

Dear Editor,

I am pleased to resubmit for publication in your journal the revised version of Manuscript NO: 34826, entitled LIVER DECOMPENSATION PREDICTS RIBAVIRIN OVEREXPOSURE IN HCV PATIENTS TREATED WITH DIRECT-ACTING ANTIVIRALS.

I really appreciated the suggestions from you and the reviewers, which I have tried to address.

Following your suggestions throughout the manuscript and the reviewers' comments, I made the following changes and additions:

- I added postal codes, institutional email address, a running title and IRB statement in TITLE PAGE
- I wrote a Core tip and added it after ABSTRACT section
- I also added Comments after the main text
- I modified the first sentence of RESULTS section in the ABSTRACT, as suggested by one of the reviewer.
- I added a little paragraph in RESULTS section (page 11), to address a reviewer's comments
- I modified REFERENCES, as requested.
- I made Table 1, 2 and 3 editable.
- I made Figures decomposable.

All the revisions have been highlighted (in red) in the revised manuscript word file.

To follow, answers to each of the two reviewers:

Reviewer's code: 02860712

Thank you for your appreciated and accurate observations. In particular, in answer to each of them

1) Child-Pugh score is a composite index. Did the Authors observe any difference in RBV overexposure according to the single items of the Child-Pugh score?

We did not observe any significant association between each of the single item of the index and ribavirin concentrations (considered at week 4, week 8 and as an average in the first 8 weeks of treatment) , as we now specify in the manuscript.

2) Creatinine levels in Child-Pugh B are not representative of the profound changes in hemodynamics associated with the progression of cirrhosis. Did the Authors observe any association between RBV clearance and the signs of portal hypertension (ascites, platelet count, esophageal varices, hypertensive gastropathy)?

Since we might consider ribavirin levels as an indirect marker of its clearance, we looked whether any correlation did exist between RBV plasma levels and signs of portal hypertension (which may be considered associated with cirrhosis progression). No association between RBV concentrations and platelet count, ascites or esophageal varices was found in our population. We had no data available on hypertensive gastropathy. We specified that in the manuscript, as well.

For either the raised questions, our sample size might represent a limit to these additional analysis.

3) *Minor change: ABSTRACT: first line of RESULTS should be: we studied 68 patients: 54 with compensated and 14 with decompensated.....*

The mistyping has been corrected.

Reviewer's code: 00071662

No specific concerns to be addressed.

Sincerely,

Viola Guardigni, MD