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Original Article

Clinical outcomes and safety evaluation of transarterial chemoembolization in patients with hepatocellular carcinoma: a retrospective observational study

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Abstract: Transarterial chemoembolization (TACE) is a major local treatment for unresectable hepatocellular carcinoma (HCC); however, clinical outcomes vary considerably among patients. This single-center retrospective observational study aimed to evaluate the clinical outcomes and safety of TACE in patients with Barcelona Clinic Liver Cancer (BCLC) stage A-B HCC and to explore factors associated with prognosis. Consecutive patients who received their first TACE between 2019 and 2024 and were unsuitable for radical treatment after multidisciplinary evaluation were included. Baseline characteristics were collected before TACE. The primary endpoints were overall survival (OS) and progression-free survival (PFS); secondary endpoints included objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) at 4-8 weeks after TACE, and time-dependent Cox regression was used to adjust for subsequent repeated TACE and systemic therapy. A total of 138 patients were included, most of whom were male (89.13%) with hepatitis B virus infection (68.12%) and BCLC stage B disease (90.58%). The median OS was 20.0 months, the median PFS was 11.0 months, and the ORR and DCR were 57.97% and 86.23%, respectively. In multivariable analysis, alpha-fetoprotein (AFP) ≥ 200 ng/mL, concomitant portal hypertension, and ≥ 4 tumor lesions were independently associated with poorer OS and PFS. Post-embolization syndrome occurred in 69.57% of patients, and severe complications occurred in 15.22%; no treatment-related deaths were observed. In conclusion, TACE achieved a certain degree of tumor control with acceptable safety in this cohort of patients with BCLC stage A-B HCC. Elevated AFP levels, portal hypertension, and greater tumor burden were associated with poorer survival outcomes. These findings should be interpreted as exploratory prognostic associations and require validation in independent cohorts.

Keywords: Hepatocellular carcinoma, transarterial chemoembolization, clinical outcomes, safety, prognostic factors, retrospective observational study

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for approximately 90% of all primary liver cancer cases [1], and has become a substantial global health burden [2]. Currently, HCC ranks sixth in incidence and third in cancer-related mortality worldwide [3]. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, long-term alcohol consumption, biliary cirrhosis, and other related conditions are major risk factors for HCC [4]. Chronic liver injury leads to persistent activation of local inflammatory microenvironment and repeated cycles of hepatocyte injury and regeneration, resulting in the accumulation of gene mutations and eventually malignant transformation of hepato-

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cytes [5]. This represents a key mechanism underlying the occurrence and development of HCC. The incidence of HCC varies considerably across populations and geographic regions. The risk of disease in males is significantly higher than that in females, and the disease is particularly prevalent in East and Southeast Asia [6]. China is a high-incidence area of liver cancer, accounting for more than 40% of new HCC cases and related deaths worldwide, posing a serious threat to public health.

The symptoms of early-stage HCC are insidious with no nonspecific clinical manifestations. By the time patients seek medical attention for obvious discomfort, the disease has already progressed to the intermediate or advanced stages, often presenting with large tumors, vascular invasion, or intrahepatic metastases, which may preclude curative treatments such as liver resection, liver transplantation, or local ablation [7]. Consequently, the overall prognosis is not optimistic. Although liver resection and transplantation can cure early-stage HCC [8], their clinical application is limited by factors such as large tumor size, insufficient hepatic functional reserve, and the shortage of donor organs. Therefore, only a limited proportion of patients are eligible for curative surgery in clinical practice. For patients with unresectable HCC who are unsuitable for curative treatment, transarterial chemoembolization (TACE) is a preferred locoregional treatment [9, 10] and has been widely used in clinical practice in China.

Normal liver tissue receives most of its blood supply from the portal vein. During the development of HCC, extensive tumor angiogenesis occurs, and the tumor blood supply predominantly dependent on the hepatic artery [11]. TACE delivers chemotherapeutic drugs directly to the tumor through the hepatic artery and simultaneously uses embolic materials to occlude tumor-feeding vessels, thereby inducing tumor ischemia and necrosis [12, 13]. This method can effectively inhibit tumor growth, delay disease progression, and prolong patient survival. Moreover, many retrospective and prospective clinical studies have demonstrated the therapeutic value of TACE in patients with unresectable HCC.

Despite its widespread use, clinical outcomes following TACE vary greatly among patients [14]. Some patients experience delayed disease progression, whereas others exhibit poor treatment responses and rapid disease progression [15]. Furthermore, TACE treatment is associated with adverse effects, including post-embolization syndrome (PES) and transient hepatic dysfunction. In severe cases, serious complications such as liver failure may even occur [16], potentially affecting subsequent treatment plans. Various clinical factors, including hepatic functional reserve, tumor burden, vascular invasion, severity of cirrhosis, and systemic inflammatory status, may significantly influence the therapeutic efficacy of TACE. Although numerous studies have evaluated TACE outcomes, their findings have been inconsistent because of differences in baseline patient characteristics, sample sizes, and inclusion and exclusion criteria. Therefore, further investigation of survival outcomes and treatment safety following TACE is warranted. Given the substantial interpatient variability in treatment efficacy, safety profiles, and the incidence of adverse reactions, effectively predicting treatment outcomes before TACE, identifying patients most likely to benefit, and recognizing those at high risk of treatment-related complications remain important challenges in clinical practice.

