



Effect of Biliary Drainage on the Prognosis of Patients with Hepatocellular Carcinoma and Bile Duct Invasion

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Background/Aims: Bile duct invasion (BDI) is rarely observed in patients with advanced hepatocellular carcinoma (HCC), leading to hyperbilirubinemia. However, the efficacy of pretreatment biliary drainage for HCC patients with BDI and obstructive jaundice is currently unclear. Thus, the aim of this study was to assess the effect of biliary drainage on the prognosis of these patients.

Methods: We retrospectively enrolled a total of 200 HCC patients with BDI from multicenter cohorts. Patients without obstructive jaundice (n=99) and those who did not undergo HCC treatment (n=37) were excluded from further analysis. Finally, 64 patients with obstructive jaundice (43 subjected to drainage and 21 not subjected to drainage) were included. Propensity score matching was then conducted.

Results: The biliary drainage group showed longer overall survival (median 10.13 months vs 4.43 months, $p=0.004$) and progression-free survival durations (median 7.00 months vs 1.97 months, $p<0.001$) than the non-drainage group. Multivariate analysis showed that biliary drainage was a significantly favorable prognostic factor for overall survival (hazard ratio, 0.42; $p=0.006$) and progression-free survival (hazard ratio, 0.30; $p<0.001$). Furthermore, in the evaluation of first response after HCC treatment, biliary drainage was beneficial ($p=0.005$). Remarkably, the durations of overall survival ($p=0.032$) and progression-free survival ($p=0.004$) were similar after propensity score matching.

Conclusions: Biliary drainage is an independent favorable prognostic factor for HCC patients with BDI and obstructive jaundice. Therefore, biliary drainage should be contemplated in the treatment of advanced HCC with BDI to improve survival outcomes. (*Gut Liver* 2024;18:877-887)

Key Words: Hepatocellular carcinoma; Bile ducts; Hyperbilirubinemia; Drainage; Survival analysis

INTRODUCTION

Hepatocellular carcinoma (HCC), the primary liver malignancy, is increasingly diagnosed at advanced stages with limited treatment effectiveness.^{1,2} Advanced HCC often involves vascular invasion, including portal and hepatic veins and liver microvascular structures.³ Bile duct invasion (BDI) is a rare but clinically relevant complication observed in advanced HCC. It is characterized by the infiltration of tumor cells into bile ducts.⁴ This infiltration

often leads to obstruction of bile flow, resulting in obstructive jaundice and hyperbilirubinemia.^{5,6}

Obstructive jaundice caused by BDI indicates poor outcomes and higher mortality in HCC in both early and progressive stages of HCC.⁷⁻¹⁰ Patients who have surgical treatment present unfavorable prognoses when BDI is pathologically confirmed.^{11,12} Obstructive jaundice complicates residual liver function evaluation and increases biliary system complications risk, including cholangitis, cholecystitis, and hemobilia.^{6,13} Furthermore, current clini-



cal guidelines for the treatment of HCC, including the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, do not clearly outline therapeutic strategies for addressing BDI.¹⁴⁻¹⁸ This gap highlights the importance of establishing more comprehensive and detailed treatment strategies for patients with BDI.

Several types of biliary drainage procedures are available for HCC patients with BDI, including endoscopic retrograde cholangiopancreatography, percutaneous transhepatic biliary drainage, and placement of covered stents.^{8,19,20} The selection of a specific drainage method is customized based on the patient's particular health status, considering factors such as liver function and the extent of bile duct dilatation. Several previous studies have reported that effective biliary drainage has a beneficial impact on prognosis of patients with HCC accompanied by obstructive jaundice.²¹⁻²⁵ However, performing biliary drainage before treating HCC is not mandatory.²⁶ Thus, whether biliary drainage should be performed for HCC with BDI is still a topic of debate.

Thus, the objective of this study was to evaluate the prognostic significance of biliary drainage in HCC patients with BDI and obstructive jaundice. This study retrospectively enrolled patients from multicenter cohorts and applied propensity score matching (PSM) to enable a balanced comparison of those who underwent biliary drainage and those who did not. This study also determined if biliary drainage could act as an independent prognostic factor for HCC patients with BDI to decide whether biliary drainage should be incorporated into treatment protocols to improve survival outcomes.

MATERIALS AND METHODS

1. Patient population

The research protocol was reviewed and approved by the Institutional Review Board of the Catholic University of Korea (IRB number: KC18RESI0399). Written informed consent was waived. A total of 200 HCC patients with concurrent BDI were retrospectively analyzed (Supplementary Methods). These patients were enrolled from six affiliated hospitals (Seoul St. Mary's Hospital, Eunpyeong St. Mary's Hospital, Uijeongbu St. Mary's Hospital, St. Vincent's Hospital, Bucheon St. Mary's Hospital, and Incheon St. Mary's Hospital) between March 2006 and April 2023. Of the total of 200 HCC patients with concurrent BDI, 101 patients presented with hyperbilirubinemia (total bilirubin ≥ 3 mg/dL). After excluding those who underwent palliative biliary drainage, 64 patients who received treatment for HCC

were included in the study (43 in the biliary drainage group and 21 in the non-drainage group).

