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NAME OF JOURNAL: World Journal of Gastroenterology

MANUSCRIPT NO.: 02953108

Manuscript Type: Topic Highlight

The authors thank editors and reviewers for their hard work and precious suggestions.

Step 1. PLEASE REVISE YOUR MANUSCRIPT ACCORDING TO THE REVIEWERS' COMMENTS.

The manuscript has been revised according to reviewers' comments (see below "Answers to Reviewers") and are in "blue color" thorough the text.

Step 2. PLEASE UPDATE THE MANUSCRIPT ACCORDING TO THE GUIDELINES AND REQUIREMENTS FOR MANUSCRIPT REVISION-TOPIC HIGHLIGHT.

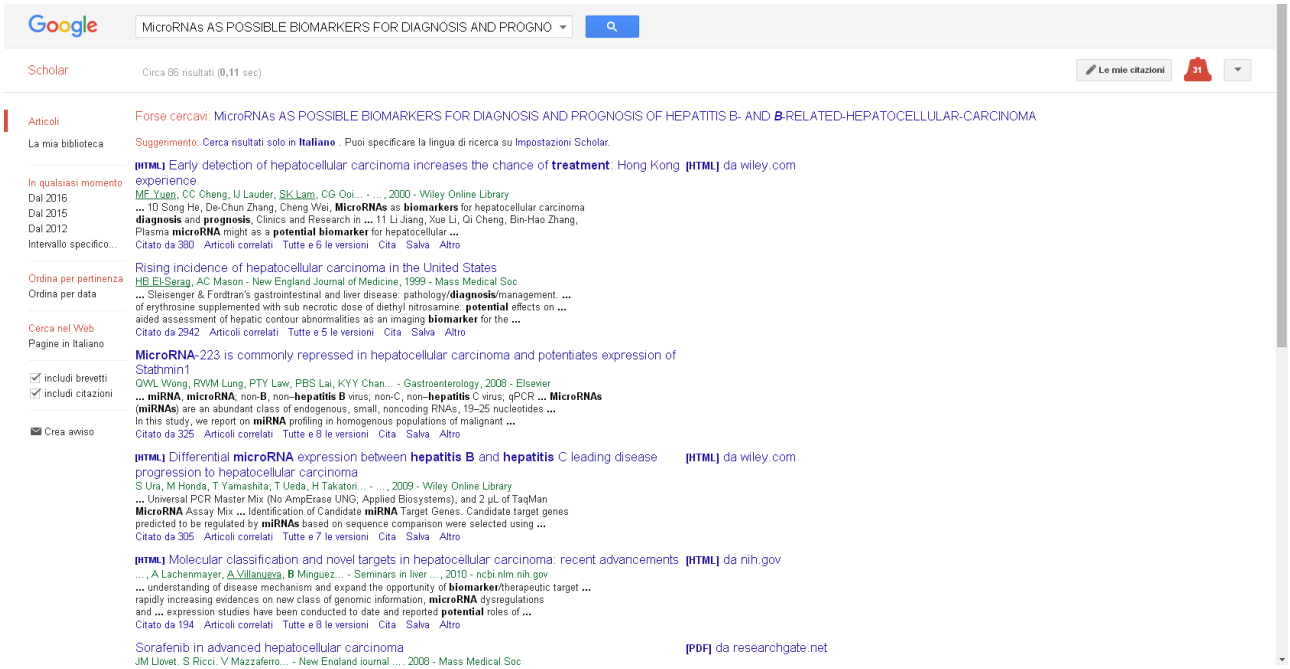
The manuscript has been updated according to the Guidelines and Requirements for Manuscript Revision-Topic Highlight.

Step 3. PLEASE PROVIDE AN AUDIO CORE TIP.

Audio Core Tip has been performed and submitted.

