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Clinical Significance of Biliary Invasion at Diagnosis in Barcelona Clinic Liver Cancer Stage B–C Hepatocellular Carcinoma: A Nationwide Cohort Analysis in South Korea

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Keywords
Hepatocellular carcinoma · Biliary invasion · Prognostic factor · Barcelona Clinic Liver Cancer

Abstract

Introduction: Evidence of biliary invasion as a prognostic factor in patients with hepatocellular carcinoma (HCC) is unclear. We aimed to verify the significance of clinically diagnosed biliary involvement in patients with Barcelona Clinic Liver Cancer stage B–C (BCLC B–C) HCC. ***Methods:*** The Korean Liver Cancer Study Group randomly extracted data of patients with HCC enrolled in the Korean Central Cancer Registry between 2011 and 2016 from approximately 50 hospitals nationwide. After excluding records without information regarding serum bilirubin level, alpha-fetoprotein (AFP) level, and Child-Pugh class, a pre-propensity score matching cohort comprising 4,077 patients was included. Considering age, sex, body mass index, viral cause, serum bilirubin level, AFP, Child-Pugh class, tumor size, multiplicity, portal invasion, and extrahepatic metastasis, patients with and without bile duct invasion at initial imaging diagnosis were matched at a ratio of 1:2 from the pre-propensity score matching cohort to form a matched cohort (propensity score matching cohort). ***Results:*** The pre-propensity score matching cohort included 4,077 patients with BCLC B–C and 165 (4.0%) with biliary invasion at diagnosis. Regarding biliary invasion at diagnosis, 1- and 2-year overall survival (OS) rates were 41.2% and 29.1% (with invasion) and 54% and 40.9% (without invasion), respectively ($p < 0.0001$). Corresponding cancer-specific survival (CSS) rates at 1 and 2 years were 43.4% and 30.7% (with invasion) and 56.6% and 44% (without invasion), respectively ($p < 0.0001$). Although biliary invasion was a significant factor affecting overall and CSS rates in a univariate analysis, it was not statistically significant in multivariate analyses for overall ($p = 0.153$) and cancer-specific ($p = 0.198$) survival rates. The propensity score matching cohort included 165 patients with biliary invasion at diagnosis and 330 without biliary invasion. In the propensity score matching cohort, biliary invasion at diagnosis was not a significant factor affecting overall ($p = 0.603$) or cancer-specific ($p = 0.960$) survival rates in the univariate analyses. One- and 2-year OS were 41.2% and 29.1% (with invasion) and 36.1% and 28.2% (without invasion), respectively. The corresponding CSS at one and 2 years were 43.4% and 30.7% (with invasion) and 39.8% and 31.4% (without invasion), respectively. Multivariate analyses revealed that AFP levels, Child-Pugh class, tumor singularity, tumor size, portal invasion, lymph node metastases, and distant metastases significantly affected both overall and CSS rates. ***Conclusion:*** Biliary invasion at

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diagnosis in patients with BCLC B–C does not affect overall or CSS rates; however, other prognostic factors associated with biliary invasion could have a greater impact.

Introduction

Although vascular invasion in hepatocellular carcinoma (HCC) is known to be a clinical factor that influences treatment decisions, and evidence of biliary invasion as a prognostic factor is unclear [1]. However, biliary tract involvement is rare (1–9%) [2, 3] and may require large data for clinical validation. More than 70% of patients with biliary involvement have Barcelona Clinic Liver Cancer (BCLC) stage B–C or higher at diagnosis [3]; therefore, nonsurgical treatment is commonly recommended in clinical practice. Furthermore, with recent developments in imaging technology, the feasibility of diagnosing bile duct invasion before treatment has become extremely high [4]. However, studies have focused on analyses based on postoperative pathology results [2], and data on treatment decisions after initial clinical diagnosis are lacking. Additionally, controlled studies that sufficiently consider factors accompanying bile duct invasion, such as vascular invasion, multiple tumors, and extrahepatic metastases [2, 5], are lacking. To date, biliary invasion has not been considered as a factor in major staging systems, except for the modified Union for International Cancer Control (UICC) classification [6, 7]. If clinical biliary invasion is an effective independent prognostic factor, decisions regarding local treatments, such as surgery, transarterial therapy, or palliative radiotherapy, can be affected [8, 9].

Therefore, in this study, we attempted to verify the significance of clinically diagnosed biliary involvement in patients with BCLC B–C HCC using propensity matching with nationwide data collected through random sampling. The clinical significance of bile duct invasion was investigated by considering the effects of accompanying clinical prognosticators, such as tumor profile, portal invasion, extrahepatic metastasis, and hepatic function.

Materials and Methods

Data Source

Nationwide data of patients with HCC were obtained from the Korean Liver Cancer Study Group. Between 2011 and 2016, approximately 25–30 hospitals were randomly selected from all hospitals (approximately 500) that registered a diagnosis of HCC in the Korean Central Cancer Registry (KCCR). At least one hospital in each of the 16 major administrative districts of Korea was stratified for selection. A probability-proportional sampling method was used to ensure that hospitals with a larger number of patients had a higher probability of selected. Patients with HCC, corresponding to approximately 16.5% of all patients with HCC in South Korea, were randomly selected from the selected hospitals based on the proportion of patients registered according to region. The data source of the present study is public open data without personal identification information from the KCCR. Institutional Review Board approval was waived; in all other respects, we recognized and adhered to the World Medical Association Declaration of Helsinki.

