Dear Editor,

We are pleased to enclosed our revision of our paper (Manuscript NO: 81402) entitled "Better performance of serum protein induced by vitamin K absence or antagonist-II for detecting hepatocellular carcinoma in patients with chronic liver disease with normal serum total bilirubin" for your consideration in *World Journal of Gastroenterology*.

We have carefully considered the insightful comments from the reviewers and revised the manuscript accordingly. A point-by-point response is enclosed follow. The revised manuscript has followed all points in the Author Guidelines of *World Journal of Gastroenterology*.

We earnestly appreciate your warm work and hope that the correction will meet with approval.

Yours sincerely,

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Point-by-point Response

Manuscript NO: 81402

Reviewer #1

1. AFP is a biomarker widely accepted in the world, while PIVKA-II is not commonly used in the western countries, although it is increasing used in China, Japan and Korea. Whether the specificity and sensitivity of PIVKA-II are superior to AFP in this population?

Reply: This is a very good question. In this population, the diagnostic performance of PIVKA-II is more superior than AFP, both in early-stage HCC (0.765 vs. 0.676, $P = 0.0183$) and late-stage HCC (0.966 vs. 0.851, $P < 0.0001$). This was consistent with prior studies demonstrating that PIVKA-II showed a better diagnostic performance than AFP in diagnosing HCC (PMID: 28620797; PMID: 30257796; PMID: 23834468).

2. Several methods are applied to PIVKA-II detection, including chemiluminescence and ELISA detection. Please provide detection methods and reagents. If multiple methods are used, how to keep the consistency in the quantitative results.

Reply: Thanks for your thoughtful suggestion. Only chemiluminescence enzyme immunoassay method was used in our study. To be specific, serum PIVKA-II levels were determined on the chemiluminescence enzyme immunoassay (LUMIPULSE®G1200, FUJIREBIO INC, Japan) by using Lumipulse® G PIVKA-II reaction cartridges according to manufacturer's instructions in the clinical laboratory of Mengchao Hepatobiliary Hospital of Fujian Medical University. We have supplemented the detection method and reagent in the manuscript. **(Please see Page 7, 2.2 Study variables)**

Reviewer #2

Major:

1. It is essential to know the reason for the exclusion of varices from the study.

Reply: Thanks for your comments. We are sorry not stating it clearly in the manuscript. Patients with **recent** esophageal and gastric varices **bleeding** will be excluded from the study because PIVKA-II levels might be overestimated in these patients. They may have coagulation disorders, accompanied with abnormal vitamin K and γ-glutamyl carboxylase synthesis and function, which further affect the production of PIVKA-II (PMID: 2555045, PMID: 3896125). Therefore, 13 patients with **recent** esophageal and gastric varices **bleeding** were excluded from the study. Actually, the 13 patients with esophageal and gastric varices **bleeding** excluded from the study had a median PIVKA-II level of 165 mAU/mL (range: 46 mAU/mL to 2185 mAU/mL), all higher than the upper limit of normal (ULN) of 40 mAU/mL.

2. Currently, the BCLC system has been widely used for guiding prognosis and treatment in patients with HCC. Could the authors analyze by stratifying the BCLC stages?

Reply: Thanks for the reviewer's thoughtful suggestion. It is well known that the BCLC staging system includes prognostic variables related to tumor status, liver function and health performance status (Eastern Cooperative Oncology Group performance status). After a careful assessment about the electronic medical records involved in this retrospective study, we found with regret that the health performance status could not be evaluated with precision, and further as well as the BCLC staging system. So we selected the Milan criteria staging system to achieve these analyses in the study (127 early-stage HCC within the Milan criteria, 140 late-stage HCC beyond the Milan

criteria). It is worth mentioning that the tumor status of Milan criteria staging system is almost same to the tumor status of the BCLC staging system, and the former is even more strict with single tumor size (single ≤ 5 cm vs single with no limitation) in early stage (PMID: 29628281).

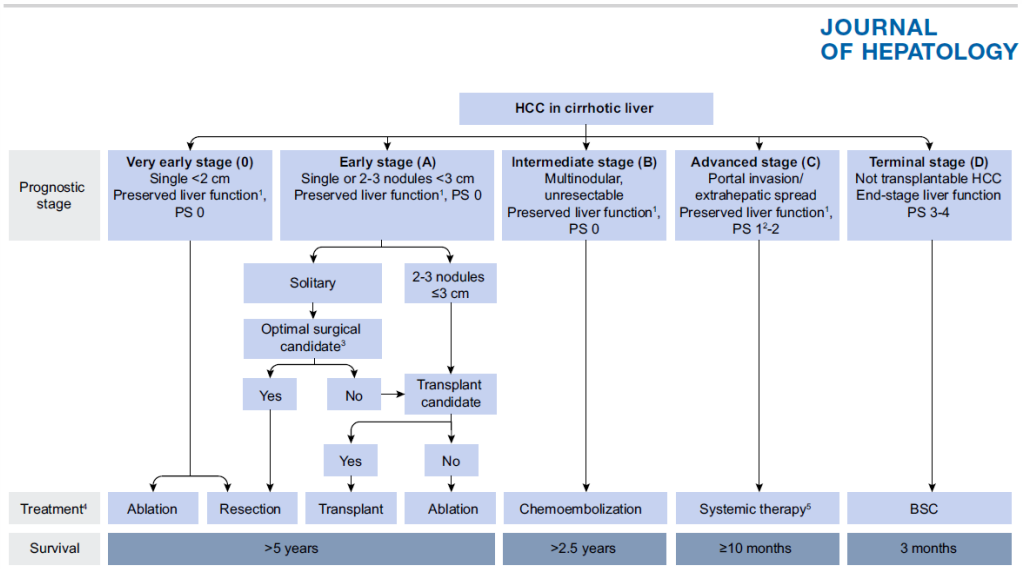

Fig. 3. Modified BCLC staging system and treatment strategy. [1]**"Preserved liver function"** refers to Child-Pugh A without any ascites, considered conditions

Minor:

1. Could the authors provide the IRB number in the ethical part of the manuscript?

Reply: We have provided the IRB number in the ethical part of the manuscript **(Please see Page 7, 2.1 Patient selection, Paragraph 5)**

2. There were varied in the cutoff level of PIVKA-II. Please cite the reference of the cutoff in the manuscript.

Reply: The "Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update (PMID: 28620797)" showed that PIVKA-II with cut-off value of 40 mAU/mL had a better performance, we have added this reference in the manuscript. **(Please see Page 7, 2.2 Study variables)**

3. Table 1: Could the authors describe the proportion of cirrhosis in percentage?

Reply: We have described the proportion of cirrhosis in percentage in Table 1 (**Please see Table 1**). Thank you.