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ORIGINAL RESEARCH

# Efficacy and Safety of Transarterial Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma Associated with Bile Duct Tumor Thrombus: A Real-World Retrospective Cohort Study



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**Background:** The occurrence of hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) is rare. The aim of the study was to evaluate the effectiveness and safety of transarterial chemoembolization (TACE) for patients with unresectable HCC with BDTT.

**Methods:** This retrospective study was conducted on newly diagnosed HCC and BDTT patients who were initially treated with TACE or conservative management (CM) from 2009 to 2018. Survival outcomes of patients treated with TACE were compared with those of patients given CM. Multivariate analyses were performed to identify independent prognostic factors related to survival.

**Results:** Out of 100 patients included in this study, 40 patients underwent TACE, while the remaining 60 received CM. The median survival time of the TACE group was 8.0 months longer than that of the CM group (13.0 versus 5.0 months, $P < 0.001$). The 6-, 12-, 18-, 24-month overall survival (OS) rates were 90.0%, 52.5%, 22.5%, and 12.5%, respectively, for the TACE group compared with 26.7%, 8.3%, 5.0%, and 3.3%, respectively, for the CM group. Multivariate analyses showed that treatment allocation (hazard ratio [HR], 0.421; 95% confidence interval [CI], 0.243–0.730; $P = 0.002$), Child–Pugh status (HR, 2.529; 95% CI, 1.300–4.920; $P = 0.006$) and total bilirubin level (HR, 1.007; 95% CI, 1.004–1.009; $P < 0.001$) on first admission were independent predictors of OS. There was no procedure-related mortality within one month after TACE treatment.

**Conclusion:** TACE is a safe and effective treatment method that may improve the OS of patients with unresectable HCC with BDTT.

**Keywords:** hepatocellular carcinoma, bile duct tumor thrombus, transarterial chemoembolization, conservative management, overall survival

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the leading cause of cancer-related death globally.[1,2] Many HCC patients seek medical care due to the presence of recognizable obstructive jaundice, which may be attributed to different etiologies, such as extrinsic compression by the tumor, metastatic lymph nodes enlargement around the porta hepatis, or bile duct tumor thrombus (BDTT).[3] Of these causes, BDTT is a rare but special clinical feature of HCC, with the incidence rate of only 1–9%.[4–6]

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With regard to the management of HCC with BDTT, surgical resection has become the main treatment method. Numerous literature have reported that surgical resection can result in better curative effect and improve long-term survival of patients compared to other palliative-intent therapy.[7,8] Some authors claim that, after curative operation, HCC patients with BDTT can even achieve similar survival outcomes compared to those without BDTT.[8–11] Nevertheless, a high proportion of HCC patients with BDTT lose the opportunity for surgery during initial hospital visit, due to liver-related (underlying hepatic dysfunction, sustained cholestasis), cancer-related (advanced tumoral disease) or patient-related (poor general conditions, uncontrollable comorbidities) factors. Current HCC practice guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have not made any treatment recommendations for this particular patient population.[12,13]

As a curative adjunct, transarterial chemoembolization (TACE) has long been held as one of the standard treatments of care for HCC patients.[14,15] Previous studies have repeatedly demonstrated that TACE, compared to conservative management (CM), provides survival benefit for advanced HCC patients.[16–18] However, due to the low incidence rate of BDTT and insufficient knowledge about BDTT, studies focusing on non-surgical treatments for unresectable HCC with BDTT are rare. In this context, we conduct a retrospective study to evaluate the efficacy and safety of TACE for patients with unresectable HCC and BDTT. Our goal is to determine whether TACE or CM is the more appropriate treatment for these patients.

# Patients and Methods

## Patients

Consecutive HCC patients with BDTT receiving initial TACE or CM at the Eastern Hepatobiliary Surgery Hospital (EHBH, Shanghai, China) from November 2009 to August 2018 were included in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the EHBH Clinical Research Ethics Committee. Written informed consent was waived in this retrospective study because the personal information of patients was anonymized and de-identified prior to analyses.

The diagnosis of HCC was made based on the characteristic enhancement pattern from the imaging data of dynamic contrast-enhanced computed tomography (CT) or multimodal magnetic resonance imaging (MRI), as recommended by the Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition).[19] BDTT was diagnosed by the presence of expansile and arterially enhancing intraductal mass connected to the intrahepatic lesion.[20] When necessary, endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) was used to make definite diagnosis of BDTT.