Inclusion criteria for this study were: (1) diagnosis of HCC based on the American Association for the Study of Liver Diseases or European Association for the Study of the Liver guidelines; (2) radiological or pathological evidence of HCC-related BDI and bile duct dilatation; (3) age of 18 years or older; and (4) absence of any other extrahepatic malignancy at the time of HCC diagnosis. Exclusion criteria were: (1) jaundice due to toxic or viral hepatitis; (2) pathological confirmation of a concurrent cholangiocarcinoma component with HCC; and (3) patients who were lost to follow-up after receiving HCC treatment. All patients in the current study were monitored until April 2023. Survival information of these patients was obtained from the National Health Insurance Service.

2. Statistical analysis

For categorical variables, statistical significance was determined using the Pearson chi-square test or Fisher exact test, as appropriate. The log-rank test was employed to compare survival distributions of the two groups and verify statistical significance of the difference in survival time. Cox regression analyses were utilized for both univariate and multivariate assessments to investigate effects of biliary drainage and other covariates on survival outcomes. The univariate analysis was conducted to identify potential prognostic factors, while the multivariate analysis was used to adjust for any confounders and assess independent effects of variables on patient outcomes. To balance baseline characteristics between the biliary drainage and non-drainage groups, we used the nearest-neighbor matching method with a 1:1 ratio and a caliper width of 0.2. This caliper, set as a proportion of the standard deviation of the logit of the propensity score, ensures closely matched pairs and minimizes baseline differences. All statistical analyses were performed using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). A p-value of less than 0.05 was considered to indicate statistical significance in all tests.

RESULTS

1. Baseline characteristics of HCC patients with BDI

In this multicenter cohort of 200 HCC patients with BDI, 101 patients were found to have hyperbilirubinemia defined as a total bilirubin level of 3 mg/dL or above (Supplementary Table 1). Demographic analysis indicated that males were the majority in both groups, showing no significant difference between the two groups ($p=0.545$).

Patients aged ≥ 60 were more prevalent in the group without hyperbilirubinemia than in the group with hyperbilirubinemia (64% vs 50%, $p=0.044$). In terms of clinical characteristics, Child-Pugh scores and Albumin-Bilirubin (ALBI) grades showed significant differences between the two groups. Those with hyperbilirubinemia showed higher percentage of patients with a Child-Pugh score ≥ 8 (indicating poorer prognosis) than those without hyperbilirubinemia (51% vs 18%, $p<0.001$). The hyperbilirubinemia group had 59% of patients with ALBI grade 1, which was lower ($p<0.001$) than the percentage (91%) of such patients in the group without hyperbilirubinemia, highlighting the impact of elevated bilirubin on liver function. However, tumor characteristics such as size and type showed no significant differences between the two groups. Regarding portal vein tumor thrombosis, groups with and without hyperbilirubinemia showed no statistically significant difference ($p=0.287$).

ference ($p=0.287$).

2. Effect of hyperbilirubinemia in HCC with BDI

Based on the results shown in Supplementary Table 1, it could be hypothesized that hyperbilirubinemia might adversely affect the prognosis of patients. Therefore, we analyzed on overall survival (OS) and progression-free survival (PFS) based on the presence of obstructive jaundice. Fig. 1A and B present Kaplan-Meier curves examining the OS and PFS according to hyperbilirubinemia (total bilirubin ≥ 3 mg/dL) in all patients with BDI ($n=200$). Patients with hyperbilirubinemia had worse OS than those without hyperbilirubinemia (median OS: 4.93 months vs 6.07 months, $p=0.027$) (Fig. 1A). However, PFS showed no significant difference between the two groups (median PFS: 3.13 months for patients with hyperbilirubinemia vs 3.70 months for patients without hyperbilirubinemia, $p=0.098$)