Study Cohorts and Propensity Matching Method

Original cohort of the data source included 9,213 patients with HCC. There were 4,519 patients with BCLC stages B and C. Among these, 4,077 patients in the pre-propensity score matching (PSM) cohort after excluding records of patients without information regarding serum bilirubin levels, alpha-fetoprotein (AFP) levels, or Child-Pugh class. When creating the pre-PSM cohort from the original cohort, records without information on tumor size and sex were not excluded because the number of patients was small (1 and 12, respectively, among the 4,519 patients). As body mass index (BMI) is clinically unrelated to HCC, records without this information were excluded. HCC is primarily diagnosed through imaging according to the KLCA-NCC (Korea Liver Cancer Association-National Cancer Center) practice guidelines, with biopsy reserved for cases where imaging findings are inconclusive. In our study, 503 out of 4,077 patients received histological confirmation in addition to imaging. Biliary invasion was defined as either radiologically confirmed by a radiologist's interpretation of computed tomography or magnetic resonance imaging scans indicating biliary invasion or histologically confirmed by the presence of tumor invasion. Considering age, sex, BMI, viral cause, serum bilirubin level, AFP level, Child-Pugh class, tumor size, multiplicity, portal invasion, and extrahepatic metastasis, patients with and without bile duct invasion at the initial imaging diagnosis were matched at a ratio of 1:2 in the pre-PSM cohort to form a matched cohort (PSM cohort).

Statistical Analyses

Descriptive statistics of the original cohort, including bile duct invasion, related portal invasion, and hyperbilirubinemia, were included to provide a wide range of

reference. Primary endpoint of this study was overall survival (OS), and secondary endpoint was cancer-specific survival (CSS). In the pre-PSM and PSM cohorts, the Kaplan-Meier estimate [10] was used for survival analysis, and the log-rank test was performed for univariate intergroup comparison. The Cox proportional hazards model was used for multivariate survival analysis [11]. The PSM was performed using the nearest neighbor method, with a minimum p value of 0.2 for all the included variables. χ^2 test was performed to compare the matched variables between the matched groups. All statistical analyses were performed using web-based R analysis (R 4.0; https://cardiomoon.shinyapps.io/webr/, accessed on February 1, 2023).

Results

Descriptive Analysis

Between 2011 and 2016, 9,213 patients with HCC were selected using random extraction. Biliary invasion at the initial imaging diagnosis was observed in 239 (2.59%) patients. Of these 239 patients, 170 (71.1%) had portal invasion at diagnosis, and 104 (43.5%) had a serum bilirubin level of 2.5 mg/dL or higher. Patients with BCLC stages B and C accounted for 49% and 4,519 of the 9,213 patients in the original cohort, respectively.

Characteristics and Results of the Pre-PSM Cohort

The pre-PSM cohort included 4,077 patients with BCLC B–C after excluding 442 patients without information on total serum bilirubin, AFP, or Child-Pugh class from the 4,519 BCLC B–C patients in the original cohort of data source. Clinical characteristics of the pre-PSM cohort are summarized in Table 1. Among the 4,077 patients, 165 (4.0%) had biliary invasion at the time of diagnosis. All 165 patients were diagnosed based on radiologic findings, and of these, 11 patients also had pathologic confirmation of the biliary invasion. Patients with biliary invasion had higher proportion of those with hyperbilirubinemia (30.3% vs. 8.5%, $p < 0.001$), high level of serum AFP (≥1,000, 40.6% vs. 33.3%, $p = 0.033$), Child-Pugh class B (48.5% vs. 29.1%, $p < 0.001$), large tumor (≥7 cm, 65.5% vs. 49.2%, $p < 0.001$), portal invasion (66.7% and 37.1%, $p < 0.001$), and lymph node metastases (20% vs. 11.8%, $p = 0.002$).

Significant factors affecting OS and CSS rates and the one- and 2-year percentile rates of OS and CSS are shown in Table 2. Regarding biliary invasion at diagnosis, the 1- and 2-year OS rates were 41.2% and 29.1% (with invasion) and 54% and 40.9% (without invasion), respectively ($p < 0.0001$, Fig. 1a). The corresponding CSS rates at one and 2 years were 43.4% and 30.7% (with invasion) and 56.6% and 44% (without invasion), respectively ($p < 0.0001$, Fig. 1b). Although biliary invasion was a significant factor affecting OS and CSS in the univariate analysis, it was not statistically significant in the multivariate analyses of OS ($p = 0.153$) and CSS ($p = 0.198$). Regarding other factors in the multivariate analyses, BMI, AFP level, Child-Pugh class, tumor singularity, tumor size, portal invasion, lymph node metastases, and distant metastases significantly affected the OS. Clinical factors, including age, BMI, viral etiology (hepatitis B and other causes), AFP level, Child-Pugh class, tumor singularity, tumor size, portal invasion, and lymph node and distant metastases, affected the CSS.

Characteristics and Results of the PSM Cohort

The characteristics and matched profiles of the PSM cohort, including 165 and 330 patients with and without biliary invasion at diagnosis, respectively, are shown in Table 1. All the clinical factors were successfully matched. Significant factors affecting the OS, CSS, and 1- and 2-year percentile rates of OS and CSS are shown in Table 3.

In the PSM cohort, biliary invasion at diagnosis was not a significant factor that affected OS ($p = 0.603$) or CSS ($p = 0.960$) in the univariate analyses. The 1- and 2-year OS rates were 41.2% and 29.1% (with invasion) and 36.1% and 28.2% (without invasion), respectively (Fig. 2a). The corresponding CSS rates at 1 and 2 years were 43.4% and 30.7% (with invasion) and 39.8% and 31.4% (without invasion), respectively (Fig. 2b). The multivariate analyses revealed that AFP levels, Child-Pugh class, tumor singularity, tumor size, portal invasion, lymph node metastases, and distant metastases significantly affected both OS and CSS.

