October 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13866-revised.doc).

Title: EVALUATION OF PROGNOSTIC VALUE OF LIVER STIFFNESS IN HEPATITIS C VIRUS PATIENTS TREATED WITH TRIPLE OR DUAL ANTIVIRAL THERAPY: A PROSPECTIVE, PILOT STUDY

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We thank the Reviewers and the Editor for their kind attention and accuracy in reviewing our work.

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers
(1) Reviewer 1

1) In the Abstract, it would be more informative to readers to highlight the direction of the differences in LS between the groups of patients rather than just to state that they "differed significantly".

- We agree with the reviewer concerning this criticism. Accordingly, we have introduced in the Methods section a paragraph highlighting the direction of the differences in LS between the groups of patients

2)In the Core Tip section the statement "improving response rates to treatment." is inappropriate since this has not been demonstrated in this study.

- This phrase has been eliminated

3)The term 'parameter ' is widely used when 'Feature' would be more appropriate; parameter should be reserved for the conditions of an experiment rather than for something that is measured.

- This has been corrected through the manuscript

4) The use of the terms "Group A" and Group B" hides the meaning and can be confusing; more informative terms such as "Dual therapy" and "Triple therapy" (as used in the Title and Table 1) would be clearer.

- As suggested, we used the terms "Dual therapy" and "Triple therapy"

5)Some minor comments follow. The running title does not highlight that this is a study of the predictive value of LS measurements.

-The running title "STIFFNESS IN HEPATITIS C VIRUS PATIENTS" has been changed with

"STIFFNESS PROGNOSTIC VALUE IN HCV PATIENTS"

6) Abstract: please define "SVR24". This term also occurs in Fig. 1.
-The "SVR24" was defined in the abstract and also in fig. 1.

7) P 4: "In this prospective," would be better as "In this prospective study,". "in clinical practice for accurate selection" would be better as "in clinical practice to improve selection". IFN should be added to the Abbreviations. "easily, reproducible and" should be "easy, reproducible and".
- These corrections have been made

8) P 6: "(F3-F4, METAVIR classification," should be "(F3-F4, METAVIR classification),". P 7: " (i.e. pregnancy)." should be " (e.g. pregnancy).". P 9: "achieving SVR 24 (9.41±5.05 vs 19.11±9.74, p=0.008) or not." would be better as "achieving SVR 24 or not (9.41±5.05 vs 19.11±9.74, p=0.008)."
- These corrections have been made

9) P9-10: "resulting higher than in Group A patients." this statement is unclear and may be incomplete.
- To enhanced clarity we added this phrase: "which is a consequence of eligibility to dual of triple therapy. In fact, therapy with boceprevir is indicated for the treatment of difficult to treat patients including patients with more advanced fibrosis."

10)P 11: "Therefore, a decline" would be better as "A decline" since this is not a consequence of the previous statement.
- This has been corrected

11) P 12: "in consideration of the high costs, has generally been restricted to patients with more advanced fibrosis stages." would be better as "has generally been restricted to patients with more advanced fibrosis stages because of their high cost."
- This phrase has been corrected

(2) Reviewer 2
Abstract:

1)-The abstract is hard to follow. The methods do not convey the analysis of the paper

- We have introduced in the Methods section a paragraph highlighting the methods used

Materials and Methods:

2) -From reading the methods, it is not clear what covariates were including in the model, nor how the model was constructed. Some of is listed in results but should be in methods and further described.

We included the model in the Method section

"Multivariate logistic regression analysis was used to assess which baseline variables were predictive of SVR. In the final model, age, gender, stiffness, and viraemia (and viral genotype as well as IL28B genotype limited to dual therapy) were considered independent predictors of SVR."

3)-Since patients in group B were treatment experienced, it would be helpful to report the nature of their tx experience (relapse, failed treatment). Also the majority of group A were genotype 2/3 (n=41 or 65), whereas all of group B were genotype 1.

- The nature of treatment experienced was specified (relapser, partial responder o non responder). The triple therapy with Boceprevir is indicated only for patients infected with HCV genotype 1, therefore the majority of patients treated with dual therapy were genotype 2/3. For the eligibility of treatment, we observed the recommendations of the Italian Association for the Study of the Liver.

4-What was defined as "eligibility for antiviral treatment"
- The eligibility for antiviral treatment was defined according to recommendations of the Italian Association for the Study of the Liver (2012).
4-It isn't clear why the authors constructed two separate regression models for group A (n=65) and group B (n=20), with LS perhaps as an independent predictors of SVR24 and controlling for covariates (e.g, genotype).
- Because the two groups, considered separately, are homogeneous and more suitable for regression analysis. We controlled for covariates, but in triple therapy group genotype was only 1 (according to Italian guidelines) and then it was omitted for collinearity.

5)-Period of recruitment is needed

-**The period of recruitment has been added**

6-Statement of patient consent and statement from ethics committee is needed

-The nature of the study was explained to patients, who provided written informed consent before the beginning of the study, in accordance with the principles of the Declaration of Helsinki (revision of Edinburgh, 2000), and the study was approved by the University of Florence Ethics Committee.

7-Was viremia a covariate in the group A model? It is listed group B, but no group A.

-Yes, it was. We added the viremia in the text. Table 2 was correct and the parameter "viremia" was present in table 2 for both dual and triple therapy.

8-Treatment discontinuation – it's not clear if patients in groups A and B completed the course of therapy or discontinued therapy for a variety of reasons.

- **The phrase "We analysed only patients that completed the course of therapy" has been added in Method section.**

It would be helpful to report duration of therapy

- **We reported duration of therapy in the Patients and Methods section.**

9-No sample size calculation.

- **The targeted study population consists of all patients that satisfy the inclusion criteria**

Results:

10-The results of the model are not included therefore it is difficult to interpret the magnitude of these associations, only a p-value is reported for group B (p=0.049).

- **We included the model in the Method section**

11-Do the +/- throughout the manuscript refer to standard deviation?

- **Yes, it does.**

Discussion:

12 The main conclusion seems to be that high values for LS are predictive of treatment success for patients pursuing triple therapy. However LS was only evaluated at baseline, not longitudinally – it is curious why the authors did not measure LS at follow-up. Moreover, the model only controlled for age, gender and viremia with an n=20 (p=0.049 for LS), but the results are not shown. The conclusion states, "LS should be considered a strong pretreatment predictor of response to both dual and triple therapy", but their results do not support this for statement for dual therapy. There is no discussion of study limitations and these may impact interpretation of findings.

- We modify the conclusions for enhanced clarity: "In conclusion, our data suggest that LS >12 kPa should be considered a strong pretreatment predictor of non response to both dual and triple therapy".

We didn't measure LS at short follow-up, because only "the changes in LS occurring in long-term follow-up definitely indicates a certain degree of fibrosis regression" as showed in a previous study (Stasi et al. 2013)

Tables and Figures:

13-Table 3 - row for male sex, do the numbers refer to M/F? Were these significantly different?

- **The difference between M and F was not statistically significant**

14-It would be helpful to have the results of the regression analysis rather than the univarate analysis in (Table 2).

- We add the table 3 "Multivariate analysis of negative prognostic factors of sustained virologic response (SVR) in both dual and triple therapy"

Other minor comments:

15-Would recommend changing "before dual/triple therapy" to "prior to initiation of dual/triple therapy" throughout the manuscript for enhanced clarity

-This has been changed

16-Inconsistencies with "PegIFN-RBV" vs "Peg-IFN/RBV"

-This has been corrected

17-Define BOC as boceprevir

- As suggested BOC has been defined as boceprevir

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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