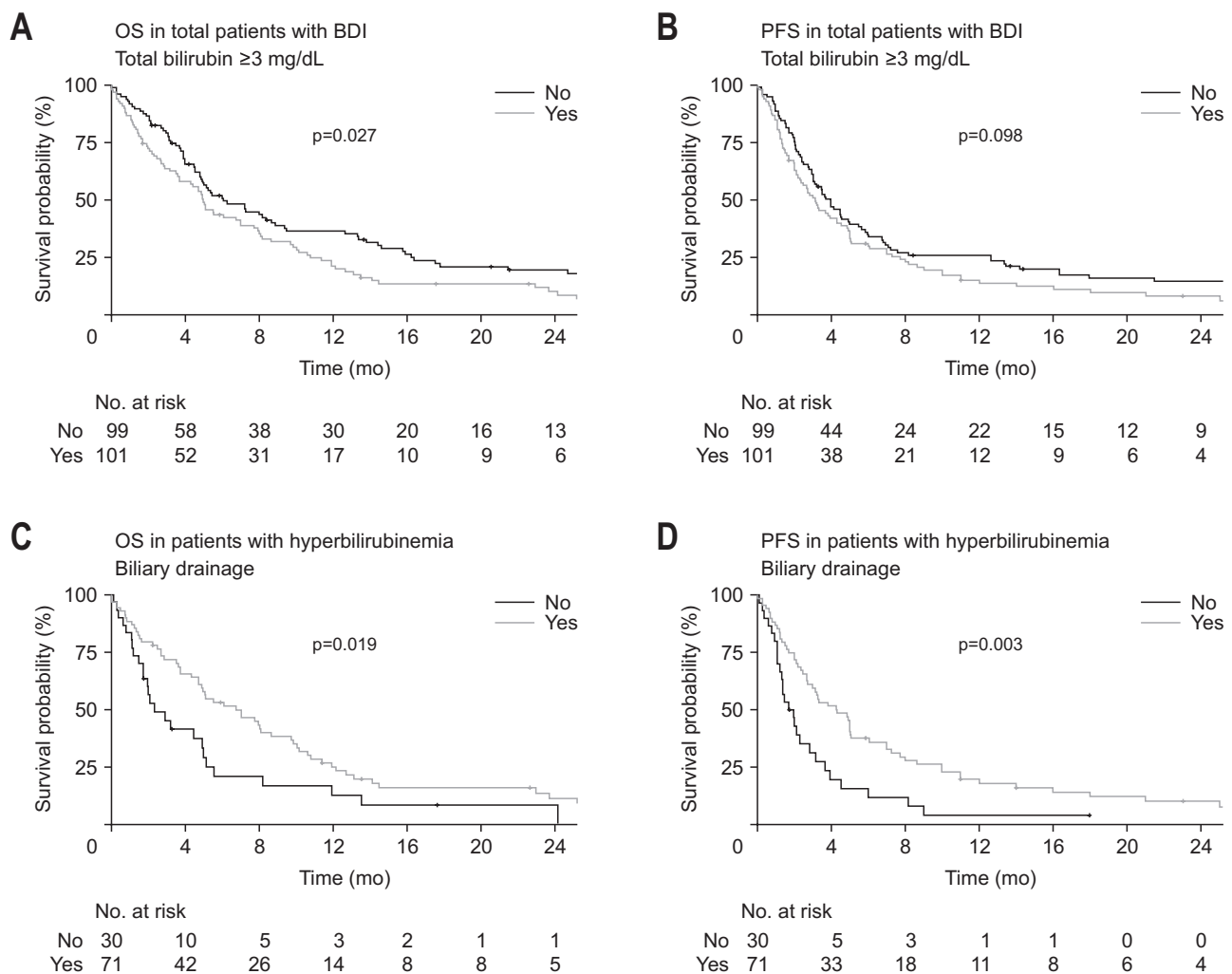


Fig. 1. Kaplan-Meier curves investigating overall survival (OS) and progression-free survival (PFS). [A, B] OS and PFS according to hyperbilirubinemia (total bilirubin ≥ 3 mg/dL) in the entire cohort ($n=200$). [C, D] OS and PFS according to biliary drainage in patients with hyperbilirubinemia ($n=101$). BDI, bile duct invasion.

(Fig. 1B). These findings led us to hypothesize that biliary drainage could potentially improve patient outcomes by alleviating hyperbilirubinemia. Thus, the impact of biliary drainage on the prognosis of HCC patients with BDI was investigated next.

3. Impact of biliary drainage on prognosis of patients with hyperbilirubinemia

We assessed the prognostic effect of biliary drainage in 101 HCC patients with BDI-induced hyperbilirubinemia. Supplementary Table 2 describes baseline characteristics of these patients. Biliary drainage was more common in males ($p=0.038$). Additionally, alpha-fetoprotein (AFP) levels were higher in the non-drainage group, with 77% having levels ≥ 400 ng/mL compared to 48% in the drainage group ($p=0.008$). Other characteristics did not show any statistically significant differences (Supplementary Table 2). We conducted a survival analysis according to biliary drainage in HCC patients with hyperbilirubinemia. Both OS (median OS: 6.73 months vs 2.30 months, $p=0.019$) and PFS (median PFS: 4.27 months vs 1.70 months, $p=0.003$) showed statistically significant improvements for patients who received biliary drainage compared to those who did not (Fig. 1C and D).

In a real-world clinical setting, biliary drainage is often performed solely for palliative purposes in HCC patients with obstructive jaundice caused by BDI. Therefore, we re-evaluated the efficacy of biliary drainage, excluding patients who underwent the procedure for palliative purposes ($n=37$) to focus on 64 patients who received HCC treatment after biliary drainage (Table 1). Before PSM, sex, age distribution, previous treatment history, etiology of HCC, and ALBI grade did not show any significant differences between the two groups. AFP levels were still higher in the non-drainage group ($p=0.037$). Tumor characteristics, including type and size, and occurrence of multiple tumors and portal vein tumor thrombosis were comparable between the two groups. Interestingly, the time from BDI diagnosis to HCC treatment was significantly shorter in the non-drainage group ($p<0.001$). In addition, a larger proportion of patients in the drainage group showed a decrease in total bilirubin after HCC treatment, although the difference between the two groups was not statistically significant. Survival analysis was performed for HCC patients with hyperbilirubinemia who underwent biliary drainage prior to HCC treatment before PSM. Results are shown in Fig. 2A and B. For OS, patients who received biliary drainage had a longer survival than those who did not (median OS: 10.13 months vs 4.43 months, $p=0.004$). Similarly, for PFS, those who received biliary drainage had longer survival than those who did not (median PFS: 7.00 months vs

1.97 months, $p<0.001$).

4. Effect of biliary drainage on first response evaluation

We conducted an analysis of first response outcomes following HCC treatment to assess the detailed efficacy of biliary drainage (Table 2, Supplementary Methods). The drainage group had 31 cases with complete response, partial response, or stable disease, compared to seven cases of progressive disease and five unknown cases. The non-drainage group had a notably different outcome, with only seven cases of complete response, partial response, or stable disease, but a higher number of progressive disease at nine cases, and five unknown cases. The Person chi-square test confirmed that these differences had p -values less than 0.005, indicating statistically significant differences in treatment responses based on whether biliary drainage was performed (Table 3). Additionally, the detailed treatment modalities of HCC were described in Supplementary Table 3, and there was no significant difference between the two groups ($p=0.132$).

