ROUND 1

#### Dear Prof. Li Ma,

Thank you for allowing me to submit a revised draft of my manuscript titled "Real-world 10-year retrospective study of Chinese guidelines for the diagnosis and treatment of hepatocellular carcinoma" with manuscript no: 82030 to the *World Journal of Gastrointestinal Oncology*. We appreciate the time and effort you and the reviewers have dedicated to providing valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments. We have studied the comments carefully and have revised the manuscript to reflect most of the suggestions provided by the reviewers, which are marked in red in the paper. Below is a detailed point-by-point response to the reviewers' comments and concerns.

This revised manuscript has been edited and proofread by Medjaden Inc.

We hope our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

# Qingfeng Tian

First, we would like to sincerely thank the reviewers for their constructive and positive comments.

#### **Replies to Reviewer 1**

REVIEW: This report is a large, retrospective study evaluating the Chinese HCC Guidelines (CNLC), conducted at a representative single center in China. The Chinese HCC guideline (CNLC) are still relatively new, and this study evaluating it may be useful. The authors attempted to clarify the reality of

HCC practice in China by presenting a large body of data from a representative Chinese institution. Practicing HCC according to the CNLC showed the possibility of prolonging recurrence-free survival after hepatic resection, although it could not be shown to prolong overall HCC survival compared to noncompliant cases. The study also demonstrated the utility of screening to detect early-stage HCC and suggested independent factors that may influence overall survival. However, this was a single-center retrospective study, so the authors concluded that future prospective studies are needed to confirm the results. However, there are several items that need to be improved. There is no definition of primary outcome and hence overinterpretation of the results is scattered (e.g. the superiority of progressive free survival in LR patients = overstating the sub-analysis). Also, some items that should be included in the methods section are not mentioned. In addition, matters not indicated by data in the 'Results' must not be stated in the 'Discussion' as the conclusion of the study. I think setting a primary outcome would make for a stylish paper.

Response: We have carefully read these comments and believe the suggestions are valuable and helpful in improving the paper's quality. We have revised the manuscript following the suggestions. Below is our detailed point-by-point response to the comments.

#### <Major> Abstract

1. How is the remaining 34% diagnosed? (on page 2, line 30-31).

Response: The remaining 33.98% of early-stage patients were diagnosed using imaging examinations and clinical statuses, and the remaining 34.12% of middle- and late-stage patients were diagnosed using pathological examinations. We have added this information to the revised manuscript based on your recommendations.

Subsequently, we changed, "The diagnosis of early-stage (Ia, Ib, and IIa) patients primarily depended on pathological examination (66.02%), while the diagnosis of middle-stage (IIb and IIIa) and late-stage (IIIb and IV) patients could mostly be made using imaging examination combined with clinical manifestations (65.88%)" to "The early-stage (Ia, Ib, and IIa) patients were primarily diagnosed by their pathological examinations (66.02%). The remaining 33.98% of patients in the early stage were diagnosed using their imaging examinations and clinical statuses. Middle-stage (IIb and IIIa) and late-stage (IIIb and IV) patients were diagnosed using imaging examinations and clinical statuses. Middle-stage (IIb and IIIa) and late-stage (IIIb and IV) patients were diagnosed using imaging examinations and clinical statuses. The remaining patients were diagnosed using imaging examinations and clinical manifestations (65.88%). The remaining patients were diagnosed using pathological examinations."

2. The data that screening reduces the risk of death was presented with COX model in the result of abstract, but data on the 'effectiveness in HCC high risk' was not provided in the result of abstract. (on page 4, line 5).

Response: Thank you for highlighting this. We have added the following relevant results and data on the "effectiveness in hepatocellular carcinoma (HCC) high risk" at the end of the abstract following your suggestion:

"Based on the Cox model survival analysis, HCC patients identified via screening had significant advantages in overall survival and tumor-free survival after hepatectomy (P < 0.01)."

### Core tip:

3. "The findings suggest that the guidelines are well-consistent with long-term clinical practice in China" (on page 4 line13-14): Delete this sentence as the research design is not representative of the whole of China. Alternatively, specify that it is a single-centre study, e.g. "70% of HCC treatment at the First

Affiliated Hospital of Zhengzhou University was performed according to guidelines".

Response: Thank you for this suggestion. We have incorporated your advice by replacing the sentence "The findings suggest that the guidelines are well-consistent with long-term clinical practice in China" in the manuscript with "The findings revealed that 70% of HCC treatment at the First Affiliated Hospital of Zhengzhou University was performed according to guidelines."