## Eligibility Criteria

Patients fulfilling the following criteria were included in this study: (I) HCC unsuitable for liver resection; (II) BDTT diagnosed by the diagnostic criteria as mentioned above; (III) Child–Pugh score in category A or B; (IV) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; (V) with no previous anti-cancer treatment.

Patients with the following conditions were excluded in this study: (I) Child–Pugh C liver function; (II) undergoing other initial anti-tumor treatments, such as local ablation, percutaneous ethanol injection or systemic treatment; (III) with refractory ascites, hepatic encephalopathy or coagulopathy; (IV) with esophagogastric variceal hemorrhage; (V) with extrahepatic metastasis; (VI) have heart, pulmonary or kidney dysfunction; (VII) with incomplete clinical data or no follow-ups.

## TACE Procedure

In patients with total bilirubin level exceeding 51.3 μmol/L, pre-TACE biliary drainage through an endoscopic or percutaneous approach was performed in order to resolve obstructive jaundice. Following successful biliary drainage (total bilirubin level decreased to ≤34.2 μmol/L within two weeks after the procedure), TACE was conducted subsequently.[21] A 4–5 French catheter was selectively introduced through a femoral artery into the hepatic artery using the Seldinger technique.[22,23] Arterioportogram was performed to detect portal patency, and to assess tumor staining and vascularity. The tip of the microcatheter was directly advanced into the tumor-feeding arteries depending on the tumor size and location. An emulsion of doxorubicin hydrochloride (20–60 mg), cisplatin (5 mg) and lipiodol (10–30 mL; 1 to 2 mL/cm diameter of the tumor; Lipiodol Ultrafluide, Guerbet, Aulnay-Sous-Bois, France) was infused. Gelfoam fragments were then injected to embolize the tumor feeding vessels until stasis of blood flow was achieved. The dosages of doxorubicin and lipiodol were determined by the body surface area and underlying liver function. The tumor

response was evaluated one month later using CT and/or MRI. Repeated TACE was performed over two or three months if residual viable tumor was detected, unless there was evidence of disease progression or hepatic decompensation. Adverse events related to TACE were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

## Conservative Management

Patients with any relative contraindications to arterial procedure (eg, platelet count $<50\times10^9$/L, prothrombin time prolongation >3s), or to chemotherapy (eg, serum total bilirubin concentration >51.3 μmol/L, leucocyte count $<3\times10^9$/L), or those requested best supportive care were treated by conservative management (CM). CM comprised biliary decompression (percutaneous transhepatic biliary drainage [PTBD], endoscopic biliary drainage [EBD], etc.), diuretic therapy, analgesic remedy, pruritus relief, nutritional supplementation and energy support, antibiotic therapy and other symptomatic treatment. Patients receiving oral small-molecular targeted agents (sorafenib, lenvatinib, etc.) or immune checkpoint inhibitors (PD-1, PD-L1, etc.) were precluded from the CM group.

## Follow-Up

All patients, after being discharged from the hospital, were recommended to attend regular follow-up visits at the outpatient clinic in accordance with a standardized follow-up protocol, in which the surveillance was performed once every 1–2 months for the first year and once every 3 months thereafter, until death or dropout from the follow-up program. At each visit, patients were assessed using routine blood test, serum AFP assay, liver functional test, chest X-ray and abdominal ultrasonography.

Besides, contrast-enhanced CT or MRI scan was performed once every 6–8 weeks during the first 3 months to evaluate tumor response and once every 4–6 months for surveillance thereafter. The dates of death or last follow-up visit were recorded. This study was censored on June 30th, 2020.

## Data Collection and Endpoint of Study

Detailed information on baseline characteristics was retrieved from the electronic system of our hospital. Demographic characteristics included age and sex. Liver function was assessed using Child-Turcotte-Pugh grading during initial hospitalization. Virological indices comprised serum hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HCV antibodies (anti-HCV), and HBV DNA load. Blood routine test, biochemistry examination and tumor biomarker comprised counts of white blood cell (WBC), hemoglobin (HGB), platelet (PLT), concentrations of albumin (ALB), total bilirubin (TBil) on admission, alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), serum creatinine (Scr), levels of carbohydrate antigen 19–9 (CA 19–9) and α-fetoprotein (AFP). Coagulation function was evaluated by prothrombin time (PT). Tumor number and diameter, and macrovascular invasion were determined radiographically. Fine-needle biopsy was not routinely carried out in our hospital, so pathological data were not available in this cohort of patients.