5. Prognostic impact of biliary drainage after PSM

PSM was performed to adjust for baseline differences and potential confounders between two groups using the nearest-neighbor method with a 1:1 matching ratio (Table 1). Variables "Time from BDI to HCC treatment" and "Decreased total bilirubin after HCC treatment" were not included as adjustment factors in the PSM because they were directly influenced by biliary drainage. After PSM, characteristics of biliary drainage and non-drainage groups in this study were largely comparable, indicating effective balancing. The proportion of males was similar in both groups (67% in non-drainage vs 76% in drainage, $p=0.495$). Age distribution, previous treatment history, and etiology showed no significant differences either, indicating effective matching (p -values ranging from 0.525 to >0.999). The ALBI grade 1 ($p=0.495$) and Child-Pugh score ≥ 8 ($p=0.355$) were also comparable between the two groups. AFP levels, which showed a significant difference before PSM ($p=0.037$), were well-adjusted after PSM ($p=0.317$). Tumor characteristics such as type, size, multiple tumors, and portal vein tumor thrombosis of the two groups showed no significant differences either after PSM (Table 1). In the survival analysis of the PSM cohort, patients who received biliary drainage had a significant higher OS than those who did not (median OS: 8.00 months vs 4.43 months, $p=0.032$) (Fig. 2C). The biliary drainage groups also had significantly higher PFS (median PFS: 5.07 months vs 1.97 months, $p=0.004$) (Fig. 2D), suggesting a beneficial effect of the treatment.

Table 1. Baseline Demographics and Clinical Characteristics of Treated HCC Patients with BDI (TB ≥ 3 mg/dL)

Characteristic	Before PSM				After PSM					
	Overall (n=64)	Biliary drainage		p-value*	SMD	Overall (n=42)	Biliary drainage		p-value*	SMD
		No (n=21)	Yes (n=43)				No (n=21)	Yes (n=21)		
Male sex	51 (80)	14(67)	37 (86)	0.099	0.47	30 (72)	14 (67)	16 (76)	0.495	0.21
Age ≥60 yr	28 (65)	9 (43)	19 (44)	0.920	0.03	16 (38)	9 (43)	7 (33)	0.525	0.20
Previous treatment history	23 (36)	9 (43)	14 (33)	0.420	0.21	18 (43)	9 (43)	9 (43)	>0.999	0.00
Etiology										
HBV	50 (78)	18 (86)	32 (74)	0.356	0.29	36 (86)	18 (86)	18 (86)	>0.999	0.00
HCV	2 (3)	0	2 (5)	>0.999	0.31	0	0	0		
Alcohol	15 (23)	7 (33)	8 (19)	0.220	0.34	13 (31)	7 (33)	6 (29)	0.739	0.10
Others	5 (7.8)	0	5 (12)	0.163	0.51	1 (2)	0 (0)	1 (5)	>0.999	0.32
ALBI grade 1	48 (75)	14 (67)	34 (79)	0.282	0.28	30 (71)	14 (67)	16 (76)	0.495	0.17
Child-Pugh score ≥8	28 (44)	12 (57)	16 (37)	0.131	0.41	21 (50)	12 (57)	9 (43)	0.355	0.22
AFP ≥400 ng/mL	37 (58)	16 (76)	21 (49)	0.037	0.59	29 (69)	16 (76)	13 (62)	0.317	0.31
PIVKA-II ≥1,000 mAU/mL	35 (55)	12 (57)	23 (53)	0.783	0.07	26 (62)	12 (57)	14 (67)	0.525	0.20
Tumor type										
Infiltrative	26 (41)	12 (57)	14 (33)	0.083	0.66	22 (52)	12 (57)	10 (48)	0.809	0.15
Massive	27 (42)	8 (38)	19 (44)			17 (41)	8 (38)	9 (43)		
Nodular	11 (17)	1 (5)	10 (23)			3 (7)	1 (5)	2 (10)		
Maximum tumor size ≥5 cm	44 (69)	16 (76)	28 (65)	0.369	0.25	29 (69)	16 (76)	13 (62)	0.517	0.25
Multiple tumors	27 (42)	10 (48)	17 (40)	0.539	0.16	20 (48)	10 (48)	10 (48)	>0.999	0.00
PVTT	52 (81)	18 (86)	34 (79)	0.736	0.18	37 (90)	18 (86)	19 (91)	>0.999	0.00
BCLC stage										
B	9 (14)	2 (10)	7 (16)	0.706	0.20	3 (7)	2 (10)	1 (5)	>0.999	0.19
C	55 (86)	19 (90)	36 (84)			39 (93)	19 (90)	20 (95)		
Time from BDI diagnosis to HCC treatment, day	24.9±32.0	12.0±22.4	31.4±34.3	<0.001	-0.68	23.5±33.0	12.0±22.4	35.0±38.1	<0.001	-0.75
Decreased TB within 7 day after HCC treatment	44 (66)	11 (52)	31 (72)	0.119	0.42	27 (64)	11 (52)	16 (76)	0.107	0.51
Decreased TB within 30 day after HCC treatment	51 (80)	14 (67)	37 (86)	0.099	0.47	32 (76)	14 (67)	18 (86)	0.147	0.46

Data are presented as number (%) or mean $\pm$ SD.

HCC, hepatocellular carcinoma; BDI, bile duct invasion; TB, total bilirubin; PSM, propensity score matching; SMD, standardized mean difference; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K antagonist; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer.

*Pearson chi-square test.