## Introduction:

4. " Patients from all over China often visit this hospital for continuous treatment after the diagnosis of HCC; therefore, we believe that the targeted participants in this study are representative of the general population of China." (on page 5 line 29-31): Single-center university hospitals are likely to be biased towards patients. For example, there will be bias for economic reasons and location, and patients with too light or too many underlying diseases and poor patient backgrounds may be excluded. Furthermore, HBV accounted for the majority of patients in the study and alcohol, NASH and HCV were less prevalent, which may not be an accurate reflection of HCC as a whole. Consider deleting or changing this sentence.

Response: We agree with your suggestion and have deleted this sentence.

#### Method

## 5. Primary and secondary outcomes should be clearly stated.

Response: We created a subheading tagged "Primary and secondary outcomes" in the methods section with the following description:

"The main research results of this paper show that the Chinese guidelines for HCC in China's real clinical practice of diagnosis and treatment compliance are good, and screening compliance is poor. According to the guidelines, screening and treatment can give patients certain survival benefits. This study found that patients who underwent hepatectomy according to the guidelines had a significant advantage in tumor-free survival compared with those who did not receive such treatment."

6. Study Design and Target Population (on page 6 line14): Please provide a definition of a definitive diagnosis of HCC and ICC. If diagnostic criteria for HCC and ICC is inaccurate, a significant number of HCCs may be removed as ICCs, or ICCs may be included as HCCs.

Response: Thank you for this suggestion. We have included the required information as follows:

"The guideline states that HCC is a malignant tumor of liver cells, while it states that intrahepatic cholangiocarcinoma (ICC) is the cancer of the intrahepatic bile duct branch lined with complex epithelial cells. The most common malignancy of ICC is adenocarcinoma. As this was a retrospective study, all included patients had been definitively diagnosed with HCC by clinicians, excluding those clinically diagnosed with ICC and HCC-ICC."

7. "(5) Survival of the patients: Patients with no clinical outcome in the hospital were followed up." (on page 7 line 26-27): Describe follow-up method.

Response: Thank you for highlighting this. We have changed this paragraph from "Patients with no clinical outcome in the hospital were followed up" to "For patients with no clinical outcome in the hospital, we followed up with their families via telephone to understand patients' survival status." 8. "Data analysis" (on page 7 line 30): Please describe the criteria for the choice of treatment method. If there are no criteria and the decision is made by the attending physician, please state that.

Response: As this was a retrospective study, data on the treatment methods received by the patients were collected from the electronic medical record system and confirmed by the attending clinicians. We have added this sentence to the end of the first paragraph in the "*Diagnosis and treatment analysis*" subsection of "MATERIALS AND METHODS."

9. Screening analysis (on page 8 line 21): What is the definition of screening methods? Please describe it on Method section.

Response: Thank you for this suggestion. The guideline recommends that early screening for HCC include liver ultrasound imaging and serum alpha-fetoprotein (AFP) level determination. We have added this description to the "*Screening analysis*" subsection of "MATERIALS AND METHODS."

### Result

10. General characteristics of patients with HCC (on page 9 line 27): Please state patient's smoking and drinking history. The drinking history is particularly important. If this data is not available, it should be stated in limitation.

Response: We have added the patient's smoking and drinking history to Table 1 and the following description into the position specified by the reviewer:

"The proportions of patients with HCC with a smoking and drinking history were 38.32% and 31.40%, respectively."

11.We collected data of 1128 clinical outcomes on page 12 line 17-18: The characteristics of those who were able to be followed should be described and a table should be created. As survival is an important outcome, the characteristics of the population for which it was analysed are also important. For example, PS, alcohol consumption, drinking, Child-pugh, stage, etc.

Response: We created Table 5 following the reviewer's suggestion, and the order of the tables in the manuscript has been adjusted. We have added to the manuscript a description of the characteristics of the patients who were able to be followed up:

"We collected 1,128 patients' clinical outcomes in total. Among the general clinical characteristics of these patients, 922 (81.74%) were male, and 798 (70.74%) were over 50. There were 992 (87.94%) patients with hepatitis B virus (HBV), 56 (4.96%) with hepatitis C virus (HCV), 62 (5.50%) with non-alcoholic fatty liver disease, and 18 (1.60%) with alcoholic liver disease. There were 226 (20.04%) patients with hypertension, 159 (14.10%) with diabetes, and 33 (2.93%) with coronary heart disease. Of the patient population, 408 (36.17%) and 337 (29.88%) had a smoking and drinking history, respectively. There were 870 (77.13%) patients who were Child–Pugh grade A, 228 (20.21%) Child–Pugh Grade B, and 30 (2.66%) Child–Pugh grade C (table 5)."