Against this background, this retrospective observational study included consecutive patients with HCC who received their first-time TACE at our hospital between 2019 to 2024. All patients were deemed unsuitable for radical treatment following multidisciplinary evaluation. This study aimed to evaluate survival outcomes, tumor response, and treatment-related adverse events and to explore the associations between pre-TACE baseline clinical characteristics and both OS and PFS. Given its single-center retrospective design and the use of subsequent systemic therapy in some patients, this study was intended as an exploratory real-world analysis of prognostic correlations rather than the development or validation of a prognostic scoring model.

Methods

Research design and subjects

This single-center retrospective observational study was conducted at Hongze District People's Hospital, Huai'an, Jiangsu, China. Conse-

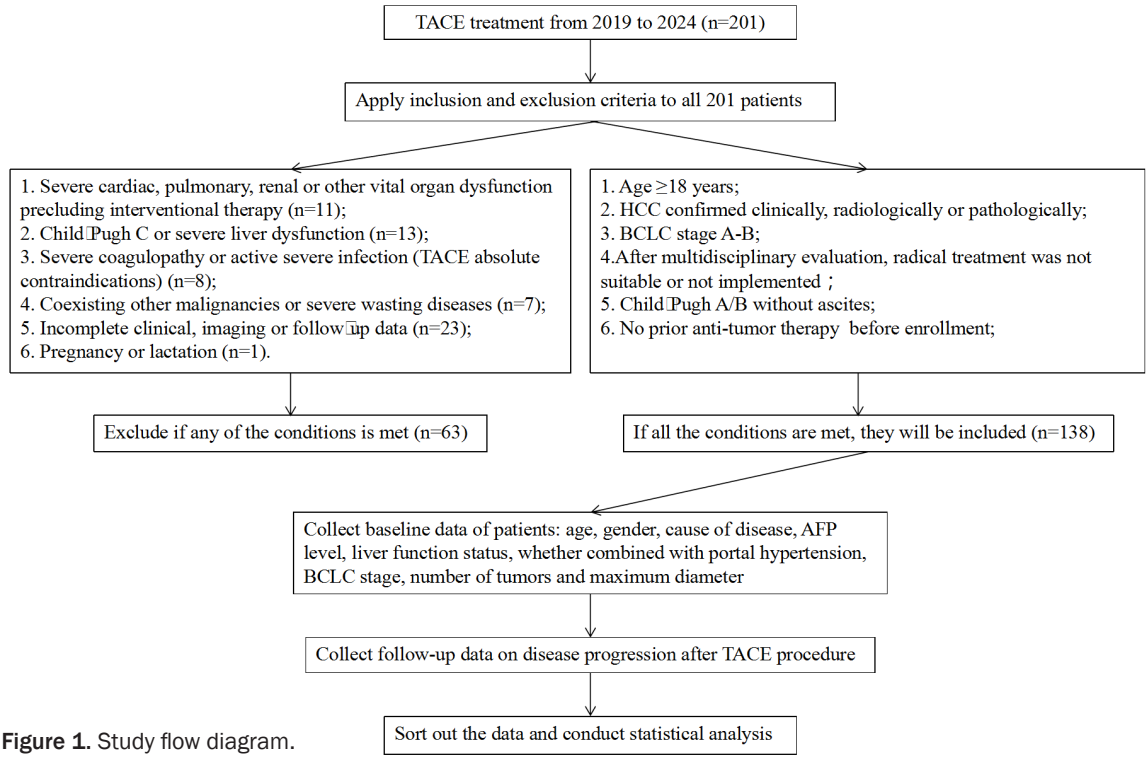


Figure 1. Study flow diagram.

cutive HCC patients who received their first TACE at the hospital between 2019 and 2024 were enrolled. All enrolled patients had Barcelona Clinic Liver Cancer (BCLC) stage A-B disease and were deemed unsuitable for radical treatment after multidisciplinary evaluation. Loss to follow-up was defined as the inability to obtain information on patient survival or disease progression from between TACE initiation and the follow-up cutoff date of December 31, 2024, with no available records of outpatient visits, hospitalizations, or telephone follow-up. During screening, eight cases were excluded due to incomplete follow-up data, and 15 cases were excluded due to missing clinical or imaging medical records. Baseline data before TACE were sourced from the hospital's electronic medical record system, including age, sex, HCC etiology, alpha-fetoprotein (AFP) levels, hepatic functional reserve, Child-Pugh classification, BCLC stage, maximum tumor diameter, number of lesions, and other tumor-related characteristics. Information on disease progression was obtained from follow-up data. The detailed study flow is presented in **Figure 1**.