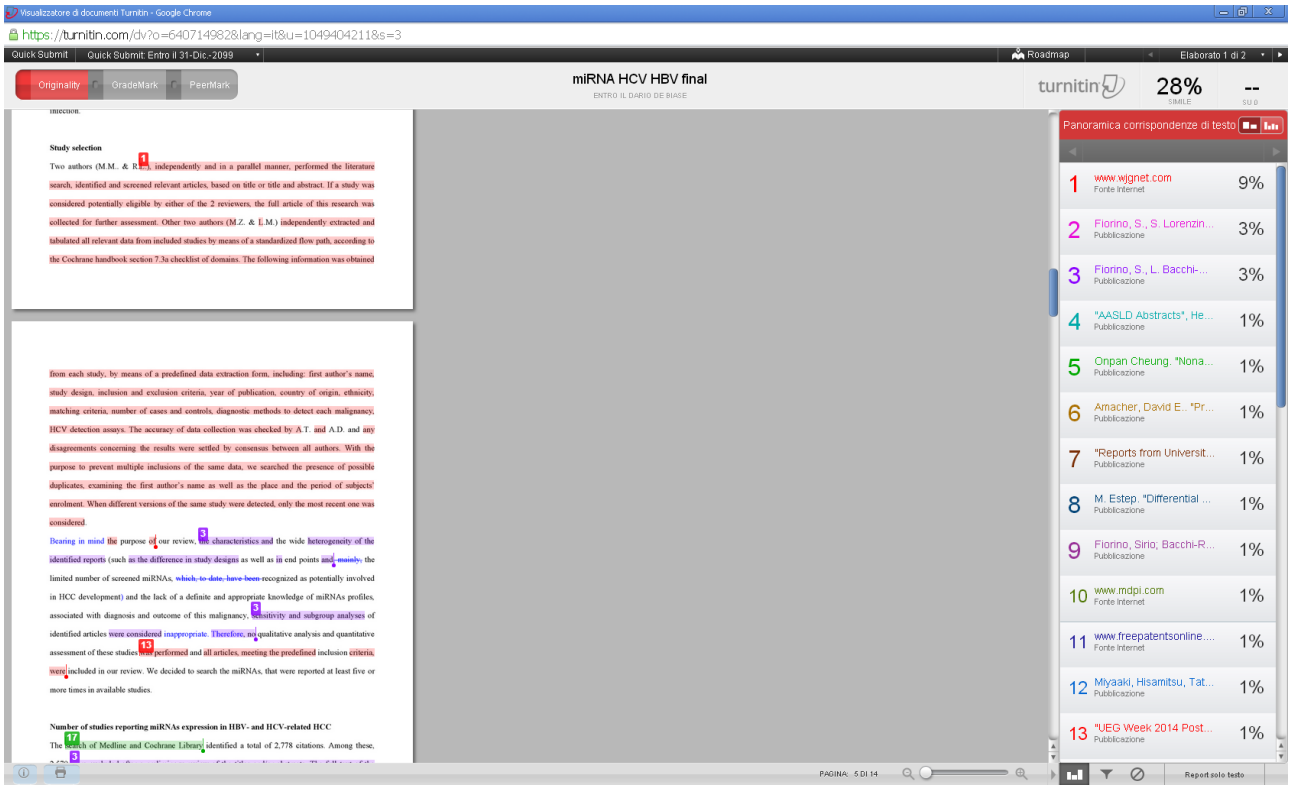
Step 4. PLEASE SUBJECT THE MANUSCRIPT TO *CROSSCHECK* ANALYSIS AND THE FINAL TITLE TO GOOGLE SCHOLAR SEARCH, AND STORE SCREENSHOT IMAGES OF THE RESULTS.

The final title has been checked using Google Scholar (see attached screenshot):



Our institution is not subscribe to "Crossref". We have used another tool to prevent scholarly and professional plagiarism (www.turnitin.com).

The highest similarity is 9% with www.wjgnet.com and as showed in figure this is due mainly to "study selection" section.



Step 5. PLEASE SIGN THE COPYRIGHT ASSIGNMENT FORM.

The Copyright Assignment form has been signed and submitted

RESPONSE TO REVIEWERS

Reviewer 1

This article describes and summarizes the potential usefulness of miRNAs for the early detection and prognosis evaluation of HBV and/or HCV related HCC through a systematic computer-based search of published articles. Moreover, the authors suggest research directions for the improvement of our knowledge on the potential role of miRNAs for HCC early detection and prognosis. This review was written very concisely and informatively and deserves to be published as its current format.

The authors thanks the reviewer for his comments

Reviewer 2

Dr. Fiorino and colleagues have presented an interesting review article based on a systematic search of the available literature to summarize the current knowledge of the relationship between miRNA expression and HBV or HCV related HCC. From the analysis of the literature the authors conclude that miRNA screening as biomarkers for hepatitis virus related HCC development needs more attention. No specific miRNA or miRNA cluster can be used to define a prognostic value. Overall, the manuscript is well written and mainly concise in its content. The study design is mainly well performed. However, the study showed some limitations which should be addressed.

Comments 1. There are some typing errors throughout the manuscript which should be corrected.

Typos throughout the text have been corrected

2. The authors performed the study from 2000 to 2015; however, miRNA analysis becomes more valid since approx. 2005/2008. For that I suggest to exclude studies before 2005.