We have also deleted the following, as it repeated the previous new description:

"According to the guidelines (hepatitis B virus [HBV] and/or hepatitis C virus [HCV] infection, excessive alcohol consumption, non-alcoholic steatohepatitis, cirrhosis from other causes, a family history of HCC, etc.).<sup>[9]</sup>"

12."The results were verified by the multivariate analysis showing that AFP > 400 ng/ml (HR = 1.612, 95% CI = 1.256-2.070), Child-Pugh B (HR = 1.771, 95%

CI = 1.243-2.524), middle stage (HR = 2.556, 95% CI = 2.032-3.215), and late stage (HR = 3.312, 95% CI = 2.113-5.192) were independent factors affecting postoperative recurrence of HCC. (Table 6)." (from page 13 line 32 to page 14 line 5): AFP and stage can be understood as an risk of postoperative recurrence in patients undergoing LR as tumor vigour, but what does it mean that Child-Pugh B is a risk of postoperative recurrence in patients undergoing LR ? Describe that in discussion section.

Response: Thank you for this suggestion. We have now added the following to the third last paragraph of the "DISCUSSION" section:

"When analyzing influencing factors for recurrence after hepatectomy, the patients with Child–Pugh grade A liver function were considered the reference because none of the patients with Child–Pugh grade C liver function received hepatectomy. Patients with Child–Pugh grade B liver function had more recurrences after hepatectomy (P < 0.01), indicating that the status of patients' liver function was an important risk factor for patients with recurrence after liver resection (LR)."

13."The guidelines recommend that imaging and pathological diagnosis can be used in the HCC diagnosis. In this study, the diagnosis methods of CNLC I a, I b, and II a stage patients were mainly pathology-based, with 70.3%, 60.4%, and 63.3% frequencies, respectively. The diagnosis methods of CNLC II b, III a, III b, and IV stage patients were mainly based on imaging examination combined with clinical features, with 67.3%, 58.6%, 69.3%, and 81.9% frequencies, respectively." (from page 14 line 30 to page 5 line 4): This sentence only repeated the results and does not describe the considerations. Please describe why approximately 30-40% of people were not diagnosed according to the guidelines. Response: The guidelines stated that pathology and imaging could be used as the basis for HCC diagnosis, and patients are not required to undergo pathological examinations to confirm the diagnosis. Doctors completed the diagnosis of all patients with HCC following the guidelines. Early-stage patients are mostly diagnosed using pathological examinations recommended by the guidelines, while the rest are diagnosed using imaging examinations recommended by the guidelines and clinical manifestations. The imaging examinations and clinical manifestations of middle-stage and advanced-stage patients are the most important diagnostic method. Most patients were diagnosed with HCC using imaging examinations, while the rest were diagnosed using pathology.

14."In this study, 304 patients were screened prior to the diagnosis of HCC." (on page 15 line 11): If the usefulness of screening is used in the conclusion, please describe in the Limitation the selection bias and confounding bias of cases undergoing screening. Items other than those identified as HCC high-risk in CNLC, such as wealth or urban area, may be factors that make people more likely to be screened.

Response: Following your suggestion, we have added the following to the limitation section:

"This study's results suggest that screening enables the early diagnosis of HCC. However, due to the retrospective study, data on patients' willingness to receive screening and influencing factors, such as wealth or urban area, could not be collected."

15."and improving the quality of life." (on page 15 line 26): Data on quality of life are not presented in the result section, so it is not possible to conclude this way.

Response: Thank you for this suggestion. We have incorporated your advice and deleted "and improving the quality of life."

16." while some patients received more active treatment, which made these patients obtain certain survival advantages." (on page 18 line 25-27): Can you present data showing this in the Result section?

Response: According to the research content, we have modified this part to:

"Depending on the actual situation, patients may receive more positive or negative treatment since various factors affect patients' treatment plans."

17."which indicated that the results of this study were well representative of the HCC patient population." (on page 19 line 9-10): Although the present study is large, it is single-center, and retrospective study. So it difficult to conclude that it is representative of HCC as a whole.

Response: Following the reviewer's advice, we have deleted this sentence.

