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Andrzej S Tarnawski

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Title: “Impact of adherence to guidelines on the prognosis of Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma”

Dear Editor:

Thank you very much for your thoughtful feedback on our manuscript. We have diligently addressed all comments and made revisions that we believe have notably enhanced the quality of our work. A detailed, point-by-point response to the reviewers' comments is included below, and changes within the manuscript are highlighted in yellow.

We hope that the revised manuscript is suitable for publication in the *World Journal of Gastroenterology*. We look forward to hearing from you regarding our resubmission and responding to any further queries you may have.

Yours sincerely,

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Reviewer #1:

Question 1: In the background of the abstract, "...non-adherent treatments to HCC guidelines, other than trans arterial chemoembolization (TACE) have...", with regards to "trans arterial", do the authors mean "transarterial" or "trans-arterial"?

Response: We sincerely appreciate your valuable feedback. We acknowledge the reviewer's observation regarding the inconsistent use of the full name 'TACE' throughout the paper. As a result, we have made revisions to standardize it as 'transarterial chemoembolization' in all relevant sections. Specifically, we have updated the abstract section, and it now states: "'transarterial chemoembolization (TACE)' has been adopted in real-world clinical practice." This change has also been implemented in other sections, including keywords, the introduction, and figure and table legends.

Question 2: The data of the manuscript could be checked through in the section (Baseline characteristics and distribution of treatment strategies according to each HCC guideline). Authors stated the average age (57.6 years) and proportion of patients with diabetes mellitus (13.7%) were lower in the upward treatment group, however, the data are inconsistent with the data in Table 1. Same as above, "42 (23.2%) of 181 patients with HCC between 2008 and 2010 received upward treatment and had higher total bilirubin levels, CPS, and MELD scores, and lower numbers of tumors" does not match the data in Table 2. Further checking by the author is required.

Response: We extend our sincere gratitude to the reviewer for their insightful comments. In response, we conducted a thorough data review, as advised. First, we made revisions to the statement: "the average age (57.6 years) and proportion of patients with diabetes mellitus (13.7%) were lower in the upward treatment group; however, the data are inconsistent with the data in Table 1." The revised version now reads: "The u

upward treatment group, compared to guideline-adherent patients, had a younger average age (57.5 vs. 60.7 years) and lower rates of diabetes (13.0% vs. 29.4%).” Additionally, we relocated this information to Table 2, alongside the inclusion of the Kinki criteria as Table 1.

Secondly, you mentioned the statement: "42 (23.2%) of 181 patients with HCC between 2008 and 2010 received upward treatment and had higher total bilirubin levels, CP S, and MELD scores, and lower numbers of tumors," which did not align with the data in Table 2. We revised to state: " For 2008-2010 HCC patients, 26.1% receiving upward treatments had fewer tumors.” These changes were made during the process of simplifying the entire manuscript and you can see in table 3.

Question3: “Compared with guideline adherence, upward treatment (HR 0.500, 95% CI 0.347–0.719) and a higher platelet count ($>10^5/\mu\text{L}$; HR 0.670, 95% CI 0.507–0.890) ...” and “Upward treatment (HR 0.673, 95% CI, 0.437–1.036) did not meaningfully improve ...” in the section “Factors affecting HCC-related mortality according to guideline adherence” were not consistent with Table 4. The author needs to make further verifications.

Response: We greatly appreciate and agree with your feedback. Following your valuable input, we conducted a comprehensive reanalysis of the incongruent data, resulting in the following findings: Upward treatment (HR 0.448, 95% CI 0.310–0.647, P-value <0.001) and a higher platelet count ($>10^5/\mu\text{L}$; HR 0.672, 95% CI 0.507–0.890, P-value = 0.006) significantly improved HCC-related survival (refer to Table 5). These findings, having undergone rigorous review, are not expected to undergo any further revisions. We highlight the revised part as yellow color in table 5.

Question4: In the discussion, the connection between this sentence “In patients with st

age B HCC, the adherence rate to each HCC guidelines did not significantly increase ...” and the following does not flow logically.