Ethics statement

The study protocol was approved by the Ethics Committee of Hongze District People's Hospital (Approval No. HZYXLL(2026)08). Given the retrospective design, no interventions were made on clinical diagnosis or treatment. All identifying information of the patients was removed, and the data were anonymized. The requirement for informed consent was waived by the hospital's Ethics Committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Inclusion criteria

Patients were eligible for inclusion if they met all of the following criteria: (1) Age ≥ 18 years; (2) Clinically, radiologically, or pathologically diagnosed HCC; (3) BCLC stage A-B; (4) Deemed unsuitable for curative treatment following comprehensive multidisciplinary (MDT) evaluation, or had not undergone radical treatment. For patients with BCLC stage A disease, the main reasons for ineligibility for radical treatment, as determined by MDT, included severe cirrhosis complicated with portal hypertension, insufficient future liver remnant volume, lesions adjacent to major blood vessels or bile ducts, or severe comorbidities that precluded surgery or ablation. Patients with BCLC stage A disease must also satisfy this criterion prior to enrollment to avoid directly assigning early-stage patients who are generally eligible for curative

treatment to the TACE cohort; (5) Child-Pugh class A or B liver function with no ascites; (6) No prior antitumor treatment, including surgery, ablation, chemoradiotherapy, targeted therapy, or immunotherapy.

Exclusion criteria

Patients were excluded if they met any of the following criteria: (1) Severe cardiac, pulmonary, renal, or other major organ dysfunction that precluded interventional therapy; (2) Child-Pugh Class C liver function or severe hepatic decompensation; (3) Absolute contraindications to TACE, such as severe coagulation disorders or active severe infections; (4) Concurrent malignancies or severe cachexia; (5) Incomplete clinical records, imaging data, or follow-up information; (6) Pregnancy or breastfeeding.

Sample size estimation

Due to the retrospective study design, no prospective sample size calculation was conducted. Based on the empirical statistical principle of at least 10 outcome events per variable (EPV) for Cox regression analysis [17], a total of 115 deaths were recorded for the OS. For the PFS endpoint, a total of 134 events were recorded in both models. In the Cox proportional hazards regression with multiple factors, six variables were ultimately retained. The resulting EPV ratio exceeded 10, meeting the conventional empirical criterion for multivariable model estimation.

Baseline clinical data collection

Clinical data were retrospectively extracted from the electronic medical records of our hospital and radiology database. Complete clinical, laboratory, and imaging data obtained before the first TACE procedure were systematically collected for all included patients. Baseline measurements were defined as clinical data obtained within one week before the first TACE to ensure that the recorded parameters reflected the treatment baseline state and were not affected by the intervention.

Baseline clinical data included age, sex, and HCC etiology (HBV, HCV, or nonviral liver disease). Major baseline variables included serum AFP levels and portal hypertension. Meanwhile, according to the cut-off values reported in previous studies, AFP levels were categorized as < 200 ng/mL and ≥ 200 ng/mL [18, 19] for subsequent analyses. Portal hypertension was defined as elevated portal venous pressure exceeding 12 mmHg or a portal venous pressure gradient exceeding 5 mmHg [20]. Baseline liver function data included liver function test results and Child-Pugh classification. Patients were classified as Child-Pugh A or B based on hepatic functional reserve. Baseline imaging data were obtained from contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) performed within one month before TACE. These data were used to assess baseline tumor characteristics, including maximum tumor diameter, number of tumor lesions, and tumor multifocality (solitary, oligo-focal, or multifocal lesions). Additionally, tumor staging data, including BCLC stage before TACE, were also collected.

A comprehensive follow-up database was established to integrate baseline information, treatment data, and follow-up outcomes for all included patients. Patients with incomplete clinical records, imaging data, or follow-up information were excluded to ensure the completeness of the data. Among the 138 included patients, all baseline variables entered into the Cox regression models, including age, sex, HCC etiology, AFP level, Child-Pugh class, BCLC stage, portal hypertension, tumor number, maximum tumor diameter, and TACE modality, were complete. Accordingly, a complete-case analysis was performed, and no imputation was undertaken. Variables that were not routinely documented, including detailed liver function indices, albumin-bilirubin (ALBI) grade, Model for End-Stage Liver Disease (MELD) scores, quantitative TACE procedural parameters, severity of cirrhosis, and esophagogastric varices, were unavailable for analysis. Multiple imputation was therefore not performed for these variables.

Treatment plan

All enrolled patients underwent TACE. Before the procedure, patients underwent comprehensive evaluation based on contrast-enhanced CT or MRI findings, hepatic functional reserve, tumor burden, and general condition. After confirming the absence of contraindications to interventional treatment, an individualized TACE

regimen was formulated. The initial TACE procedure primarily involved two modalities: conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE) [21]. The difference between the two treatment modalities lies in the type of embolization agent used and the drug delivery method [22].