18.Limitations on page 19 line 20: Is the exclusion of ICCs certain in this study? If not certain, the statement should be listed under limitation.

Response: Patients with ICC have definitely been excluded from this study.

19." which indicates that the guidelines have a good effect on the treatment of patients with HCC in China." (on page 20 line 7-8): This sentence is unnecessary. "Despite the limited survival benefit for patients receiving the treatment recommended by the guidelines, patients who underwent LR in accordance with the guidelines had a significant survival advantage." is enough as conclusion. Redundant statements should be avoided.

#### Response: Thank you for this comment. We have deleted this sentence.

20."limited survival benefit" (on page 20 line 9): Survival benefits in the whole patients of HCC were not proven in the result section. Only patients who underwent LR in accordance with the guidelines had a significant progressive free survival advantage. Please consider changing "limited benefit in HCC patients as a whole" to "No benefit was demonstrated in HCC patients as a whole". The data described in the Result section should refrain from being overstated. I think that the lack of definition of primary outcome and secondary outcomes led to an over-interpretation of results.

Response: Following your advice, we have changed "the limited survival benefit" to "no benefit was demonstrated in patients with HCC as a whole."

#### Abstract

1. This sentence should be stated in the CONCLUSION. (from page 3 line 31 to page 4 line 3)

Response: Thank you for this suggestion. The journal requires the conclusion section to be no more than 30 words; however, if this sentence is included, the

number of words will not meet the requirement. Hence, we did not incorporate this suggestion.

#### Introduction

2. CNLC on page 5 line 10 is first appearance in main text. Spelling out.

Response: Thank you for highlighting this. The abbreviation for China liver cancer (CNLC) staging has been spelled out where it first appeared in the main text.

## Method

3. "(4) The treatment information collected included" (on page 7 line23): There appears to be no mention of TACE or RFA. Please add it.

Response: Following your advice, we have changed "1) whether the patients accepted surgical treatment and the surgical method" to "1) whether the patients accepted surgical treatments and methods, including LR, radio frequency ablation (RFA), liver transplantation (LT), transcatheter arterial chemoembolization (TACE)".

Result

4. "significantly elevated AFP levels (> 400 ng/ml)" (on page 10 line 7): Please describe the rationale for the" significantly elevated AFP levels defined as > 400 ng/ml" in Method section.

Response: Following your suggestion, we have added the following expression after the "(3) The serological reports of the patients included" in the "*Data collection*" subsection in "MATERIALS AND METHODS" as follows:

"According to the CNLC staging as recommended by the guideline, AFP levels are divided into three categories:  $\leq 20$ , 20–400, and  $\geq 400$  (ng/mL). As advised by the guidelines, an AFP level  $\geq 400$  ng/mL is significantly increased.

5. "clinical features" (on page 10 line 21): Please describe in detail.

Response: Table 1 presents clinical features. Furthermore, the description of patients' characteristics and clinical features were described in the "*General characteristics of patients with HCC*" subsection in "RESULTS." In addition to the characteristics presented in Table 1, it also includes the number of tumors in the patient, the maximum diameter of a single tumor, and whether there was extrahepatic metastasis, vascular cancer thrombus, and ascites. The above clinical features were included and analyzed when we performed Child-Pugh grading and CNLC staging for patients. However, due to numerous indicators, they are not shown in Table 1. We have changed "clinical features" to "clinical features (Table 1)."

### Discussion

6. "Staging of liver cancer is very important for the selection of treatment options and the evaluation of prognosis. There are many staging systems, such as the BCLC, EASL, APASL, JSH, HKLC[3-7]. Among them, the most widely used staging is the BCLC. CNLC staging was established according to the patients' PS, liver tumor, and liver function by the National Health Commission in combination with China's specific national conditions and practice accumulation, including CNLC I a, I b, II a, II b, III a, III b, and IV stages[9-10]." (on page 14 line 8-15).

Response: Following your suggestion, we have revised this sentence in the "DISCUSSION" section as follows:

"Liver cancer staging is important in selecting treatment options and evaluating prognosis. Many staging systems exist, such as the Barcelona Clinic Liver Cancer (BCLC), the European Association for the Study of the Liver, the Asian Pacific Association for the Study of the Liver, the Japan Society of Hepatology, and Hong Kong Liver Cancer staging systems <sup>[3-7]</sup>. Among them, the most widely used staging is the BCLC. China liver cancer staging was established for Chinese people by the National Health Commission in combination with China's specific national conditions and practice accumulation<sup>[9,10]</sup>."

