Prognostic importance of bile duct invasion in surgical resection with curative intent for hepatocellular carcinoma using PSM analysis

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Abstract. There is not yet a consensus regarding a difference in prognosis for patients with hepatocellular carcinoma (HCC) with and without bile duct invasion (BDI). The present study aimed to clarify the prognostic importance of BDI on the short and long-term outcome of patients with HCC who underwent surgical resection. The present study evaluated HCC with BDI, including peripheral microscopic biliary invasion and revealed that the prognosis of patients with BDI was poorer compared with those without BDI. It should be noted that peripheral BDI also had a negative impact on the prognosis of patients with HCC. The clinical prognosis assessment revealed that BDI should be considered when assigning a disease stage. BDI, either macroscopic or microscopic, indicated a poor prognosis in patients with HCC who underwent curative resection, however it was not a surgical contraindication. Macroscopic BDI and hyperbilirubinemia were significantly associated with a dismal prognosis, which should alert surgeons.

Introduction

Jaundice is common in patients with hepatocellular carcinoma (HCC), and it can be detected in 19-40% of patients at the time of diagnosis (1). It is usually a result of insufficient functioning of the reduced normal hepatic parenchyma resulting from the underlying cirrhosis and tumor replacement (2). The prognosis is extremely poor, and no effective treatment option is available. However, obstructive jaundice secondary to tumor invasion of the major bile ducts or biliary tumor thrombus may benefit from surgical resection (1,3-5). It is important to distinguish hepatic and obstructive jaundice, because the latter is treatable with the potential to prolong patient survival and even in some cases curable. The literature describing experiences with the management of HCC with obstructive jaundice includes mainly case reports and a few reports of large series of patients (5-10). In addition, most previous studies focused only on tumor invasion of the large bile ducts, such as the common bile ducts up to the first branches of the biliary duct, which commonly manifested as obstructive jaundice (3,11-13). However, invasion of the peripheral branches of the bile duct has not been well characterized and is not preoperatively diagnosable due to non-specific clinical manifestations, which usually do not include jaundice.

In this study, the relationships between the clinicopathological factors of HCC and prognosis after curative resection were analyzed retrospectively. The aim was to clarify the prognostic impact of bile duct invasion (BDI), including microscopic invasion of the peripheral branches of the bile duct, on short- and long-term outcomes in HCC patients after curative resection.

Patients and methods

Patients. A prospectively maintained database that includes HCC patients admitted to Eastern Hepatobiliary Hospital was reviewed. This study enrolled a cohort of 270 patients who were diagnosed with HCC and underwent surgical resection with curative intent performed by a single surgical team between February 2003 and January 2011. Approval from the Institutional Review Board of the Second Military Medical University (Shanghai, China) was obtained prior to data review. Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines.

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R0 or R1 resections were designated as resection with curative intent (14). Of these 270 cases, macroscopic or microscopic BDI, including biliary tumor thrombus, were identified in 107 cases. Since our surgical team is specialized in the diagnosis and treatment of biliary tract tumors, most HCC patients with preoperative jaundice were admitted to our department. We compared the characteristics of the HCC cases with BDI (b⁺ group, n=107) with those of cases without BDI (b⁻ group, n=163), and we used propensity score matching (PSM) analysis to avoid bias between the b⁺ and b⁻ groups.

Pre-operative assessment. Laboratory data for HCC patients were obtained upon admission before surgery. Possible BDI of HCC was noted when peripheral bile duct dilatation or tumor thrombus was detected by ultrasonography (US) or computed tomography (CT), and the BDI was further assessed by direct cholangiography or magnetic resonance cholangiopancreatography (MRCP) of the obstruction or stenosis of the biliary trees. In patients with BDI who presented with obstructive jaundice, biliary drainage was performed first, and the hepatic functional reserve was evaluated after the serum bilirubin level was lower than 5 mg/dl. Liver resection was performed next.

Operative procedures. The extent of hepatectomy was selected based on the location and size of the tumor, liver function, and volume of liver parenchyma. Hepatectomies included partial resection, subsegmentectomy, segmentectomy, lobectomy, and extended lobectomy, and they were performed with the intent to remove the entire tumor and the concomitant bile ducts. When the tumor invasion extended to the extrahepatic bile duct or contralateral hepatic duct, the resection was accompanied by removal of extrahepatic bile ducts or by cholangiotomy.

Pathological assessment. Resected specimens were evaluated macroscopically and microscopically according to TNM stage (UICC 7th edition) (15). Two pathologists independently reviewed all sections and reached a consensus on the pathologic features of all cases. Macroscopic BDI was defined as tumor thrombus in the common hepatic ducts or the first to second branches of the bile duct. Microscopic BDI was defined as tumor thrombus in the third order or lower peripheral branches of the bile duct. Patients with these two types of BDI were included in the BDI (b⁺) group. Survival was measured from the time of hepatic resection, and death marked the endpoint. Outcomes in this cohort were reviewed in January 2016.

