Dear Dr. / Lian-Sheng Ma,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled [Circulating microRNA 9-3p and serum endocan as potential biomarkers for hepatitis C virus-related hepatocellular carcinoma] to [*World Journal of Hepatology*]. We appreciate the time and effort that you and the reviewers have dedicated for providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on my paper. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. Here is a point-by-point response to the reviewers' comments and editorial office's concerns**.**

Comments from Reviewer 1

1- Major concerns: 1. It is not clear from the study, can miR-9-3p target endocan gene? Since the expression levels of miR-9-3p and endocan are inversely correlated, it would be useful to study the ability of miR-9-3p to target ESM1.	Response: Thank you for this suggestion. It would have been interesting to explore this aspect. However, in our case control study on humans we aimed mainly to study the diagnostic and prognostic value of both biomarkers in the same patients in a blood sample while testing if miR-9-3p can target endocan gene will need totally different approach using cell lines and culture or studying it on animals
Minor concerns: *1. It is recommended to subdivide the "Results" section into subsections.*	Thank you for pointing this out. We agree with this comment. Therefore, we have subdivided it into sections matching the order of tables and figures
2. MiR-9-3p has been identified in HCC as a tumor suppressor. Therefore, it would be useful to discuss this in "Introduction" and "Discussion" sections (for example, see Higashi T, Hayashi H, Ishimoto T, Takeyama H, Kaida	Agree. We have, accordingly, revised and modified introduction to add a paragraph to emphasize this point. [Page number 6, paragraph 4, and line 4-6.]. Regarding discussion section it was already discussed and

T, Arima K, Taki K, Sakamoto K, Kuroki H, Okabe H, Nitta H, Hashimoto D, Chikamoto A, Beppu T, Baba H. miR-9-3p plays a tumour-suppressor role by targeting TAZ (WWTR1) in hepatocellular carcinoma cells. Br J Cancer. 2015 Jul 14;113(2):252-8. doi: 10.1038/bjc.2015.170. Epub 2015 Jun 30. PMID: 26125451; PMCID: PMC4506379).	mentioned. [Page number 14, paragraph 2, and 4].
3. It would be better to capture data presented in Table 4 as a figure.	Thank you for this suggestion. It would have been interesting to explore this aspect. However, we consulted two statistical consultants who clarify that this data cannot be presented clearly as a figure
4. There are some technical errors in the text: (i) Introduction, paragraph 1, line 2: HCC is the third leading cause of cancer death, not the fourth one; (ii) Introduction, paragraph 2, line 2: The word "epigenetic" should be removed. (iii) The authors use both terms "microRNA" and "miRNA" – this should be unified. (iv) Introduction, last paragraph: since endocan is implicated in inflammation and HCV is associated with inflammation, this linkage between endocan and HCV-related YCC should be emphasized in the last sentence.	We have revised the text to address your concerns and hope that it is now satisfying. Please see page 6 of the revised manuscript, paragraph 1, and line 2, and paragraph 2, line 2. microRNA was unified in the revised manuscript. The last paragraph in the introduction section was modified to clarify this linkage

Comments from Reviewer 2

1. The sentence "To the best of our knowledge, the roles of miR-9-3p and endocan have not been evaluated in HCC" seems incorrect. eg. Higashi T, Hayashi H, Ishimoto T, et al. miR-9-3p plays a tumour-suppressor role by targeting TAZ (WWTR1) in hepatocellular carcinoma cells. British journal of cancer. 2015 Jul;113(2):252-8.	You have raised an important point here. However, We believe that the roles of both microRNA 9-3p and endocan have not been evaluated in HCC because the paper you mentioned studies microRNA 9-3p targeting protein other than endocan which is TAZ
2. How was the sample size calculated in each group? What were the inclusion and exclusion criteria?	Thank you for pointing this out. We agree with this comment. According to previous studies at a power of 80%, CI 95% sample size was calculated. The inclusion criteria was added in subject and method section [Page number 7, paragraph 2, and line 7-9]. The exclusion criteria was modified to be clearer. [Page number 8, paragraph 1, and and line 1-5].
3. Was matching done between the case and control groups ?	Case and control groups are matched regarding age and gender mentioned in subject and method section [Page number 7, paragraph 2, and line 6]
4. As cirrhosis was diagnosed based on history, clinical examination, laboratory results, and imaging that included abdominal ultrasonography and CT, it would be more appropriate to use the term chronic liver disease	Thank you for pointing this out. We agree with this comment and we replaced the term liver cirrhosis with the term chronic liver disease in the revised manuscript
5. The aim and objectives of the study need to be more clear and	We have revised the text to address your concerns and hope

