Response to reviewers' comments

Manuscript title: ***"Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients"***

We thank the reviewers for their constructive and valuable comments which have helped us to improve the content and the structure of our manuscript, which we hope is now acceptable for publication in the *World Journal of Gastroenterology*.

Below, we address point-by-point all the reviewers' comments.

Reviewer 1:

1. *"The authors state that this study is planned prospectively. However, the inclusion criteria for the participants are not clear to me: what grade of cirrhosis was necessary for inclusion? Please comment in the method section."*

Response: In the revised manuscript, we have now addressed this point in the methods section, in line with the reviewer comment: *"One hundred and thirty-nine newly diagnosed cirrhotic patients (Child-Turcotte-Pugh of at least 5-13)....."* (Page 7, lines 97-98).

2. *"The number of control patients seems to be very low. Was the number of control patients calculated while planning the prospective study design?"*

Response: Indeed, the number of control patients turned out to be quite low. As a matter of fact, the number of control patients was not calculated beforehand, because we enrolled all consecutive patients who were newly diagnosed with liver cirrhosis (page 7, lines 88-89), regardless of their esophageal varices presence.

3. *"It would have been interesting to report a second time point for the measurement of the non-invasive parameters – this might have increased the sensitivity and specificity!? Were the non-invasive parameters only measured once?"*

Response: Point well-taken. In the revised manuscript, we acknowledge this limitation: *"Also, assessment of the sensitivity and specificity upon a second-time measurement would have provided an additional insight into the predictive power of the non-invasive parameters included in our analysis."* (Page 14, lines 290-292).

4. *"How did you monitor the compliance of patients who were subjected to medical treatment of the esophageal varices?"*

Response: In the revised manuscript, we now clarify that: *"Treatment compliance of the patients was monitored by measuring the resting pulse rate and interviewing them periodically if any side effects occurred"* (Page 8, lines 112-113).

Reviewer 2:

1. *"Red sign of EV is a crucial sign predicting EVB; however, there is no description about red sign. The author should describe the number of EV with red sign in Table 4."*

Response: Point well-taken. In the revised manuscript, we have now added a new row in both Table 1 and Table 4 (we leave the decision upon editor's discretion) presenting the distribution of red signs by esophageal variceal bleeding status. In addition, we have also amended the methods section respectively: *"Presence of red signs was also recorded in all patients."* (Page 9, lines 139-140). Also, in the results section, we now state that: *"Among patients with esophageal varices, 19 (17%) presented red signs compared with 94 (83%) patients without red signs."* (Page 10, lines 172-173).

2. *"Table 4 indicated that 4 (11.8%) patients experienced EVB in None EV. Did these patients experience bleeding from EV? This description confuses the readers."*

Response: We thank the reviewer for pointing this out. In the revised manuscript, we now clarify this issue as follows: *"Of these, 4 (11.8%) patients were without EV upon enrollment, but experienced EV in the course of the follow-up."* (Page 11, lines 202-203).

3. *"The authors should describe whether antiplatelet and anticoagulant agents were administrated in these patients."*

Response: No, none of the patients included in our study were prescribed antiplatelet or anticoagulant agents. We now acknowledge this issue in the methods section (Page 8, lines 113-115).

Reviewer 3:

<u>Material and Methods section</u>

1. *"Page 6, lines 13-14: "newly diagnosed ….. hospitalized at the…. 2005-2017". What does "newly" mean exactly? For the first time? Does it mean that 33 patients in Child C class have diagnosis of liver cirrhosis for the first time? Or they were admitted newly in this hospital?"*

Response: Yes, "newly diagnosed" stands for the "first time" hospitalized patients. In the revised manuscript, we have now clarified this issue (page 7, lines 88-89). In addition, 33 patients in Child C class had a diagnosis of liver cirrhosis for the first time and were also newly admitted in our hospital.

2. *"Why 43 patients in Child class A were hospitalized? Perhaps as outpatients?"*

Response: In fact, 43 patients in Child A class were also hospitalized due to the fact that they were diagnosed for the first time with liver cirrhosis.

3. *"Follow up period of the patients that have been recruited in 2017 could not be long enough to allow their inclusion, and in my opinion such data must be eliminated."*

Response: Instead of 2017, it should read 2007. We thank the reviewer for pointing this out and apologize for this typographic error, which we have now corrected (Page 7, lines 90).

4. *"Page 6 line 24: Why were patients with current or past history of treatment for chronic B or chronic C hepatitis excluded?"*

Response: We excluded patients with current or past history of treatment for chronic B or chronic C hepatitis because these conditions may alter the hematological and biochemical parameters. We have now elaborated on this issue in the methods section (Page 8, lines 103-104).

Discussion section

5. *"Page 12 lines 7-9: "Our study demonstrate sufficient ……. ranged from 0.45 to 0.55". These statements are in contrast to what is said just after, i.e., that none of the non-invasive marker is useful …" and therefore must be re-written or eliminated."*

Response: Again, we deeply apologize and thank the reviewer for spotting this typo. In the revised manuscript, we have now replaced the word "sufficient" with "insufficient" as follows: "Our study demonstrated insufficient accuracy of AST/ALT, APRI, PC/SD, FIB-4, FI and King's score for the prediction of EVB which ranged from 0.45 to 0.55." (Page 13, lines 265-267).

6. *"Page 12, lines 11-15: This sentence is inappropriate, because this study demonstrates that none of the non-invasive markers of fibrosis that were assessed is useful for predicting EVB. Yet, lines 23-25: 'In our study, the …. in cirrhotic patients'. This is not true, at least for first variceal bleeding."*

Response: Point well-taken. In the revised manuscript, we have now elaborated on this issue as follows: *"However, only FIB -4 turned out to be a useful predictor in this sample of Albanian patients and, therefore, the usefulness and applicability of these noninvasive markers should be considered cautiously."* (Page 13-14, lines 274-276).
Furthermore, we have now reworded the other sentence as follows: *"In our study, the multivariate model allowed us to assess important variables most of which, nevertheless, did not predict the presence of EV and the risk of first variceal bleeding in cirrhotic patients"* (Page 14, lines 284-286).