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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Impact of Bile Duct Tumor Thrombus on the Long-Term Surgical Outcomes of Hepatocellular Carcinoma Patients: A Propensity Score Matching Analysis

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ABSTRACT

Background. Hepatectomy with tumor thrombectomy is the preferred treatment option for hepatocellular carcinoma (HCC) patients with bile duct tumor thrombus (BDTT); however, the impact of BDTT on their prognosis is unclear.

Objective. We aimed to investigate the long-term surgical outcomes of HCC patients with BDTT.

Methods. The data of HCC patients with and without BDTT who underwent hepatectomy were retrospectively reviewed and the long-term outcomes were compared. For propensity score matching (PSM) analysis, patients were matched in a 1:1 ratio. Subgroup analysis was conducted according to the American Joint Committee on Cancer (AJCC) staging system.

Results. Before PSM, HCC patients with BDTT had more advanced tumor stages and adverse clinicopathological features. Recurrence-free survival (RFS) and overall survival (OS) were significantly higher in the non-BDTT group before PSM (RFS, $p < 0.001$; OS, $p < 0.001$), while after PSM, the BDTT group had significantly poorer RFS ($p = 0.025$). There was no difference in OS between the groups ($p = 0.588$). Subgroup analysis showed that RFS and OS in AJCC stage I–II patients were significantly poorer in the BDTT group; no differences were found in the AJCC stage III group before or after PSM. When the presence of BDTT was recommended to increase the AJCC staging system by one stage in AJCC stage I–II patients, the predictive ability for RFS and OS was higher.

Conclusions. BDTT was associated with significantly poorer long-term surgical outcomes in AJCC stage I–II patients. A modified AJCC staging system including BDTT status in stage I–II might have a better prognostic ability.

Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers and a leading cause of cancer-related death worldwide.[1] Vascular invasion, especially portal vein invasion, is common in HCC patients and is recognized as a strong negative prognostic factor.[2,3] HCC with bile duct tumor thrombus (BDTT) is rarer than HCC with vascular invasion, and its incidence ranges from 0.4 to 12.9%.[4–7] Although surgical resection is the preferred treatment for HCC with BDTT, the impact of BDTT on prognosis after surgery remains unknown. Only a limited number of studies with a small sample size have studied

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this issue, but their conclusions have been inconsistent.[7–18] Some studies reported that HCC patients with BDTT had worse prognosis after surgery than those without BDTT;[7–14] however, other studies reported no significant difference in prognosis between patients with and without BDTT.[15–18] To the best of our knowledge, no randomized controlled trials have compared the prognostic outcomes of HCC patients with and without BDTT; therefore, the prognosis of HCC patients with BDTT after surgery remains unknown and requires further investigation.

In the past few decades, multiple staging systems have been developed to enhance prognostic ability.[19,20] Of the proposed systems, the American Joint Committee on Cancer (AJCC) staging system is the most widely applied.[21] The variables incorporated in the AJCC staging system are tumor size and number, vascular invasion, intrahepatic and extrahepatic metastases, surrounding tissue invasion, and portal vein tumor thrombosis;[21] however, BDTT is not included as a variable in the AJCC staging system. Because the biological features of BDTT are likely similar to those of portal vein tumor thrombus,[6,22] it is possible to incorporate BDTT into the AJCC staging system.

This study aimed to investigate the long-term surgical outcomes of HCC patients with and without BDTT, and the impact of BDTT on the AJCC staging system, using a propensity score matching (PSM) analysis method to reduce possible selection bias.

METHODS

Patients

We retrospectively reviewed HCC patients who underwent hepatectomy between July 2009 and October 2018 at five high-volume institutions—Fujian Provincial Hospital (Fuzhou, China), Eastern Hepatobiliary Surgery Hospital (Shanghai, China), West China Hospital of Sichuan University (Chengdu, China), Zhongshan Hospital of Xiamen University (Xiamen, China), and the First Affiliated Hospital of Fujian Medical University (Fuzhou, China). A diagnosis of BDTT in patients with HCC was pathologically confirmed by two experienced pathologists at each participating hospital. In addition, BDTT has been classified into two types: macroscopic BDTT, which indicates that invasion of the tumor thrombus was in the first branches of the bile duct and the common hepatic duct, and microscopic BDTT, which indicates that invasion of the tumor thrombus was in the second and more peripheral branches of the bile duct. Baseline demographics, including preoperative, operative, and postoperative demographic details, as well as outcomes, were collected retrospectively. This study was approved by the Institutional Review Board of each institution. All patients or their guardians provided informed consent for their data to be collected and used for research purposes.