The primary endpoint of this study was overall survival (OS), which was calculated from the date of the first TACE session (for the TACE group) or the date of the first in-hospital work-up results (for the CM group) to the date of death or the date of last follow-up. The secondary endpoints were in-hospital mortality of the TACE group, defined as any death within 30 days following the first course of treatment, and TACE-related complications.

## Statistical Analysis

Continuous variables, reported as means with standard deviations (SD) or medians with interquartile range (IQR), were compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical data, displayed as frequencies and percentages (%), were compared using chi-square test or Fisher's exact test, as appropriate. OS was analyzed using Kaplan–Meier method and compared using Log rank test. Univariate analysis and multivariate Cox regression analysis with backward stepwise selection were performed to identify independent prognostic factors of OS. Subgroup analysis was subsequently conducted by stratifying patients according to independent risk factors. A two-tailed $P$ value of $<0.05$ was considered statistically significant throughout. Statistical analyses were performed using SPSS software, version 26.0 (IBM Corporation, Armonk, NY, USA) and R program, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

# Results

## Study Population

The flowchart in Figure 1 illustrates the patient selection process in this study. Out of 195 patients with unresectable HCC and BDTT who underwent initial TACE or CM during

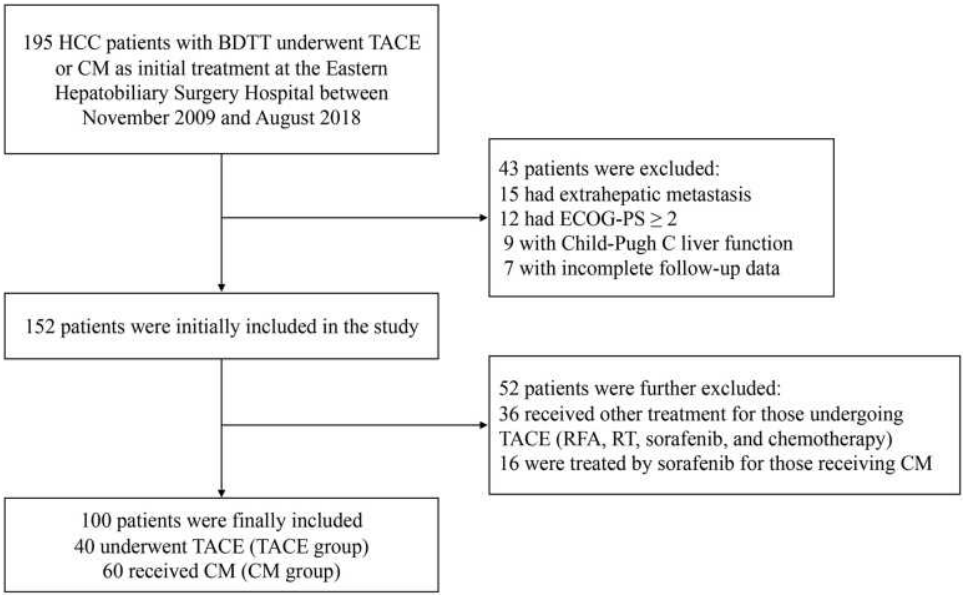


**Figure 1** Flowchart of screening all HCC patients with BDTT who underwent either TACE or CM as initial treatment.
**Abbreviations**: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management; ECOG-PS, Eastern Cooperative Oncology Group performance status; RFA, radiofrequency ablation; RT, radiotherapy.

the study period, 95 patients were excluded from this study cohort based on the predefined eligibility criteria. From the total number of 100 patients included in this study, 40 received TACE and the remaining 60 underwent CM.

Patients in the TACE group received either one session (n = 26), two sessions (n = 12), three sessions (n = 1) or four sessions (n = 1) of TACE. The mean session of TACE was 1.4. Adverse events related to TACE are shown in Table S1. There was no TACE-related mortality. Meanwhile, 35 patients developed complications at different degrees (all grade 3 or below), resulting in a morbidity rate of 87.5% in the TACE group. No major complications such as acute cholangitis, liver abscess, and hepatic failure were observed.

## Baseline Characteristics

The baseline characteristics of patients in the TACE and CM groups are shown in Table 1. Compared to the CM group, the TACE group had a significantly higher proportion of Child–Pugh grade A patients (70.0% vs 16.7%; $P < 0.001$), a lower concentration of total bilirubin on admission (27.3 vs 211.8 μmol/L; $P < 0.001$), a lower level of CA 19–9 (71.5 vs 259.0 U/mL; $P = 0.001$), a larger tumor diameter (7.0 vs 4.7 cm; $P = 0.017$); a higher occurrence of multiple tumors (35.0% vs 13.3%; $P = 0.010$), and higher presence of major vascular invasion (25.0% vs 5.0%; $P = 0.004$). The other demographic and clinical profiles were comparable between the two groups.