Statistical analysis. The two groups were compared using Mann-Whitney U test for non-parametric data. The Chi-square test was used for categorical data. Survival curves were estimated with the Kaplan-Meier method and compared by the log-rank test. Cox regression analysis was carried out to determine which factor was the best prognostic determinant. P<0.05 was considered to indicate a statistically significant difference. Calculations were done using SPSS version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). After comparing the demographic data between the two groups, we performed PSM analysis using logistic regression to create a propensity score for patients in the b⁺ and b⁻ groups. One-to-one matching between the two groups was done using the nearest-neighbor

matching method. The PH assumption was checked. The caliper value was 0.2.

Results

Demographic data. The clinical features of the b⁺ and b⁻ groups are presented in Table I. A typicl clinical case of HCC with BDI was described in Fig. 1. No differences in sex, age, serum AFP level, prothrombin time (PT), and the percentages of viral hepatitis and cirrhosis were observed between the b⁺ and b⁻ groups. The levels of serum total bilirubin (sTBIL; P<0.001), serum albumin (sALB; P<0.001), and serum alanine transaminase (sALT; P<0.001) as well as tumor size (P=0.012) and presence of multiple tumor lesions (P=0.031) were significantly higher in the b⁺ group than in the b⁻ group. In addition, BDI may not always cause jaundice. There were 42 cases in b⁺ group who did not present with jaundice.

Postoperative complications and mortality. Two cases of in-hospital deaths occurred in each group, and these patients died of hepatic failure within 1 month after surgery. Thirteen of the 107 HCC patients in the b⁺ group (13/107, 12.1%) developed postoperative complications. These cases included 5 patients with pleural effusions, 3 with hemobilia, 1 with a biliary tract infection, 1 with bile leakage, 1 with upper gastrointestinal ulcer bleeding, 1 with a thoracic epidural hematoma, and 2 with infection at the incision site. During the same period, only five patients in the b⁻ group (5/163, 3.1%) had postoperative complications, including 4 cases of pleural effusion and 1 of incision site infection (Table II).

Comparison of survival between the b⁺ group and b⁻ group. The median disease-free survival (DFS) times in the b⁺ and b⁻ groups were 8 and 33 months, respectively. The cumulative 1-, 3-, and 5-year DFS rates in the b⁺ group (37.2, 11.5, and 0%, respectively) were significantly worse than those in the b⁻ group (59.4, 47.9, and 24.5%, respectively; P<0.001). The median overall survival (OS) times were 16.6 and 84.0 months in the b⁺ and b⁻ groups, respectively. The cumulative 1-, 3-, and 5-year survival rates in the b⁺ group (60.5, 20.1, and 12.0%, respectively) were significantly poorer than those in the b⁻ group (84.9, 69.9, and 57.6%, respectively; P<0.001, Fig. 2).

Risk factors for reduced DFS. Univariate analysis revealed that age, BDI, portal vein tumor thrombosis (PVTT), sAFP level, viral hepatitis, cirrhosis, tumor size, multiple tumor lesions, sTBIL level, and sALB level significantly affected DFS (Table III). Prognostic factors for poor DFS were further identified by multivariate analysis and included BDI (P<0.001), PVTT (P<0.001), high sAFP level ≥20 ng/ml (P=0.001), and age ≥60 years (P=0.037; Table IV). However, tumor size and multiple tumor lesions were not an independently significant factor by multivariate analysis.

Risk factors for reduced OS. Univariate analysis revealed that sex, BDI, PVTT, AFP level, multiple tumor lesions, tumor differentiation, sALB level, sTBIL level, and sALT level significantly affected OS (Table V). Multivariate analysis showed that sex (P=0.034), BDI (P=0.001), PVTT (P=0.007),

Table I. Demographic data of b⁺ group and b⁻ group.

Variables	b⁺ group (n=107)	b⁻ group (n=163)	P-value
Male sex	88	140	0.419
Mean age (years)	50.6±10.5	49.5±10.6	0.388
TBIL, mg/dl (range)	3.57 (0.50-28.01)	0.84 (0.33-2.82)	<0.001
ALB (g/l)	39.4±4.3	42.5±3.9	<0.001
ALT grade (U/l)			<0.001
<40	17	82	
≥40	90	81	
AFP grade (ng/ml)			0.163
<20	30	59	
≥20	77	104	
PT grade (second)			0.753
<14	98	151	
≥14	9	12	
Tumor size (cm)			0.012
<5	49	50	
≥5	58	113	
Multiple tumor lesions			0.031
Yes	22	18	
No	85	145	
PVTT			0.747
Yes	13	22	
No	94	141	
Presence of hepatitis			0.084
Yes	105	152	
No	2	11	
Presence of cirrhosis			0.508
Yes	58	95	
No	49	68	
UICC 7th edition			0.796
I	16	23	
II	24	40	
III	62	92	
IV	5	8	