Response: We appreciate your insightful feedback. As you mentioned, after thorough reevaluation, we identified areas where the content lacked a logical transition between preceding and subsequent sections. In response to your feedback, we have incorporated additional explanations (the real clinical practice for stage B HCC in Korea and the plausible reasons behind the lack of significant increase in guideline adherence rates) following the mentioned sentence, aiming to offer a coherent rationale for the gap between guideline recommendations and real-world treatment practices as follows;

“This study explores the reasons behind this gap and examines the implications for treatment decisions in stage B HCC. Notably, the present study revealed that liver resection is commonly adopted as a treatment option for stage B HCC in real-world clinical practice in Korea, deviating from guidelines...”, and as following paragraph to clarify the reasons behind the lack of significant increase in guideline adherence rates;

“Achieving significant increase in guideline adherence rates over time remains elusive in East-Asian countries. One plausible explanation for this lies in the complex and multifaceted nature of HCC, often necessitates tailored treatment strategies that may not always align with standardized recommendation of guidelines. Moreover, the historical expertise in curative or aggressive treatments for stage B HCC in East Asian countries compared to Western countries can be attributed to another pivotal factor. East-Asian countries have historically grappled with a higher incidence of HCC, largely due to a higher prevalence of chronic hepatitis B, which has necessitated the development of specialized treatment approaches. The establishment of specialized liver centers and multidisciplinary teams has cultivated expertise in various treatment modalities. Over

time, the tradition of aggressive HCC treatment, including liver resection and transplantation, has become ingrained based on continuous researches and clinical trials, and leading to innovative strategies. ... Variations in clinical practice, differences in treatment preferences across regions, and the heterogeneous nature of stage B HCC. Despite could be attributed to non-adherence to guideline.”

We believe these amendments accurately incorporates the reviewer’s suggestion and provides clarified explanation about our study. Once again, we extend our gratitude to the reviewer for this insightful observation, and we hope that our amendments address the concerns raised.

Reviewer #2:

Abstract: “Clearly define the research's objective in the Aim section; provide a concise summary of the methodology used; mention the key findings regarding guideline adherence rates, treatment effectiveness, and factors impacting survival outcomes; conclude with a succinct statement summarizing the study's main outcome and its potential implications for HCC treatment.”

Response: We are very thankful for providing crucial insights that have greatly influenced the overall flow of this study. Taking your advice into consideration, we have made the following revisions;

Background; Hepatocellular carcinoma (HCC) patients with Barcelona Clinic Liver Cancer (BCLC) stage B have considerable heterogeneity of tumor burden, liver function, and performance status within the group. To improve the poor survival outcomes of HCC patients with BCLC stages B, non-adherent treatment approach to HCC guidelines, other than transarterial chemoembolization (TACE) have being adopted in real-world

d clinical practice.

Aim; To assess guideline adherence trends in Korean stage B HCC patients and study its impact on their survival.

Methods; A retrospective analysis was conducted using data from the Korea Central Cancer Registry from 2008 to 2016. Stage B HCC patients were categorized into three treatment groups: guideline-adherent, upward, and downward, based on HCC guidelines from Asian Pacific, European, and American associations for the study of liver diseases. The primary outcomes were HCC-related deaths and tumor recurrence served as the secondary outcome. Survival among the groups was compared using the Kaplan-Meier method and log-rank test. Predictors of survival outcomes were identified using multivariable Cox regression analysis.

Results; In Korea, from 2008 to 2016, adherence to Hepatocellular Carcinoma (HCC) treatment guidelines for BCLC stage B patients showed variation but didn't improve over time. Adherence rates differed: 77-80% (2008-2012) for EASL guidelines, 71.7-75.9% (2008-2010) for AASLD guidelines, and remained steady at 90.14-94.5% (2010-2016) for APASL guidelines. Upward treatments like liver resection or transplantation and radiofrequency ablation significantly improved HCC-related survival compared to TACE ($P < 0.001$). 5-year survival rates for TACE vs. upward treatments varied by guidelines. Patients receiving upward treatments were typically <70 years old, had platelet counts $>105/\mu\text{L}$, and serum albumin levels $\geq 3.5\text{g/dL}$.

Conclusions; Adherence to guidelines significantly influenced survival in Korean stage B HCC patients. Curative treatments outperformed TACE, but liver resection selection should be cautious due to disease heterogeneity.

Introduction: “ Specify the significance of studying stage B HCC, emphasizing its heterogeneity; mention the global impact of HCC and its ranking among cancer-related deaths; highlight the multiple existing international guidelines for HCC treatment; emphasize the challenges in predicting prognosis for stage B patients due to tumor and patient heterogeneity; stress the importance of efforts to improve prognosis for stage B HCC patients, even if it means diverging from guidelines; clarify the role and scope of the Korea Central Cancer Registry (KCCR); state the study's objectives: assessing changes in guideline adherence rates and investigating the impact of non-adherence on survival outcomes; convey the potential contribution of the study to refining HCC guidelines for real-world stage B HCC management.”