The inclusion criteria were as follows: (1) underwent surgical resection; (2) pathological diagnosis of HCC with or without BDTT; (3) no anticancer treatment for HCC before surgery; (4) no distant metastasis; and (5) aged 18–75 years with good operative tolerance. Because the sample size was too large, we performed a random sampling from each of the enrolled centers for HCC patients without BDTT. Overall, 1670 HCC patients without BDTT were randomly collected from each of the enrolled centres, and 268 HCC patients with BDTT were collected from each of the enrolled centers. Of these patients, 1358 and 227 HCC patients without and with BDTT were included. The exclusion criteria in HCC without BDTT were (1) combined HCC and cholangiocarcinoma (47 patients); (2) other serious malignant diseases (59 patients); (3) Child–Pugh class C (57 patients); (4) extrahepatic bile duct resection (16 patients); (5) AJCC stage IV (39 patients); and (6) incomplete data (135 patients). Included patients were divided into two groups: patients without BDTT (non-BDTT group) and those with BDTT (BDTT group). Tumor stage was assessed using the 8th edition of the AJCC staging manual.

Surgery and Pathology

Patients with HCC who presented with obstructive jaundice (total bilirubin level >5 mg/dL) or acute cholangitis had percutaneous transhepatic biliary drainage placed in their contralateral intrahepatic bile duct to reduce the level of total bilirubin to <5 mg/dL before surgery. Resection was considered R0 if the specimen and bile duct margins were histologically negative, R1 if the margins were histologically positive, and R2 if the margins were macroscopically positive. The tumor size was defined as the maximum diameter of the largest tumor, regardless of the number of tumors. Macrovascular invasion was defined as the presence of a tumor in the portal vein or the hepatic vein. The degree of liver damage, tumor size, tumor number, tumor differentiation, capsule formation, vessel invasion, lymph node metastasis, and surgical margins were determined by pathological examination. Because there is still controversy on whether extrahepatic duct resection has to be performed for HCC with BDTT, HCC patients who underwent extrahepatic duct resection were excluded to avoid the influence of extrahepatic duct resection on our analysis.

Follow-Up

Patients with multiple tumors, R1/R2 resection, or vascular invasion were treated with preventive transarterial chemoembolization (TACE) 4 weeks after surgery. Follow-up occurred every 3 months for the first year and every 6 months thereafter, and included the following tests: α-fetoprotein (AFP), liver function, and contrast-enhanced computed tomography or magnetic resonance imaging. Recurrence was managed with multimodality treatments, including surgical resection, TACE, radiofrequency ablation, or systemic therapy, based on the functional liver reserves and recurrence pattern. All patients were followed until either death or the study end date of October 2020.

Statistical Analyses

Statistical analyses were performed using SPSS software version 17.0 (SPSS, Inc., Chicago, IL, USA) and R3.1.2 software (Institute for Statistics and Mathematics, Vienna, Austria). Categorical variables were expressed as percentages and were compared using the Chi-square test or Fisher's exact test. Univariate and multivariate analyses of prognostic factors were performed using the Cox proportional hazard model, and factors with a p-value <0.05 in univariate analysis were then incorporated into the multivariate analysis. Overall survival (OS) and recurrence-free survival (RFS) rates between patients with or without BDTT were calculated using the Kaplan–Meier method and compared using the log-rank test.

PSM analysis was used to reduce possible selection bias from an imbalance in the variables that could potentially influence the outcomes. PSM was performed using a 1:1 matching method with a caliper width of 0.02 times the standard deviation. The variables entered into the PSM included clinicopathological characteristics (sex, age, hepatitis B surface antigen [HBsAg] status, liver cirrhosis, Child–Pugh class, AFP, tumor size, tumor number, microvascular invasion, macrovascular invasion, tumor differentiation, and R0 resection). After PSM, Kaplan–Meier analyses were performed. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Clinicopathological Characteristics

A total of 7753 HCC patients underwent surgical treatment in the five institutions, of whom, 265 (3.42%) presented with BDTT during the study period (between July 2009 and October 2018). Of the total patients, 1585 consecutive HCC patients who underwent hepatectomy were included in our study—1358 patients in the non-BDTT group and 227 in the BDTT group. The clinicopathological baseline characteristics of the HCC patients are shown in Table 1. Before PSM, the two groups differed significantly in age (< 65 years), liver cirrhosis, AFP (> 400 ng/U), liver function, tumor number, tumor differentiation, microvascular invasion, macrovascular invasion, and tumor-node-metastasis (TNM) stage. There were no significant differences in sex, HBsAg, tumor diameter, or rate of R0 resection between the groups. After PSM, there were 184 patients in each of the groups. Details of the baseline clinicopathological characteristics of the two groups before and after PSM are shown in Table 1. PSM compensated for the differences in age (< 65 years), liver cirrhosis, AFP (> 400 ng/U), liver function, tumor number, tumor differentiation, microvascular invasion, and macrovascular invasion.