Male sex, mean age (years), TBIL (mg/dl) and ALB (g/l) were compared using Mann-Whitney U test. ALT grade (U/l), AFP grade (ng/ml), PT grade (second), tumor size (cm), multiple tumor lesions, PVTT, presence of hepatitis, presence of cirrhosis and UICC 7th edition were compared using Chi-square test. TBIL, total bilirubin; ALB, albumin; ALT, alanine transaminase; PT, prothrombin time; AFP, alpha-fetoprotein.

Table II. Postoperative complications in b⁺ group (n=107) and b⁻ group (n=163).

Complications	b⁺ (n=107)	b⁻ (n=163)	P-value
Pleural effusions	5	4	
Hemobilia	3	0	
Biliary tract infections	1	0	
Bile leakage	1	0	
Upper gastrointestinal bleeding	1	0	
Thoracic epidural hematoma	1	0	
Incision infection	2	1	
Total	13	5	0.003

to compare them directly to determine whether BDI was an independent factor for poor prognosis. The overall balance between the two matched groups was excellent (P=1.00), and no unbalanced covariates (|d| >25) were found. Despite matching for sex, age, PVTT, tumor size, multiple tumor lesions, sALT, sPT, sAFP, sALB, and sTBIL levels, the b⁻ and b⁺ patients showed significant differences in DFS and OS.

The cumulative 1-, 3-, and 5-year DFS rates in the b⁺ group (39.2, 16.6, and 0%, respectively) were significantly worse than those in the b⁻ group (64.3, 40.7, and 25.4%, respectively; P=0.006). The cumulative 1-, 3-, and 5-year survival rates in the b⁺ group (75.6, 34.0, and 25.5%, respectively) were significantly poor than those in the b⁻ group (87.9, 70.2, and 55.3%, respectively; P=0.024, Fig. 3). Therefore, BDI was verified as a critical prognostic factor associated with both poor DFS and OS in this cohort.

Differences in DFS and OS between HCC patients with microscopic and macroscopic BDI. Postoperative DFS was similar between the groups of HCC patients with microscopic BDI (n=10) and macroscopic BDI (n=97; P=0.401, Fig. 4), but the DFS rates for both these groups were poorer than that in the b⁻ group (P=0.048 and P<0.001, respectively). Postoperative OS in HCC patients with macroscopic BDI was significantly worse than that in those with microscopic BDI (P=0.008) and that in the b⁻ group (P<0.001). Postoperative OS did not differ significantly between HCC patients with microscopic BDI and those in the b⁻ᵛ group (P=0.412, Fig. 4).

Differences in postoperative DFS and OS between HCC patients with BDI and those with PVTT. There were no significant differences in the postoperative DFS and OS between HCC with single BDI (n=93) and those with single PVTT (n=19; P>0.05, Fig. 5).

Tumor recurrence in 107 HCC patients with BDI (b⁺ group). Seventy-five patients in the b⁺ group experienced HCC recurrence during follow-up. Most cases of recurrence occurred in the liver, including 58 cases (58/75, 77.3%) in the remnant liver and 53 cases (53/75, 70.7%) in the bile ducts. The other sites included lung in 10 cases (13.3%), bone in 3 cases (4%),

sAFP ≥20 ng/ml (P=0.014), sALB (P=0.005), and high sTBIL ≥2 mg/dl (P=0.008) were independent risk factors for reduced OS (Table VI).

