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***Retrospective Cohort Study*****Impact of adherence to guidelines on the prognosis of Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma**

Guideline adherence and HCC prognosis

**Abstract****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 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  $>10^5/\mu\text{L}$ , and serum albumin levels  $\geq 3.5\text{g/dL}$ .

## CONCLUSION

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.

**Key Words:** hepatocellular carcinoma; Barcelona Clinic Liver Cancer stage B; guideline adherence; liver neoplasms; transarterial chemoembolization; liver resection

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**Core Tip:** The current HCC guidelines do not recommend curative treatments, except liver transplantation, for patients with BCLC stage B HCC. Our study, however,

suggests survival benefits for selected patients aged <70 years, with platelet counts >105/ $\mu$ L and albumin levels  $\geq$ 3.5 g/dL, even if the liver function is up to CPS B7, beyond the Milan criteria and outside the up-to-7 criteria. As for the B2 group of the Kinki criteria, which presents a highly diverse population of patients with stage B HCC, curative strategies should be considered with caution through multidisciplinary approach.<sup>8</sup>

## INTRODUCTION

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, pose 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.<sup>1</sup> 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.<sup>41</sup>

To ensure effective management and treatment of HCC, various international guidelines including the Asian Pacific Association for the Study of the Liver (APASL),<sup>1</sup> European Association for the Study of the Liver (EASL), and American Association for the Study of Liver Diseases (AASLD).<sup>2-7</sup> The AASLD and EASL guidelines are based on the Barcelona Clinic Liver Cancer (BCLC) staging system, which considers factor such as tumor characteristics (number, size, vascular invasion, and extrahepatic localization),<sup>3</sup> 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.<sup>8</sup> 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 optimizing the prognosis for patients with stage B HCC.<sup>9-15</sup>

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 within the program.<sup>16</sup>

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.

## **MATERIALS AND METHODS**

### **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.<sup>2</sup> 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).<sup>3-7</sup>

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 mo between consecutive treatments.

#### Definition of guideline adherence

Guideline adherence was defined differently for each guideline based on the grades of evidence and recommendations.<sup>3-7,17</sup> 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.

#### Anthropometric and laboratory evaluation

Age, sex, body mass index (BMI, kg/m<sup>2</sup>), etiology (hepatitis B or C, alcohol consumption), presence of diabetes mellitus and hypertension, ascites, CPS, and Mayo End-Stage Liver Disease (MELD) score were collected as anthropometric parameters. The values of serum creatinine, sodium, alanine aminotransferase (ALT), platelets, serum albumin, total bilirubin, and international normalized ratio (INR) were collected as laboratory parameters. Tumor number, maximum tumor diameter, and alpha-

fetoprotein (AFP) levels were collected as tumor factors. All laboratory marker levels were measured using a conventional automated analyzer.

#### 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  $\chi^2$ -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).<sup>18,19</sup> 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  $P < 0.05$ .

## RESULTS

### RESULTS

#### Baseline characteristics and distribution of treatment strategies according to each HCC guideline

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, and 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.



### Changes in guideline adherence with time

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).

### Factors affecting HCC-related mortality according to guideline adherence

#### 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 ( $>10^5/\mu\text{L}$ ; 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 ( $>10^5/\mu\text{L}$ ; 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 = 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 guide-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.

**Comparison of PFS according to guideline adherence**

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 ( $\geq 3.5$ 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 ( $\geq 3.5$ g/dL;  $\geq 3.5$ 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 ( $> 10^5/\mu\text{L}$ ; 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.

#### **Subgroup analysis of the impact of guideline adherence on overall survival according to BCLC subclassification**

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

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.<sup>33-35</sup> 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.<sup>36-38</sup> Overall, these findings suggest that curative treatments may significantly improve the prognosis of stage B HCC patients, even after accounting for potential selection bias.

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.

In 2022, the BCLC group updated their recommendations for HCC treatment, subclassifying 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.<sup>32</sup> 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.<sup>24</sup> Potential survival benefits of liver resection over TACE in selected patients with stage B HCC were verified through systematic reviews and meta-analyses.<sup>25-31</sup> Considering real-world scenarios<sup>33-35</sup> 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.

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.

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.

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  $>10^5/\mu\text{L}$ , and serum albumin levels  $\geq 3.5$  g/dL, even in cases where the liver function is up to CPS 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.

## **CONCLUSION**

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.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Hepatocellular carcinoma (HCC) <sup>6</sup> is a major global health concern, ranking as the second leading cause of cancer mortality worldwide. Treatment guidelines are based on the Barcelona Clinic Liver Cancer (BCLC) staging system, but in East-Asian countries, hepatic resection is often adopted over Transarterial chemoembolization (TACE) for stage B HCC due to better survival outcomes.

### ***Research motivation***

The need for regional adaptations in HCC treatment guidelines for stage B HCC to improve prognosis of stage B HCC.

### ***Research objectives***

This study aims to evaluate adherence to international HCC guidelines in Korea using 2008-2016 data, investigate the preference for hepatic resection over TACE for stage B HCC, analyze the impact of guideline non-adherence on survival in Korean stage B HCC patients, and identify patient subgroups benefiting from guideline deviations to improve real-world management recommendations.

### ***Research methods***

In this retrospective analysis, data from the Korea Central Cancer Registry from 2008 to 2016 were utilized. Stage B HCC patients were categorized into treatment groups based on adherence to HCC guidelines from Asian Pacific, European, and American associations for the study of liver diseases. The primary outcome was on HCC-related deaths, with tumor recurrence as a secondary outcome, and statistical methods such as

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Kaplan-Meier with log-rank tests, and multivariable Cox regression analysis were used to analyze survival outcomes and predictors of survival.

### *Research results*

The adherence to HCC treatment guidelines for EASL and AASLD exhibit a declining trend over time in Korea. Curative treatments, deviating from guideline recommendations led to significantly better survival rates. Patients receiving upward treatments were age <70 years old, had platelet counts  $>10^5/\mu\text{L}$ , and serum albumin levels  $\geq 3.5\text{g/dL}$ .

### *Research conclusions*

This study, based on real-world data in Korea, revealed a persistent gap between recommendation of treatment guidelines and real clinical practice for HCC patients with stage B and liver resection often chosen over guideline recommendations, resulted in better survival for selected patients.

### *Research perspectives*

The findings suggest that expanding the eligibility criteria for liver resection in specific patient groups may be beneficial. The study also highlights the need for careful patient selection through multidisciplinary approach when considering curative treatments for stage B HCC. However, prospective studies are needed to further evaluate the clinical implications of curative treatments in stage B HCC.

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### **ACKNOWLEDGEMENTS**

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