Response: We sincerely thank the reviewer for the insightful comments. As you mentioned, we revised our study to make it clear and emphasized as follows according to each comment;

“Specify the significance of studying stage B HCC, emphasizing its heterogeneity; mention the global impact of HCC and its ranking among cancer-related deaths;”

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, poses a significant threat to worldwide public health as second leading cause of cancer mortality. It is particularly alarming that liver cancer ranks as the second most common cause of premature death from cancer in 2020 among persons aged 30 to 69 years, even in high-income countries.¹ Also in Korea, HCC is responsible for the second highest mortality rates across all age groups and places a heavy burden on the working-age population, contributing to substantial economic consequences.

“Highlight the multiple existing international guidelines for HCC treatment; emphasize the challenges in predicting prognosis for stage B patients due to tumor and patient

heterogeneity. stress the importance of efforts to improve prognosis for stage B HCC patients, even if it means diverging from guidelines;”

To ensure effective management and treatment of HCC, various international guidelines including the Asian Pacific Association for the Study of the Liver (APASL), European Association for the Study of the Liver (EASL), and American Association for the Study of Liver Diseases (AASLD). The AASLD and EASL guidelines are based on the Barcelona Clinic Liver Cancer (BCLC) staging system, which considers factors such as tumor characteristics (number, size, vascular invasion, and extrahepatic localization), liver function (Child–Pugh score [CPS]), and performance status (PS; defined by the Eastern Cooperative Oncology Group scale) to determine appropriate treatment options and predict patient prognosis.

The BCLC staging system strictly recommends transarterial chemoembolization (TACE) for stage B HCC, which typically includes patients with multinodular tumors, Child–Pugh scores of A or B, performance status of 0, and no vascular invasion or extrahepatic spread. However, in East-Asian countries, there's a notable deviation from this recommendation, with hepatic resection being considered a viable treatment option for patients with stage B HCC. In these countries, nonrandomized controlled trials have revealed that around half of the stage B HCC patients undergo TACE, while an equal proportion opt for hepatic resection. Intriguingly, even after conducting sensitivity analyses, hepatic resection consistently demonstrates superior survival outcomes compared to TACE for patients with stage B HCC. ⁸ This deviation from the BCLC staging system reflects the potential benefits of adopting non-adherent treatment modalities to improve the prognosis of patients with stage B HCC. Consequently, HCC guidelines have continuously evolved in response to global clinical evidences, with the aim of optimi

zing the prognosis for patients with stage B HCC.

“Clarify the role and scope of the Korea Central Cancer Registry (KCCR);”

The Korea Central Cancer Registry (KCCR), established in 1980, serves as a hospital-based nationwide cancer registry initiated by the Ministry of Health and Welfare. Its primary goal is to accurately record cancer incidence in Korea, facilitating essential cancer research and treatment planning through the development of a comprehensive cancer incidence database. Each year, newly diagnosed cancer patients are registered with in the program.

“State the study's objectives: assessing changes in guideline adherence rates and investigating the impact of non-adherence on survival outcomes; convey the potential contribution of the study to refining HCC guidelines for real-world stage B HCC management;”

This study aims to evaluate the adherence rates to each HCC guideline (EASL, AASLD, and APASL) in Korea, using data from the KCCR between 2008 and 2016. Additionally, we aim to assess the impact of guideline non-adherence on the survival outcomes of patients with stage B HCC. By identifying specific patient subgroups that benefit from treatments deviating from the HCC guidelines, this study could significantly contribute to the refinement of guidelines for real-world management of patients with stage B HCC.

Methods: “provide a brief rationale for the retrospective multicenter cohort study; clarify the criteria used for patient selection and inclusion; define stage B (intermediate stage) HCC according to the BCLC staging system; describe the criteria used to classify patients into guideline-adherent, upward, and downward treatment groups; explain th

e primary and secondary endpoints clearly; simplify and rephrase the definition of guideline adherence for each guideline; mention the statistical software used for analysis; describe the presentation of continuous variables with normal distribution; explain the purpose and methodology of Kaplan-Meier analysis; simplify the explanation of the modified Bolondi or Kinki criteria for classifying patients with stage B HCC.”

Response: We extend our sincere gratitude to the reviewer for their insightful comments. In response to your suggestions, we have revised according to each comment:

1. We have provided clearer and rephrased explanations regarding the classified groups and the definition of guideline adherence.

