

May, 2018

Dear Editor,

enclosed, you'll find the revised manuscript in Word format (file name: Review\_HCC\_DAA may). The modified sentences are highlighted in green.

**Name of Journal:** World Journal of Gastroenterology

**MS:** 39311

**Title:** Direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C: a few lights and many shadows.

**Point-by point response to reviewers comments.**

**Editor:**

1. Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

*Done*

2. Please revise and perfect your manuscript according to peer-reviewers' comments.

*Done*

3. Please add some figures, or we cannot accept it.

*Done. Two figures have been provided and the figure legends is in the manuscript file, before the tables section.*

4. Add postcode here

*Done*

5. Full name (Orcid number)

*Done*

6. Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance.

Please refer to Instruction to authors on our website or attached Format for detailed information.

*Done*

7. Please provide all authors abbreviation names and manuscript title here. World J Gastroenterol 2018; In press

*Done*

8. Please correct all references numbers like this

*Done*

9. Please check and confirm that there are no repeated references! Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI. PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.\*\*)

*Done*

#### **Reviewer #1:**

1. Authors described “Studies from the IFN-era taught us that HCV eradication reduces but does not eliminate the risk of HCC once cirrhosis has been established (5).” However, **Nishiguchi** et al. [Lancet. 1995] demonstrated that interferon-alpha improved liver function and that its use could be associated with a reduction of HCC in patients with chronic HCV infection and cirrhosis. Authors should discuss more carefully.

*Done. See page 5*

2. HCV-DAA and HCC recurrence Authors should refer the recent editorial of **Hepatology International** (2018 Mar;12(2):90-93. doi: 10.1007/s12072-018-9862-1.) at the point of recurrence after DAA treatment.

*Done. See page 15*

#### **Reviewer #2:**

The review entitled “Direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C: a few lights and many shadows” by Guarino et al., has been assessed as follows; This review analyses the scientific literature regarding the risk of HCC in terms of its recurrence and occurrence after the use of DAAs to eradicate HCV infection., this review does not suggest that there is a higher rate of

de novo HCC occurrence or recurrence after DAA therapy in patients with previous HCV infection.

**Reviewer #3:**

Shimizu et al. published an article regarding the relationship of occult HBV infection and HCC recurrence after DAA. **Shimizu**, H., Matsui, K., Iwabuchi, S. et al. Relationship of hepatitis B virus infection to the recurrence of hepatocellular carcinoma after direct acting antivirals Indian J Gastroenterol (2017) 36: 235. They found a striking association between anti-HBc positivity and HCC recurrence after DAA therapy. Please include their insights into your manuscript.

*Done. See page 12 and Table 2*

**Reviewer #4:**

1- It could be useful to update the literature search until April 2018 instead of February 2018 and so to cite the following papers recently published and:

- Does interferon-free direct-acting antiviral therapy for hepatitis C after curative treatment for hepatocellular carcinoma lead to unexpected recurrences of HCC? A multicenter study by the Japanese Red Cross Hospital Liver Study Group. **Mashiba** T, Joko K, Kurosaki M, Ochi H, Osaki Y, Kojima Y, Nakata R, Goto T, Takehiro A, Kimura H, Mitsuda A, Kawanami C, Uchida Y, Ogawa C, Kusakabe A, Narita R, Ide Y, Abe T, Tsuji K, Kitamura T, Okada K, Sohda T, Shigeno M, Satou T, Izumi N. PLoS One. 2018 Apr 16;13(4):e0194704. doi: 10.1371/journal.pone.0194704.
- Incidence of Hepatocellular Carcinoma in Patients with HCV-associated Cirrhosis Treated with Direct-Acting Antiviral Agents. **Calvaruso** V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, Tinè F, Distefano M, Licata A, Giannitrapani L, Prestileo T, Mazzola G, Di Rosolini MA, Larocca L, Bertino G, Digiacomio A, Benanti F, Guarneri L, Averna A, Iacobello C, Magro A, Scalisi I, Cartabellotta F, Savalli F, Barbara M, Davì A, Russello M, Scifo G, Squadrito G, Cammà C, Raimondo G, Craxì A, Di Marco V; Rete Sicilia Selezione Terapia- HCV (RESIST-HCV). Gastroenterology. 2018 Apr 12. pii: S0016-5085(18)30441-4
- Liver Angiopoietin-2 is a key predictor of de novo or recurrent hepatocellular cancer after HCV direct-acting antivirals. **Faillaci** F, Marzi L, Critelli R, Milosa F, Schepis F, Turola E, Andreani S, Vandelli G, Bernabucci V, Lei B, D'Ambrosio F, Bristot L, Cavalletto L, Chemello L, Sighinolfi P, Manni P, Maiorana A, Caporali C, Bianchini M, Marsico M, Turco L, de Maria N, Del Buono M, Todesca P, di Lena L, Romagnoli D, Magistri P, di Benedetto F, Bruno S, Taliani G, Giannelli G, Martinez-Chantar ML, Villa E. Hepatology. 2018 Mar 31
- **Abenavoli** L, Boccuto L. New serum markers for detection of early hepatocellular carcinoma. Panminerva Med. 2017 Dec;59(4):281-282.

*Done. See pages 7; 14; 16 and Tables 1 and 2*

2- There are some typographical errors in the Reference paragraph: please, check them. The authors answered my comments.

*Done.*

Thank you again for revising our manuscript.  
Sincerely yours,

Nicola Caporaso  
Full Professor of Gastroenterology  
Department of Clinical Medicine and Surgery, Gastroenterology Unit,  
University of Naples "Federico II"  
Via S. Pansini,5- 80131 Naples  
Tel.:+390817462761; fax:+390817464746  
e-mail address: nicola.caporaso@unina.it