

## ANSWERING REVIEWERS

June 24, 2019

Dear Editor and Reviewers,

Please find enclosed the edited manuscript in Word format (file name: 48753-edited.doc).

**Title:** The impact of the national Human Development Index on liver cancer outcomes: transition from 2008 to 2018

**Authors:** Shi-Yi Shao, Qi-Da Hu, Meng Wang, Xin-Yu Zhao, Wang-Teng Wu, Ting-Bo Liang

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

**Manuscript NO:** 48753

Thank you for your letter and reviewers' precious comments concerning our manuscript. We have studied those comments carefully and made revisions according to the suggestions of reviewers which we hope would meet with approval.

1   Format has been updated.

2   Answer to reviewers' questions

(1) Q (Number ID 03648086): Would the authors be able to justify why choosing the 15% cutoff for an increase and decrease in the MIR value (the

mortality-to-incidence ratio) when describing the transition from 2008 to 2018 (In results section 3.3 and Fig 3a)?

A: We appreciate this great question. We initially intended to describe that countries with decreasing MIR were far more than those with rising MIR values. In particular, MIR in some countries have declined substantially, even more than 15%. So the number 15% is not a cutoff line, we just chose this as an supporting evidence to describe the phenomenon that the overall trend of MIR was declining. Furthermore, the detailed transition of MIR from 2008 to 2018 of certain countries was shown in **Table 1**.

(2) Q (Number ID 03648086): Figure 2 and 3 are showing very important data points. In order to improve the overall intuition, the authors should keep a consistent color schema in figures. Could authors use RED for the data points of 2018, and BLUE for those of 2008 in Figure 2a-e (“e” is missing in the current version) and in Figure 3b? The same color change could be made for word “2018” and “2008” in the figures.

A: It is our negligence and we are so sorry about this. We have made color changes according to reviewer’s advice and now Figure 2 and 3 are in a consistent color schema, “E” is added in Figure 2 as well.

(3) Q (Number ID 03648086): the parts (a -e) in Figure 2 are too crowded. More space should be available if the authors intend to make it a 2-column figure

A: As the reviewer’s good advice, we have modified the layout of Figure 2 to make it a better version.

(4) Q (Number ID 02998194): The only thing I would like to mention is that a noticeable part of discussion is about details of treatment of HCC which are not mentioned before.

A: As we mentioned in **Introduction** (*Page 6, Para. 2*), the manner in which social development and medical advances have benefited liver cancer patients

and the degree of the impact in the past decade are still unknown. The new therapeutic regimens for HCC are emerging. Especially immunotherapy, many preclinical and clinical studies showed immune checkpoint blockades are effective treatment strategy for HCC (Mizukoshi E, Hepatology 2011; 53:1206–1216; Flynn MJ, Hepatology 2018, DOI: 10.1002/hep.30337). For example, encouraging clinical outcomes were reported from ongoing phase I/II trials of the anti-PD-1 antibody nivolumab for HCC patients (Kudo, Liver Cancer 2016; 6(1):1-12; El-Khoueiry AB, Lancet. 2017; 389(10088):2492-2502). As for cancer vaccine, a series of clinical trials testing cancer vaccines as adjuvant therapy for HCC patients are currently ongoing (UMINCTR: 000002614; NCT03203005). Furthermore, clinical trials have shown that the combination of cancer vaccines and immunomodulatory drugs, such as chemotherapy and checkpoint inhibitors, induces a better clinical outcome than individual treatments (Sharma P, Cell 2015; 161: 205–214; NCT01522820; Greten TF, BMC Cancer 2010;10:209). While nucleotide-based regulation, including miRNA, lncRNA and circRNA, *via* nanoparticle-mediated drug delivery is also showing promising therapeutic perspectives, though has not been put into clinical practice yet (Bogorad RL, Nat Commun 2014;5:3869; Varshney A, Hepatology 2018;67(4):1392-1407).

- 3 Formula in *Statistical analysis* was revised into an editable version.
- 4 References and typesetting were corrected.
- 5 The manuscript has been copyedited by Springer Nature Author Services for SCI Biomedical Editing and Publishing for language polishing.
- 6 Figures were changed into a decomposable edition. These figures were in a separate MICROSOFT POWERPOINT file.
- 7 We have conducted this secondary analysis based on existing public data. Our major data resources are (1) GLOBOCAN database 2018 and 2008, (2)

HDI: UNDP database, (3) the CONCORD-3 report. This study does not involve any human or animal subjects, nor personal or medical data.

Approval file of institutional review board is not applicable.

- 8 One of the author Bing-Feng Huang was replaced with Jun-Ming Huang, the latter colleague has made great contribution in revising the manuscript and giving important suggestions.

Thank you again for your great suggestions and considering to publish our manuscript in *World Journal of Gastroenterology*.

Sincerely yours,

Ting-bo Liang