“Provide a brief rationale for the retrospective multicenter cohort study; clarify the criteria used for patient selection and inclusion; define stage B (intermediate stage) HCC according to the BCLC staging system; describe the criteria used to classify patients into guideline-adherent, upward, and downward treatment groups; explain the primary and secondary endpoints clearly; simplify and rephrase the definition of guideline adherence for each guideline;”

Study population and study outcome

This was a retrospective multicenter cohort study that included 13,838 treatment-naïve HCC patients registered in the KCCR from 2008 to 2016. The patients were followed up until December 2019. Diagnosis of HCC was made based on pathological findings from surgical specimens, liver biopsies, or radiologic findings through liver dynamic computed tomography (CT) or magnetic resonance imaging (MRI). Stage B HCC was defined as multinodular tumors with a CPS of A or B, PS of 0, and absence of vascular invasion or cancer-related symptoms according to the BCLC staging system.²

A total of 650 patients with BCLC stage B HCC were selected and divided into three groups: guideline-adherent, upward, and downward treatment groups according to guidelines, including the EASL (2000, 2012), AASLD (2005, 2010), and APASL (2010) guidelines (Figure 1).

The primary endpoint was HCC-related death, and the secondary endpoint was tumor recurrence after the first HCC treatment. HCC-related survival was measured from the date of first treatment until HCC-related death or the last follow-up. Progression-free survival (PFS) was measured from the date of the first to the second treatment. Tumor recurrence was defined as a period longer than 1 month between consecutive treatments.

Definition of guideline adherence

Guideline adherence was defined differently for each guideline based on the grades of evidence and recommendations. Among non-adherent treatments, upward treatment referred to more aggressive or curative treatments than recommended in the BCLC staging system or updated treatments with proven efficacy. Downward treatment referred to moving from left to right in the BCLC staging system or treatments under clinical trials with no proven efficacy. All guidelines recommended TACE as standard therapy for unresectable, large, or multifocal stage B HCCs. The APASL guidelines stated that liver resection could be considered if HCC is confined to the liver, anatomically resectable, and the patient has satisfactory liver function reserve.

“Mention the statistical software used for analysis; describe the presentation of continuous variables with normal distribution; explain the purpose and methodology of Kaplan-Meier analysis;”

2. Additionally, we have elaborated on the purpose and methodology of the statistical analysis as follows:

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables with normal distribution (age, BMI, CPS, MELD score, Serum creatinine, Sodium, ALT, platelet, serum albumin, total bilirubin, INR, tumor number, maximum tumor diameter and AFP level) are expressed as mean \pm standard deviation. The χ^2 -test with Fisher's exact test was used for categorical variables (sex, etiology and ascites). HCC-related death and HCC progression-free survival was compared using the Kaplan–Meier method with log-rank test. Univariate Cox regression analysis was performed and multivariate Cox regression analysis was conducted using selected variables sorted through stepwise selection to identify reliable predictors of survival in patients with stage B HCC. The modified Bolondi or Kinki subclassification system was used to categorize patients based on liver function and tumor status as follows: B1 (CPS 5-7 and within up-to-7), B2 (CPS 5-7 and beyond up-to-7), and B3 (CPS 8, 9, and any tumor status) (Table 1).^{18,19} Propensity score matching (PSM) analysis for variables such as age, etiology, platelet count, serum albumin level, tumor burden, and MELD score was performed to balance differences of baseline characteristics between patients who underwent hepatic resection and TACE during the subgroup analysis based on Kinki criteria. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was defined as $P < 0.05$.

“Simplify the explanation of the modified Bolondi or Kinki criteria for classifying patients with stage B HCC;”

3. We have included an explanatory table regarding Kinki criteria as table 1 to facilitate

ate the comprehension of reviewers and readers.

TABLE 1 Modified Bolondi or Kinki subclassification system

Subclassification	B1	B2	B3	
Child-Pugh score	5–7	5–7	8, 9	
'Beyond Milan' and within 'up to 7 criteria'	in	out	any	
			in	out
Concept of treatment strategy	Curative	Noncurative	Curative intent if within up-to-7 criteria	Palliative, no treatment
Treatment option	Resection Ablation Superselective cTACE	TACE with DC beads HAIC Sorafenib	Transplantataion Ablation Superselective cTACE	HAIC Selective TACE with DC beads

Results: “clarify the significance of specific percentages and statistics in the results section; simplify the presentation of baseline characteristics; highlight the most significant differences and trends within the baseline characteristics; present the changes in guideline adherence rates over time more concisely; summarize key findings regarding factors affecting HCC-related mortality for each guideline; provide a more concise and straightforward explanation of the impact of guideline adherence on PFS; simplify and clarify the results of subgroup analysis according to BCLC subclassification, focusing on the most relevant findings; avoid excessive repetition of statistical information; ensure that all relevant information and variables are explained clearly for each analysis.”