Survival analysis in 36 pairs of patients from the two groups matched with PSM. Because the demographic data were diverse between the b⁺ and b⁻ patients, we opted to match 36 pairs of cases for all risk factors except BDI through PSM analysis and
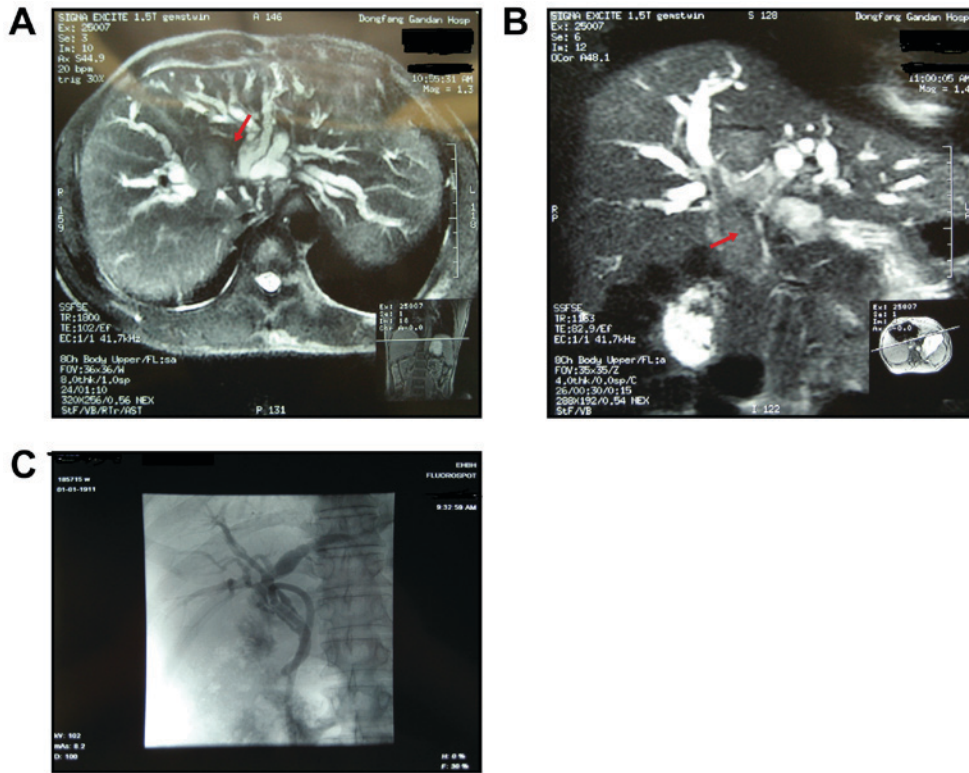
Figure 1. Typical imaging features of hepatocellular carcinoma with bile duct invasion. (A) MRI indicates a tumor mass in the right of the liver. (B) Preoperative magnetic resonance cholangiopancreatography reveals a biliary tumor thrombus extending superficially from an intrahepatic to an extra hepatic bile duct. The red arrows indicate a biliary tumor thrombus. (C) T tube angiography was performed 2 months following surgery and revealed normal results without recurrence.
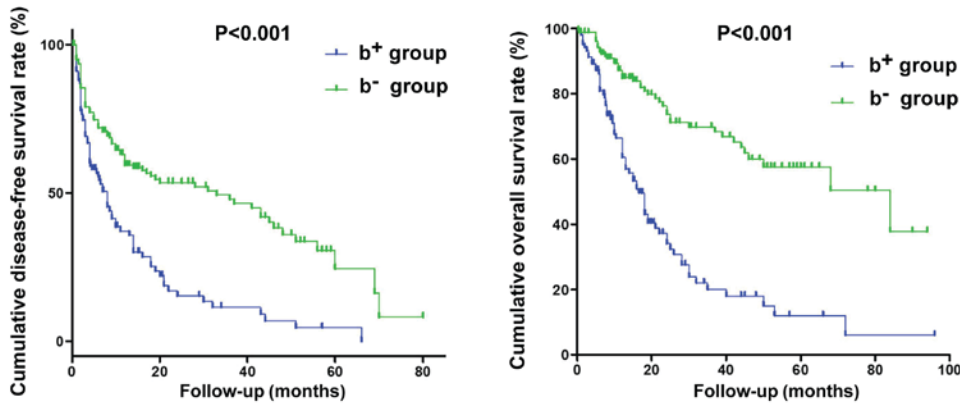

Figure 2. Postoperative disease-free survival and overall survival curves for the b+ and b- groups. The cumulative 1-, 3-, and 5-year survival rates in the b+ group were significantly poorer than those in the b- group.

abdomen in 2 cases (2.7%), and brain in 2 cases (2.7%), and 7 cases (9.3%) experienced retroperitoneal metastasis.

Discussion

We retrospectively analyzed risk factors for poor prognosis in a cohort of 270 HCC patients who underwent curative resection performed by our single surgical team. Of the 270 patients, 107 had BDI. This study is one of the largest investigations of the effects of BDI that has been published. We found BDI was constistently identified as a risk factor for reduced survival together with others variables. Furthermore, we directly compared the outcomes associated with BDI after matching for all other risk factors and verified that BDI was the determining risk factor for poor prognosis of HCC by comparing DFS and OS after curative hepatectomy. Our findings provide two implications for the clinical management of HCC patients. One is that jaundice in HCC could be associated with BDI and is surgically treatable (16,17). Jaundice is present in 19-40% of patients with HCC at the time of diagnosis and is caused by diffuse tumor infiltration of the liver parenchyma, progressive liver failure, hepatic hilar invasion, severe cirrhosis, or a combination of these factors (1-4). There is no good treatment option for jaundice resulting from insufficient liver function. On the other hand,

Table III. Univariate analysis of 13 variables associated with DFS in patients with HCC who underwent surgical resection with curative intent (n=270).

