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Editors-in-Chief

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Dear editors,

We have received your decision letter regarding our manuscript titled "Fibrosis regression following Hepatitis C antiviral therapy". We were happy to hear that the manuscript might be accepted for publication pending the completion of satisfactory revisions. We have revised the manuscript as much as possible in accordance with the reviewer comments. We wish to thank you and the reviewers for the valuable comments and helpful suggestions, which have contributed significantly to the improvement of our paper. We are also sending our point-by-point responses to the comments of the reviewers below.

Sincerely,

Mohamed El-Kassas

On behalf of the authors

REVIEWERS' COMMENTS

Responses to Reviewer #1

Dear Editor, the paper by Elsharkawy et al. entitled "Fibrosis regression following hepatitis C antiviral therapy" is a mini review of literature on regression of liver fibrosis in patients with chronic HCV infection after SVR. The paper can be improved.

R 1-1. An extensive revision of English is required. the meaning of several sentence appears unclear and must be better explained.

Response:

Thank you dear reviewer for the valuable suggestion. An English editing and revision has been made aiming to improve the quality of the manuscript.

R 1-2. Many studies evaluating the regression of hepatic fibrosis (and liver stiffness) after viral eradication have been omitted. Please add a table on the outcome reported in different study. And please add a second table on the histological outcome in this setting. - better explain the Histopathological features of fibrosis regression.

Response:

Thank you dear reviewer. Two tables have been added to the manuscript describing the outcome of different studies in literature regarding liver fibrosis both by invasive and non-invasive modalities.

R 1-3. Add the role of overlapping -better explain the pathogenesis and the burden of liver steatosis and inflammation on the liver stiffness.

Response:

Thank you dear reviewer. The role of overlapping the burden of liver steatosis and inflammation on liver stiffness has been added and explained.

Responses to Reviewer #2

R 2-1. In the manuscript "Fibrosis regression following hepatitis C antiviral therapy", Elsharkawy et al. presented a review of the literature focused on the topic of the possible regression of liver fibrosis in patients with chronic HCV infection after viral eradication. The topic is of great interest, especially in light of the need for more information on the correct management and follow-up of patients with SVR. The authors carefully analyze most aspects of the topic. However, the paper can be improved, both in content and form. Specifically, main issues are: - An extensive revision of English is required. Many sentences appear unclear and the vocabulary needs to be implemented. - At the end of the paragraph "HCV and liver fibrosis", a sentence is repeated consecutively. Moreover, the meaning of this sentence and the following ones (up to the end of the aforementioned paragraph) appears unclear and must be better explained, in order to avoid errors of understanding.

Response:

Thank you dear reviewer for the valuable comment. The sentence has been clarified and modified so as to avoid errors of understanding.

R 2-2. Many studies evaluating the regression of hepatic fibrosis (and liver stiffness) after viral eradication have been omitted. A more careful analysis of the relevant literature is needed. As an example: Rosato V et al. Factors affecting long-term changes of liver stiffness in direct-acting anti-hepatitis C virus therapy: A multicentre prospective study. J Viral Hepat. 2022 Jan;29(1):26-34. doi: 10.1111/jvh.13617. PMID: 34582610. - Similarly, several studies evaluating the clinical significance of liver stiffness regression following clearance of HCV have been omitted. For

example Rinaldi et al. show how the degree of improvement in liver stiffness after SVR can be a predictor of HCC risk (Rinaldi L et al. Role of Liver Stiffness Measurement in Predicting HCC Occurrence in Direct-Acting Antivirals Setting: A Real-Life Experience. Dig Dis Sci. 2019 Oct;64(10):3013-3019. doi: 10.1007/s10620-019-05604-8. PMID: 30937719).

Response:

Thank you dear reviewer for the valuable suggestion. A more careful analysis of literature has been attempted; and tables of outcome of fibrosis and fibrosis regression following HCV treatment have been added. The suggested studies have also been added and explained.

R 2-3. In the paragraph "Fibrosis regression following HCV treatment: does fibrosis really regress?", no reference was made about the potential impact of the damage cofactors (eg: obesity, diabetes mellitus) in influencing the regression of fibrosis. In my opinion this concept is crucial and needs to be discussed.

Response:

Thank you dear reviewer for the comment. The reference was added to the paragraph. The concept of factors influencing fibrosis regression has been added and highlighted.

R 2-4. The paragraphs "Antiviral treatment for HCV" and "Evaluation of fibrosis" show contents that need to be anticipated for the correct reading and understanding of the manuscript. It is therefore advisable to insert these paragraphs (or part of them) in the first part of the paper.

Response:

Thank you dear reviewer for the suggestion. These paragraphs have been added and inserted in the first part of the manuscript.

R 2-5. The acronym LSM at the end of the paragraph "Fibrosis regression following HCV treatment: does fibrosis really regress?" it has never previously been fully explained.

Response:

Thank you dear reviewer. This acronym has been modified.

R 2-6. In the section "Effect of fibrosis regression on clinical outcomes" the impact of viral eradication on some of the most important HCV-related extrahepatic manifestations (eg diabetes and atherosclerosis) is omitted. Numerous works deal with this theme. Eg: - Adinolfi LE, et al. Reduced incidence of type 2 diabetes in patients with chronic hepatitis C virus infection cleared by direct-acting antiviral therapy: A prospective study. Diabetes Obes Metab. 2020 Dec;22(12):2408-2416. doi: 10.1111/dom.14168. PMID: 32761721. - Adinolfi LE, et al. Impact of hepatitis C virus clearance by direct-acting antiviral treatment on the incidence of major cardiovascular events: A prospective multicentre study. Atherosclerosis. 2020 Mar;296:40-47. doi: 10.1016/j.atherosclerosis.2020.01.010. PMID: 32005004.

Response:

Thank you dear reviewer for the worthy suggestion. The impact of viral eradication on HCV-related extrahepatic manifestations have been added. Additionally, the suggested studies have been added and explained.

R 2-7. Finally, in my opinion, it is necessary to better explain why the interpretation of the improvement of liver stiffness must be evaluated with caution and not assimilated to the regression of liver fibrosis. In particular, it is necessary to better explain the role of steatosis and especially inflammation, which appear to significantly influence liver stiffness.

Response:

Thank you dear reviewer for the valuable suggestion. The role of steatosis and inflammation has been added and explained.

Responses to Reviewer #3

R 3-1. My detailed comments are as follows: 1.Could you review more about the specific pathophysiological mechanisms of liver fibrosis regression after Hepatitis C therapy?

Response:

Thank you dear reviewer. We have added details about the pathophysiological mechanisms of liver fibrosis regression after HCV therapy.

R 3-2. Could you draw diagrams or tables about the key points of the article?

Response:

Thank you dear reviewer for the worthy suggestion. A table with the key points of the article has been added.

Again, we would like to express our appreciation to the Editors and the reviewers for the comments on our paper. If you have any further queries, please do not hesitate to contact us.

Thank you