7. "The method of CNLC staging was first published in 2017[9]. Due to the short period since the publication, there are currently no real-world studies on the diagnosis and treatment of patients based on CNLC staging, and only a few studies have been performed on specific treatment methods in different CNLC staging [11-13]." (on page 14 line 16-20): Moving to the intro would help readers understand the strengths of the paper earlier.

Response: We have moved "The method of CNLC staging was first published in 2017<sup>[9]</sup>. Due to the short period since its publication, there are currently no real-world studies on diagnosing and treating patients based on CNLC staging, and only a few studies have been performed on specific treatment methods in different CNLC staging<sup>[11-13]</sup>" to the beginning of the sentence. We have also moved "The screening of high-risk HCC groups and the diagnosis and treatment of patients with HCC are also recommended by the guidelines. Some studies have analyzed the situation of patients with HCC undergoing LR or interventional therapy based on CNLC staging<sup>[11-13]</sup>" to the second paragraph of the introduction.

8. "As China is the country with the largest number of liver cancer cases in the world," (on page 14 line 20-21): A supporting citation is needed.):

#### Response: Based on your suggestion, we have inserted a reference.

9. "The strength of this study is that we collected data of a large sample of patients with HCC from the real world and conducted CNLC staging for the patients to evaluate the compliance between CNLC staging and real clinical diagnosis and treatment in China. We also performed a systematic review and an analysis of the diagnosis and treatment choices of Chinese patients with HCC in the real world." (on page 14 line 24-29): This should also be mentioned in the intro.

Response: Based on your suggestion, we have added the following to the beginning of the last sentence in the "INTRODUCTION" section:

"The collected data of the large sample of patients with HCC were classified into CNLC stages to evaluate the compliance between CNLC staging and real clinical diagnosis and treatment in China."

10. "The guidelines have identified high-risk groups for HCC: people with HBV and/or HCV infection, excessive alcohol consumption, non-alcoholic steatohepatitis, cirrhosis caused by other causes, and a family history of liver cancer, especially men older than 40 years of age[10]. Regular screening of high-risk groups for HCC is recommended by the guidelines to detect more patients in the early-stage HCC." (on page 15 line 5-10): These sentence

should be included in the Introduction or Method section. In the discussion section, you should in principle write a discussion of the data based on your own research.

Response: Following your advice, we have moved the following to the second sentence of the *"Screening analysis"* subsection in *"MATERIALS AND METHODS"*:

"Furthermore, the guideline has identified high-risk groups for HCC: people with HBV and/or HCV infection, excessive alcohol consumption, non-alcoholic steatohepatitis, cirrhosis caused by other causes, and a family history of liver cancer, especially men older than 40 years<sup>[9,10]</sup>."

11. "Taiwan of China" (on page 15 line 31): This sentence may be politically misleading. This is a scientific paper, so I recommend just stating 'Taiwan' so that any interpretation is acceptable. However, I am not a politician, so I cannot judge how this paper could be criticized because of this statement. The editorial board should decide whether to allow this wording or require a correction.

Response: We have changed "Currently, in Asia, for example, Korea and Japan have unified national screening programs, and Taiwan of China" to "Currently, some Asian countries and regions, for example, Korea and Japan, have unified national screening programs and stratified and phased screening programs have been implemented for high-risk groups of people with HCC in Taiwan."

ROUND 2

Dear Prof. Jia-Ru Fan,

We are grateful to the reviewer for their insightful comments. We have gone over the comments carefully and revised the manuscript to reflect most of the suggestions provided by the reviewer. These revisions are marked in red in the paper. Below is a detailed point-by-point response to the reviewer's comments and concerns.

With best wishes,

Yours sincerely,

Qingfeng Tian

First, we sincerely thank the reviewer for their constructive and positive

comments.

# **Replies to Reviewer 1**

Reviewer #1: RESPONSE to Authors. I think it is well corrected. However, there are still a few areas of concern.

**Response:** We have read your comments carefully and believe the suggestions are valuable and helpful in improving the paper's quality. We have revised the manuscript following the suggestions. Below is our detailed point-by-point response to the comments.

(Previous Point of View) The data that screening reduces the risk of death was presented with COX model in the result of abstract, but data on the 'effectiveness in HCC high risk' was not provided in the result of abstract. (on page 4, line 5). Author's Response: Thank you for highlighting this. We have added the following relevant results and data on the "effectiveness in hepatocellular carcinoma (HCC) high risk" at the end of the abstract following your suggestion: "Based on the Cox model survival analysis, HCC patients in our study identified via screening had significant advantages in overall survival and tumor-free survival after hepatectomy (P < 0.01)."