All patients underwent right femoral artery puncture under local anesthesia. After catheter placement, digital subtraction angiography (DSA) of the celiac trunk and common hepatic artery was performed in sequence to assess tumor vascularity, tumor blush, and portal venous flow status. The catheter was advanced superselectively into the tumor-feeding branches whenever technically feasible. In the cTACE group, epirubicin was the primary chemotherapeutic agent. No standardized fixed dose was prescribed; instead, the dosage was individualized according to the patient's hepatic function and tumor burden. The chemotherapeutic agent was thoroughly emulsified with lipiodol and infused into the target artery, followed by embolization with gelatin sponge or polyvinyl alcohol particles. In the DEB-TACE group, doxorubicin-loaded drug-eluting microspheres were mainly applied as both drug carrier and embolic agent. No standardized fixed dose was prescribed, and the dose was individualized according to tumor characteristics. The drug-loaded microspheres were slowly infused through the superselectively catheterized tumor-feeding artery until blood flow in the target vessel was nearly ceased. No additional particulate embolic materials were routinely used for DEB-TACE. In both groups, the procedural endpoint was defined as near-complete resolution of the abnormal tumor blush and near-complete interruption of blood flow in the tumor-feeding arteries [23].

All patients routinely received postoperative hepatoprotective therapy, acid-suppressing therapy, analgesics, fluid replacement, and symptomatic supportive care. Vital signs, liver function, complete blood counts, and renal function were closely monitored, and PES and other treatment-related adverse reactions were promptly managed. During follow-up, specialist physicians comprehensively assessed imaging findings, hepatic functional recovery, and tumor progression to determine whether repeat TACE or other subsequent treatments should be performed. Among the 138 patients in this cohort, 18 patients (13.04%) received repeated TACE during follow-up, with a median interval of 15.0 months [interquartile range (IQR): 11.5-15.0]. In addition, 22 patients (15.94%) received targeted therapy and/or immunotherapy, with a median interval from the initiation of TACE to treatment initiation of 15.5 months (IQR: 12.8-19.3).

Clinical outcome measures

Primary outcomes: (1) Overall survival (OS): defined as the interval from the first TACE procedure to death. Patients who remained alive at the cutoff date were censored at their most recent follow-up contact; (2) Progression-free survival (PFS): defined as the interval from the TACE procedure to the first occurrence of tumor progression or death, whichever occurred first. Patients who were alive without tumor progression were censored at the date of their last tumor assessment or follow-up, according to the prespecified study protocol.

Secondary outcomes: (1) Tumor response: the first post-TACE contrast-enhanced CT or MRI examination was performed 4-8 weeks after the procedure. Tumor response was assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines. The objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) or partial response (PR); the disease control rate (DCR) was defined as the percentage of patients achieving CR, PR or stable disease (SD). (2) Treatment-related adverse events: PES and severe complications were the primary recorded events. The main clinical manifestations of PES included non-infectious fever, abdominal pain, and vomiting.

Statistical analysis

The statistical analyses were conducted using SPSS 26.0. The normality was assessed using the Shapiro-Wilk test. Continuous variables that followed a normal distribution are presented as the mean ± standard deviation (SD), whereas normally distributed variables were presented as the median and IQR. Categorical variables are presented as counts and percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. Survival outcomes, including median OS, median PFS, and OS and PFS rates at 1, 2 and 3 years,

were estimated using the Kaplan-Meier method. Cox proportional hazards regression was used to identify baseline prognostic factors associated with OS and PFS. All candidate variables were initially assessed using univariable Cox regression, and variables with $P < 0.05$ in the univariable analysis were included into the multivariable models. Because maximum tumor diameter and tumor number both reflect tumor burden and may be correlated, only tumor number was included in the final multivariable model to reduce potential collinearity. To account for immortal time bias induced by subsequent repeated TACE and systemic targeted therapy and/or immunotherapy, these post-TACE treatments were incorporated into the multivariable Cox models as time-dependent covariates. For each time-dependent covariate, a value of 0 was assigned before treatment initiation, and a value of 1 from the time of treatment initiation onward. Patients who did not receive such treatment during follow-up were assigned a value of 0 throughout the entire follow-up period. The multivariable models were fitted using the enter method.

The Cox models were restricted to variables that were available and consistently recorded in this retrospective database (age, sex, etiology, AFP, Child-Pugh class, BCLC stage, portal hypertension, tumor number, and time-dependent subsequent treatments). Other potentially relevant confounders were not available in a standardized form and therefore could not be included in the models. These included detailed liver functional indices [albumin, bilirubin, international normalized ratio/prothrombin time (INR/PT)]; composite liver function scores, such as the albumin-bilirubin (ALBI) grade and Model for End-stage Liver Disease (MELD) score; quantitative TACE procedural parameters, including embolization degree, specific chemotherapeutic agents and doses, lipiodol dose, and completeness of embolization; baseline cirrhosis severity; and portal hypertension-related complications, such as esophagogastric varices. These factors should be regarded as potential sources of residual confounding when interpreting the findings.

