Dear Editor,

We appreciated your great efforts during evaluation of our research which added too much to our knowledge; we will do our best to respond to the reviewers comments properly. All the changes were made in the text by word track changes.

Much Obliged

Reviewer 1

Manuscript overall is very good.... but the authors need to summarise the data into tables and the conclusion can be a little more elaborate.....add a note on limitations of the study

Response to Reviewers' comment

Thanks sir for your positive feedback, and we really appreciate your valuable and important comments.

We tried to summarize more the study results, however, we are still limited with the journal recommendation regarding number of allowed tables. We tried also to elaborate the conclusion section as per your advice. Additionally, we added to the limitations section in the study discussion.

Once again, thanks for the valuable comments and support.

Reviewer 2

Dear authors This in an important issue that has created doubts in

the hepatology community. However, it is now recognized that the effect of higher

rates of HCC after treatment with DAA could be related to treat worse patients that would never tolerate IFN-based therapies. Your study is very interesting as it presents different results, but there are some question that should be clarified:

- Why were patients from group II not treated with DAA?

  Response: Thanks sir for your positive feedback, and we really appreciate your valuable and important comments.

  Thanks for elaborating this point. Patients in group II were presented to our institute with HCC as the first presentation without previous diagnosis with HCV. This was clarified in the manuscript.

- Were they treated with IFN-based therapies? Had they achieved SVR?

  Response: Being presenting with HCC as the first presentation, None of group II patients were previously treated with any antiviral agents including interferon.

- Were there other cause-related deaths in group II?

  Response: Thanks for your comment, and we totally agree with you that the survival and other fate related data is so important. However, it wasn't reported during the study conduction, as being a case-control cross sectional study without further longitudinal follow up. This was added to limitation section, and a recommendation for further follow up of the studied cohort to detect and compare the survival was provided.

- As they had more advanced liver disease, they could not have time to develop HCC.

Response: Thanks for raising this. As stated in the previous point, most of them weren't under a surveillance program for early detection of HCC, neither for their chronic liver disease.

- In the case of your results, how would you explain higher rates of HCC with DAA treated patients?

  Response: We didn't intend to measure the rates of HCC development in each group, as we included all coming patients with HCC and then divided them according to history of DAAs exposure. Alternatively, HCC in DAAs treated patients had more tendency to present with multifocal lesions (53%) in comparison to (25%) in DAAs naive patients. Moreover, HCCs in group I patients tended to present with bigger tumor size at the initial presentation than group II patients. The same findings were reported in similar studies, suggesting a possible DAAs role in such aggressive behavior.

  We added this paragraph to the discussion section to clarify this point: Many theories have been proposed to explain this unexpected event; some researchers have related the development of HCC to baseline risk factors such as advanced fibrosis grade, HBV co-infection, or age. Another theory proposes that DAAs cause immune surveillance mechanisms to become dysregulated as a result of the rapid viral clearance; and this behavior has been confirmed by several investigations. With the downregulation of type II and III IFNs, their receptors, and IFN-stimulated genes, this dysregulation may result in the re-establishment of innate immunity. Due to the anti-angiogenic and anti-proliferative capabilities of IFN, which DAAs lack, a

reduction in IFN activation may promote the proliferation of malignant cells. Furthermore, after HCV eradication, one of the immune system alterations observed is a decrease in the number of cytotoxic activity of natural killer (NK) cells in the liver, which favours a faster progression of HCC foci.

Reviewer3

The work by Magdy Fouad et al. retrospectively analyzed the differences in basic clinical, radiological and laboratory characteristics as well as tumor behavior upon HCC diagnosis between patients with and without a previous history of DAAs exposure. The authors reported that aggressive tumours were more common in DAAs exposed patients and anti-HCV therapy in HCC patients should be postponed until a consistent risk-benefit ratio is established through further research. This work is interesting and instructive. There are several questions should be addressed before acceptance.

1. The third paragraph in introduction is obscure. First, I could not retrieve the cited paper in Pubmed (ref 6); second, the author should have cited the paper by the Italian group. So, "This study included 344 patients with HCV-related cirrhosis who received different DAA regimens", who conducted this study?

   Response: Thanks a lot for this constructive comment. We worked on this to complete the missing data and clarify what is meant. The

reference number 6 was corrected, and the missing reference (number 9), was added.

2. What is the final outcome (Overall survival, RFS) of these patients? Follow-up data are required.

   Response: Thanks for your comment, and we totally agree with you that the survival and other fate related data is so important. However, it wasn't reported during the study conduction, as being a case-control cross sectional study without further longitudinal follow up. This was added to limitation section, and a recommendation for further follow up of the studied cohort to detect and compare the survival was provided.

3. The statement "group 1/I", "group 2/II" should be consistent throughout the paper. There are several writing errors in this manuscript.

   Response: Thanks for your comment. We have revised the paper thoroughly to correct this, and to improve the language and fix grammar mistakes.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar,

sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response: Additional English language revision was performed.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly. Now we list the abbreviations rules as follows.

(1) Title: Please spell out any abbreviation in the title. Abbreviations are not permitted.

(2) Running title: Please shorten the running title to no more than 6 words. Abbreviations are permitted.

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

(4) Key words: Abbreviations must be defined upon first appearance in the Key words.

(5) Core tip: Abbreviations must be defined upon first appearance in the Core tip. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(8) Figures: Please verify the abbreviations used in figures and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

(9) Tables: Please verify the abbreviations used in tables and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

Response: Thanks for that. We did our best to stick to the journal style and recommendations.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) ***Science editor:*** 1 Scientific quality: The manuscript describes a Case Control Study of the hepatocellular carcinoma after direct-acting antivirals. The topic is within the scope of the WJH. (1) Classification: Grade B, C and C; (2) Summary of the Peer-Review Report:Manuscript overall is very good, but the authors need to summarise the data into tables and the conclusion. Some points need to be clarified.

The questions raised by the reviewers should be answered; (3) Format: There are 4 tables and 1 figure; (4) References: A total of 22 references are cited, including 6 references published in the last 3 years; (5) Self-cited references: There are 3 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated. 2 Language evaluation: Classification: Grade B, B and B. A language editing certificate issued by Helwan University, Research Support Center was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form and theWritten informed consent. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJH. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (2) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; (3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text. 6 Recommendation: Conditional acceptance.

(2) ***Company editor-in-chief:*** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thanks for that. We did our best to correct all the mentioned details and to stick to the journal style and recommendations.