Discussion

Currently, studies on bile duct invasive HCC are lacking. In real-world clinical practice, more than two-third of patients with bile duct invasion have BCLC stage B or higher. Furthermore, most studies that have been conducted are based on postoperative pathological reports, and studies based on clinical diagnoses are lacking.

If biliary invasion is detected on imaging studies at the time of diagnosis in patients with HCC, it should be considered when making treatment decisions. In the past, there were few treatment options for HCC other than surgery; however, many treatment options, including local treatment options (transarterial chemoembolization,

Table 1. Characteristics of the pre-PSM and PSM cohorts

Variables	Pre-PSM cohort			PSM cohort		
	no biliary invasion (n = 3,912)	biliary invasion (n = 165)	p value	no biliary invasion (n = 330)	biliary invasion (n = 165)	p value
Age	61.4±12.0	62.3±12.5	0.349	61.2±12.4	62.3±12.5	0.352
Sex			0.972			0.344
Male	3,233 (82.6%)	137 (83.0%)		286 (86.7%)	137 (83.0%)	
Female	678 (17.3%)	28 (17.0%)		44 (13.3%)	28 (17.0%)	
Unknown	1	0		0	0	
BMI			0.334			0.982
<25	2,506 (64.1%)	115 (69.7%)		231 (70.0%)	115 (69.7%)	
≥25	1,155 (29.5%)	41 (24.8%)		80 (24.2%)	41 (24.8%)	
Unknown	251 (6.4%)	9 (5.5%)		19 (5.8%)	9 (5.5%)	
Etiology			0.558			0.54
Hepatitis B	2,307 (59.0%)	93 (56.4%)		197 (59.7%)	93 (56.4%)	
Other cause	1,605 (41.0%)	72 (43.6%)		133 (40.3%)	72 (43.6%)	
Serum bilirubin			<0.001			0.519
≥2.5	332 (8.5%)	50 (30.3%)		111 (33.6%)	50 (30.3%)	
<2.5	3,580 (91.5%)	115 (69.7%)		219 (66.4%)	115 (69.7%)	
AFP level			0.033			0.766
<400	2,357 (60.3%)	83 (50.3%)		172 (52.1%)	83 (50.3%)	
400–1,000	253 (6.5%)	15 (9.1%)		24 (7.3%)	15 (9.1%)	
≥1,000	1,302 (33.3%)	67 (40.6%)		134 (40.6%)	67 (40.6%)	
PIVKA-II			0.039			0.236
<40	525 (13.4%)	12 (7.3%)		114 (34.5%)	66 (40%)	
≥40	2,391 (61.1%)	99 (60%)		216 (65.5%)	99 (60%)	
Child-Pugh class			<0.001			0.427
A	2,773 (70.9%)	85 (51.5%)		156 (47.3%)	85 (51.5%)	
B	1,139 (29.1%)	80 (48.5%)		174 (52.7%)	80 (48.5%)	
Tumor singularity			0.576			0.824
Single	1,774 (45.3%)	79 (47.9%)		163 (49.4%)	79 (47.9%)	
Multiple	2,138 (54.7%)	86 (52.1%)		167 (50.6%)	86 (52.1%)	
Tumor size			<0.001			0.407
<7 cm	1,977 (50.5%)	57 (34.5%)		131 (39.7%)	57 (34.5%)	
≥7 cm	1,923 (49.2%)	108 (65.5%)		198 (60.0%)	108 (65.5%)	
Unknown	12 (0.3%)	0 (0.0%)		1 (0.3%)	0 (0.0%)	
Portal invasion			<0.001			0.973
Yes	1,452 (37.1%)	110 (66.7%)		218 (66.1%)	110 (66.7%)	
No	2,460 (62.9%)	55 (33.3%)		112 (33.9%)	55 (33.3%)	
Lymph node metastases			0.002			1
Yes	461 (11.8%)	33 (20.0%)		66 (20.0%)	33 (20.0%)	
No	3,451 (88.2%)	132 (80%)		264 (80%)	132 (80%)	
Distant metastases			0.407			0.968
Yes	695 (17.8%)	34 (20.6%)		66 (20.0%)	34 (20.6%)	
No	3,217 (82.2%)	131 (79.4%)		264 (80.0%)	131 (79.4%)	
First treatment			<0.001			0.265
Surgical resection	596 (15.2%)	16 (9.7%)		35 (10.6%)	16 (9.7%)	
Liver transplantation	31 (0.8%)	1 (0.6%)		0 (0.0%)	1 (0.6%)	
RFA	124 (3.2%)	1 (0.6%)		7 (2.1%)	1 (0.6%)	

Table 1 (continued)

Variables	Pre-PSM cohort			PSM cohort		
	no biliary invasion (n = 3,912)	biliary invasion (n = 165)	p value	no biliary invasion (n = 330)	biliary invasion (n = 165)	p value
TACE	1,704 (43.6%)	53 (32.1%)		130 (39.4%)	53 (32.1%)	
TARE	27 (0.7%)	1 (0.6%)		1 (0.3%)	1 (0.6%)	
Systemic treatment	475 (12.1%)	30 (18.2%)		47 (14.2%)	30 (18.2%)	
Radiation therapy	93 (2.4%)	7 (4.2%)		8 (2.4%)	7 (4.2%)	
Second treatment			0.132			0.190
Surgical resection	82 (2.1%)	5 (3.0%)		6 (1.8%)	5 (3.0%)	
Liver transplantation	21 (0.5%)	0 (0.0%)		2 (0.6%)	0 (0.0%)	
RFA	130 (3.3%)	1 (0.6%)		9 (2.7%)	1 (0.6%)	
TACE	1,004 (25.7%)	38 (23.0%)		70 (21.2%)	38 (23.0%)	
TARE	10 (0.3%)	0 (0.0%)		1 (0.3%)	0 (0.0%)	
Systemic treatment	249 (6.4%)	7 (4.2%)		16 (4.8%)	7 (4.2%)	
Radiation therapy	220 (5.6%)	13 (7.9%)		12 (3.6%)	13 (7.9%)	

