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06 July, 2016

Shui Qiu

Scientific editor

World Journal of Hepatology

Dear Editor:

I, along with my coauthors, would like to re-submit the attached manuscript entitled "**Retrospective study of the associations between hepatitis C infection and metabolic factors**" as a Retrospective Study. The manuscript ID is 27057.

The manuscript has been carefully rechecked and appropriate changes have been made in accordance with the reviewers' suggestions. All the changes are represented as **underlined,** text in the revised manuscript. The responses to their comments have been prepared and attached herewith.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a

more balanced and better account of the research. We hope that the revised manuscript is suitable for publication in your journal.

I look forward to your reply.

Sincerely,
Shira Yair Sabag

Reviewer #1: Reviewer's code: 00004603

1. Comment: " Why patients with HCV genotype 3 are not analyzed separately from patients with other genotypes (at least, genotype 1)? May be if these patients are grouped based on genotype, more significant differences will be found in all tables.".

Response: Some of our tables were stratified according to differences between patients with genotype 3 and non-genotype 3. However, as presented in our study most of the cohort included patients with genotype 1. Therefore stratified data for genotype 3 in responders and non-responders could not be analyzed owing to the low number of patients in the responders and non-responders groups as presented below.

For DM

Case Processing Summary

Genotype 3	Response to treatment	Total N	N of Events	Censored	
				N	Percent
Genotype_none3	None Responder	41	12	29	70.7%
	Responder	51	5	46	90.2%
	Overall	92	17	75	81.5%
Genotype3	None Responder	3	0	3	100.0%
	Responder	20	5	15	75.0%
	Overall	23	5	18	78.3%
Overall	Overall	115	22	93	80.9%

For IFG

批注 [A1]: Same notes as above.

Case Processing Summary

Genotype 3	Response to treatment	Total N	N of Events	Censored	
				N	Percent
Genotype_none3	None Responder	41	29	12	29.3%
	Responder	51	20	31	60.8%
	Overall	92	49	43	46.7%
Genotype3	None Responder	3	2	1	33.3%
	Responder	20	10	10	50.0%
	Overall	23	12	11	47.8%
Overall	Overall	115	61	54	47.0%

2. Comment: " There are lot of repetitions between Introduction and Discussion. If the authors want to discuss possible mechanisms how MS and T2DM are related to the responsiveness to HCV-infection treatment, it should be moved to the Discussion, but then there is no reason to mention it in Introduction, especially because none of these mechanisms are studied in this manuscript. ".

Response: We thank to the reviewer for this comment. According to this comment, the manuscript was edited and shortened, repetitions were excluded, and the discussion was re-edited.

3. Comment: " The data presented in the Tables 3,4,5 need to be better explained. ".

Response:

According to this comment, Tables 3, 4, and 5 were better presented to clarify the data.

4. Comment: " The conclusions should me condensed and should not look like a part of Discussion. ".

Response: We agree with the reviewer and therefore separated the conclusions in the last paragraph of the discussion.

5. Comment: " There are lot of misspellings, and some sentences are too long.".

Response: The manuscript was revised again for spelling, and the English language was edited by a native speaker.

Reviewer #2: **Reviewer's code:** 00503560

1. Comment: " The manuscript was overly long. Please think through to reduce the volume of both introduction and discussion. ".

Response: We thank the reviewer for his/her comment. The manuscript was edited and shortened.

2. Comment: " The number of references (63 references) were too much. Please limit the number of references; for example within 40 references. ".

Response: Following the comment, the reference list was shortened along with the manuscript.

3. Comment: " To evaluate glucose tolerance in patients with chronic liver diseases is not found to be simple. Please provide the measure(s) of blood sugar control over a long period. Restricted to the short-term parameter, HbA1c and GA can be used in the same individuals.".

Response: This study was conducted as a retrospective study.

Due to the retrospective design of our study, we could assess parameters that were evaluated during the follow-up. Glycated albumin (GA) is not a parameter routinely measured for diabetes, and HbA1c values were not available in many patient charts. Moreover, liver cirrhosis or treatment with IFN alpha may falsely decrease HbA1c levels (in relation to glycemia) due to the shortened erythrocyte half-life due to hypersplenism and hemolytic anemia, respectively*. Additionally, GA may be overestimated in relation to glycemic control in patients with chronic liver disease due to decreased synthesis of albumin and prolonged albumin half-life*. Therefore, our data evaluation allowed us to only present data as they were presented to the physicians on routine follow-up with the patients.

We do recognize the drawbacks of this retrospective evaluation and have listed those limitations of our study.

***References:**

Hammerstad SS, Frankel Grock S, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and hepatitis C: a two-way association. *Front Endocrinol* 2015; **6:** 1–19.

Dinu IL, Mota E. Glycated albumin-- More than the missing link in the evaluation of diabetes control. *Rom J Nutr Metab Dis* 2014; **21:** 137–150.