Comment to Authors: Is this analysis focused on the HCC high-risk group? If

so, it should be stated as such.

**Response:** All patients with HCC were enrolled in this study and the study sample was not limited to high-risk patients with HCC alone. The COX

model's analysis object also included all patients with HCC. To clarify this, we have modified the original expression "Based on the Cox model survival analysis, HCC patients identified via screening had significant advantages in overall survival and tumor-free survival after hepatectomy (P <0.01)." as follows: "Based on the Cox model survival analysis, in our study, patients with HCC identified via screening had significant advantages in overall and tumor-free survival after hepatectomy."

(Previous Point of View) Primary and secondary outcomes should be clearly stated. Author's Response: We created a subheading tagged "Primary and secondary outcomes" in the methods section with the following description: "The main research results of this paper show that the Chinese guidelines for HCC in China's real clinical practice of diagnosis and treatment compliance are good, and screening compliance is poor. According to the guidelines, screening and treatment can give patients certain survival benefits. This study found that patients who underwent hepatectomy according to the guidelines had a significant advantage in tumor-free survival compared with those who

did not receive such treatment." Comment to Authors: This describes it as if it

were an outcome; it should be changed to say that, for example, the PFS extension was set as the PRIMARY OUTCOME.

Response: Thank you for the valuable suggestion. We have deleted the "Primary and secondary outcomes" section that was created previously in the methods section with the description: "The main research results of this paper show that the Chinese guidelines for HCC in China's real clinical practice of diagnosis and treatment compliance are good, and screening compliance is poor. According to the guidelines, screening and treatment can give patients certain survival benefits. This study found that patients who underwent hepatectomy according to the guidelines had a significant advantage in tumor-free survival compared with those who did not receive such treatment."

The primary outcome was overall survival time and the secondary outcome was tumor-free survival time. We have added this sentence to the end of the first paragraph in the "Statistical analysis" subsection of "MATERIALS AND METHODS".

(Previous Point of View) "The results were verified by the multivariate analysis showing that AFP > 400 ng/ml (HR = 1.612, 95% CI = 1.256-2.070), Child-Pugh B (HR = 1.771, 95% CI = 1.243-2.524), middle stage (HR = 2.556, 95% CI = 2.032-3.215), and late stage (HR = 3.312, 95% CI = 2.113-5.192) were independent factors affecting postoperative recurrence of HCC. (Table 6)." (from page 13 line 32 to page 14 line 5): AFP and stage can be understood as an risk of postoperative recurrence in patients undergoing LR as tumor

vigour, but what does it mean that Child-Pugh B is a risk of postoperative recurrence in patients undergoing LR ? Describe that in discussion section. Author's Response: Thank you for this suggestion. We have now added the following to the third last paragraph of the "DISCUSSION" section: "When analyzing influencing factors for recurrence after hepatectomy, the patients with Child–Pugh grade A liver function were considered the reference because none of the patients with Child–Pugh grade C liver function received hepatectomy. Patients with Child–Pugh grade B liver function had more recurrences after hepatectomy (P <0.01), indicating that the status of patients' liver function was an important risk factor for patients with recurrence after

liver resection (LR)." Comment to Authors: Are there any previous reports

that support the statement of higher postoperative recurrence rates in Child-pugh B? Please cite references.

**Response:** Based on your suggestion, we have inserted a reference.

(Previous Point of View) Limitations on page 19 line 20: Is the exclusion of ICCs certain in this study? If not certain, the statement should be listed under limitation. Author's Response: Patients with ICC have definitely been

excluded from this study. Comment to Authors: Pathological examinations

have not been performed in all cases. Although the attending physician followed the guidelines to distinguish between HCC and ICC, it is impossible to rule out ICC or HCC-ICC perfectly because the guidelines are not 100% accurate. It would be better to state in the Limitation that a certain number of ICCs may have been mixed or some HCCs may have been excluded, to gain the reader's confidence.

**Response:** Following your suggestion, we have added the following to the limitation section:

"Some patients with ICCs may have been included while some with HCC may have been excluded because pathological examinations were not performed in all cases. The attending physician followed the guidelines used to distinguish HCC and ICC; however, it is impossible to rule out ICC or HCC-ICC absolutely because the guidelines are not 100% accurate."