The proportional hazards (PH) assumption was validated using Schoenfeld's residuals. A non-significant test result indicates that no obvious violation of the proportional hazards assumption was detected but does not rule out residual confounding or other sources of bias. Tumor response was evaluated based on contrast-enhanced CT or MRI performed 4-8 weeks after TACE, according to the mRECIST criteria [24]. Two-sided 95% confidence intervals (CIs) for ORR and DCR were calculated using the Clopper-Pearson exact method. TACE modality (cTACE vs DEB-TACE) was treated as a potential confounding variable rather than as a primary exposure of interest, as the study was neither designed nor powered to compare the two modalities. Accordingly, no between-modality comparisons of efficacy or safety were performed.

Treatment-related adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Grade 3-5 events were classified as severe adverse events. To quantify the robustness of the observed associations to unmeasured confounding, E-values were calculated for AFP ≥ 200 ng/mL, portal hypertension, and ≥ 4 tumor lesions using the corresponding hazard ratios and confidence limits, following the approach described by VanderWeele and Ding.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Basic clinical characteristics of patients

A total of 138 HCC patients who underwent their first TACE were included in the study. The median age was 59.00 years, and 89.13% of patients were male. HBV infection (68.12%) was the primary etiology. Child-Pugh class A accounted for 56.52% of patients, and 90.58% had BCLC stage B disease. Among the 13 patients with BCLC stage A disease, 7 had AFP ≥ 200 ng/mL, 4 had concomitant portal hypertension, and none had ≥ 4 tumor lesions. In comparison, among the 125 patients with BCLC stage B disease, the corresponding numbers were 93, 96, and 87, respectively. Overall, 72.46% of the patients had AFP ≥ 200 ng/mL, 72.46% presented with concomitant portal hypertension, and 63.04% had ≥ 4 tumor lesions. The maximum tumor diameter exceeded 5 cm in 42.03% of patients. At the initial TACE procedure, cTACE and DEB-TACE were performed in 50.72% and 49.28% of patients, respectively, indicating a balanced distribution

Table 1. Baseline characteristics of included patients

Variable		Total (n = 138)
Age (years), M (Q_1, Q_3)		59.00 (55.00, 64.00)
Sex, n (%)	Male	123 (89.13)
	Female	15 (10.87)
Etiology, n (%)	HBV	94 (68.12)
	HCV	10 (7.25)
	Alcoholic liver disease	12 (8.70)
	Others	22 (15.94)
Child-Pugh, n (%)	A	78 (56.52)
	B	60 (43.48)
AFP, n (%)	< 200 ng/mL	38 (27.54)
	≥ 200 ng/mL	100 (72.46)
BCLC, n (%)	A	13 (9.42)
	B	125 (90.58)
Portal hypertension, n (%)	Yes	100 (72.46)
	No	38 (27.54)
The number of tumors, n (%)	< 4	51 (36.96)
	≥ 4	87 (63.04)
Maximum tumor diameter (cm), n (%)	≤ 5	80 (57.97)
	> 5	58 (42.03)
The first TACE treatment method, n (%)	cTACE	70 (50.72)
	DEB-TACE	68 (49.28)

Notes: HBV, Hepatitis B virus; HCV, Hepatitis C virus; AFP, Alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, Transcatheter Arterial Chemoembolization; cTACE, Conventional TACE; DEB-TACE, Drug-Eluting Bead TACE.

Table 2. Tumor response

Variable	Total (n = 138)	95% CI (%)
CR, n (%)	5 (3.62)	
PR, n (%)	75 (54.35)	
SD, n (%)	39 (28.26)	
PD, n (%)	19 (13.77)	
ORR (CR+PR), n (%)	80 (57.97)	49.28-66.32
DCR (CR+PR+SD), n (%)	119 (86.23)	79.34-91.50

Notes: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; CI, confidence interval.

between the two treatment modalities. The baseline characteristics are summarized in **Table 1**.

Assessment of tumor response in HCC patients

Tumor response was assessed according to the mRECIST criteria 4-8 weeks after the first TACE. As shown in **Table 2**, CR was observed in 5 patients (3.62%), PR in 75 cases (54.35%), SD in 39 cases (28.26%), and PD in 19 cases (13.77%). The ORR was 57.97% (95% CI: 49.28%-66.32%), and the DCR was 86.23% (95% CI: 79.34%-91.50%).

Analysis of survival outcomes following TACE

Survival outcomes after TACE were analyzed using the Kaplan-Meier method, and the median follow-up duration was estimated using the reverse Kaplan-Meier approach. As shown in **Table 3**, the median OS was 20.0 months (95% CI: 16.5-23.5), the median PFS was 11.0 months (95% CI: 9.2-12.8), and the median follow-up duration was 38.0 months (95% CI: 36.7-41.3) in the overall cohort. The 1-, 2-, and 3-year OS rates were 71.7%, 40.0%, and 15.4%, respectively (**Figure 2**).