Response: We sincerely appreciate your valuable recommendations, which have greatly contributed to highlighting our research findings. We have meticulously incorporated all suggestions into our revisions as follows;

“Clarify the significance of specific percentages and statistics in the results section;”

“Simplify the presentation of baseline characteristics; highlight the most significant differences and trends within the baseline characteristics;”

The study groups' baseline characteristics, as per the EASL, AASLD, and APASL guidelines, are detailed in Tables 2 and 3, and Supplementary Table 2. Under the 2000 EASL guidelines, 76.2% of 353 HCC patients had guideline-compliant treatment, while 21.8% received upward treatments. For the 2012 EASL guidelines, 27.6% received upward treatments, with seven patients in the downward group excluded due to low sample size. The upward treatment group, compared to guideline-adherent patients, had a younger average age (57.5 vs. 60.7 years) and lower rates of diabetes (13.0% vs. 29.4%). They also had lower ALT levels, CPS, MELD scores, and tumor numbers, along with higher sodium levels, platelet counts, and serum albumin levels. Under the 2005 AASLD guideline, nine patients in the downward group were excluded. For 2008-2010 HCC patients, 26.1% receiving upward treatments had fewer tumors. Under the 2010 AASLD guidelines (2011-2016 HCC patients), 32.8% receiving upward treatments were younger (average age: 59.6 vs. 62.6 years) and had fewer diabetic cases (21.4% vs. 30.3%) and tumors. In contrast, according to the 2010 APASL guidelines (2010-2016 HCC patients), only 4.2% received upward treatment, with the majority (91.7%) adhering to the guidelines. The upward treatment group had higher BMI and serum sodium levels (Supplementary Table 2).

Regarding treatment strategies, a significant portion of stage B HCC patients underwent liver resection, liver transplantation, or radiofrequency ablation (RFA). Based on EASL guidelines, among 155 patients with upward treatment, 72.9% underwent liver resection, 9.7% received liver transplantation, and 8.4% had RFA. The results according to AASLD guidelines resulted in 56.5% liver resection, 7.5% liver transplantation, an

d 7% RFA out of 200 patients with upward treatment. Additionally, 58 patients were classified as upward treatment due to CPS B liver function while receiving transcatheter chemotherapy (TACE, DEB-TACE, TARE). Under APASL guidelines, most stage B HCC patients (486 out of 530) adhered to guidelines. Within this group, 94 underwent liver resections. Among the 22 receiving upward treatment, 50% had liver transplantation, and 50% had RFA (Table 4). These findings underscore the diverse treatment approaches for stage B HCC, highlighting the need for personalized management strategies.

“Present the changes in guideline adherence rates over time more concisely;”

Over the study period (2008-2016), there was a discernible trend in adherence rates to the different HCC guidelines among patients with stage B HCC. Adherence to the EASL guidelines initially ranged from 77% to 80% (2008-2012) but showed a downward trend to 58.8% to 71.6% (2013-2016). Similarly, adherence to the AASLD guidelines started at 71.7% to 75.9% (2008-2010) and exhibited variability ranging from 49.2% to 73.8% (2011-2016). In contrast, adherence to the APASL guidelines maintained a consistently high, ranging from 90.14% to 94.5% throughout the study duration (Figure 2).

“Summarize key findings regarding factors affecting HCC-related mortality for each guideline;”

1. 2000 EASL Guidelines:

Upward treatment showed significantly better 5-year survival rates (63.4% vs. 27.2, log-rank P-value < 0.001, Figure 3A). Risk factors for HCC-related death included >4 tumors and a maximum tumor diameter >10 cm. Upward treatment (HR 0.448, 95%

CI 0.310–0.647, P-value <0.001) and a higher platelet count (>105/ μ L; HR 0.672, 95% CI 0.507–0.890, P-value = 0.006) significantly improved HCC-related survival (Table 5).

2. 2012 EASL Guidelines:

Upward treatment demonstrated the best survival outcome (5-year survival rates: 57.3% vs 35.2%, log-rank $p < 0.001$, Figure 3B). Risk factors for HCC-related death included Age >70 years, male sex, total bilirubin level >1.2 mg/dL, AFP >200 ng/mL, >4 tumors, maximum tumor diameter >5 cm, and downward treatment. Upward treatment (HR 0.720, 95% CI 0.478–1.086, P-value = 0.117) did not meaningfully improve HCC-related survival (Table 5).