Risk Factors Influencing Overall Survival and Recurrence-Free Survival

Univariate analysis revealed that sex (male), age (> 65 years), AFP (> 400 ng/mL), maximum tumor size (> 5.0 cm), tumor number (multiple), microvascular invasion (positive), macrovascular invasion (positive), BDTT (positive), tumor differentiation (poor), R0 resection (no), and AJCC stage III were independently associated with OS. HBsAg (positive), liver cirrhosis (positive), Child–Pugh class (B), AFP (> 400 ng/mL), maximum tumor size (> 5.0 cm), tumor number (multiple), microvascular invasion (positive), macrovascular invasion (positive), BDTT (positive), tumor differentiation (poor), R0 resection (no), and AJCC stage III were independent risk factors for RFS rates (electronic supplementary material [ESM] Table 1). Multivariate analysis revealed that AFP (> 400 ng/mL), maximum tumor size (> 5.0 cm), microvascular invasion (positive), macrovascular invasion (positive), BDTT (positive), tumor differentiation (poor), R0 resection (no), and AJCC stage III were independent risk factors for poor OS, while liver cirrhosis (positive), maximum tumor size (> 5.0 cm), microvascular invasion (positive), BDTT (positive), tumor differentiation (poor), R0 resection (no), and AJCC stage III were independent risk factors for poor RFS (ESM Table 2).

Long-Term Outcomes

Before PSM, the 1-, 3-, and 5-year OS rates were 84.2%, 64.2%, and 50.3%, respectively, in patients without BDTT, and 78.4%, 43.4%, and 37.4%, respectively, in those with BDTT ($p < 0.001$) (Fig. 1a). The 1-, 3-, and 5-year RFS rates were 58.3%, 43.0%, and 34.1%, respectively, in patients without BDTT and 41.0%, 21.1%, and 20.3%,

TABLE 1 Patient demographics and tumor characteristics

Variables	Before PSM [$n = 1585$]			After PSM [$n = 370$]		
	Without BDTT [$n = 1358$]	With BDTT [$n = 227$]	P value	Without BDTT [$n = 185$]	With BDTT [$n = 185$]	P value
Sex			0.832			0.326
Male	1156	192		150	157	
Female	202	35		34	27	
Age, years			0.011			0.651
≤ 65	1081	197		160	157	
> 65	277	30		24	27	
HBsAg			0.880			0.326
Yes	1101	185		157	150	
No	257	42		27	34	
Liver cirrhosis			< 0.001			0.916
Yes	975	125		106	105	
No	383	102		78	79	
Child–Pugh class			< 0.001			0.473
A	1285	135		140	134	
B	73	92		44	50	
AFP, ng/mL			< 0.001			0.211
≤ 400	903	106		85	97	
> 400	455	121		99	87	
No. of tumors			0.001			0.503
Single	1045	151		128	122	
Multiple	313	76		56	62	
Tumor diameter			0.084			0.453
≤ 5	622	90		67	74	
> 5	736	137		117	110	
Microvascular invasion			0.006			0.677
Yes	533	111		89	93	
No	825	116		95	91	
Macrovascular invasion			0.016			0.509
Yes	171	42		38	33	
No	1187	185		146	151	
Tumor differentiation			< 0.001			1.000
Well/moderate	772	52		47	47	
Poor	586	175		137	137	
AJCC stages			< 0.001			0.449
I/II	1017	140		120	113	
III/IV	341	87		64	71	
R0 resection			0.102			0.862
Yes	1159	203		166	165	
No	199	24		18	19	

PSM propensity score matching, *BDTT* bile duct tumor thrombus, *HBsAg* hepatitis B surface antigen, *AFP* α-fetoprotein, *AJCC* American Joint Committee on cancer

