Point-to-point response

Dear Song-Zhu Yang and co-authors, I would like to mention some comments regarding your manuscript. It is well written, presented and the methods and results are good. However, I would suggest including some key points:

1-The conclusion of the abstract is very simple. Try to conclude with some future perspectives applying your findings in the clinical practice.

Thank you for this valuable comment. We revised the abstract. (Page 4)

2-Methods: please define which clinicopathologic parameters were used.

We have defined which clinicopathologic parameters were used in Page 7 Line 10.

3-The authors mention that the inclusion criteria were those patients with HCC confirmed during pathology who were treated in the ..... Treated with what???? Surgery, transplantation, radio frequency ablation?? It is not clear.

All patients were treated with surgery in the Department of Hepatobiliary Surgery, Yantaishan Hospital, between January 2012 and June 2012.

4-How the initial HCC diagnosis was done? Imaging criteria? AASLD, EASL criteria? Please define this key point.

The diagnosis of HCC was made based on guidelines from the Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association.

Ref: The guidelines of prevention and treatment for chronic hepatitis B (In Chinese). Chin J Hepatol 2005; 13:881e91.

5-Which were the exclusion criteria.

The exclusion criteria were 1. Patients received other treatment (TACE, RFA or others) before surgery. 2. Patients have other tumor diseases.

6-Which HCC related stratification method (eg: HKLC or BCLC) was applied?

We didn't apply the HCC related stratification method. From our clinical point of view, BCLC is not suitable for patients with HCC who need resection.

7-Did tumor invasion was diagnosed during imaging or only during pathologic analysis? Tumor vein invasion: macrovascular or microvascular invasion?

Tumor invasion was diagnosed only during pathologic analysis. Tumor vein invasion was mainly microvascular invasion.

8-What about tumor grade or nuclear grade, Edmonson steiner grading system, and microvascular invasion??? Did KIF1B expression correlated with serum AFP??

Our hospital is not performed tumor grade, nuclear grade and Edmonson steiner grading system. Tumor vein invasion means microvascular invasion. We only have serum AFP values of 31 patients. The correlated analysis shows that KIF1B expression

has no correlated with serum AFP based on the limited data. So we did not show this result because of no significant.

9-How the follow-up was assessed in all patients. The authors did not clearly describe this key point because tumor recurrence might be influenced by how the follow up and tumor recurrence assessement was performed. I cannot consider if this lead to a time bias. The author mention that the patients with tumor invasion and with low KIF1B expression had worst prognosis, but they did not clearly show at what time point the imaging follow up was performed in all patients. This was a retrospective analysis and I feel that the imaging assessment was not uniform in all the patients. Please clarify this.

After discharge, 68 patients were followed up regularly at our outpatient clinic, every 3 months in the first year and every 6 months thereafter. The visit consisted of liver function tests, levels of AFP, chest radiography, ultrasonography, CT, and/or MRI. A diagnosis of recurrence was based mainly on a combination of increased AFP level; typical manifestations on CT, MRI, or hepatic arteriograph; and, if necessary, percutaneous needle biopsy.

10- The main finding is that those patients with low KIF1B expression had higher tumor invasion and worst survival and higher recurrence rate. However, does this finding add any new data? We already know that those patients with tumor invasion are prone to develop recurrence and worst outcomes after liver resection. Indeed, liver resection in the US, european and latinamerican countries is not performed and it is consider BCLC stage C: sorafenib only. What are the main clinical messages and application of your findings?

In this study, we found that those patients with low KIF1B expression had higher tumor invasion and worst survival and higher recurrence rate. We didn't have any new data. We hypothesized that KIF1B genes may associate with tumor invasion and metastasis. To clarify this presumption, further well-designed clinical studies are needed.

Minor comments:
1-Correct "Prognoses" for prognosis. Page 4.
We have modified this word.

2-"..but not significantly so." ??? What is this? Page 8
KIF1B mRNA expression in HCC tissues with vein invasion (1.41±0.25) was also lower than in those without vein invasion (1.50±0.30) without no significantly.

In this paper, the authors aimed at investigating the relationship between KIF1B expression and clinicopathologic parameters, and its prognostic value for patients with hepatocellular carcinoma (HCC). There are some SPECIFIC CONCERNS worth being addressed to improve the quality of the manuscript:

1, The amount of HCC samples is too little to support the results.

The amount of HCC samples is 68. The results showed that the survival difference between patients with up-regulated expression of KIF1B mRNA in HCC tissues and down-regulated expression of that had statistical significance. It could support the conclusion.

2, If the author show the protein level of KIF1B in Figure 1, they should also show the mRNA levels of KIF1B.

In this study, we use quantitative real-time reverse transcription-polymerase chain reaction to detect the mRNA levels of KIF1B. It were showed as $2^{-\Delta Ct}$. We did not carry out RNA electrophoresis. So there was no figure about mRNA levels of KIF1B.

3, The author did not define “up/down-regulated expression of”. We don’t know how they grouped these patients.

We found ratios of KIF1B mRNA expression in HCC/adjacent PC tissues were correlated with OS and DFS. So the KIF1B mRNA expression in HCC tissue was higher than that of adjacent PC tissue were up-regulated. In contrary, the KIF1B mRNA expression in HCC tissue was lower than that of adjacent PC tissue were down-regulated.

Dear prof Shu-Guang Chen

1- The significance of your research in manipulating KIF1B expression in hcc might have therapeutic implication but your results cannot conclude that KIF1B for the 1st time is a liver cancer suppressor gene and further studies on large scale must be recommended

Thank you for the reviewer's comments. We revised the manuscript and recommended the further studies on large scale in Discussion Part. (Page 13)

2- The manuscript's presentation and readability is good but the abbreviations must be mentioned

We have revised the abbreviations.

3-discussion is not well organized because the results drawn not appropriately supported by the literature and your reasoned explanations must be provided

We increased the content of Discussion in order to better explain the results. (Shown in Page 13)

4- references are appropriate and up to date

Thanks a lot.

5- tables and figures clearly present the major amount of information in clear manner

Thanks a lot.