Variables	Cut off values	Total	Disease-free survival time (months)	P-value
Sex				0.143
	Male	228	14.0±2.5	
	Female	42	6.0±2.8	
Age (years)				0.006
	<60	222	11.0±2.2	
	≥60	48	48.0±21.8	
Bile duct invasion				<0.001
	Yes	107	8.0±1.2	
	No	163	33.0±9.9	
PVTT				<0.001
	Yes	35	5.0±1.4	
	No	235	18.0±2.6	
Presence of hepatitis				0.003
	Yes	257	12.0±2.4	
	No	13	60.2±9.8	
Presence of cirrhosis				0.052
	Yes	153	18.0±3.4	
	No	117	11.0±1.9	
Tumor size (cm)				0.021
	<5	99	21.0±2.0	
	≥5	171	9.0±1.6	
Multiple tumor lesions				0.010
	Yes	40	4.2±1.9	
	No	230	17.0±2.8	
AFP (ng/ml)				<0.001
	<20	89	43.0±7.4	
	≥20	181	9.0±1.4	
PT (sec)				0.328
	<14	249	14.0±2.6	
	≥14	21	10.0±3.6	
TBIL (mg/dl)				0.001
	<2	203	18.0±5.7	
	≥2	67	8.0±2.0	
ALB (g/l)				0.001
	<35	22	3.6±3.2	
	≥35	248	16.0±2.5	
ALT (U/l)				0.039
	<40	99	18.0±11.9	
	≥40	171	12.0±2.4	

DFS, disease-free survival ; HCC, hepatocellular carcinoma; TBIL, total bilirubin; PVTT, portal vein tumor thrombosis; ALB, albumin; ALT, alanine transaminase; PT, prothrombin time; AFP, α-fetoprotein.

obstructive jaundice resulting from BDI of a major bile duct is an uncommon, but treatable, cause of jaundice in HCC patients. It is important to recognize this cause and devise an appropriate treatment that will benefit patients, including prolonging their survival, and even occasionally provide a cure (1,3-5,18).

In our study, the typical clinical features of BDI in HCC are repeated episodes of cholangitis and fluctuating jaundice, and it is often misdiagnosed as cholangiocarcinoma. In addition, BDI may not always cause jaundice. There were 10 cases of HCC with microscopic BDI and 32 cases with macroscopic

Table IV. Multivariate analysis for DFS in patients with HCC who underwent surgical resection with curative intent (n=270).

Variable	Regression coefficient	Standard error	P-value	Relative risk	95% CI
Age	-0.542	0.260	0.037	0.582	0.350-0.968
Bile duct invasion	0.828	0.163	<0.001	2.290	1.664-3.150
PVTT	0.948	0.217	<0.001	2.580	1.687-3.946
AFP	0.665	0.193	0.001	1.944	1.332-2.838

DFS, disease-free survival; HCC, hepatocellular carcinoma; CI, confidence interval; PVTT, portal vein tumor thrombosis; AFP, α-fetoprotein.

BDI in our cohort who did not present with jaundice. Strictly speaking, these two conditions should be distinguished in further studies.

Only a few reports with a small number of cases of HCC with BDI have been published (3,5-9). Surgical resection has been considered the preferred treatment for HCC with BDI; however, there has been no consensus regarding the differences in prognosis of HCC with and without BDI. In the present study, we found that macroscopic BDI and hyperbilirubinemia were significantly associated with an adverse prognosis in HCC patients. Thus, the second implication of our findings is that hepatologists should be informed of the detection of BDI, because BDI was an indicator of poor prognosis in HCC patients who underwent curative resection in this study.

Previous studies (3,11-13) focused on tumor invasion of the large bile ducts, such as the common bile ducts up to the first branches of the hepatic duct. HCC invasion of a peripheral bile duct has not been well studied. In the present study, we evaluated HCC with BDI, including peripheral microscopic biliary invasion, and found that it was also associated with poor outcomes. Thus, even peripheral BDI has a negative impact on DFS in HCC patients. A further analysis showed that macroscopic BDI was significantly associated with poor prognosis, whereas microscopic BDI was not. However, macroscopic BDI was dominantly responsible for obstructing jaundice. In clinical assessment of prognosis, macroscopic BDI should be considered in the assignment of clinical stage.