## Univariate and Multivariate Analyses of Predictors of OS

As shown in Table 2, treatment allocation (TACE vs CM, HR = 0.42, 95% CI = 0.24–0.73; $P = 0.002$), Child–Pugh grade (class B vs A, HR = 2.53, 95% CI = 1.30–4.92; $P = 0.006$), and total bilirubin level on first admission (per 1 μmol/L increase, HR = 1.007, 95% CI = 1.004–1.009; $P < 0.001$) were identified as independent prognostic factors of OS for patients with unresectable HCC with BDTT.

## Survival Analysis in All Patients

During the follow-up period with a median of 7 months (range, 1–49), 8 (20.0%) patients in the TACE group and 47 (78.3%) patients in the CM group died. A significant difference in OS was observed between the two groups. The median survival time (MST) was 13.0 months in the TACE group and 5.0 months in the CM group, respectively. Compared to CM, TACE showed significantly better OS at 6 months (90.0% vs 26.7%), 12 months (52.5% vs 8.3%), 18 months (22.5% vs 5.0%), and 24 months (12.5% vs 3.3%) ($P < 0.001$; Figure 2).

## Subgroup Analysis Stratified by Independent Risk Factors

Although baseline Child–Pugh grade and total bilirubin concentration were identified as independent risk factors

**Table 1** Baseline Characteristics of HCC Patients with BDTT

| Clinical Variables | TACE Group (n=40) | CM Group (n=60) | Statistic | *P* |
|---|---|---|---|---|
| Age, years | 55 (45–62) | 55 (42–61) | 0.232 | 0.816 |
| Sex | | | 0.009 | 0.923 |
| Male | 31 (77.5%) | 46 (76.7%) | | |
| Female | 9 (22.5%) | 14 (23.3%) | | |
| Child–Pugh class | | | 28.976 | < 0.001 |
| A | 28 (70.0%) | 10 (16.7%) | | |
| B | 12 (30.0%) | 50 (83.3%) | | |
| HBsAg | | | 0.082 | 0.774 |
| Positive | 31 (77.5%) | 45 (75.0%) | | |
| Negative | 9 (22.5%) | 15 (25.0%) | | |
| HBeAg | | | 0.915 | 0.339 |
| Positive | 9 (22.5%) | 9 (15.0%) | | |
| Negative | 31 (77.5%) | 51 (85.0%) | | |
| Anti-HCV | | | 0.916 | 0.338 |
| Positive | 2 (5.0%) | 1 (1.7%) | | |
| Negative | 38 (95.0%) | 59 (98.3%) | | |
| HBV DNA, copies/mL | | | 0.032 | 0.857 |
| ≤ 1000 | 28 (70.0%) | 43 (71.7%) | | |
| > 1000 | 12 (30.0%) | 17 (28.3%) | | |
| WBC, $10^9$/L | 5.2 (3.8–7.2) | 6.4 (4.8–7.6) | 1.787 | 0.074 |
| HGB, g/L | 128 (119–134) | 123 (108–136) | 0.827 | 0.408 |
| PLT, $10^9$/L | 169 (120–220) | 177 (128–263) | 0.697 | 0.486 |
| ALB, g/L | 37.7 (4.5) | 36.2 (5.8) | 1.555 | 0.123 |
| TBil on admission, μmol/L | 27.3 (19.7–44.1) | 211.8 (82.8–334.4) | 6.294 | < 0.001 |
| ALT (U/L) | 50.5 (29.8–104.8) | 68.6 (47.6–116.8) | 1.763 | 0.078 |
| GGT (U/L) | 324.0 (188.3–523.3) | 269.5 (126.0–527.0) | 1.031 | 0.303 |
| ALP (U/L) | 179.5 (133.5–269.5) | 198.0 (141.0–308.8) | 1.270 | 0.204 |
| PT (s) | 12.3 (11.5–13.8) | 12.3 (11.6–14.0) | 0.011 | 0.992 |
| Scr (μmol/L) | 65.3 (14.1) | 64.1 (16.6) | 0.398 | 0.691 |
| CA 19–9 (U/mL) | 71.5 (29.9–145.2) | 259.0 (56.5–932.6) | 3.380 | 0.001 |
| AFP (ng/mL) | | | 0.245 | 0.621 |
| ≤ 400 | 24 (60.0%) | 33 (55.0%) | | |
| > 400 | 16 (40.0%) | 27 (45.0%) | | |
| Tumor diameter (cm) | 7.0 (4.5–8.9) | 4.7 (3.1–6.8) | 2.396 | 0.017 |
| Tumor number | | | 6.566 | 0.010 |
| Solitary | 26 (65.0%) | 52 (86.7%) | | |
| Multiple | 14 (35.0%) | 8 (13.3%) | | |
| Major vascular invasion | | | 8.488 | 0.004 |
| Presence | 10 (25.0%) | 3 (5.0%) | | |
| Absence | 30 (75.0%) | 57 (95.0%) | | |

