To the reviewers,

Thank you for your constructive and thorough review of our manuscript entitled "Lessons from "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy" submitted to World Journal of Hepatology.

Please find below responses to your questions and comments.

Name of journal: World Journal of Hepatology
Manuscript NO: 48519
Title: Lessons frome "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy

Reviewer's code: 00037028

1. … with a somewhat small sample size. That is probably the major limitation of the study.

Thank you for your comments and your consideration. The small sample size constitutes actually a major limitation of the study and was added page 16. Nevertheless, we found results in accordance with the literature when rifaximin was used in patients with recurrent HE and without persistent HE.

2. I would recommend rewording the statement on line 367 as either "we cannot attest to the effectiveness," or "we cannot conclude that rifaximin is effective," for better clarity.

The statement has been reformulated (now line 376, page 16) taking into account the proposal, for better clarity.

Reviewer's code: 03730829

1. In introduction;

You should add more data about the roles of rifaximin in patients with chronic liver diseases; e.g. prevention of SBP. 1) Elfert A, Abo Ali L, Soliman S, et al. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis. Eur J Gastroenterol Hepatol. 2016 Dec;28(12):1450-1454.

You should add more data about other antibiotics that may have beneficial role in hepatic encephalopathy e.g. nitazoxanide. 2) Abd-Elsalam S, El-Kalla F, Elwan N, et al. A Randomized Controlled Trial Comparing Nitazoxanide Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy. J Clin Gastroenterol. 2019 Mar;53(3):226-230.

Thank you for your suggestions: this information has been added into the main text (page 6).

2. In methods; Sample size calculation and the power of the study are so important in the study design and in the methods section as you are investigating rifaximin use in the management of recurrent hepatic encephalopathy and in the prevention of acute exacerbations recurrence on persistent HE. ; so is this sample sufficient or not? It is important question to answer to get a valid conclusion.

Thank you for your comment on the sample size. We fully agree with the concern you have pointed out.

The number of patients does not allow to draw definitive conclusions mostly in subgroup analyses (patient with persistent EH or patients treated by TIPS). So we need to be cautious before being confident that rifaximin is not useful in these situations. Further RCT are needed in these particular indications. However the positive effect in the "real life whole cohort" is encouraging and in accordance with previous trials.

A sentence was added in the discussion section regarding this limitation.

3. In discussion; you should clarify more to the readers the limitations of the study.

The limitations of the study were revised, using the various comments.

Reviewer's code: 00503572

1. Definition of "HE event" in not precised. Authors say that they used West Haven Criteria for detection of HE nevertheless there are several grades of HE. I want to think that they called" HE event" when clinical evident HE was detected. What happened if patient showed a significant improvement of HE without complete disappearance of the WH criteria? How was it considered?

HE events corresponded to episodes of HE and acute exacerbations in patients with a persistent form (page 9, lines 199-200) and could be characterized as grade I to IV, according to clinical examination based on West Haven criteria. The highest West Haven grade of each HE event was considered and described in baseline characteristics for example (Table 1). The primary effectiveness endpoint was the total number of HE events; it did not take into account the improvement of HE but it was assessed by the probability of persistent HE cessation for the persistent form.

2. The retrospective analysis of pretreatment period and prospective analysis of therapeutic one may be source of bias in the absence of blind evaluation of results. Treatment patients may be unintentionally favored. How can you assure that it did not happened?

For the two periods, data were collected in the same way, using hospitalization and consultation reports via electronic medical records, to avoid any source of bias.

3. The connotation of "real life experience" does not justify lack some rigorous evaluation and definitions of objectives.

The objective of this study was to assess the effectiveness of rifaximin in the management of recurrent HE especially in the persistent form, using defined effectiveness endpoints. However, this study provides some major limitations described in the manuscript.

4. English language of the manuscript needs some corrections.

An additional proofreading was performed after the manuscript's revision.

5. I recommend authors modify the manuscript according with the comments and include discussion of limitations of this study.

The comments were taken into consideration and the limitations of the study were revised.