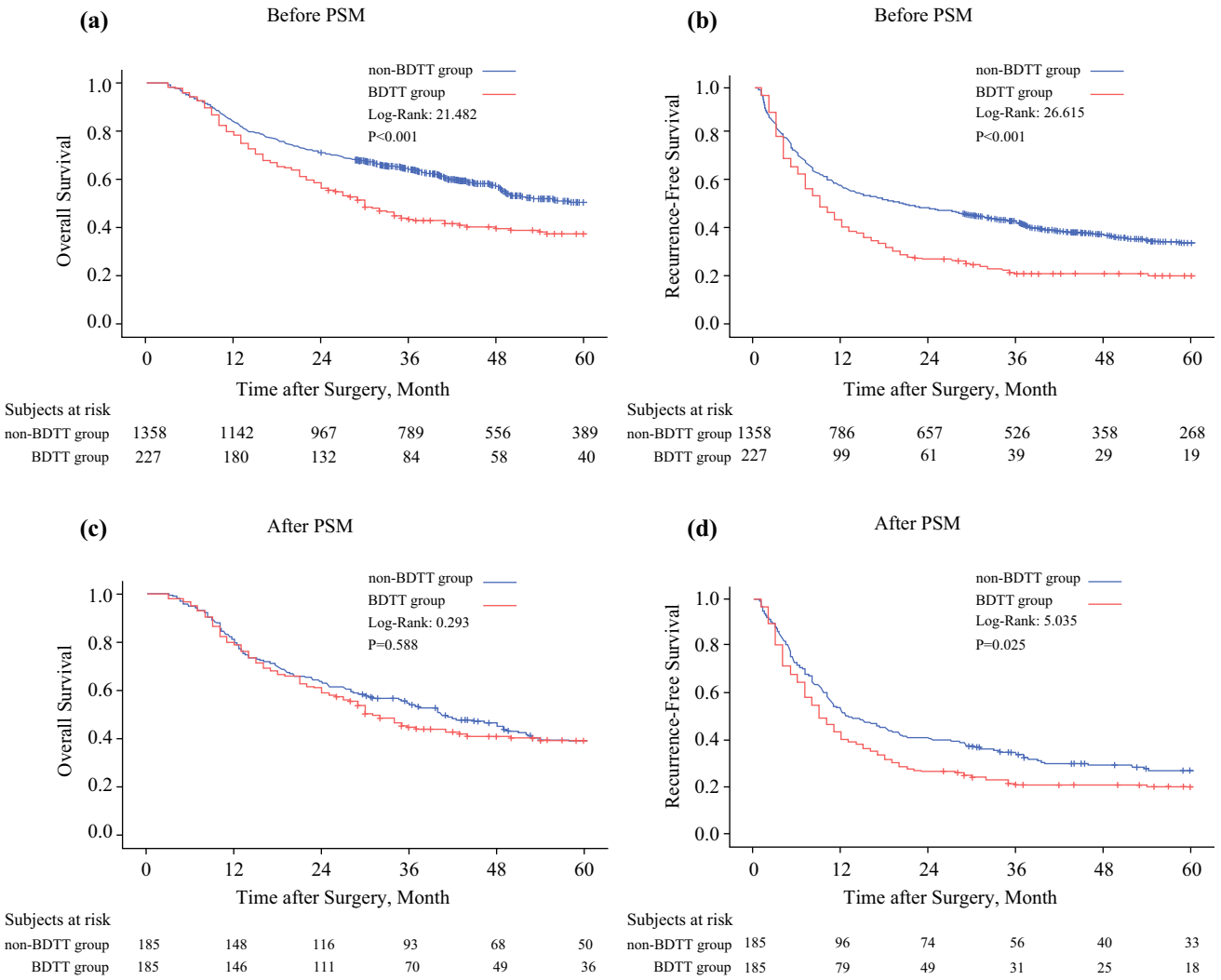

FIG. 1 Kaplan–Meier analysis of OS and RFS for all HCC patients with and without BDTT. **a** OS and **b** RFS of HCC patients with and without BDTT before PSM. **c** OS and **d** RFS of HCC patients with and without BDTT after PSM. *BDTT* bile duct tumor thrombus, *HCC* hepatocellular carcinoma, *OS* overall survival, *PSM* propensity score matching, *RFS* recurrence-free survival

respectively, in those with BDTT ($p < 0.001$) (Fig. 1b). OS and RFS were significantly worse in patients in the BDTT group than in those without BDTT. After 1:1 PSM, there was no significant difference in OS between the two groups (OS: 81.0% vs. 78.8%; 3 years, 54.2% vs. 44.4%; 5 years, 38.7% vs. 39.0%; $p = 0.588$) (Fig. 1c). However, the 1-, 3-, and 5-year RFS rates were 52.6%, 34.3%, and 26.9%, respectively, in patients without BDTT, and 40.2%, 20.9%, and 20.0%, respectively, in those with BDTT ($p = 0.025$) (Fig. 1c). The median survival time after resection after PSM was 40.3 months in HCC patients without BDTT and 31 months in those with BDTT. Moreover, there was no significant difference in OS and RFS between the microscopic and macroscopic BDTT groups (ESM Fig. 1a, b). In HCC patients with BDTT, the number of patients who underwent major hepatectomy, BDTT thrombectomy, presented with jaundice, and had macroscopic or microscopic BDTT in each stage were provided (ESM Table 3). There was no significant difference between the AJCC stage I–II group and the AJCC stage III group.