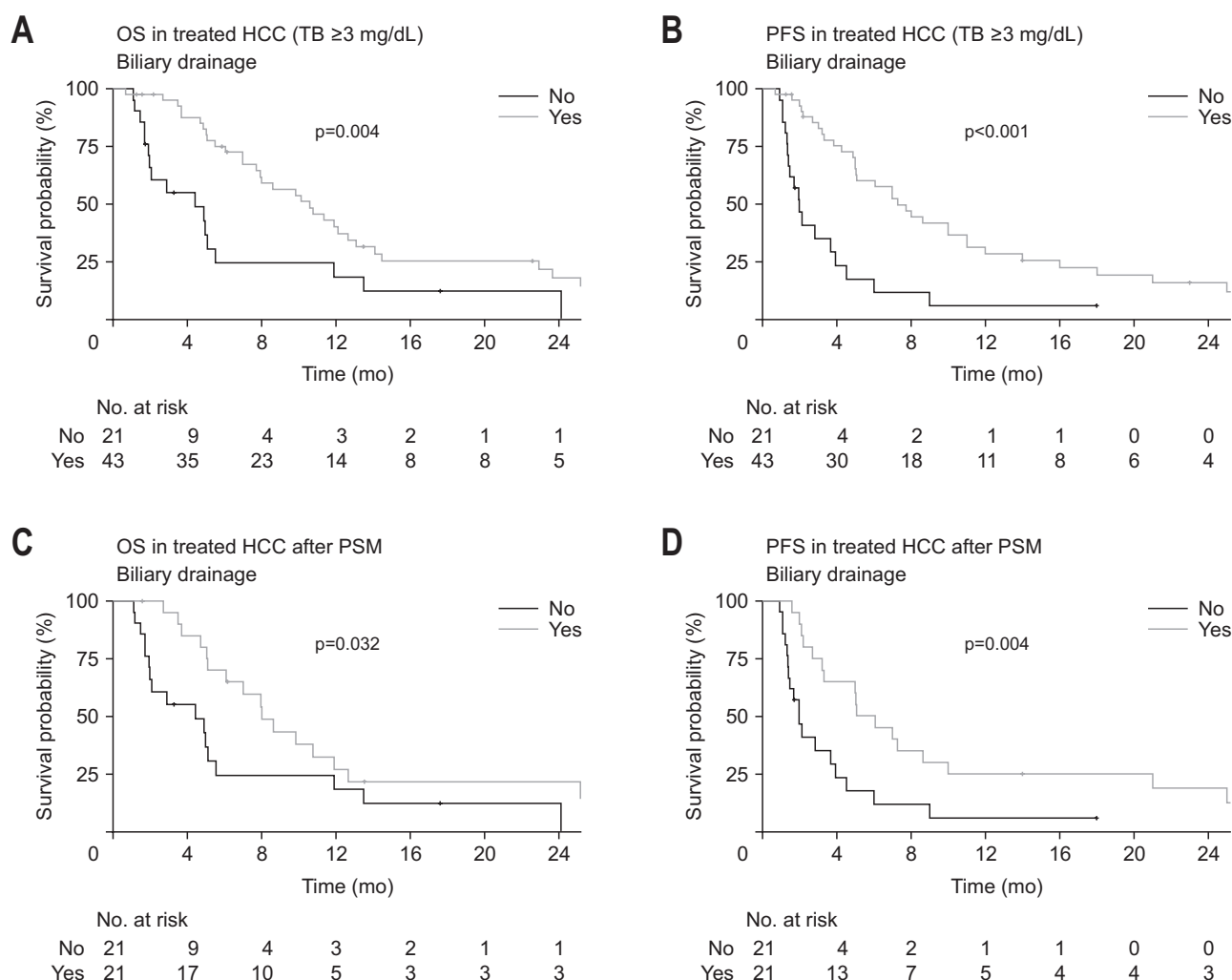


Fig. 2. Kaplan-Meier curves showing prognostic impact of biliary drainage in the treated HCC patients with hyperbilirubinemia. Before PSM: OS (A) and PFS (B). After PSM: OS (C) and PFS (D). HCC, hepatocellular carcinoma; PSM, propensity score matching; OS, overall survival; PFS, progression-free survival; TB, total bilirubin.

Table 2. Evaluation of First Response Following HCC Treatment: Treated HCC Patients with Hyperbilirubinemia (TB ≥ 3 mg/dL)

Response	Overall	Biliary drainage		p-value*
		No	Yes	
CR, PR, SD	38	7	31	0.005
CR		1	2	
PR		0	5	
SD		6	24	
PD	16	9	7	
Unknown	10	5	5	

HCC, hepatocellular carcinoma; TB, total bilirubin; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

*Pearson chi-square test.