PSM, propensity score matching; BMI, body mass index; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

radiofrequency ablation, and radiotherapy) and systemic chemotherapy, are currently being developed and studied. Various treatment options should be considered, depending on whether biliary invasion is present on imaging findings. Currently, biliary invasion is not considered in most staging systems, except the UICC staging system. This is because studies and prognostic information on biliary invasion at the time of diagnosis are lacking. For example, chemotherapy or radiotherapy may be added to the treatment of patients with biliary invasion at the time of diagnosis.

According to the results of our study, biliary invasion was a prognostic factor related to both OS and CSS in the univariate analysis of the pre-PSM cohort. However, this factor did not have a significant effect on these indicators in the multivariate analysis. Moreover, in the matched profiles of the PSM cohort, biliary invasion was not a significant factor for OS and CSS. This suggests that other prognostic factors associated with biliary invasion have a greater effect than those associated with biliary invasion at diagnosis. According to a report by Ikenaga et al. [5], biliary invasion is more often accompanied by infiltration, intrahepatic metastasis, and portal vein thrombosis.

Because many existing studies on bile duct invasion are based on postoperative data, most early-stage patients were inevitably included in these studies. Several studies have claimed the clinical usefulness of biliary invasion, but it differs by clinical stage. Ikenaga et al. [5] reported that biliary invasion has prognostic significance in early-stage patients but has little usefulness in advanced-stage patients. According to a study by Lu et al. [9], postoperative biliary invasion showed significant OS rate in early-stage patients with BCLC 0–A but not in patients with BCLC B. The reason why our study did not show significant results is presumed to be because BCLC B–C was the subject. In a multicenter study, Huang et al. [8] found that OS was worse in a HCC with bile duct invasion group than in a HCC without bile duct invasion group ($p < 0.001$). In this study, 90.7% of the patients had BCLC stage A, and early-stage patients accounted for the majority of the patients. Huang et al. [8] modified the China Liver Cancer staging system, a HCC staging system in China, by considering bile duct invasion as a poor prognostic factor. It is presumed that our study did not produce significant results because it targeted patients with BCLC stage B–C.

Our study has the advantage of being the first large-scale study to compare PSM with a control group in patients with intermediate or higher stage disease. Our study provided the following clinical and study findings: when biliary invasion is found at the time of diagnosis in an intermediate or higher stage disease, it should be investigated whether additional treatment should be considered if there are no cofactors, such as portal vein invasion or high serum bilirubin levels.

A major limitation of our study is the inability to account for the full range of treatments received by patients with biliary invasion throughout their disease course. Due to the retrospective nature of our cohort, we were only able to collect data on the initial and second

Table 2. Results of analysis in the pre-PSM cohort

	n (total *n* = 4,077)	1-year OS	2-year OS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value	1-year CSS	2-year CSS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value
Age <60	2,186 (53.6%)	55.9% (53.9–58.1)	41.5% (39.5–43.7)			59.6% (57.6–61.8)	45.8% (43.7–48.0)		
Age ≥60	1,891 (46.4%)	50.7% (48.5–53.0)	39.1% (36.9–41.3)	0.975, 0.4712		52.1% (49.9–54.4)	40.9% (38.7–43.2)	1.061, 0.106	0.834, <0.0001
Sex									
Male	3,370 (82.7%)	52.8% (51.2–54.6)	39.0% (37.4–40.7)			55.6% (53.9–57.3)	42.3% (40.6–44.0)		
Female	706 (17.3%)	56.7% (53.1–60.4)	47.0% (43.5–50.9)	0.839, 0.0002	0.991, 0.859	58.7% (55.1–62.5)	49.1% (45.5–53.0)	0.861, 0.0025	1.009, 0.870
Unknown	1								
BMI									
<25	2,621 (64.3%)	50.7% (48.9–52.7)	37.5% (35.7–39.4)			54% (44.6–48.5)	41.1% (39.2–43.0)		
≥25	1,196 (29.3%)	64.6% (62.0–67.4)	50.8% (48.0–53.7)	0.736, <0.0001	0.853, <0.0001	66.1% (63.4–68.8)	52.9% (50.2–55.9)	0.762, <0.0001	0.889, 0.0056
Unknown	260 (6.4%)								
Etiology									
Hepatitis B	2,400 (58.9%)	50.8% (48.9–52.9)	38.5% (36.6–40.5)			52.8% (50.8–54.8)	40.8% (38.9–42.9)		
Other cause	1,677 (41.1%)	57.3% (55.0–59.7)	43.1% (40.8–45.5)	1.017, 0.642		61.0% (58.6–63.4)	47.4% (45.0–49.9)	1.101, 0.0107	1.077, 0.089
Serum bilirubin									
≥2.5	382 (9.4%)	28.3% (24.1–33.2)	22.8% (18.9–27.4)			30.3% (25.9–35.4)	24.7% (20.6–29.5)		
<2.5	3,695 (90.6%)	56.1% (54.5–57.7)	42.2% (40.7–43.8)	1.918, <0.0001	0.895, 0.109	58.8% (57.2–60.4)	45.4% (43.8–47.1)	1.974, <0.0001	0.947, 0.454
AFP level									
<400	2,440 (59.8%)	66.6% (64.8–68.5)	52.5% (50.5–54.5)			69.6% (67.8–71.5)	56.3% (54.3–58.4)		
400–1,000	268 (65.7%)	47.0% (41.4–53.4)	32.1% (27.0–38.2)			48.9% (43.2–55.3)	34.1% (28.8–40.4)		
≥1,000	1,369 (33.6%)	31.3% (29.0–33.9)	20.5% (18.5–22.8)	1.452, <0.0001	1.158, <0.0001	33.2% (30.8–35.9)	22.3% (20.1–24.6)	1.505, <0.0001	1.198, <0.0001
Child-Pugh class									
A	2,858 (70.1%)	64.3% (62.6–66.1)	49.4% (47.6–51.2)			66.5% (64.7–68.2)	52.4% (50.6–54.3)		
B	1,219 (29.9%)	28.1% (25.7–30.8)	19.4% (17.3–21.7)	2.416, <0.0001	2.201, <0.0001	31.2% (28.7–34.0)	22.0% (19.7–24.5)	2.421, <0.0001	2.126, <0.0001