3. 2005 AASLD Guidelines:

Upward treatment had significantly better 5-year survival rates (63% vs. 30%, log-rank P-value < 0.001, Figure 4A). Risk factors for HCC-related death included >4 tumors and a maximum tumor diameter >5 cm. Upward treatment (HR 0.465, 95% CI, 0.322–0.670, P-value <0.001) and a higher platelet count (>105/ μ L; HR 0.684, 95% CI 0.518–0.904, P-value = 0.008) significantly improved HCC-related survival outcomes in patients with HCC between 2008 and 2010.

4. 2010 AASLD Guidelines:

Upward treatment demonstrated better 5-year survival rates (50% vs. 29.3%, log-rank P <0.001, Figure 4B). Factors associated with HCC-related death included age >70 years, CPS >7, >4 tumors, and a maximum tumor diameter >5 cm. Upward treatment (HR 0.478, 95% CI 0.333–0.685, P-value <0.001) compared with guideline-adherent treatment and serum albumin levels >3.5 g/dL (HR 0.596, 95% CI 0.416–0.855, P-value

e = 0.005) were associated with improved HCC-related survival (Table 6).

5. 2010 APASL Guidelines:

Guideline-adherent treatment showed the highest survival rates (1-year survival rates: 84.1%, 77.3%, and 36.4%, in the guideline-adherent, upward, and downward treatment groups, log-rank $P < 0.001$, Supplementary Figure 1). Risk factors for HCC-related death included age >70 years, INR >1.2 , total bilirubin level >1.2 mg/dL, >4 tumors, maximum tumor diameter >5 cm, and downward treatment. Upward treatment (HR 0.704, 95% CI 0.372–1.333, P-value = 0.281) was not associated with better survival outcomes (Supplementary Table 3), may be attributed to the relatively limited number of patients included in the upward treatment group compared to guideline-adherent group.

These findings highlight that adherence to different guidelines and specific treatment choices played a crucial role in the prognosis of HCC patients, with common risk factors including tumor characteristics, patient age and liver function influencing survival outcomes.

“Provide a more concise and straightforward explanation of the impact of guideline adherence on PFS;”

Following the 2000 EASL guidelines, there was no significant difference in PFS between guideline-adherent and upward treatment groups. However, according to the 2012 EASL guidelines, the guideline-adherent group had notably improved 1-year PFS (60.5% vs 39.8%, log-rank $P < 0.001$, Supplementary Figure 2B). Between 2013 and 2016, upward treatment (HR 0.648, 95% CI 0.461–0.909, P-value = 0.012) and higher serum albumin levels (≥ 3.5 g/dL; HR 0.74, 95% CI 0.568–0.964, P-value = 0.026) were related to better PFS.

For the 2005 AASLD guidelines, no significant difference in PFS was observed between guideline-adherent and upward treatment groups. However, following the 2010 AASLD guidelines, upward treatment was associated with superior 1-year PFS (58.6% vs. 38.9%, log-rank $P < 0.001$, Supplementary Figure 3B). Between 2011 and 2016, upward treatment (HR 0.556, 95% CI 0.426–0.726, P -value < 0.001), and higher serum albumin levels (≥ 3.5 g/dL; ≥ 3.5 g/dL; HR 0.689, 95% CI 0.511–0.928, P -value = 0.014) were correlated with improved PFS (Supplementary Table 5).

Regarding the 2010 APASL guidelines, the upward treatment group exhibited the highest 1-year PFS rate (75%, 44.8%, and 31.3% in upward treatment group, guideline-adherent group and downward treatment group, respectively, log-rank $P = 0.028$, Supplementary Figure 4). Risk factors for tumor progression included age > 70 years, > 4 tumors, maximum tumor diameter > 5 cm, and downward treatment. Compared to guideline adherence, between 2010 and 2016, upward treatment (HR 0.561, 95% CI 0.313–1.004, P -value = 0.052) and a higher platelet count ($> 105/\mu\text{L}$; HR 0.740, 95% CI 0.587–0.932, P -value = 0.011) were associated with significant PFS improvement (Supplementary Table 6).

In summary, regardless of the specific guidelines followed, factors such as adherence to guidelines, treatment choice (especially upward treatments), serum albumin levels, and platelet count consistently played pivotal roles in determining the prognosis of HCC patients, particularly in terms of PFS.

“Simplify and clarify the results of subgroup analysis according to BCLC subclassification, focusing on the most relevant findings; avoid excessive repetition of statistical information;”

Participants were categorized into BCLC stage B1 (40.6%, $n = 263$), B2 (55.1%, $n =$

357), and B3 (4.3%, n = 28). The majority fell into stages B1 and B2 (96.7%). Among B1 and B2 patients, a significant portion received upward treatment (66.7% and 70%, respectively).