Subgroup Analysis of Survival According to Disease Stage

We conducted a subgroup analysis of our patients using the AJCC staging system. HCC patients were subcategorized into AJCC stage I, II, and III groups. Before PSM, OS and RFS were significantly worse in BDTT patients in the AJCC stage I and II groups than those in the non-BDTT group (ESM Fig. 2a, b: AJCC I—OS: $p < 0.001$, RFS: $p < 0.001$; ESM Fig. 3a, b: AJCC II—OS: $p = 0.001$, RFS: $p = 0.006$). However, there was no significant difference between BDTT and non-BDTT patients in the AJCC stage III group (ESM Fig. 4a, b: OS: $p = 0.341$,

RFS: $p = 0.188$). After PSM, OS and RFS were still significantly worse in the patients with BDTT than in those without BDTT in the AJCC stage I and II groups (ESM Fig. 2c, d: AJCC I—OS: $p = 0.034$, RFS: $p = 0.018$; ESM Fig. 3c, d: AJCC II—OS: $p = 0.030$, RFS: $p = 0.040$). In the AJCC stage III group, there was no significant difference between the BDTT and non-BDTT groups after PSM (ESM Fig. 4c, d: OS: $p = 0.643$, RFS: $p = 0.934$). To explore the influence of BDTT in the AJCC staging system, we compared the long-term outcomes between AJCC stage I patients with BDTT and AJCC stage II patients without BDTT, as well as AJCC stage II patients with BDTT and AJCC stage III patients without BDTT. The results indicated that there were no significant differences in OS and RFS between AJCC stage I patients with BDTT and AJCC stage II patients without BDTT (Fig. 2a, b: OS: $p = 0.326$, RFS: $p = 0.318$). Moreover, there were also no significant differences in OS and RFS between AJCC stage II patients with BDTT and AJCC stage III patients without BDTT (Fig. 2c, d: OS: $p = 0.308$, RFS: $p = 0.190$).

Modification of the American Joint Committee on Cancer Staging System for Prognostic Prediction

Based on our results, the addition of BDTT to the AJCC staging system was recommended. We recategorized AJCC stage I BDTT patients to AJCC stage II. In addition, AJCC stage II BDTT patients were recategorized to AJCC stage III. Table 2 presents the retrospective staging results of the 1585 patients using both the original and the modified AJCC staging systems. Survival rates based on the AJCC staging system were calculated using the Kaplan–Meier method and were analyzed using the log-rank test. Our