Table 2 (continued)

	n (total *n* = 4,077)	1-year OS	2-year OS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value	1-year CSS	2-year CSS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value
Tumor singularity									
Single	1,853 (45.5%)	60.4% (58.3–62.7)	48.5% (46.2–50.8)			63% (60.8–65.3)	51.7% (49.4–54.0)		
Multiple	2,224 (54.5%)	47.7% (45.7–49.8)	33.7% (31.8–35.7)	1.468, <0.0001	1.414, <0.0001	50.4% (48.3–52.5)	36.6% (34.6–38.7)	1.510, <0.0001	1.450, <0.0001
Tumor size									
<7 cm	2,034 (49.9%)	73.7% (71.9–75.7)	59.0% (56.9–61.2)			76.1% (74.3–78.0)	62.2% (60.1–64.4)		
≥7 cm	2,031 (49.8%)	33.4% (31.4–35.5)	22% (20.2–23.8)	2.443, <0.0001	1.876, <0.0001	35.9% (33.8–38.1)	24.4% (22.6–26.4)	2.537, <0.0001	1.904, <0.0001
Unknown	12								
Portal invasion									
Yes	1,562 (38.3%)	27.7% (25.6–30.0)	17.8% (16.0–19.8)			29.8% (27.6–32.2)	19.5% (17.6–21.7)		
No	2,515 (61.7%)	69.5% (67.7–71.3)	54.4% (52.5–56.4)	2.529, <0.0001	1.771, <0.0001	72.1% (70.4–73.9)	58.1% (56.1–60.1)	2.685, <0.0001	1.863, <0.0001
Lymph node metastases									
Yes	494 (12.1%)	22.5% (19.1–26.5)	12.1% (9.6–15.4)			25.6% (21.9–29.9)	14.5% (11.6–18.2)		
No	3,583 (87.9%)	57.8% (56.2–59.4)	44.3% (42.7–45.9)	2.509, <0.0001	1.507, <0.0001	60.2% (58.6–61.8)	47.3% (45.7–49.0)	2.513, <0.0001	1.476, <0.0001
Distant metastases									
Yes	729 (17.9%)	16.1% (13.6–18.9)	8.2% (6.5–10.5)			18.4% (15.7–21.6)	9.6% (7.6–12.2)		
No	3,348 (82.1%)	61.6% (60–63.3)	47.4% (45.7–49.1)	3.461, <0.0001	2.006, <0.0001	64.0% (62.4–65.6)	50.5% (48.8–52.3)	3.527, <0.0001	2.002, <0.0001
Biliary invasion									
Yes	165 (4.0%)	41.2% (34.3–49.5)	29.1% (22.9–36.9)			43.4% (36.4–51.9)	30.7% (24.3–38.8)		
No	3,912 (96%)	54.0% (52.5–55.6)	40.9% (39.4–42.4)	1.422, <0.0001	0.879, 0.153	56.6% (55.1–58.2)	44.0% (42.5–45.6)	1.492, <0.0001	0.887, 0.198

OS, overall survival; HR, hazards ratio; CSS, cancer-specific survival; PSM, propensity score matching; BMI, body mass index; AFP, alpha-fetoprotein.

