed reduction in mortality of patients with acute on chronic liver failure (ACLF) [1]. We agree with Ustungad and colleagues that the hypothesis that the mechanism of beneficial effects is through reduction in bacterial translocation is hypothetical. However, the significant differences in the white cell count between those patients that were treated with NSBB and those that were not is certainly supportive of the hypothesis but we completely agree that this needs to be verified in prospective studies.

The second point they raise is about potential confounders. Active alcoholism, platelet count and previous decompensations and in particular, GI bleeding, cannot really be considered as potential confounders. All of these were associated with the use of NSBB (Table 1), but none were associated with differences in mortality rates (Table 3) [1]. By definition, a potential confounder must show a clear association with both the outcome and the factor, which is obviously not the case here. Despite this, the multivariate analysis included both previous decompensations and active alcoholism in the previous 3 months, since they were the only two factors showing an imbalance between NSBB and non-NSBB groups (together with age). Platelet count was not considered for this purpose since lab parameters and the evaluation of organ failures, scores and ACLF grades were taken at patients' enrolment, so they can be considered as the effect of being treated with NSBB during the previous 3-months.

The authors rightly suggest that the CLIF-C ACLF score is the best-validated scoring system for patients with ACLF [2]. The data presented in our paper helps to understand the score better. As is illustrated in Figure 3, the predicted mortality of ACLF patients for a given CLIF-C ACLF score between the patients treated with NSBB or not was best differentiated between the score values of about 30-60 indicating that at CLIF-C ACLF score of <30 or >60, the discriminating value of the score is limited and new biomarkers are needed to provide better discrimination [1]. Nevertheless, as Ustungad et al. suggest, NSBB use should be accounted for when judging the predictive value of the CLIF-C ACLF score.

Finally, there were no statistically significant differences between the use of lactulose (NSBB 61.1%; No NSBB 52.2%; p=0.1), Rifaximin (NSBB 17.2%; No NSBB 11.7%; p=0.16) or norfloxacin (NSBB 4.4%; No NSBB 2.4%; p=0.61) between the groups treated or not treated with NSBBs.

References

1. Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol. 2016;64(3):574-82.
2. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61(5):1038-47.