The authors agree with the reviewer. However including paper before 2005 allows to focus on the big issue of miRNA studies: the high variability in miRNA analysis and results observed between studies.

3. To give the reader any idea which of the miRNAs or miRNA panels would be useful as biomarkers for HBV/HCV related HCC and/or worthy for further analysis, the authors should give more detailed information concerning this issue. A table listing or ranking the miRNAs would be helpful

The authors agree with the reviewer and several tables ranking the miRNAs have been added (Tables 2 and 4, Supplementary Tables 1-3).

4. The catalogue of literature shown as table is not useful for the reader, however, could be shortened dramatically. It would be better to focus on the miRNAs and their impact on HCC development showing subsequently the references.

The authors agree with the reviewer and several tables ranking the miRNAs have been added (Tables 2 and 4, Supplementary tables 1-3). However the overall tables allow to examine in depth each miRNA.

5. No comparison has been made concerning non-viral HCC as control panel but would be of high interest if there do exist any differences in miRNA profiles of virus related HCC.

A paragraph has been included in the main text concerning the issue highlighted by the reviewer (pages 11-13).

6. What are viral miRNAs in contrast to host miRNAs (page 13, para d)? Should be explained.

A paragraph at point d) of discussion has been added to explain this concept.

7. Why didn′t the authors search for RNA-interference or RNAi? These terms might also be relevant for the presented study.

The authors agree with the reviewer. However the aim of the present review was to focus on miRNA more than RNAi.

8. The authors should present a clear statement and conclusion of their findings giving any idea of their preference for potentially useful miRNAs.

See Table 2 and 4 and the new paragraphs at page 10.

Reviewer 3

The review paper by Sirio et al. describes the possibility of microRNAs as a diagnostic tool of HBV and HCV related liver diseases. As the authors concluded, there is no relationship between microRNA and HBV-HCV related liver diseases according to their analysis.

Although this manuscript concluded a negative result, their analysis result can be open to the public. This paper can be published after correction of a few mistyping; p. 12, l. 9: “a) study” should be “a) Study.” p. 13, l. 15: “.prognostic tools” should be “prognostic tools.”

The authors thanks the reviewer for the comments. Typos thorough the manuscript have been corrected

Reviewer 4

Dear editor Thanks for inviting me to review this manuscript from your prestigious journal. It is a nice review article that investigates correlation between miRNAs and hepatitis B and C viruses induced HCC development both in its diagnosis and prognosis. The search strategy and its protocol seem to be appropriate. Eligibility criteria have been described well. The results are very comprehensive however it would be very nice if the authors can summarize data about some of the miRNAs which have enough related studies in a table. I mean authors can design a table based on miRNAs not based on study and evaluate studies for and against a special miRNAs. I think this thing can be done for some of miRNAs and it can give a better view to the readers I have no other comments and I think that the manuscript can be accepted after considering aforementioned comment. Best Regards Mohammad Saeid Rezaee-Zavareh Middle East liver Disease Center, Tehran IR Iran Students’ Research Committee, Baqiyatallah University of Medical Sciences, Tehran IR Iran

The authors thanks the reviewer for the comments. The authors agree with the reviewer and a table ranking the miRNAs has been added (Tables 2 and 4, supplementary tables 1-3).

Reviewer 5

please see minor edits in the attached documents.

My major issues are

1) Is any MiRNA levels or SNP used for any cancer decision/prognostication yet? I suspect not in. If you think this is a area worth further study you should state what cancer has the best MiRNA data behind it and what the HCC field would need to get there.

In this moment clinical use of miRNAs are still under debate. The big issue is the high variability observed in miRNA results obtained by different studies, not only in HCC but also in all other tumors investigated for miRNAs expression (e.g. pancreas, brain tumors, …). According to the authors the habitual use of miRNAs in clinical practice is far to be applied.

2) despite cataloging a large number of papers, you never really quantitate the strength of current evidence for miRNAs. You state one is likely not enough but it would be useful for you to "rank" them in some rough order of which has the highest potential/ best current evidence

The authors agree with the reviewer and different tables ranking miRNAs (Tables 2 and 4, supplementary Tables 1-3) and a new paragraph at page 10 have been added.

3) Is there any MiRNA data in nonhepatitis virus HCC (or alcoholic liver disease wo HCC?) Often HCC is not a matter of just viral hepatitis but also steatohepatitis +/- alcohol

A paragraph has been included in the main text concerning the issue highlighted by the reviewer (pages 11-13).