**Abbreviations**: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HBV DNA, hepatitis B virus deoxyribonucleic acid; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB, albumin; TBil, total bilirubin; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PT, prothrombin time; Scr, serum creatinine; CA19-9, carbohydrate antigen 19–9; AFP, α-fetoprotein.

**Table 2** Univariate and Multivariate Analysis for Prognostic Factors of OS in HCC Patients with BDTT

| Clinical Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Treatment allocation, TACE vs CM | 0.365 (0.238–0.560) | < 0.001 | 0.421 (0.243–0.730) | 0.002 |
| Age (per 1 year increase) | 0.998 (0.979–1.018) | 0.871 | | |
| Sex, male vs female | 1.006 (0.627–1.614) | 0.979 | | |
| Child–Pugh class, B vs A | 1.639 (1.081–2.485) | 0.020 | 2.529 (1.300–4.920) | 0.006 |
| HBsAg, positive vs negative | 1.063 (0.664–1.700) | 0.800 | | |
| HBeAg, positive vs negative | 1.457 (0.845–2.512) | 0.176 | | |
| Anti-HCV, positive vs negative | 2.854 (0.685–11.889) | 0.150 | | |
| HBV DNA, >1000 vs ≤1000 copies/mL | 1.377 (0.875–2.167) | 0.167 | | |
| WBC (per $1*10^9$/L increase) | 1.077 (0.995–1.165) | 0.066 | | |
| HGB (per 1 g/L increase) | 1.001 (0.994–1.009) | 0.781 | | |
| PLT (per $1*10^9$/L increase) | 1.001 (0.999–1.003) | 0.352 | | |
| ALB (per 1 g/L increase) | 0.990 (0.951–1.032) | 0.647 | | |
| TBil on admission (per 1 μmol/L increase) | 1.006 (1.004–1.007) | < 0.001 | 1.007 (1.004–1.009) | < 0.001 |
| ALT (per 1 U/L increase) | 0.999 (0.996–1.002) | 0.366 | | |
| GGT (per 1 U/L increase) | 1.000 (0.999–1.001) | 0.652 | | |
| ALP (per 1 U/L increase) | 1.001 (0.999–1.002) | 0.354 | | |
| PT (per 1 second increase) | 1.030 (0.941–1.126) | 0.523 | | |
| Scr (per 1 μmol/L increase) | 1.006 (0.993–1.019) | 0.357 | | |
| CA 19–9, > 40 vs ≤ 40 U/mL | 1.276 (0.800–2.038) | 0.306 | | |
| AFP, > 400 vs ≤ 400 ng/mL | 1.051 (0.699–1.581) | 0.811 | | |
| Tumor diameter, > 5 vs ≤ 5 cm | 1.264 (0.845–1.890) | 0.255 | | |
| Tumor number, multiple vs solitary | 1.036 (0.642–1.673) | 0.884 | | |
| Major vascular invasion, yes vs no | 1.519 (0.842–2.743) | 0.165 | | |

**Abbreviations**: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HBV DNA, hepatitis B virus deoxyribonucleic acid; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB, albumin; TBil, total bilirubin; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; PT, prothrombin time; Scr, serum creatinine; CA19-9, carbohydrate antigen 19–9; AFP, α-fetoprotein.

related to OS, they were not comparable between the TACE and CM groups. It can be argued that the survival benefits from TACE were biased due to imbalance in these covariates. Therefore, we stratified the patients into 4 subgroups by baseline liver function and bilirubin level.

