January 14, 2021

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 61832-Review.docx).

Title: Early Diagnosis and Therapeutic Strategies for Hepatocellular Carcinoma: From Bench to Bedside

Author: Ming-Cheng Guan, Ming-Da Wang, Si-Yu Liu, Wei Ouyang, Lei Liang, Timothy M. Pawlik, Qiu-Ran Xu, Dong-Sheng Huang, Feng Shen, Hong Zhu, Tian Yang

Name of Journal: World Journal of Gastrointestinal Oncology

ESPS Manuscript NO: 61832

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) **Reviewer #1:** *HCC is among the most common and mortality cancers in many countries of the world. HCC mostly develops secondary to some underlying diseases. Today, the best screening method for HCC is US + AFP measurements. however, it is known that some HCCs do not produce AFP. So it is obvious that there is a need for a new biomarker in screening. However, epidemiologically, a biomarker must be cheap and easily accessible in order to be used in screening. Markers used in current studies are quite expensive. Considering that the countries where HCC is most common are the underdeveloped countries, it is obvious that this issue should be discussed. I think the article is publishable*

Response:

We greatly appreciate the reviewer #1 for the positive and constructive comments and suggestions.

(2) Reviewer #2: *This is an interesting and comprehensive review on early diagnosis of hepatocellular carcinoma (HCC). The detailed information of miR-125b, miR-122 and miR-21 as biomarkers for the early detection of HCC may be added in non-coding RNA section.*

Response:

We thank Reviewer #2 for the favorable comments. The following sentences have been added in the revised paper (Page 10, Line 21).

Subgroup analysis in a recent meta-analysis noted that the pooled sensitivity, specificity, and AUC of miR-125b for detecting HBV-related HCC patients were 0.95, 0.79, and 0.95, respectively[32]. Another meta-analysis of 13 studies including 920 HCC patients and 1217 controls revealed that the pooled sensitivities, specificities, and AUCs of serum miR-122 were 0.76, 0.75, and 0.82 for distinguishing HCC patients from overall controls; and 0.79, 0.82, and 0.87 for differentiating HCC from HBV or HCV infection; respectively[33]. MiR-21 might be another useful biomarker for early detection of HCC, with the pooled sensitivity, specificity, and AUC of 85.2%, 79.2%, and 0.89, respectively[35]. However, prospective population-based studies with larger sample sizes and different ethnic groups are needed to further validate these findings.

32 Jin X, Cai C, Qiu Y. Diagnostic Value of Circulating microRNAs in Hepatitis B Virus-Related Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. J Cancer 2019; 10(20): 4754-4764 [PMID: 31598147 PMCID: PMC6775527 DOI: 10.7150/jca.32833]

33 Zhao XF, Li N, Lin DD, Sun LB. Circulating MicroRNA-122 for the Diagnosis of Hepatocellular Carcinoma: A Meta-Analysis. Biomed Res Int 2020; 2020: 5353695 [PMID: 32309434 PMCID: PMC7139899 DOI: 10.1155/2020/5353695]

35 Qu J, Yang J, Chen M, Cui L, Wang T, Gao W, Tian J, Wei R. MicroRNA-21 as a diagnostic marker for hepatocellular carcinoma: A systematic review and meta-analysis. Pak J Med Sci 2019; 35(5): 1466-1471 [PMID: 31489028 PMCID: PMC6717466 DOI: 10.12669/pjms.35.5.685]

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Oncology.*

Sincerely yours,

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