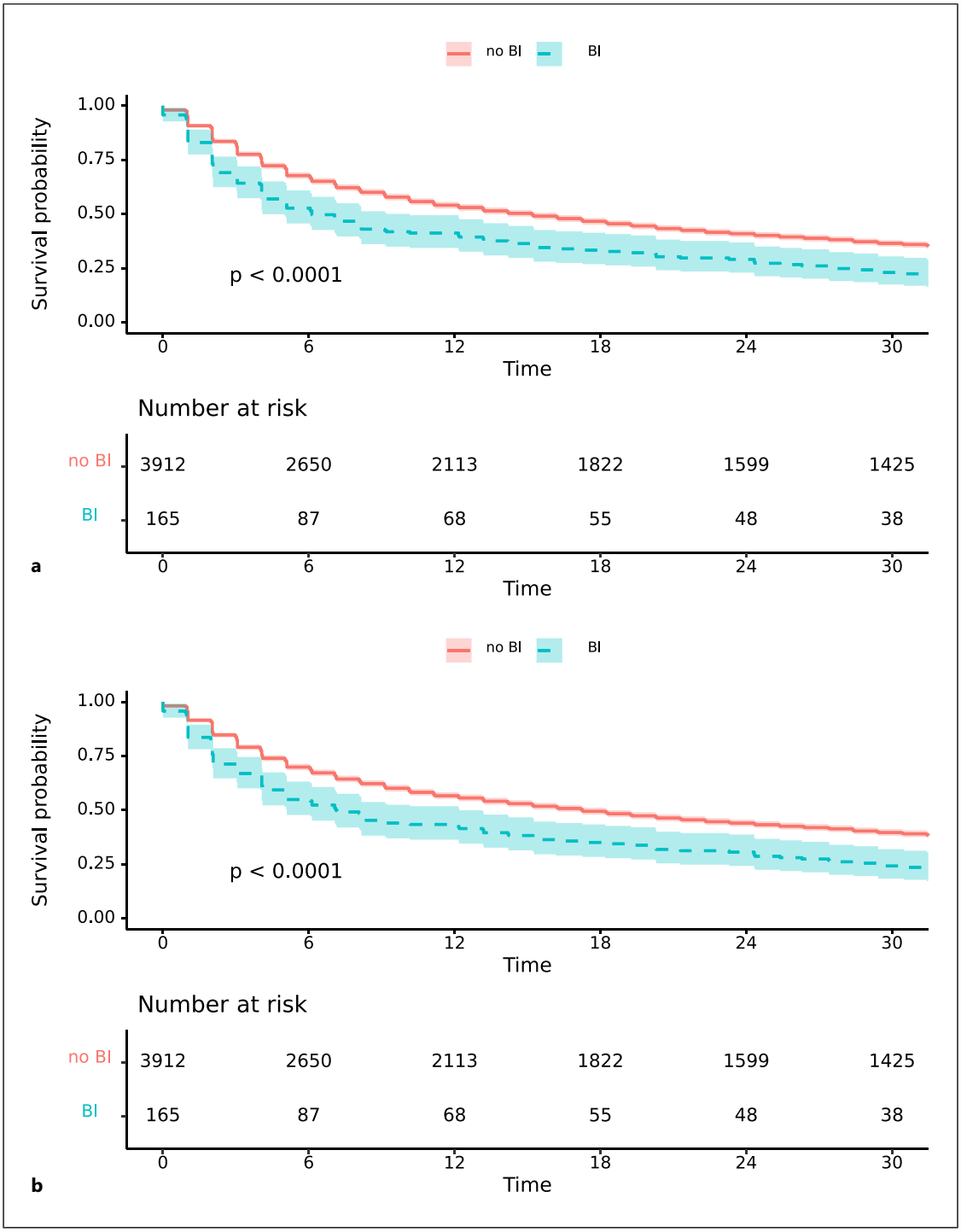

Fig. 1. a Kaplan-Meier curve illustrating the 1- and 2-year overall survival (OS) rates according to the presence or absence of biliary invasion (BI) at diagnosis. The 1- and 2-year OS rates were 41.2% and 29.1% (BI) and 54% and 40.9% (no BI), respectively ($p < 0.0001$). **b** Kaplan-Meier curve illustrating the 1- and 2-year cancer-specific survival (CSS) rates according to the presence or absence of biliary invasion (BI) at diagnosis. The corresponding CSS rates at 1 and 2 years were 43.4% and 30.7% (BI) and 56.6% and 44% (no BI), respectively ($p < 0.0001$).

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Table 3. Results of analysis in the PSM matched cohort

	n (total *n* = 495)	1-year OS	2-year OS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value	1-year CSS	2-year CSS	Univariate HR, *p* value	Multivariate exp (coefficient), *p* value
Age <60	260 (52.5%)	38.5% (33.0–44.9)	28.8% (23.8–34.9)			42.5% (36.8–49.2)	31.9% (26.5–38.4)		
Age ≥60	235 (47.5%)	37.0% (31.3–43.7)	28.1% (22.9–34.5)	0.922, 0.401		39.4% (33.6–46.3)	30.3% (24.9–37.0)	0.966, 0.734	
Sex									
Male	423 (85.5%)	36.9% (32.6–41.8)	27.9% (23.9–32.5)			40.3% (35.8–45.4)	30.7% (26.5–35.6)		
Female	72 (14.5%)	43.1% (33.0–56.2)	31.9% (22.8–44.8)	0.903, 0.460		45.5% (35.2–58.9)	33.8% (24.3–47.0)	0.898, 0.455	
Unknown									
BMI									
<25	346 (69.9%)	36.7% (32.0–42.2)	26.3% (22.0–31.4)			40.6% (35.6–46.3)	29.1% (24.5–34.5)		
≥25	121 (24.4%)	44.6% (36.6–54.4)	37.2% (29.5–46.9)	1.031, 0.658		46.2% (38.1–56.2)	39.3% (31.4–49.2)	1.062, 0.392	
Unknown	3								
Etiology									
Hepatitis B	205 (41.4%)	37.6% (31.5–44.8)	29.3% (23.7–36.2)			42.1% (35.6–49.7)	33.3% (27.1–40.8)		
Other cause	290 (58.6%)	37.9% (32.7–43.9)	27.9% (23.2–33.6)	0.942, 0.535		40.3% (35.0–46.5)	29.7% (24.8–35.6)	1.021, 0.841	
Serum bilirubin									
≥2.5	334 (67.5%)	23.0% (17.3–30.5)	16.8% (11.9–23.7)			48.7% (43.5–54.5)	37.3% (32.3–43.0)		
<2.5	161 (32.5%)	44.9% (39.9–50.6)	34.1% (29.4–39.6)	1.789, <0.0001	1.086, 0.532	25.2% (19.2–33.1)	18.4% (13.1–25.7)	1.866, <0.0001	1.191, 0.205
AFP level									
<400	255 (51.5%)	52.2% (46.4–58.7)	40.4% (34.8–46.9)			55.8% (49.9–62.4)	43.6% (37.7–50.3)		
400–1,000	39 (7.9%)	28.2% (17.1–46.5)	17.9% (9.2–35.1)			29.6% (18.1–48.4)	18.8% (9.7–36.6)		
≥1,000	201 (40.6%)	21.4% (16.4–27.9)	15.4% (11.2–21.3)	1.343, <0.0001	1.184, 0.002	24.3% (18.9–31.4)	17.5% (12.8–24.0)	1.362, <0.0001	1.191, 0.002
Child-Pugh class									
A	241 (48.7%)	56.4% (50.5–63.1)	43.6% (37.7–50.3)			59.1% (53.1–65.7)	46.0% (40.0–52.8)		
B	254 (51.3%)	20.1% (15.7–25.7)	14.2% (10.5–19.2)	2.554, <0.0001	2.355, <0.0001	23.4% (18.6–29.6)	16.6% (12.4–22.2)	2.529, <0.0001	2.329, <0.0001