6. Univariate and multivariate analyses

Next, we conducted univariate and multivariate analyses to determine factors associated with the favorable impact

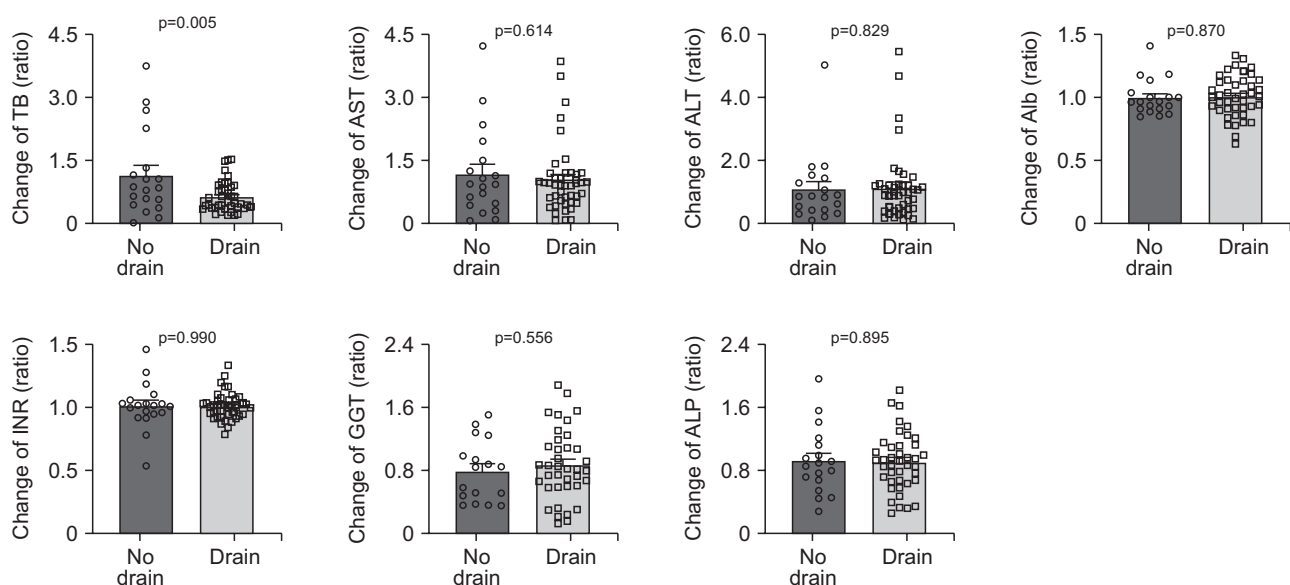
of biliary drainage in HCC patients with BDI. In univariate analysis before PSM, ALBI grade 1, the presence of multiple tumors, AFP levels ≥ 400 ng/mL, and biliary drainage were identified as statistically significant factors associated with OS. Subsequent multivariate analysis revealed that ALBI grade 1 (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.18 to 0.75; $p=0.006$), the presence of multiple tumors (HR, 2.19; 95% CI, 1.01 to 3.59; $p=0.047$), and biliary drainage (HR, 0.42; 95% CI, 0.22 to 0.78; $p=0.006$) maintained their significance (Supplementary Table 4). Regarding PFS, the univariate analysis showed that AFP level ≥ 400 ng/mL, the presence of multiple tumors, and biliary drainage were statistically significant factors associated with PFS. However, in the subsequent multivariate analysis, only biliary drainage (HR, 0.30; 95% CI, 0.16 to 0.56; $p<0.001$) remained as a significant factor for favorable PFS (Supplementary Table 4).

After PSM, in univariate analysis, significant factors as-

Table 3. Univariate and Multivariate Analyses of Factors Affecting Overall Survival and Progression-Free Survival after Propensity Score Matching

Characteristic	Overall survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	1.01 (0.48–2.12)	0.983			1.04 (0.50–2.12)	0.926		
Age ≥ 60 yr	1.24 (0.60–2.55)	0.557			1.30 (0.65–2.60)	0.455		
Previous treatment history	1.58 (0.79–3.14)	0.193			1.96 (0.99–3.88)	0.044	2.38 (1.15–4.92)	0.019
Etiology								
HBV	1.72 (0.60–4.95)	0.314			1.37 (0.52–3.56)	0.524		
Alcohol	0.64 (0.30–1.35)	0.236			0.67 (0.33–1.37)	0.272		
ALBI grade 1	0.38 (0.18–0.83)	0.015	0.41 (0.18–0.91)	0.029	0.74 (0.36–1.51)	0.405		
Child-Pugh score ≥ 8	0.68 (0.34–1.34)	0.265			0.57 (0.29–1.11)	0.096		
AFP ≥ 400 ng/mL	2.26 (1.01–5.05)	0.046	1.71 (0.74–3.96)	0.208	2.13 (0.99–4.57)	0.034	2.13 (0.97–4.60)	0.054
PIVKA-II $\geq 1,000$ mAU/mL	0.76 (0.37–1.54)	0.446			0.57 (0.29–1.11)	0.096		
Tumor type								
Massive	1.38 (0.68–2.77)	0.374			1.13 (0.57–2.25)	0.726		
Nodular	1.44 (0.32–6.49)	0.633			1.73 (0.49–6.07)	0.396		
Maximum tumor size ≥ 5 cm	1.34 (0.62–2.89)	0.459			1.48 (0.72–3.02)	0.286		
Multiple tumors	2.04 (1.02–4.10)	0.045	2.03 (0.96–4.29)	0.064	1.84 (0.93–3.66)	0.081		
PVTT	0.99 (0.34–2.85)	0.983			0.58 (0.22–1.53)	0.267		
BCLC stage C	1.00 (0.30–3.33)	0.997			0.69 (0.28–2.30)	0.549		
Biliary drainage	0.47 (0.23–0.95)	0.036	0.40 (0.19–0.83)	0.014	0.28 (0.11–0.67)	0.004	0.29 (0.13–0.61)	0.001
Time from BDI diagnosis to HCC treatment	1.00 (0.99–1.01)	0.518			1.00 (0.99–1.01)	0.711		
Decreased TB within 7 day after HCC treatment	0.59 (0.29–1.20)	0.144			0.75 (0.37–1.50)	0.412		
Decreased TB within 30 day after HCC treatment	0.49 (0.22–1.12)	0.090			0.52 (0.23–1.17)	0.113		

HR, hazard ration; CI, confidence interval; HBV, hepatitis B virus; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; PIVKA, protein induced by vitamin K antagonist; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer; BDI, bile duct invasion; HCC, hepatocellular carcinoma; TB, total bilirubin.