BDI indicates a high degree of HCC invasiveness. In this study, the DFS and OS of the b⁺ group were significantly poorer than those of the b⁻ group. The incidence of postoperative complications in patients with HCC complicated with biliary tumor invasion is higher, which may be related to the higher degree of malignancy and stronger invasive ability. To understand the cancer biology responsible for this observation, we noted that both the size and numbers of tumors differed significantly between the two groups (P=0.012 and P=0.031, respectively). The b⁺ group was characterized by a high proportion of patients with multiple tumors and a small primary lesion <5 cm in diameter, and these two factors were also found to be closely related to postoperative prognosis in HCC. In addition, a considerable number of patients in the b⁺ group presented with jaundice upon admission due to bile duct tumor thrombosis. A possible link between the presence of multiple tumors and BDI suggests a quick spreading and invasive nature of the HCC in this group and the number of tumors was more ominous than the size of the tumors.

In our view, the biology of BDI is similar to that of vascular invasion, especially PVTT, which is often present and recognized as a prognostic factor in HCC patients (19-22). The median survival time among HCC patients with PVTT has been reported to be 2.7-4.0 months without intervention (19). Although an increasing variety of therapeutic options that offer survival benefits are available for HCC patients with PVTT (20), the long-term prognosis remains poor due to the extensive spreading of the tumor throughout the liver and the increased portal blood pressure that results in variceal ruptures, ascites, hepatic encephalopathy, liver failure, and death (21,22). As expected, PVTT was found to be an independent negative risk factor for both DFS and OS (P<0.001 and P=0.005, respectively) in this study. These findings suggest that HCC with BDI shares a similar degree of invasiveness as HCC with PVTT. Once a tumor thrombus forms in the remnant bile ducts and causes hyperbilirubinemia, few treatment options are available. On the contrary, multiple adjuvant therapies can be used to treat the relapsed PVTT.

TBIL level is an important factor in assessing the prognosis of HCC. In this study, the preoperative serum TBIL level was found to be a significant independent prognostic factor for OS (P=0.001). Hyperbilirubinemia is an important clinical feature of HCC with BDI. We have reported that the preoperative BIL level is a significant prognostic factor for DFS and OS after liver transplantation (P=0.046 and P=0.002, respectively) (23). In the present study, we also identified that hyperbilirubinemia was an indicator of advanced HCC with poor prognosis.

Liver surgery in these patients may not be safe because of the hepatic and systemic changes caused by hyperbilirubinemia and the resultant cholangitis (24,25). Thus, preoperative biliary drainage (PBD) is essential for safe hepatectomy. PBD can increase cholestatic liver tolerance to ischemia and reduce blood loss (26,27). The clinical success rate of PBD (endoscopic or percutaneous) ranges from 48.4-100% in the literature (28,29). Percutaneous transhepatic cholangial drainage (PTCD) is more commonly applied at our center as both the risks associated with PTCD and the economic burden are lower. Drainage of the remnant liver is mandatory, and the drainage of obstructed segments is not necessary unless cholangitis is present. When BDI is located in the secondary or even a more proximal part of the biliary tree, PTBD will be easier than PBD. Thus, we do not necessarily view hyperbilirubinemia as a surgical contraindication. In our experience, TBIL levels were decreased in several patients with hyperbilirubinemia after PBD, leading to the increased survival rates following resection. In our

Table V. Univariate analysis of 13 variables associated with OS in patients with HCC who underwent surgical resection with curative intent (n=270).

Variables	Cut off value	Total	Overall survival time (months)	P-value
Sex				0.035
	Male	228	37.0±7.0	
	Female	42	21.0±3.3	
Age (years)				0.345
	<60	222	44.5±3.2	
	≥60	48	52.9±6.7	
Bile duct invasion				<0.001
	Yes	107	16.6±1.7	
	No	163	84.0±21.6	
PVTT				0.006
	Yes	35	18.0±1.5	
	No	235	40.0±6.7	
Presence of hepatitis				0.041
	Yes	257	44.9±3.1	
	No	13	66.5±8.2	
Presence of cirrhosis				0.534
	Yes	153	37.0±8.6	
	No	117	28.0±6.9	
Tumor size (cm)				0.184
	<5	99	42.0±8.3	
	≥5	171	25.0±7.9	
Multiple tumor lesions				0.029
	Yes	40	17.0±1.9	
	No	230	37.0±6.9	
AFP (ng/ml)				<0.001
	<20	89	68.0±21.0	
	≥20	181	24.0±4.1	
PT (sec)				0.078
	<14	249	39.0±6.9	
	≥14	21	25.0±4.6	
TBIL (mg/dl)				<0.001
	<2	203	50.0±10.9	
	≥2	67	13.0±1.7	
ALB (g/l)				<0.001
	<35	22	8.0±3.3	
	≥35	248	39.0±6.5	
ALT (U/l)				0.002
	<40	99	61.7±5.4	
	≥40	171	38.2±3.2	

TBIL, total bilirubin; PVTT, portal vein tumor thrombosis; ALB, albumin; ALT, alanine transaminase; PT, prothrombin time; AFP, α-fetoprotein.

experience, a routine PBD via PTCD and oral bilirubin for several days before operation will mitigate hyperbilirubinemia in most cases of obstructive jaundice.