As shown in Figure 3, for patients with Child–Pugh class A liver function, the MST in the TACE and CM groups was 13.0 and 5.5 months, respectively. The OS of TACE was superior to that of CM ($P < 0.001$; Figure 3A). Similarly, for patients with Child–Pugh grade B liver function, the TACE group had longer MST than the CM group (9.5 vs 5.0 months, $P = 0.003$; Figure 3B). Stratification by total bilirubin amount suggested that in patients whose total bilirubin level was 51 μmol/L or lower, the MST was not statistically significantly different between the TACE and CM groups (13.0 vs 6.0 months, $P = 0.079$; Figure 3C). Nevertheless, in patients with total bilirubin level exceeding 51 μmol/L, the TACE group had significantly longer MST than the CM group (9.0 vs 5.0 months, $P = 0.005$; Figure 3D).

## Discussion

It is estimated that the prevalence rate of obstructive jaundice in HCC induced by BDTT ranges from 26.7% to 72.5%.[6,24–27] Thus, HCC with BDTT is termed "icteric type of HCC" or "cholestatic type of HCC". Surgical resection is currently the first-line treatment when HCC and BDTT are both resectable and the liver function is well preserved. Previous studies have demonstrated the survival benefit of curative surgery compared to palliative treatment for patients with resectable HCC and BDTT.[7,8] However, a relatively large proportion of HCC patients with BDTT have been diagnosed when the disease progresses to intermediate or late stage, which prevents the chance for surgical resection. Under these circumstances, TACE, radiofrequency ablation and other loco-regional treatments have been considered as potentially useful treatment interventions.[28,29]

It has been well accepted that TACE is an important curative adjunct for HCC patients fulfilling the criteria of

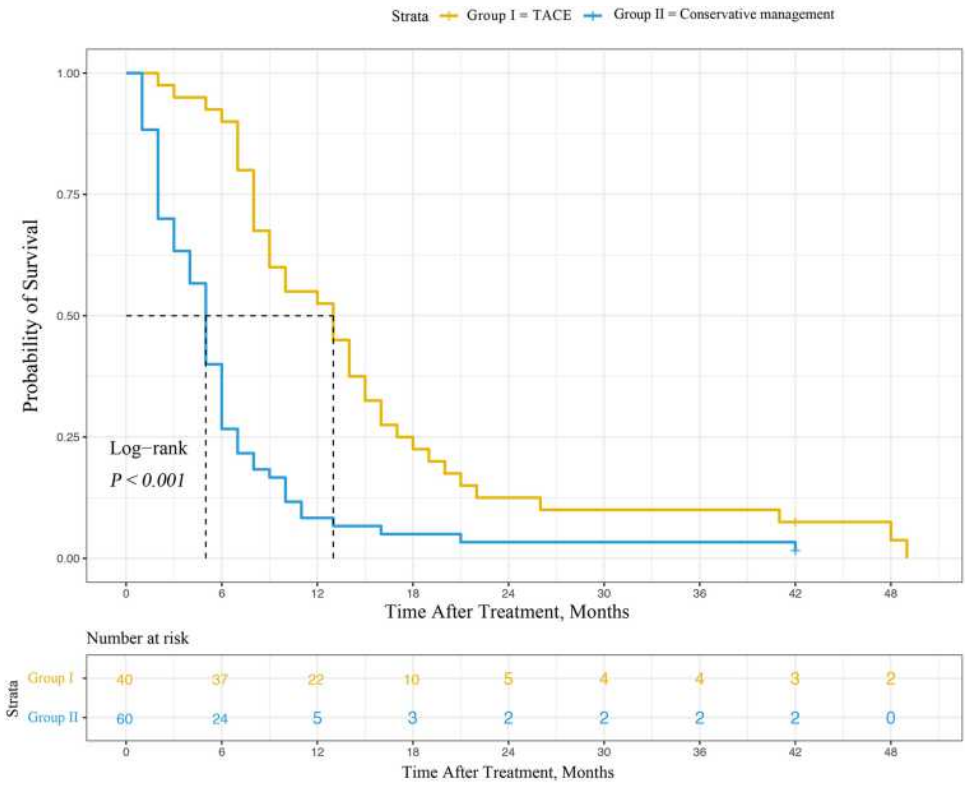


**Figure 2** Kaplan–Meier curves of overall survival in HCC patients with BDTT who underwent TACE or CM ($P < 0.001$).
**Abbreviations**: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management.

intermediate stage of BCLC staging system.[15,30] A recent meta-analysis has demonstrated that TACE plus radiofrequency ablation (RFA) is able to deliver equivalent oncologic outcomes as surgical resection in HCC patients, with the added benefit of decreased morbidity. TACE combined with RFA may be considered a curative alternative to surgical resection.[15] Moreover, radioembolization with Yttrium-90 microspheres is a safe and effective therapy for HCC patients with or without portal vein invasion.[31,32]