**Fig. 3.** Ratios of changes in serological markers within 1 month after hepatocellular carcinoma treatment. TB, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; Alb, albumin; INR, international normalized ratio; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

sociated with OS were ALBI grade 1, AFP level ≥ 400 ng/mL, the presence of multiple tumors, and biliary drainage. In the multivariate analysis, ALBI grade 1 (HR, 0.41; 95% CI, 0.18 to 0.91; $p=0.029$) and biliary drainage (HR, 0.40; 95% CI, 0.19 to 0.83; $p=0.014$) retained their significance as predictive factors for better OS (Table 3). In the analysis of PFS, previous treatment history of HCC, AFP levels ≥ 400 ng/mL, and biliary drainage were significant factors associated with PFS in the univariate analysis. In the multivariate analysis, both previous treatment history of HCC (HR, 2.38; 95% CI, 1.15 to 4.92; $p=0.019$) and biliary drainage (HR, 0.29; 95% CI, 0.13 to 0.61; $p=0.001$) were confirmed as independent predictors for better PFS (Table 3).

7. Changes in serological markers after HCC treatment

We analyzed ratios of changes in serological markers associated with liver function (total bilirubin, aspartate transaminase, albumin, international normalized ratio, alanine transaminase, gamma-glutamyl transferase, and alkaline phosphatase) within 1 month after HCC treatment in patients who underwent biliary drainage and those who did not (Fig. 3). The baseline for analyzing changes in serological markers after HCC treatment was not the date of BDI diagnosis, but the date of HCC treatment. Interestingly, we observed significant changes only in total bilirubin, with the biliary drainage group showing a notable decrease ($p=0.005$). The absence of statistically significant differences for other serological markers suggests that biliary drainage prior to HCC treatment might have a selective short-term impact on total bilirubin levels following HCC treatment.

DISCUSSION

This study evaluated the prognostic impact of biliary drainage in HCC patients with BDI and obstructive jaundice. We conducted a comprehensive analysis of a cohort of 200 HCC patients with BDI. After excluding specific subsets of patients, we focused our analysis on a subset of 64 individuals who underwent HCC treatment after biliary drainage. Within this cohort, we observed that biliary drainage emerged as a significant and independent favorable prognostic factor. Patients who underwent biliary drainage exhibited better OS and PFS than those who did not. Furthermore, our analysis revealed significant reductions in total bilirubin levels following HCC treatment in the biliary drainage group.

Our study provides critical insights into the management of HCC with BDI, an area that is currently not ex-

plicitly addressed in existing clinical guidelines. According to recent HCC guidelines such as American Association for the Study of Liver Diseases and European Association for the Study of the Liver, various treatment options could be used for HCC.¹⁴⁻¹⁸ However, these guidelines offer limited directives when it comes to the specific scenario of HCC with BDI. Our findings underscore the prognostic significance of biliary drainage in patients with HCC and BDI, highlighting the potential of using this approach to improve survival outcomes. This is particularly noteworthy considering the lack of clear recommendations in major clinical guidelines regarding the management of this subgroup of HCC patients. Furthermore, recent research has indicated that BDI should be considered when redefining HCC staging systems. The prognosis of HCC patients with BDI varies significantly from those without BDI, particularly in early stages, suggesting that BDI could be a critical factor when making staging and treatment decisions.¹⁰

In advanced HCC, the evaluation of residual liver function is crucial for determining treatment options and predicting patient outcomes. The Child-Pugh score, a widely used tool for assessing liver function, incorporates several parameters, including total bilirubin levels. However, when BDI occurs, it can lead to obstructive jaundice and hyperbilirubinemia, making it difficult to interpret bilirubin levels. Results of our study aligned with findings of a previous 12-year prospective study involving 2,095 HCC patients, of which 530 presented with jaundice.²⁷ In that study, patients with hepatic insufficiency had poor prognosis, while those with obstructive jaundice showed better outcomes, with some undergoing curative resection and others receiving palliative biliary stents.²⁷ Similarly, our research underscores the importance of distinguishing the cause of jaundice in HCC patients, as appropriate treatment such as biliary drainage can significantly improve prognosis.

Previously, several studies have collectively reported the role of effective biliary drainage in improving the prognosis of HCC patients with BDI and obstructive jaundice. Successful biliary drainage, whether through percutaneous transhepatic biliary drainage or endoscopic retrograde cholangiopancreatography, can significantly enhance clinical outcomes and survival times, especially when it is coupled with additional HCC treatments such as transarterial chemoembolization or radiotherapy.^{21,22} Another study has reinforced this finding, emphasizing that effective drainage is particularly beneficial in patients with preserved liver function and in cases where high bilirubin levels are attributed to bile duct obstruction rather than liver dysfunction.²⁴ Overall, these findings aligned well with our research, which also concluded that biliary drainage could act as an independent favorable prognostic factor for

HCC patients with BDI and obstructive jaundice, leading to favorable outcomes. Effective biliary drainage not only can mitigate obstructive jaundice, but also can potentially enable further anti-cancer treatments, thereby improving survival prospects.