Are bile duct resection and bilioenteric anastomosis required for managing HCC with BDI? Another controversy is whether extrahepatic bile duct resection is necessary in the treatment of HCC with BDI. In the present study, there seemed to be no correlation between bile duct resection and prognosis or HCC recurrence. Noda *et al* (30) reported that bile duct resection might be avoided in favor or non-operative treatments such as percutaneous ethanol injection therapy (PEIT), ablation, and

Table VI. Multivariate analysis for OS in HCC patients who underwent surgical resection with curative intent (n=270).

Variable	Regression coefficient	Standard error	P-value	Relative risk	95% CI
Sex	-0.536	0.253	0.034	0.585	0.357-0.960
Bile duct invasion	0.856	0.251	0.001	2.353	1.437-3.852
PVTT	0.688	0.257	0.007	1.990	1.203-3.293
AFP	0.580	0.236	0.014	1.785	1.125-2.852
ALB	-0.813	0.292	0.005	0.444	0.250-0.786
TBIL	0.695	0.263	0.008	2.004	1.196-3.359

OS, overall survival; HCC, hepatocellular carcinoma; CI, confidence interval; PVTT, portal vein tumor thrombosis; AFP, α-fetoprotein; TBIL, total bilirubin; ALB, albumin.
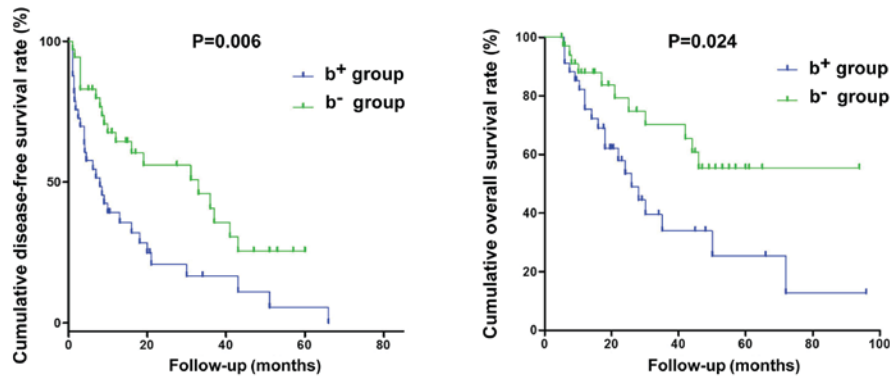
Figure 3. Postoperative OS and DFS curves for 36 pairs of patients matched using PSM analysis. BDI was verified as a critical prognostic factor associated with both poor DFS and OS in this cohort. DFS, disease-free survival; OS, overall survival; BDI, bile duct invasion; PSM, propensity score matching.
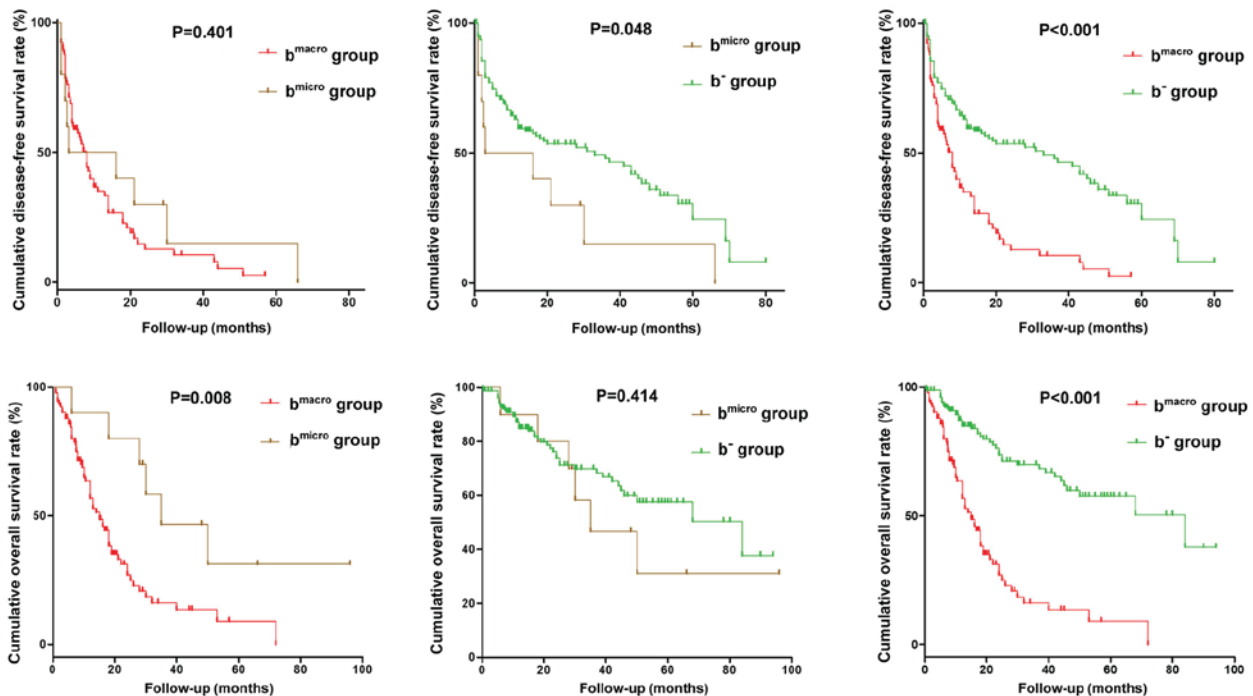