Hyperbilirubinemia in HCC with BDTT is considered a relative contraindication for TACE due to the high risk of post-procedural liver failure.[3] Besides, high serum total bilirubin level has always been used as a representative of bad hepatic functional reserve. Nonetheless, abnormal concentration of bilirubin in HCC patients with BDTT may be independent of poor liver function. In such circumstances, hyperbilirubinemia may simply reflect the obstruction of bile ducts. Furthermore, the development of interventional therapies has safely paved the way for subsequent anti-tumor treatment of TACE in patients with obstructive jaundice.

Survival benefits of TACE over CM for unresectable HCC have been demonstrated by two randomized controlled trials (RCTs).[33,34] In addition, a series of retrospective cohort studies have demonstrated that TACE is related to significantly better OS in selected HCC patients with portal vein tumor thrombus (PVTT).[35–38] However, due to the low incidence of BDTT, there have been very few studies that compare the survival outcomes between patients with unresectable HCC with BDTT who underwent TACE and those who received CM. Choi and colleagues[28] reported that patients with unresectable HCC with central bile duct invasion who received TACE had 1-year survival rate of 50.9%, and median survival of 12.2 months. Another retrospective study demonstrated that, under the condition of successful biliary drainage, patients with unresectable HCC with obstructive jaundice who underwent TACE had substantially prolonged median survival compared to patients with conservative treatment (410 vs 77 days, $P < 0.001$).[21]

In the present study, survival analysis showed that the MST of the TACE group was 13.0 months, which was remarkably longer than that of the CM group of 5.0 months. The 12-month survival rate of the TACE group was significantly better compared to that of the CM group