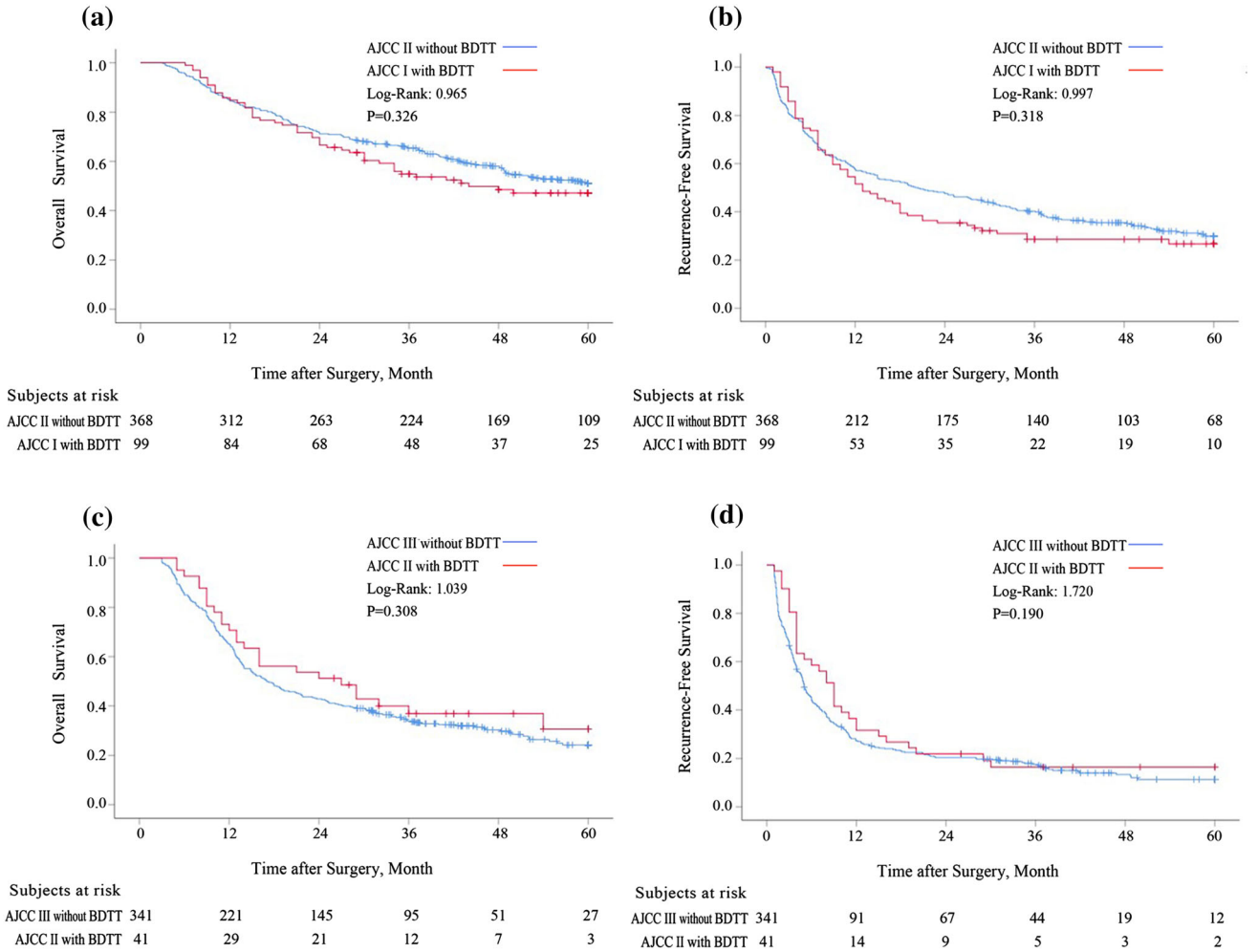

FIG. 2 Comparison of **a** OS and **b** RFS between HCC patients with BDTT in AJCC stage I and those without BDTT in AJCC stage II according to the AJCC staging system. Comparison of **c** OS and **d** RFS between HCC patients with BDTT in AJCC stage II and those without BDTT in AJCC stage III according to the AJCC staging system. *AJCC* American Joint Committee on Cancer, *BDTT* bile duct tumor thrombus, *HCC* hepatocellular carcinoma, *OS* overall survival, *PSM* propensity score matching, *RFS* recurrence-free survival

TABLE 2 Distribution of the 1585 HCC patients using both the original and modified AJCC staging systems

	Original AJCC	Modified AJCC	*P* value
AJCC			< 0.001
I	748	649	
II	409	467	
III	428	469	

HCC hepatocellular carcinoma, *AJCC* American Joint Committee on cancer

results found that the modified AJCC staging system was better at predicting OS and RFS than the original AJCC staging system (Fig. 3a–d; original AJCC staging system: OS: Chi-square = 231.765, $p < 0.001$; RFS: Chi-square = 257.363, $p < 0.001$; modified AJCC staging system: OS: Chi-square = 249.311, $p < 0.001$; RFS: Chi-square = 279.501, $p < 0.001$). In this group of patients, higher Chi-square values demonstrated a better prognostic prediction ability. When the presence of BDTT was recommended to increase the AJCC staging system by one stage in AJCC stages I–II patients, the ability to predict the RFS and OS was higher using the modified AJCC staging system.