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Table 3 (continued)

	n (total n = 495)	1-year OS	2-year OS	Univariate HR, p value	Multivariate exp (coefficient), p value	1-year CSS	2-year CSS	Univariate HR, p value	Multivariate exp (coefficient), p value
Tumor singularity									
Single	242 (48.9%)	49.2% (43.3–55.9)	40.9% (35.2–47.6)			52.6% (46.6–59.4)	43.8% (37.8–50.7)		
Multiple	253 (51.1%)	26.9% (21.9–32.9)	16.6% (12.6–21.9)	1.749, <0.0001	1.400, <0.001	29.8% (24.5–36.2)	18.7% (14.3–24.5)	1.816, <0.0001	1.450, 0.0004
Tumor size									
<7 cm	188 (38.0%)	60.6% (54.0–68.0)	50.5% (43.9–58.2)			63.4% (56.8–70.8)	53.3% (46.6–61.1)		
≥7 cm	306 (61.8%)	23.9% (19.5–29.1)	15.0% (11.5–19.6)	2.139, <0.0001	1.691, <0.0001	27.0% (22.3–32.7)	17.0% (13.1–22.1)	2.180, <0.0001	1.698, <0.0001
unknown	1								
Portal invasion									
Yes	328 (66.3%)	27.1% (22.7–32.4)	18.9% (15.1–23.7)			30.1% (25.4–35.7)	21.2% (17.1–26.4)		
No	167 (33.7%)	58.7% (51.7–66.6)	47.3% (40.3–55.5)	1.967, <0.0001	1.378, 0.005	62.2% (55.2–702)	50.2% (43.0–58.6)	2.088, <0.0001	1.452, 0.002
Lymph node metastases									
Yes	99 (20%)	12.1% (7.1–20.6)	8.1% (4.2–15.7)			14.5% (8.7–24.3)	9.7% (5.1–18.6)		
No	396 (80%)	44.2% (39.6–49.4)	33.6% (29.2–38.6)	2.458, <0.0001	1.424, 0.009	47.3% (42.5–52.6)	36.2% (31.6–41.4)	2.448, <0.0001	1.417, 0.013
Distant metastases									
Yes	100 (20.2%)	10% (5.6–18.0)	6% (2.8–13)			12.7% (7.3–22.2)	7.6% (3.6–16.2)		
No	395 (79.8%)	44.8% (40.2–50.0)	34.2% (29.8–39.2)	3.080, <0.0001	1.755, <0.0001	47.8% (43.1–53.1)	36.7% (32.3–41.9)	3.060, <0.0001	1.705, <0.001
Biliary invasion									
Yes	165 (33.4%)	41.2% (34.3–49.5)	29.1% (22.9–36.9)			43.4% (36.4–51.9)	30.7% (24.3–38.8)		
No	330 (66.6%)	36.1% (31.2–41.6)	28.2% (23.7–33.5)	0.948, 0.603		39.8% (34.7–45.6)	31.4% (26.6–37.0)	0.995, 0.960	

OS, overall survival; HR, hazards ratio; CSS, cancer-specific survival; PSM, propensity score matching; BMI, body mass index; AFP, alpha-fetoprotein.