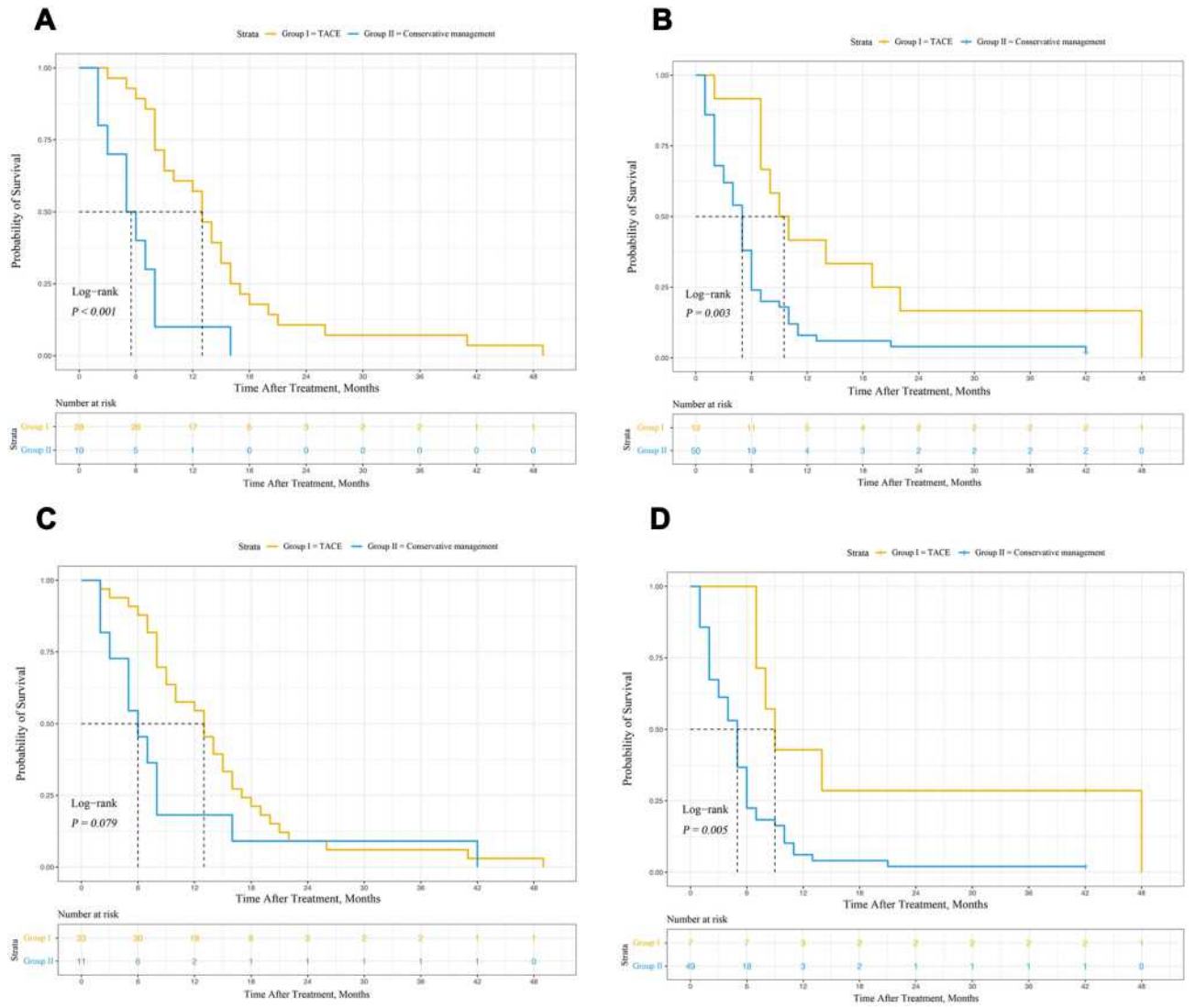


**Figure 3** Subgroup analysis of overall survival in HCC patients with BDTT who underwent initial TACE or CM stratified using baseline liver function (Child–Pugh class A or B) and total bilirubin concentration (≤51 or >51 μmol/L). (**A**) survival curves for HCC patients with BDTT with Child–Pugh class A liver function ($P < 0.001$); (**B**) survival curves for HCC patients with BDTT with Child–Pugh class B liver function ($P = 0.003$); (**C**) survival curves for HCC patients with BDTT with total bilirubin level ≤51 μmol/L ($P = 0.079$); (**D**) survival curves for HCC patients with BDTT with total bilirubin level >51 μmol/L ($P = 0.005$).

**Abbreviations**: HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management.

(52.5% vs 8.3%; $P < 0.001$). These results were consistent with findings in previous studies.[21,28] Multivariate analysis showed that treatment allocation (TACE vs CM, HR = 0.42, 95% CI = 0.24–0.73; $P = 0.002$) was independently related to OS. All the findings suggested that TACE was associated with improved OS for patients with unresectable HCC and BDTT.

The safety of TACE was also assesses in our study. Patients with complications were all recovered without any permanent adverse sequelae after dedicated medical care. In addition, no life-threatening (grade 4 or 5) adverse effects related to TACE were observed in this study, indicating that TACE is safe to be used for this subset of patients. Specifically, a rare complication of BDTT caused by TACE should be highlighted. When necrotic debris of tumor thrombus is separated from the main BDTT and floats into the common bile duct following TACE, clinical symptoms of obstructive jaundice will appear, which should be distinguished from jaundice caused by temporary liver insufficiency after TACE. This complication can be relieved by endoscopy-assisted thrombectomy or stent implantation. In this study, no such complication was found. However, in order to make an accurate diagnosis and provide prompt interventions, clinicians must be aware of such cases.

The present study has some limitations. Firstly, the retrospective nature of this study may introduce potential

selection bias. Secondly, the disparities of the baseline clinical characteristics may have an impact on the observed benefits of TACE in unresectable HCC with BDTT. Although propensity score matching analysis has been widely used in retrospective studies to minimize confounding effects, the small number of patients in this study restricts its application. Thus, prospective, large-scale studies from multiple centers should be designed in the future to overcome these limitations.

## Conclusions

In conclusion, TACE may be a safe and effective treatment option for patients with unresectable HCC with BDTT. Child–Pugh score and total bilirubin level of patients on first admission to hospital can be used as important prognostic factors for overall survival.

## Abbreviations

HCC, hepatocellular carcinoma; BDTT, bile duct tumor thrombus; TACE, transarterial chemoembolization; CM, conservative management; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; OS, overall survival; MST, median survival time.

## Data Sharing Statement

Research data are not shared, owing to the privacy or ethical restrictions.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki and the Eastern Hepatobiliary Surgery Hospital (EHBH) Clinical Research Ethics Committee approved this retrospective study. The requirement for informed consent was waived due to the retrospective nature of the study, and no personal information was disclosed.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Jin-Kai Feng, Ju-Xian Sun, Zong-Han Liu, and Jing-Wen Gu are co-first authors for this study. The authors declare that they have no conflicts of interest related to this study.

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