Analysis of factors associated with OS in HCC patients

Cox proportional hazards regression was performed to identify factors associated with OS in

Table 3. Survival outcomes of HCC patients after TACE

Survival indicators	Median time (95% CI)	1-year SR (%)	2-year SR (%)	3-year SR (%)
OS	20.0 (16.5-23.5)	71.7	40.0	15.4
PFS	11.0 (9.2-12.8)			
FU	38.0 (36.7-41.3)			

Notes: OS, overall survival; PFS, progression-free survival; FU, follow-up time; SR, survival rate; CI, confidence interval.

HCC patients treated with TACE (**Table 4**). In the overall cohort, AFP ≥ 200 ng/mL, BCLC stage B, portal hypertension, and ≥ 4 tumor lesions were significantly associated with poorer OS (all P < 0.05), whereas age (per one-year increment), sex, etiology, Child-Pugh class, maximum tumor diameter > 5 cm, and TACE treatment modality were not significantly associated with OS (all P > 0.05).

Variables with statistical significance in Univariable test were selected for inclusion in the multivariable Cox regression model. To adjust for time bias induced by subsequent repeated TACE and systemic targeted therapy/immunotherapy, these treatments were incorporated into the model as time-dependent covariates. After adjustment for these subsequent treatments, AFP ≥ 200 ng/mL, portal hypertension, and ≥ 4 tumor lesions remained significantly associated with poor OS (all P < 0.05), whereas BCLC stage B was no longer significantly association with OS (P > 0.05). As time-dependent covariates, neither repeated TACE nor systemic targeted therapy and/or immunotherapy (P > 0.05) was significantly associated with OS. Schoenfeld residual tests revealed no significant evidence of violations of the PH assumption for AFP levels (P = 0.323), ≥ 4 tumor lesions (P = 0.077), or portal hypertension (P = 0.089).

The E-values for the three factors retained in the OS model were 3.65 for AFP ≥ 200 ng/mL (CI-limit E-value 1.90), 3.10 for portal hypertension (1.56), and 2.70 for ≥ 4 tumor lesions (1.28). These estimates suggest that, under the assumptions of the E-value framework, an unmeasured confounder would need to be associated with both the exposure and OS by risk ratios of roughly 2.7-3.7 each, to fully explain away these associations, whereas moderate confounding (RR ≈ 1.3-1.9) could potentially shift the lower confidence limits to include the null. The detailed results are presented in **Table 5** and Supplementary Table 2.

Analysis of factors associated with PFS prognosis in HCC patients

Cox proportional hazards regression was performed to identify variables associated with PFS in HCC patients treated with TACE. **Table 6** presents the univariable Cox regression results for PFS. In the overall cohort, AFP ≥ 200 ng/mL, BCLC stage B disease, portal hypertension, ≥ 4 tumor lesions, and maximum tumor diameter > 5 cm were significantly associated with poorer PFS (all P < 0.05). In contrast, age (per one-year increment), sex, etiology, Child-Pugh class, and TACE treatment modality were not significantly associated with PFS (all P > 0.05).

Because tumor number and maximum tumor diameter both reflect tumor burden and may be correlated, only tumor number was retained in the multivariable model to reduce potential collinearity. To account for potential immortal time bias associated with subsequent repeated TACE and systemic targeted therapy/immunotherapy, these treatments were incorporated into the multivariable Cox regression model as time-dependent covariates. AFP ≥ 200 ng/mL, portal hypertension, and ≥ 4 tumor lesions (P < 0.05) remained significantly associated with poor PFS, whereas BCLC stage B showed no significant association with PFS (P > 0.05). As time-dependent covariates, neither repeated TACE nor systemic targeted therapy/immunotherapy (P > 0.05) showed a significant association with PFS. Schoenfeld residual tests revealed no obvious violation of the PH assumption for AFP (P = 0.678), ≥ 4 tumor lesions (P = 0.723), or portal hypertension (P = 0.376) in the model. The corresponding E-values were 2.97 for AFP ≥ 200 ng/mL (CI-limit E-value 1.57), 2.74 for portal hypertension (1.34), and 3.46 for ≥ 4 tumor lesions (1.74). The detailed results are presented in See **Table 7** and Supplementary Table 2.