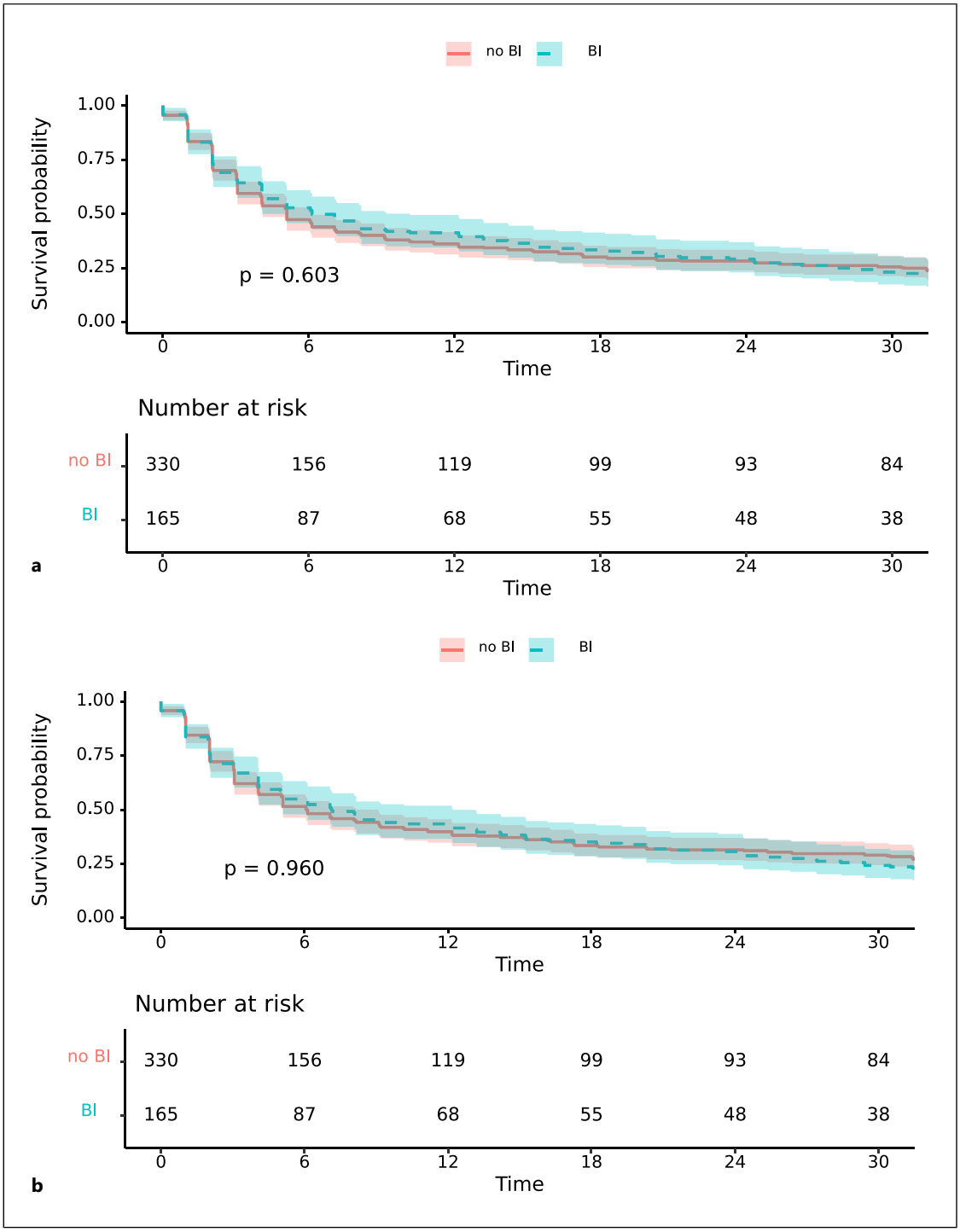

Fig. 2. a Kaplan-Meier curve depicting the 1- and 2-year overall survival (OS) rates based on the presence or absence of biliary invasion (BI) at diagnosis in the propensity score matching (PSM) cohort. The 1- and 2-year OS rates were 41.2% and 29.1% (BI) and 36.1% and 28.2% (no BI), respectively. **b** Kaplan-Meier curve illustrating the 1- and 2-year cancer-specific survival (CSS) rates according to the presence or absence of biliary invasion at diagnosis in the propensity score matching (PSM) cohort. The corresponding CSS rates at 1 and 2 years were 43.4% and 30.7% (BI) and 39.8% and 31.4% (no BI), respectively.

treatments after diagnosis. Since HCC with biliary invasion often involves multiple rounds of locoregional and systemic therapies, analyzing survival based solely on early treatments could yield incomplete or misleading conclusions. Future studies with comprehensive longitudinal data on all treatments are needed to better understand the impact of therapeutic interventions on survival outcomes in this specific patient population. Another limitation of our study is that biliary invasion at diagnosis was investigated as a single factor. Additionally, whether there is a difference in the prognosis of OS and CSS, depending on the site of biliary invasion, needs to be investigated. Moreover, although rare, HCC can present as mixed tumors with cholangiocarcinoma or metastases, and accurate diagnosis may benefit from biopsy or tumor markers such as carbohydrate antigen 19-9. Due to the retrospective nature of our study, carbohydrate antigen 19-9 data were unavailable, though levels of AFP and protein induced by vitamin K absence or antagonist-II were included. Given that over 70% of HCC cases in South Korea are HBV- or HCV-related [12], imaging alone was often sufficient for diagnosis, which is reflected in the fact that only 12.3% of patients underwent biopsy in our study. Additionally, the lack of data on specific etiologies such as cholestatic liver diseases (PSC, PBC), due to the limitations of the KCCR, may constrain the comprehensiveness of our findings regarding less common causes of HCC. Furthermore, our study is limited by the absence of data on the proportion of patients with biliary invasion who underwent biliary drainage. An et al. [3] reported that patients with obstructive jaundice due to biliary invasion who underwent successful biliary drainage demonstrated better survival outcomes. Future research is warranted to investigate this important clinical factor further.

Conclusions

Biliary invasion at diagnosis in patients with BCLC B–C does not affect the prognosis of OS and CSS; however, other prognostic factors associated with biliary invasion could be a greater impact.

Acknowledgments

This study was conducted with data provided by the Korea Central Cancer Registry (KCCR) and the Korean Liver Cancer Association.

Statement of Ethics

The present study utilized public open data sourced from the KCCR, devoid of personal identification information. Institutional Review Board approval was waived by the Institutional Review Board of Korea University Medical Center, with full adherence to the principles outlined in the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

Material preparation and data collection were performed by Chi Hong Rim, and analyses were performed by Sunmin Park and Won Sup Yoon. The first draft of the manuscript was written by Sunmin Park. All authors contributed to the study conception and design, commented on previous versions of the manuscript, and read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. The data that support the findings of this study are available upon reasonable request (contact e-mail: sunmini815@korea.ac.kr).

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