Notably, in the B1 group, those who received upward treatment had a significantly higher 5-year survival rate compared to those adhering to guidelines (71.1% vs 41.4%, log-rank $P < 0.001$, Figure 5A). Upward treatment was associated with a significant improvement in survival outcomes (HR 0.470, 95% CI 0.288–0.766, P-value = 0.002), even after propensity score matching in a 1:1 ratio for variables such as platelet count, serum albumin, MELD score, number of tumors, and maximum tumor diameter. (Supplementary table 8 and 9, Supplementary figure 5). In the B2 group, a similar trend was observed, with a higher 5-year survival rate for those receiving upward treatment compared to guideline adherence (51.2% vs 21.6%, log-rank $P < 0.001$, Figure 5B).

Upward treatment remained robust factor related to greater survival outcome (HR 0.553, 95% CI 0.317–0.965, P-value = 0.037, Supplementary table 11 and 12, supplementary figure 6) after 1:1 PSM for variables such as age, etiology, sodium, platelet count, serum albumin, MELD score, number of tumors, and maximum tumor diameter. Interestingly, despite the Kinki criteria recommending TACE, HAIC, and systemic chemotherapy as treatment options for B2 HCC patients, liver resection, LT, or RFA resulted in better outcomes for over 70% of B2 patients compared to those following guidelines. These findings highlight the potential benefits of individualized treatment approaches beyond guideline recommendations for certain BCLC subgroups.

Discussion: “provide a more concise and clear introduction to the discussion; summarize the main findings of the study in a more straightforward manner; clarify the reasons behind the lack of significant increase in guideline adherence rates; discuss the im

lications of these findings in the context of real-world clinical practice; highlight the importance of multidisciplinary opinions in treatment decisions for stage B HCC; address the limitations of the study more explicitly and discuss their potential impact on the results; consider discussing the potential clinical implications and recommendations based on the findings; ensure that the discussion is well-organized and flows logically from one point to the next; Provide a clear and concise conclusion summarizing the key takeaways from the study.”

Response: We sincerely thank you for your valuable guidance, which has contributed significantly to our study's ability to offer essential clinical insights for guiding treatment decisions in Stage B HCC patients. We have carefully integrated all your recommendations into our revisions to emphasize these implications.

“Summarize the main findings of the study in a more straightforward manner;”

This large-scale, longitudinal study examined real-world data of patients with stage B HCC in Korea over an 8-year period. Since this was a nationwide and multicenter study using data from the KCCR, random and representative selection of patients with HCC was performed. The adherence rate to guidelines for stage B HCC has not significantly increased over time, highlighting a gap between guideline recommendations and clinical practice. This study explores the reasons behind this gap and examines the implications for treatment decisions in stage B HCC.

Notably, the present study revealed that liver resection is commonly adopted as a treatment option for stage B HCC in real-world clinical practice in Korea, deviating from guidelines. This reflects the trend of Asian countries adopting more aggressive HCC treatment strategies compared to Western countries.³³⁻³⁵ Furthermore, it demonstrated that curative treatments, including liver resection, yield better survival outcomes than

TACE in selected patients. Prognostic factors for stage B HCC patients after curative treatment included age, tumor number, maximum tumor diameter, and underlying liver function, aligning with prior large-scale studies.³⁶⁻³⁸ Overall, these findings suggest that curative treatments may significantly improve the prognosis of stage B HCC patients, even after accounting for potential selection bias.

“Clarify the reasons behind the lack of significant increase in guideline adherence rates;” Achieving significant increase in guideline adherence rates over time remains elusive in East-Asian countries. One plausible explanation for this lies in the complex and multifaceted nature of HCC, often necessitates tailored treatment strategies that may not always align with standardized recommendation of guidelines. Moreover, the historical expertise in curative or aggressive treatments for stage B HCC in East Asian countries compared to Western countries can be attributed to another pivotal factor. East-Asian countries have historically grappled with a higher incidence of HCC, largely due to a higher prevalence of chronic hepatitis B, which has necessitated the development of specialized treatment approaches. The establishment of specialized liver centers and multidisciplinary teams has cultivated expertise in various treatment modalities. Over time, the tradition of aggressive HCC treatment, including liver resection and transplantation, has become ingrained based on continuous researches and clinical trials, and leading to innovative strategies. Robust healthcare infrastructure, have further contributed to this expertise. In contrast, Western countries, with different demographics and healthcare contexts, may have different treatment strategies for HCC. Variations in clinical practice, differences in treatment preferences across regions, and the heterogeneous nature of stage B HCC Despite could be attributed to non-adherence to guideline.