Figure 4. Postoperative disease-free survival and OS curves for hepatocellular carcinoma patients with microscopic or macroscopic BDI. Postoperative OS in HCC patients with macroscopic BDI was significantly worse than that in those with microscopic BDI and that in the b⁻ group. BDI, bile duct invasion; OS, overall survival.

transcatheter arterial chemoembolization (TACE), based on the potential for serious complications such as liver abscess

after bile duct resection and bilioenteric anastomosis (31,32). Moreover, because postoperative recurrence after resection of
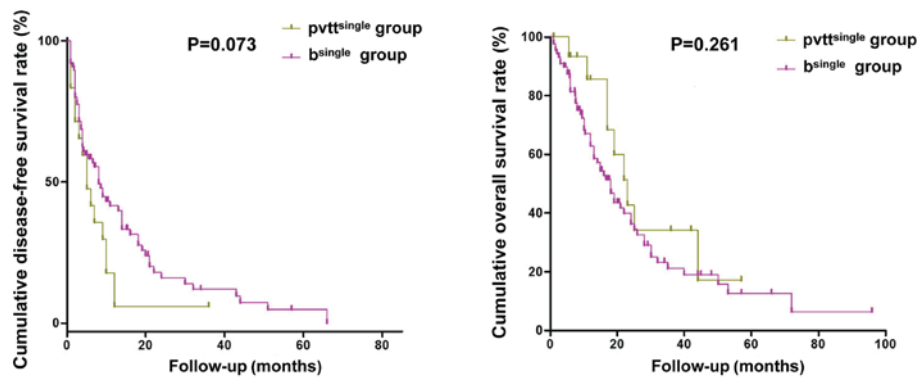
Figure 5. Postoperative DFS and OS curves for hepatocellular carcinoma patients with single BDI or single portal vein tumor thrombosis. There were no significant differences in the postoperative DFS and OS between two groups. DFS, disease-free survival; OS, overall survival; BDI, bile duct invasion.

HCC with BDI often occurs in the remanent liver, bile duct resection and bilioenteric anastomosis should be avoided whenever possible to avoid limiting later treatment options.

Recently, Yamamoto *et al* (25) reported a bile duct-preserving surgery termed the 'peeling off technique' for HCC with BDI, which is similar to our surgical approach. Preservation of the bile duct is important for two reasons. First, bile duct tumor thrombus demonstrates extensive growth potential and does not usually adhere to the bile duct wall. Second, treatments for recurrence, such as TACE or radio-frequency ablation (RFA), are restricted after resection of the extrahepatic bile duct because liver abscess formation after TACE and RFA is relatively common when an underlying bilioenteric anastomosis is present (33,34). In the current study, only three patients with BDI underwent extrahepatic bile duct resection and bilioenteric anastomosis.

This study has several limitations. Despite the large number of patients included in the present study, the enrolled patients represented a highly selected cohort, as only a fraction of the total number of HCC patients diagnosed during the study period had BDI. Additional investigations with a large patient population carried out in multiple centers are needed to verify the main findings. In addition, the proposed cancer biology, i.e., the high degree of invasiveness of HCC with BDI, should be further investigated in a laboratory setting.

In conclusion, BDI, including macroscopic and microscopic BDI, reflects a high degree of HCC aggressiveness but does not represent a surgical contraindication. Macroscopic BDI and hyperbilirubinemia were indicative of poor prognosis for HCC patients, which should alert surgeons. Extrahepatic bile duct resection and bilioenteric anastomosis are not required for managing HCC patients with BDI.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XY, ZQ and RR performed the majority of the research and collected all the clinicopathological data. XY wrote the manuscript. LC, XL and RR assisted with the analysis and edited the manuscript. W-FT, XJ and MW designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Second Military Medical University. Written informed consent was obtained from all patients prior to surgical treatment, pathological examinations and further analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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