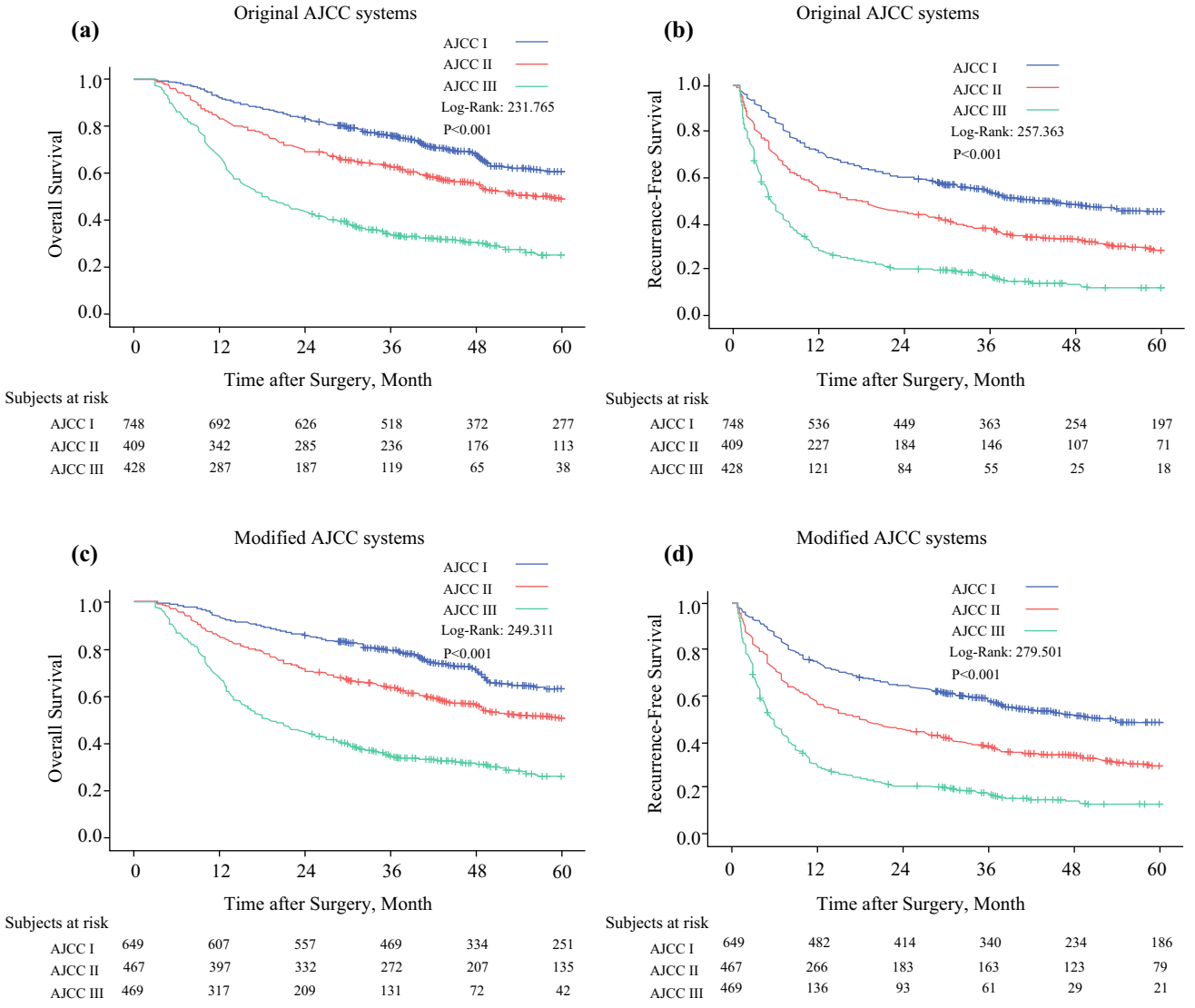

FIG. 3 Kaplan–Meier analysis of **a** OS and **b** RFS in all HCC patients according to the original AJCC staging system. Kaplan–Meier analysis of **c** OS and **d** RFS in all HCC patients according to the modified AJCC staging system. *AJCC* American Joint Committee on Cancer, *HCC* hepatocellular carcinoma, *OS* overall survival, *RFS* recurrence-free survival

DISCUSSION

HCC with BDTT was first reported as 'icteric hepatocellular carcinoma' in 1947;[23] however, the impact of BDTT on surgical outcomes in HCC is still an area of speculation and controversy owing to the low incidence of BDTT in HCC.[4–7] In our data, the incidence of BDTT in HCC was 3.42%, which was similar to the incidence reported in previous studies.[4–7] Over the past several decades, studies have investigated the clinicopathological features and prognosis of HCC patients with BDTT;[7–18] however, these studies have not conclusively indicated whether these patients had a poorer long-term outcome after surgery. Rammohan et al. indicated that the 1-, 3-, and 5-year survival rates in HCC patients with BDTT were 82%, 48%, and 10%, respectively, with a median survival of 28.6 months, which was significantly poorer than patients without BDTT.[11] A study by Kim et al. also found that BDTT could be used as an independent prognostic factor for survival in early-stage HCC.[10] Meng et al.,[7] Yu et al.,[8] and Wang et al.[9] observed significantly poorer survival outcomes of patients with HCC and BDTT after hepatectomy. In contrast, Shiomi et al.[16] and Satoh et al.[17] found that HCC patients with BDTT had no significant difference in survival when compared with those without BDTT. In addition, Wong et al. also reported that HCC patients with and without BDTT had comparable OS and RFS after being matched for conventional adverse prognostic factors.[15] These results suggest that the long-term survival of patients with HCC and BDTT is satisfactory after radical surgery;[15] however, this study only included a small number (37 cases) of HCC patients with BDTT. The argument on the impact of BDTT after surgery may be due to differences in the clinicopathological characteristics between HCC patients with and without BDTT.

According to previous studies, HCC patients with BDTT had a higher grade of tumor differentiation in 40.9–93.3% of cases, a higher rate of portal vein invasion in 28.8–76.5% of cases, and intrahepatic multiple lesions in 20–80% of cases.[16,17] In a recent study, Navadgi et al. also found that patients with HCC and BDTT who underwent hepatectomy had a higher proportion of poorly differentiated tumors, lymphovascular invasion, and macrovascular invasion in a systematic review and meta-analysis.[5] Our data corroborated this and also indicated that HCC patients with BDTT had comparatively poorer tumor differentiation, younger age (< 65 years), higher rate of liver cirrhosis, higher level of AFP (> 400 ng/U), worse liver function, higher rate of multiple tumors, higher rate of macrovascular invasion, and advanced TNM stage than those without BDTT. The incidence of macrovascular invasion was estimated to occur in approximately 28.8–76.5% of cases, which was significantly higher than that seen in HCC patients without BDTT.[11,16,17] This might be because the portal vein and bile duct are enclosed in the same Glisson sheath, and tumors can invade these structures at the same time. These different pathologic features suggested that HCC patients with BDTT had more aggressive features that were associated with a more advanced tumor stage. Therefore, the pre-existing conditions present in HCC patients with BDTT have more aggressive features that impact long-term survival. Thus, if researchers ignore the aggressive features associated with BDTT and only compare with 'average' HCC patients without matching, the comparison between the two groups would not be accurate.