Postoperative - TACE safety outcomes

Following the analysis of prognostic factors for survival outcomes, the safety profile of TACE was further evaluated, with attention focused on the incidence of PES and severe treatment-related complications. PES is the most common transient adverse reaction following TACE, primarily manifested as fever, abdominal pain, and vomiting [25]. In this study, 69.57% of patients developed PES, with concurrent fever and abdominal pain being the most common

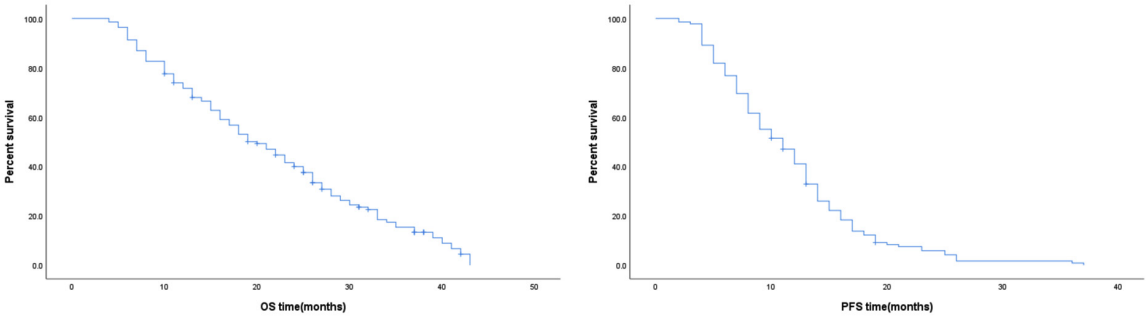


Figure 2. Kaplan-Meier survival curves for OS and PFS (n = 138). Notes: OS, overall survival; PFS, progression-free survival.

Table 4. Univariable Cox-regression of OS-related factors in HCC patients

Variable	Group	β	SE	Wald χ^2	HR	HR (95% CI)	*P* value
Age	Consecutive	0.008	0.013	0.330	1.008	0.982-1.034	0.565
Sex	Male				1.000		0.498
	Female	0.195	0.288	0.460	1.216	0.691-2.139	
Etiology	HBV				1.000		0.925
	HCV	0.038	0.353	0.012	1.039	0.520-2.076	
	Alcoholic liver disease	-0.198	0.337	0.345	0.820	0.424-1.589	
	Others	0.169	0.258	0.428	1.184	0.714-1.961	
AFP	< 200 ng/mL				1.000		< 0.001
	≥ 200 ng/mL	1.113	0.239	21.637	3.045	1.905-4.867	
Child-Pugh	A				1.000		0.110
	B	0.304	0.190	2.555	1.356	0.933-1.969	
BCLC	A				1.000		< 0.001
	B	1.053	0.393	7.185	2.866	1.327-6.188	
Portal hypertension	No				1.000		< 0.001
	Yes	1.068	0.244	19.150	2.911	1.804-4.697	
The number of tumors	< 4				1.000		< 0.001
	≥ 4	0.924	0.212	19.083	2.520	1.665-3.816	
Tumor size (cm)	≤ 5				1.000		0.074
	> 5	0.348	0.195	3.190	1.416	0.967-2.075	
The first TACE treatment method	cTACE				1.000		0.579
	DEB-TACE	0.104	0.188	0.309	1.110	0.768-1.604	

Notes: OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; cTACE, conventional TACE; DEB-TACE, drug-eluting bead TACE; SE, standard error.

presentation. Symptoms gradually resolved following routine symptomatic and supportive treatment, and the overall prognosis was favorable. A total of 21 patients (15.22%) experienced Grade 3-4 severe treatment-related adverse events. Among them, 18 patients (13.04%) experienced grade 3 events, including severe liver function injury in 11 cases, liver abscess in 5 cases, and severe renal function injury in 2 cases; Three patients (2.17%) developed grade 4 events, including ectopic embolization in 3 cases. Most events occurred within 1 week after TACE. Management included antimicrobial therapy, hepatoprotective and nephroprotective measures, symptomatic and supportive care, as well as necessary interventional and surgical interventions. Most affected patients improved following active treatment, although a small number of patients with severe hepatic and renal dysfunction required prolonged symptomatic treatment. Overall, 117 patients (84.78) experienced no grade 3-4 treatment-related adverse events. Details are shown in **Table 8**.

Table 5. Multivariable Cox regression of OS-related factors in HCC patients

Variable	Group	β	SE	Wald χ^2	HR	HR (95% CI)	*P* value
AFP	< 200 ng/mL				1.000		0.004
	≥ 200 ng/mL	0.748	0.258	8.398	2.113	1.274-3.505	
BCLC	A				1.000		0.547
	B	0.262	0.436	0.362	1.300	0.554-3.053	
Portal hypertension	No				1.000		0.018
	Yes	0.617	0.261	5.589	1.853	1.111-3.091	
The number of tumors	< 4				1.000		0.032
	≥ 4	0.507	0.236	4.609	1.660	1.045-2.637	
Repeat TACE (time-varying)		-0.446	0.292	2.336	0.640	0.360-1.134	0.126
Systemic targeted/immunotherapy (time-varying)		-0.323	0.304	1.130	0.724	0.399-1.314	0.288

Notes: OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; SE, standard error.