specific.	that it is now satisfying. Please see [page 7 of the revised manuscript, paragraph 1, line 11-14]
6. The sentence "In the HCC group, 62.9% of patients were classified as grade A according to Child-Pugh classifications; and four (11.4%) patients were in BCLC stage, 18 (51.4 %) patients in stage B and 13 (37.1%) patients were in stage C " seems to be incomplete. BCLC staging and CHILD class should be mentioned separately. Also in table, please include all BCLC and CHILD class even if a particular group has no patients.	Thank you for pointing this out. We agree with this comment and we replaced that sentence with another full sentence. Please see [page 11, paragraph 4, and line 18-22] in the revised manuscript. Also in tables, we included all BCLC and CHILD class.
7. Limitations of the study needs to be mentioned. eg. only HCV related cirrhosis and HCC were included in the study	Thank you for pointing this out. We agree with this comment and we added this point in the end of discussion section. Please see [page 15, paragraph 1, line 1-4] in the revised manuscript
8. The cost and availability of tests like "Endocan" and "miR-9-3p" need to be discussed.	Endocan levels were measured by ELISA technique, which is an easy, available and a highly specific antibody-antigen interaction. MicroRNA-9-3p is measured by RT-PCR which is rapid, accurate and cost-effective method. We believe these markers are costly effective to pick up HCC patients especially the early cases. HCV-related HCC especially the advanced stage constitutes an economic burden to the Egyptian society which already has a higher prevalence of HCV. So, using these markers for early detection of HCV-induced HCC is valuable and for screening of high-risk group.

Editorial Office's comments

1. The authors use both terms "microRNA" and "miRNA" – this should be unified.	We have revised the text to address your concerns and hope that it is now satisfying. microRNA was unified in the revised manuscript.
2. It is not clear from the study, can miR-9-3p target the endocan gene? Since the expression levels of miR-9-3p and endocan are inversely correlated, it would be useful to study the ability of miR-9-3p to target ESM1.	Thank you for this suggestion. It would have been interesting to explore this aspect. However, in our case control study on humans we aimed mainly to study the diagnostic and prognostic value of both biomarkers in the same patients in a blood sample while testing if microRNA-9-3p can target endocan gene will need totally different approach using cell lines and culture or studying it on animals
3. BCLC staging and CHILD class should be mentioned separately. Also in the table, please include all BCLC and CHILD classes even if a particular group has no patients.	Thank you for pointing this out. We agree with this comment and we replaced that sentence with another full sentence. Please see [page 11, paragraph 4, and line 18-22] in the revised manuscript. Also in tables, we included all BCLC and CHILD class.
4. Cost-effectiveness of measuring these markers should be discussed.	Endocan levels were measured by ELISA technique, which is an easy, available and a highly specific antibody-antigen interaction. MiR-9-3p is measured by RT-PCR which is rapid, accurate and cost-effective method. We believe these markers are costly effective to pick up HCC patients especially the early cases. HCV-related HCC

	especially the advanced stage constitutes an economic burden to the Egyptian society which already has a higher prevalence of HCV. So, using these markers for early detection of HCV-induced HCC is valuable and for screening of high-risk group.

In addition to the above comments, all spelling and grammatical errors pointed out by the reviewers have been corrected.

We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Sincerely,