“Discuss the implications of these findings in the context of real-world clinical practice”

e;”

In 2022, the BCLC group updated their recommendations for HCC treatment, sub-classifying stage B HCC patients into three groups based on tumor characteristics and potential benefits: those eligible for extended liver transplantation criteria despite multiple HCCs, those suitable for TACE due to well-defined HCC nodules and preserved portal flow, and those with diffuse, infiltrative, and extensive HCC that may benefit from systemic therapy.³² However, the updated BCLC staging system still does not recommend liver resection as a feasible therapy for stage B HCC due to the lack of prospective studies. Notably, a Chinese randomized controlled trial and a Korean retrospective cohort study have shown potential survival benefits of liver resection over TACE in selected patients with multiple HCCs. In a Korean retrospective cohort study, two periods (2003-2005 and 2008-2010) were compared to assess changing treatment trends. The results indicated that patients with stage 0-C HCC who underwent curative treatments in the later cohort achieved superior 5-year survival outcomes compared to those who received non-curative therapy.²⁴ Potential survival benefits of liver resection over TACE in selected patients with stage B HCC were verified through systematic reviews and meta-analyses.²⁵⁻³¹ Considering real-world scenarios³³⁻³⁵ that demonstrate superior outcomes with liver resection, a multidisciplinary approach can optimize survival for stage B HCC patients and establish robust evidences for adopting curative treatments in patients with more advanced HCC. We also highlight the need to careful patient selection considering individual patient characteristics and institutional expertise to maximize the survival benefit from liver resection.

“Highlight the importance of multidisciplinary opinions in treatment decisions for stage

B HCC;”

Patients with chronic liver disease face an increased risk of post-hepatectomy liver failure; however, advances in preoperative assessments such as portal hypertension evaluation, future liver remnant volume or function prediction, portal vein embolization, surgical techniques, and postoperative management have expanded the possibilities of hepatic resection even in more advanced stages. These advancements enable the consideration of curative treatments in stage B HCC through a multidisciplinary approach. As a result, portal hypertension, multifocal HCCs or portal vein thrombosis are now recognized as manageable challenges manageable obstacles in the realm of HCC treatment. Overall, the importance of multidisciplinary evaluation and meticulous planning cannot be overstated in the treatment decisions for stage B HCC, where surgical resection remains a vital option whenever technically feasible.

“Address the limitations of the study more explicitly and discuss their potential impact on the results;”

Our study has several limitations that warrant consideration when interpreting the results. Firstly, given its retrospective nature, there is a possibility that treatment strategies were influenced by expert opinions or patient preferences, introducing inherent bias. To establish the safety and effectiveness of curative treatment for stage B HCC, well-designed prospective studies are essential. Secondly, our study excluded certain patients with stage B HCC who may benefit from alternative treatments or systemic therapy according to the 2022 BCLC staging system due to the limited number of participants. This exclusion could impact the generalizability of our findings. Thirdly, we were unable to account for potential confounding factors such as tumor location, pathology, degree of differentiation, and imaging characteristics, as this data was unavailable from the KCCR. These factors can influence treatment choices and prognosis, potentially

affecting our results. Lastly, due to the small sample size, we did not conduct a survival analysis comparing the B3 group with the B1 and B2 groups. While our study offers valuable insights into stage B HCC treatment and prognosis, well-designed prospective studies overcoming these limitations through well-designed prospective studies is necessary for a more comprehensive understanding of the disease and its management.

“Discuss the potential clinical implications and recommendations based on the findings.”

We propose that the eligibility criteria for liver resection be expanded to patients with stage B HCC in selected patients aged <70 years, with platelet counts >105/ μ L, and serum albumin levels \geq 3.5 g/dL, even in cases where the liver function is up to CP S B7 or the HCC status is beyond the Milan criteria and outside the up-to-7 criteria. However, careful patient selection considering liver function, tumor location, and burden is crucial.

“Provide a clear and concise conclusion summarizing the key takeaways from the study.”

The present study verified that there is a discrepancy between guideline recommendations and real-world clinical practice in the treatment of stage B HCC and liver resection often chosen over guideline recommendations, resulted in better survival for selected patients. Multidisciplinary evaluation is crucial for decisions of curative treatments in stage B HCC, especially considering patient characteristics and institutional expertise. Prospective studies are required to further assess the clinical implications of curative treatments in stage B HCC.

Finally, we added acknowledgment part as follows;

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Once again, we deeply appreciate the reviewers for their valuable feedback. We believe that the revised manuscript presents a more accurate and comprehensive depiction of our findings and have crucial clinical implications for guiding treatments of stage B HCC.