27 June 2016

Dear Dr. Ma,

Re: Resubmission of manuscript reference No. 25849

Please find attached a revised version of our manuscript "**Hepatocellular Carcinoma (HCC) Screening and Surveillance in 2,293 Chronic Hepatitis B (CHB) Patients in an Endemic Area**", which we would like to submit for consideration for publication as a Prospective Study in the *World Journal of Gastroenterology*.

The comments of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. Our point-by-point responses to each of the comments of the reviewers are detailed below.

Revisions to the text are shown using yellow highlight for additions. We hope that the revisions to the manuscript and our accompanying responses will be sufficient to ensure that our manuscript is now suitable for publication in the *World Journal of Gastroenterology*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Response to the comments of Reviewer #02445074

My recommendation is accept with minor modifications.

GENERAL COMMENTS: This study has important implications for government policy in Thailand in relationship to treating HCC, a major cause of death. This society does not have options for liver transplantation. The AUS screening program followed by surveillance and treatment if necessary, was shown to be sufficient and valuable for patients of >40 years.

SPECIFIC COMMENTS: Abstract Remove use of first person. Abstract higher survival rate

Response: *Thank you for your suggestion. We no longer use the first person in the revised Abstract. Regarding the survival rate in HCC patients, it was as high as that reported in another study (ref. 26); we have concluded as such in the revised Abstract.*

Response to the comments of Reviewer #00012216

Teerapat U et al carry out a retrospective descriptive longitudinal analysis to describe the incidence and prevalence of hepatocellular carcinoma (HCC) in chronic HBV infected patients from Thailand. They also define the role of liver ultrasound and alphe-fetoprotein for the early HCC detection. The work is interesting with a big sample size, and the method is appropriate. Nevertheless, I would add some comments. Authors should define their gold standard for HCC diagnosis, in order to calculate properly the sensitivity and specificity. If the gold standard of the HCC diagnosis is the absence of developing a symptomatic tumour during follow-up, they should only use for the analysis, the new cases among those patients with a long enough follow-up as to develop symptoms in case they were not correctly diagnosed. They obtain a high sensitivity for the US screening that could be biased if they have not used and appropriated gold standard to be sure that the patient does not have an HCC. They carry out an MRI or CT only in those cases with a solid nodule in the US, but could be possible that in some cases, HCC were not seen in US but visible with a CT and this would change the sensitivity. In my opinion, with the design of the study they cannot define the sensitivity and specificity of US for HCC screening. In fact, other studies show lower sensitivities for US to detect HCC (ClinGastroenterolHepatol. 2011

Feb;9(2):161-7). In any case, the manuscript is interesting because describe the incidence and prevalence of HCC among chronic HBV Thai patients.

1. "Authors should define their gold standard for HCC diagnosis, in order to calculate properly the sensitivity and specificity"

   Response: *Thank you for your comment. Our HCC diagnostic criteria was in accordance with the AASLD guidelines 2011 (**ref. 18**), which was stated in the original manuscript (**page 8, lines 11-13**). The gold standard for HCC diagnosis in this study was thus defined by either of the following criteria:*

   1) *Histologic criteria (14 out of 17 HCCs in our study) or*
   2) *Radiologic criteria: Nodules >1 cm in size with arterial hypervascularity and venous or delayed phase washout, using more than one contrast-enhanced study (3 out of 17 HCCs in our study).*

2. "If the gold standard of the HCC diagnosis is the absence of developing a symptomatic tumour during follow-up, they should only use for the analysis, the new cases among those patients with a long enough follow-up as to develop symptoms in case they were not correctly diagnosed. They obtain a high sensitivity for the US screening that could be biased if they have not used and appropriated gold standard to be sure that the patient does not have an HCC"

   Response: *Thank you for your comment. The HCC diagnosis does not depend on the presence of symptomatic or asymptomatic tumors. We strictly followed the AASLD criteria as mentioned above (**ref. 18**). Therefore, our data could not be biased because we used the appropriate gold standard.*

3. "They carry out an MRI or CT only in those cases with a solid nodule in the US, but could be possible that in some cases, HCC were not seen in US but visible with a CT and this would change the sensitivity. In my opinion, with the design of the study they cannot define the sensitivity and specificity of US for HCC screening"

   Response: *Thank you for your concern. We have clarified that CT/MRI or biopsy was undertaken in any case with a visible nodule revealed using AUS in our study (**page 8, lines 1-4**).*

*We used all of the HCC patients to calculate the sensitivity and specificity of AUS; thus, the validity of the AUS should not be compromised (**page 8, lines 22-26**). In addition, in our study there was good patient adherence to follow-up; 85% of the patients were followed up as scheduled. Therefore, we are confident that the calculation of sensitivity and specificity is accurate.*

4. "In my opinion, with the design of the study they cannot define the sensitivity and specificity of US for HCC screening. In fact, other studies show lower sensitivities for US to detect HCC (ClinGastroenterolHepatol. 2011 Feb;9(2):161-7).

Response: *We used the same design as in previous studies. The sensitivity of AUS varied among most previous studies, ranging from 71 to 84% depending on the operator's performance (**as discussed on page 6, lines 6-8 and ref. 15**).*

*The study mentioned above (Clin Gastroenterol Hepatol. 2011 Feb;9(2):161-7) recruited all patients with cirrhosis, which markedly differed from our study (only 3% of our patients had cirrhosis, therefore, the sensitivity of AUS may be different because of the different recruited population. In addition, the sensitivity was high in our study because our radiologists were specially trained in AUS and have extensive experiences in HCC screening (they perform >4000 AUS/year), which could explain our high sensitivity. Nevertheless, we have now added your recommended reference (Clin Gastroenterol Hepatol. 2011 Feb;9(2):161-7) as **ref. no. 16**.*

Responses to the comments of Reviewer #00001541

This is a well designed and presented work conveying useful clinical information on the value of US screening of HBV-infected patients for early detection of HCC in Thailand. Minor point: in the abstract and in the text it should be made clear that the values of HCC prevalence or incidence refer to the HBV-infected population

Response: *Thank you for your suggestion. We have also mentioned the high prevalence and incidence of HCC associated with HBV-infection in our study in the Abstract (**page 4, lines 20-21**) and in the Discussion section (**page 11, lines 6-9**).*