Author's response to reviews

Title: Serum hyaluronate as a Non-invasive Marker of Hepatic Fibrosis and Inflammation in HBeAg-negative Chronic Hepatitis B

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Author's response to reviews: see over
Dear editors

Thank you very much for your kind message informing us of the encouraging decision of the editorial board regarding our manuscript. We are very thankful to the reviewers for their thoughtful and precise critics, observing which has helped us to improve the quality of the manuscript. Attached please find the second revised version of our manuscript. Our new sentences come in red color font in the revised paper. You will find below the point by point response to reviewers’ comments.

Best regards
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Response to reviewer 1:

Thank you very much for your constructive comments

1. The suggested correction was made in the introduction of the second revised manuscript. (We aimed to find out the utility of serum hyaluronate to evaluate the presence of extensive liver fibrosis …).

2. On the Ishak scoring system stage 5 is defined as marked bridging fibrosis with occasional nodule formation, and stage 6 as multiple well defined nodules (1). Our pathologist was able to differentiate stage 5 and 6. However, we saw several cases of inter-observer variability for stage 5 and 6 of liver fibrosis, among different pathologists. As we described in the first revised
manuscript it is not unfair to call stage 5 as compensated cirrhosis. In fact, stage 5 and 6 are considered as cirrhosis by some investigators (2). We added the following sentence to the “Methods” of the second revised manuscript: “Stage 3 or more was considered as significant fibrosis, and stage 5 or 6 was considered as cirrhosis”.

3. The referees can see below the box and whisker plot of HA plotted against levels of liver fibrosis (Figure 1), as well as the related scattergram (Figure 2). The figure of box and whisker plot of the HA serum levels against fibrosis scores was added in the second revised manuscript.

4. We added the following sentences in the discussion of the second revised manuscript: “Also, it should be noted that the cut-off value for a given variable depends upon the sample in which it has been identified. In order to be reproducible, a cut-off value should be obtained in a sample representative of the population with the disease”.

5. In our study, stages of liver fibrosis had strong correlation with grades of liver necroinflammation. (Correlation coefficient: 0.57; P<0.001 on the spearman correlation test)

6. This important point corrected in the discussion of the second revised manuscript. (HA was correlated with stage and predictive for the presence of extensive fibrosis).

7. The suggested correction was made in the abstract of the second revised manuscript (Serum hyaluronate was the best predictor of extensive liver fibrosis ….).
**Figure 1:** Box and whisker plot of HA levels against different stages of liver fibrosis

**Figure 2:** Scatter gram of HA levels against different stages of liver fibrosis
Response to reviewer 2:

Thank you very much for your constructive comments.

1. Box plot of hyaluronate according to each fibrosis stage was added (Figure 1 in the second revised manuscript)

2. The suggested sentence by the reviewer 2 was added in the second revised manuscript: “However, hyaluronic acid may have a lower sensitivity for minimal fibrosis (as in chronic hepatitis C) as well as an absence of independent assessment of both fibrosis and activity as given by FibroTest-Actitest”.

3. The price of each kit of hyaluronic acid is 600 US Dollars in Iran as well as in Europe. Every kit can be applicable for 96 samples (7 control and 89 patients). Thus the price is less than 7 US Dollars per patient. Obviously, when duplicate tests are used for every patient, the price is doubled. We considered the average price of 10 US Dollars in the revised manuscript.

References:
