

4<sup>th</sup> of March 2020

Dear Editor

Thank you for pointing out the oversights for the manuscript no 53381, entitled „*Circulating miRNAs as noninvasive biomarkers for hepatitis B virus liver fibrosis*”.

To answer to all your comments, I will take the liberty to enumerate each of these in the same order:

- The audio core tip was reuploaded in an mp3 format
- Figure 1 was mistakenly missing. It was reuploaded as suggested. We have also included it in the manuscript in an embedded power point slide, in case there is a problem with the uploaded slide
- The font and spacing was rechecked as indicated
- The work is supported by only one programme but with a longer name and multiple specifications. It reads as follows: sponsored by the Ministry of Research and innovation, developed as part of programme 1, subprogramme 1.2 focusing on Institutional performance, followed by the number of this programme and its name. The official website of the programme is <https://umfcd.ro/cercetare-si-dezvoltare/proiecte/proiecte-de-dezvoltare-institutionala/cresterea-performantei-institutionale-si-a-competentelor-cdi-in-domeniul-sanatate-ale-universitatii-de-medicina-si-farmacie-carol-davila-bucuresti/>
- The observation regarding the institution of the corresponding author was addressed
- Regarding the peer-reviewers comments we have critically analyzed the paragraphs dedicated to the importance of an early treatment and to the non-invasive diagnostic methods to ensure that these issues are well understood. The other paragraphs were not changed (See below for the response to the comments)
- Each reference was manually checked, adding the PMID and making sure that the reference template is respected. The repeated reference 138 was deleted.
- The indications for table 1 were respected and the up and down were replaced with arrows, which were afterwards explained in the legend below.

Thank you for your support during the review process. Please let me know if I can be of any further assistance.

Sincerely yours,

Simona Maria Ruta, MD, PhD

18<sup>th</sup> of January 2020

Dear Editor,

Thank you for transmitting the reviewers' comments derived from the evaluation of manuscript no 53381, entitled „*Circulating miRNAs as noninvasive biomarkers for hepatitis B virus liver fibrosis*”.

We highly appreciate the reviewers' comments and suggestion that helped us improve the quality of the manuscript. We hope that this revised version will answer to all the recommended corrections.

Attached please find a detailed point by point response, together with the modifications (in red) of the manuscript.

Thank you for your support during the review process. Looking forward for your decision on the publication of the above mentioned manuscript.

Sincerely yours,  
Simona Maria Ruta, MD, PhD

#### **Response for reviewer number 4**

We are grateful for the constructive review; we consider that the comments and suggestions had helped improve the quality of our article. We tried to clarify all the points as follows:

1. *INTRODUCTION- it is advisable to emphasize the followings:*

- *The significance of early detection of fibrosis to start treatment as an absence of (early) treatment can lead to the development of liver cirrhosis and hepatocellular carcinoma.*
- *Evaluation of other non-invasive scoring systems for assessment of liver fibrosis.*

**Further details highlighting the above mentioned points have been added in red in the introduction section of the manuscript, supplementary references related to this information were added.**

- *The way of measurement & analysis of MicroRNAs*

**A specific paragraph on this topic has been added in the manuscript body, summarizing the detection and quantification methods and the methodologic challenges of miRNA quantification.**

○ *“HBV-associated liver fibrosis occurs 10-15 years after infection, and its progression depends on viral characteristics (HBV genotype, viral load, HBV*

mutations) and host-related factors (age, gender, other comorbidities or coinfections).” A reference has to be cited

**The paragraph was revised in accordance with the EASL guidelines and the corresponding reference has been added . The and bibliography has been reformatted accordingly.**

2. *TEXT:- the followings points have to be considered:*

○ *EVs: Has to be fully written as a subheading. **The manuscript has been reorganized accordingly, with a specific paragraph with a subheading on miRNAs in EV inserted in the text***

*Also in the last paragraph within this subheading, place of reference 89 & 88 have to be revised. It seems that they are exchanged. Table (3): Zhang et al<sup>[133]</sup>, : It is 134 not 133; ○ Table (4): Numbering of references in this table is incorrect & has to be carefully revised **References have been revised, thank you for signaling the discrepancies.***

**3. References:** *Revision of this section is mandate to be comparable with the text; Ref. 88 & 89*

**The references have been revised, we have corrected the previous numbering errors throughout the manuscript .**