Our study revealed a notable finding regarding the time interval between diagnosis of BDI and subsequent treatment of HCC and its relationship to the effectiveness of biliary drainage. Specifically, although the group that underwent biliary drainage experienced a longer duration from BDI diagnosis to HCC treatment (after PSM: 35 days for drainage group vs 12 days for non-drainage, $p < 0.001$), they still showed better OS and PFS (Table 3). One possible explanation for such improved survival outcomes, despite a delayed treatment, could be the role of biliary drainage in stabilizing patients' general conditions before HCC treatment. By alleviating obstructive jaundice, biliary drainage might have enhanced patients' residual liver functions and reduced the possibility of biliary-origin infection, thus making them better candidates for subsequent HCC therapies. Another intriguing result was that patients who underwent biliary drainage exhibited a significant decrease in total bilirubin level at 1 month after receiving HCC treatment, as opposed to those who did not receive drainage ($p = 0.005$) (Fig. 3). Therefore, reduced bilirubin levels after HCC treatment could suggest that the biliary drainage group might have a more controlled disease process since hyperbilirubinemia is often associated with a poor prognostic predictor and extensive liver involvement in HCC.

In univariate and multivariate analyses, several significant prognostic factors were identified in HCC patients with BDI (Table 3 and Supplementary Table 4). ALBI grade and AFP levels emerged as significant prognostic predictors in our study, aligning with findings of previous research that underscored its utility in assessing liver function and disease status in HCC patients.²⁸⁻³¹ Our study also revealed that the presence of multiple tumors significantly predicted poorer outcomes, highlighting the aggressive nature of HCC characterized by multiple lesions, particularly when compounded by BDI. The impact of previous treatments on the prognosis of HCC patients with BDI is another novel aspect explored in our study. We found that a history of previous HCC treatments negatively impacted the prognosis, which might reflect a more advanced disease or an inherent tumor aggressiveness. Our study demonstrates that these factors are especially important in cases of HCC with BDI, emphasizing their significance for this specific subgroup of patients.

In the present study, we aimed to accurately differentiate jaundice caused by BDI from that resulting from liver function decline, using a combination of clinical assess-

ments and imaging techniques. Our initial evaluation involved a thorough examination of clinical symptoms and biochemical tests, where jaundice resulting from liver function decline often presents with elevated liver enzymes, decreased albumin levels or prothrombin time prolongation, while jaundice due to BDI is characterized by increased direct bilirubin, alkaline phosphatase or gamma-glutamyl transferase levels. Even when imaging confirmed BDI, we carefully investigated the impact of other factors such as hepatic parenchymal invasion by HCC, sepsis, or bleeding, which could independently impair liver function. These factors could significantly impair liver function independently of the degree of biliary obstruction.

While our study provides valuable insights into the prognostic efficacy of biliary drainage in HCC patients with BDI, several limitations should be considered. Firstly, as a retrospective study, our findings are inherently limited by potential selection bias and the inability to control for all confounding variables. Moreover, since findings were derived from a single-country cohort, they might not be generalizable to diverse geographic or ethnic populations. Although we analyzed a considerable number of cases, the overall sample size, particularly after applying PSM, might still be too small to draw definitive conclusions. Additionally, heterogeneity in patient characteristics, such as varying stages of liver disease and different treatment histories, might have significantly influenced outcomes. Given the study's extensive time span, changes in diagnostic tools and therapeutic strategies over time might have affected results, leading to potential variability in treatment approaches and outcomes. Another limitation of our study is the inability to perform detailed subgroup analyses based on the location or level of BDI due to the limited number of enrolled patients. Further detailed analyses involving a larger cohort of patients are necessary. Selection bias could arise from various sources, such as the criteria used to include or exclude patients from the study, differences in the availability or quality of medical records, or in the way that treatments were decided upon. For instance, patients who were selected for biliary drainage might have had different baseline characteristics or prognostic factors compared to those who did not undergo drainage. Moreover, the findings of the study might not be fully representative of all patients with HCC and BDI due to the specific inclusion and exclusion criteria applied. Despite efforts to mitigate these biases through statistical methods like PSM, selection bias remains a limitation of our study, affecting the strength and generalizability of our conclusions.

In conclusion, our study contributes to the understanding of the prognostic efficacy of biliary drainage in patients with HCC and BDI. It clearly demonstrates that biliary

drainage is an independent favorable prognostic factor associated with improved survival outcomes such as OS and PFS. These findings emphasize the specific importance considering the current gap in clinical guidelines for the treatment of HCC with BDI. Future studies, particularly prospective and randomized controlled trials, are necessary to further validate and refine these findings so that they could contribute to more effective management and improved outcomes for HCC patients with BDI.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: K.Y., H.Y.K. Data acquisition: K.Y., H.Y., C.W.K., H.C.N., J.H.K., A.L., J.M.Y., U.I.C., H.L.L., J.H.K., S.W.N., S.K.L., P.S.S., J.W.H., J.W.J., S.H.B., J.Y.C., S.K.Y. Data analysis and interpretation: K.Y. Drafting of the manuscript: K.Y. Critical revision of the manuscript for important intellectual content: C.W.K., H.C.N., J.H.K., A.L., J.M.Y., U.I.C., H.L.L., J.H.K., S.W.N., S.K.L., P.S.S., J.W.H., J.W.J., S.H.B., J.Y.C., S.K.Y. Statistical analysis: K.Y., H.Y. Administrative, technical, or material support: Study supervision: H.Y.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at <https://doi.org/10.5009/gnl240032>.

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