In our study, OS and RFS were significantly worse in patients with BDTT than in those without BDTT. After PSM, the RFS rate was still worse in patients with BDTT than in those without BDTT. However, there was no significant difference in OS between the two groups. In addition, there was no significant difference in OS and RFS between the microscopic and macroscopic BDTT groups. The subgroup analysis using the AJCC staging system showed that BDTT was a significant risk factor that influenced OS and RFS in HCC in AJCC stage I–II, both before and after PSM, but not in those with AJCC stage III. These findings are similar to those presented in the study by Jang et al., who also found that BDTT could be used as an independent prognostic factor for survival in early-stage HCC.[24] The results may be associated with HCC, with AJCC stage III exhibiting high tumor malignancy and poor prognosis. In addition, HCC patients with AJCC stage III usually had macrovascular invasion and surrounding tissue infiltration. The impact of common prognostic factors, such as vascular invasion, may be greater than that of BDTT. In BDTT in conjunction with these factors, the impact of BDTT appeared to be less prominent. However, in HCC patients with AJCC stage I–II, BDTT was found to be a significant prognostic factor for OS and RFS. This may be due to the fact that if BDTT does not accompany vascular invasion, there may be undetected or hidden microvascular invasion. This suggests that BDTT could be used as a poor prognostic factor for HCC patients with AJCC stage I–II.

Notably, according to the 8th edition of the AJCC Cancer Staging Manual, BDTT is not currently considered a prognostic factor.[21] The prognostic factors typically used in TNM staging include vascular invasion, tumor size and number, lymph node involvement, and distant metastasis.[21] However, BDTT is considered in the Japanese staging system for HCC.[25] The presence of BDTT based on preoperative imaging findings increases the T classification by one grade.[25,26] In addition, Lu et al. also found that modification of the Barcelona Clinic Liver Cancer system to include the BDTT status might further enhance its prognostic ability.[27] However, whether BDTT should be

considered a staging factor for HCC patients requires further research owing to the small patient cohorts and lack of a clear characterization of HCC patients with BDTT. In our study, our results suggested that BDTT was a significant prognostic factor for OS and RFS in HCC patients with AJCC stage I–II. Moreover, we found there were no significant differences in RFS and OS between AJCC stage I patients with BDTT and AJCC stage II patients without BDTT, or between AJCC stage II patients with BDTT and AJCC stage III patients without BDTT. Therefore, in patients with BDTT in AJCC stage I–II, the presence of BDTT is recommended as a factor in the AJCC staging system. The presence of BDTT may increase the AJCC staging system by one stage in AJCC stage I–II patients. In addition, this modified AJCC staging system had better performance in predicting OS and RFS than the original AJCC staging system. Herein, we hypothesized that BDTT in patients with AJCC stage I–II may be included in the HCC staging system.

Our study had some limitations. First, this study utilized a retrospective design, therefore, although we used PSM to balance for baseline characteristics and operative details, a risk of selection bias remained between the two groups. Second, the number of HCC patients with BDTT was small. However, to the best of our knowledge, our study had the largest cohort of studies that used PSM to compare the prognosis between HCC patients with and without BDTT. Third, surgical treatment and postoperative management were performed by different clinicians from different centers, which may have affected the prognosis of patients. In addition, we excluded HCC patients who underwent extrahepatic duct resection because in our data, the proportion of patients who underwent extrahepatic duct resection was very low. Therefore, in cases where hepatectomy was used for the treatment of HCC with BDTT, the effect of extrahepatic bile duct resection remained unclear and requires further research. Fourth, most HCC patients in our study had a history of hepatitis B virus infection and this may not be able to be extrapolated to other etiologies of HCC. Therefore, more well-designed multicenter randomized controlled trials to further verify the impact of BDTT on surgical outcomes for HCC are warranted.

CONCLUSION

Overall, our study indicated that BDTT was associated with significantly worse long-term surgical outcomes in HCC patients in AJCC stages I and II. In addition, we propose that HCC patients with BDTT may increase the AJCC staging system by one stage in AJCC stage I–II patients. Our modified AJCC staging system, including BDTT status, had a better prognostic ability in AJCC stage I–II.

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