Table 6. Univariable Cox-regression of PFS-related factors in HCC patients

Variable	Group	β	SE	Wald χ^2	HR	HR (95% CI)	*P* value
Age	Consecutive	0.006	0.013	0.235	1.006	0.981-1.032	0.628
Sex	Male				1.000		0.116
	Female	0.434	0.276	2.475	1.544	0.899-2.652	
Etiology	HBV				1.000		0.947
	HCV	0.090	0.335	0.071	1.094	0.567-2.109	
	Alcoholic liver disease	-0.130	0.321	0.164	0.878	0.468-1.648	
	Others	0.074	0.249	0.088	1.076	0.661-1.752	
AFP	< 200 ng/mL				1.000		< 0.001
	≥ 200 ng/mL	0.780	0.213	13.409	2.182	1.437-3.313	
Child-Pugh	A				1.000		0.602
	B	0.091	0.175	0.272	1.096	0.778-1.543	
BCLC	A				1.000		0.002
	B	1.032	0.336	9.418	2.808	1.452-5.429	
Portal hypertension	No				1.000		< 0.001
	Yes	0.860	0.208	17.092	2.363	1.572-3.551	
The number of tumors	< 4				1.000		< 0.001
	≥ 4	0.992	0.200	24.690	2.695	1.823-3.985	
Tumor size (cm)	≤ 5				1.000		0.041
	> 5	0.364	0.178	4.194	1.440	1.016-2.041	
The first TACE treatment method	cTACE				1.000		0.222
	DEB-TACE	0.213	0.174	1.493	1.237	0.879-1.741	

Notes: PFS, progression-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; cTACE, conventional TACE; DEB-TACE, drug-eluting bead TACE; SE, standard error.

Discussion

TACE is an important locoregional therapy for patients with unresectable HCC [26]. It controls tumor progression by embolizing tumor-feeding arteries, thereby inducing tumor ischemia and necrosis. However, survival outcomes vary greatly among patients, and treatment-related adverse events may also affect treatment tolerance and overall clinical benefit [27]. Although TACE can achieve local tumor control, patients with intermediate- and advanced-stage HCC generally have a substantial tumor burden, underlying liver fibrosis, and potential micro-metastatic disease [28]. Consequently, TACE is insufficient to eradicate all tumor lesions, and tumor recurrence and disease progression remain major causes of mortality in these patients [29]. The 3-year OS rate remains low, particularly among patients at high risk of disease

Table 7. Multivariable Cox regression of PFS-related factors in HCC patients

Variable	Group	β	SE	Wald χ^2	HR	HR (95% CI)	*P* value
AFP	< 200 ng/mL				1.000		0.011
	≥ 200 ng/mL	0.582	0.229	6.464	1.789	1.143-2.804	
BCLC	A				1.000		0.238
	B	0.438	0.371	1.391	1.549	0.749-3.206	
Portal hypertension	No				1.000		0.024
	Yes	0.517	0.229	5.117	1.677	1.071-2.625	
The number of tumors	< 4				1.000		0.001
	≥ 4	0.708	0.220	10.392	2.030	1.320-3.122	
Repeat TACE (time-varying)		0.043	0.262	0.027	1.044	0.624-1.746	0.870
Systemic targeted/immunotherapy (time-varying)		0.233	0.263	0.784	1.262	0.754-2.115	0.376

Notes: PFS, progression-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; SE, standard error.

Table 8. Incidence of post-embolization syndrome and grade 3-4 treatment-related adverse events after TACE

Variable	Total (n = 138)
PES, n (%)	96 (69.57)
Fever	18 (13.04)
Abdominal pain	12 (8.70)
Emesis	9 (6.52)
Fever+Abdominal pain	28 (20.29)
Abdominal pain+Emesis	21 (15.22)
Fever+Abdominal pain+Emesis	8 (5.80)
Severe complication, n (%)	
Yes	21 (15.22)
No	117 (84.78)

Notes: TACE, transarterial chemoembolization; PES, post-embolization syndrome.

progression, highlighting the limitation of TACE alone in this population. In clinical practice, tumor burden and liver functional reserve should be carefully assessed, and systemic therapies, including targeted therapy and immunotherapy, may be considered to further improve long-term survival [30].

This study retrospectively analyzed 138 HCC patients with BCLC stage A-B who underwent TACE. We characterized OS, PFS, tumor response, and treatment-related adverse events, and explored the associations between pre-TACE baseline characteristics and survival outcomes. Importantly, this study was not designed to develop or externally validate a prognostic scoring model for patients undergoing TACE. Furthermore, some patients received repeated TACE or targeted therapy and/or immunotherapy after the initial procedure. Accordingly, the long-term outcomes in the overall cohort reflect real-world treatment pathways and should not be interpreted as the net therapeutic effect of TACE. The median OS of the overall cohort was 20.0 months (95% CI: 16.5-23.5), with 1-, 2-, and 3-year OS rates of 71.7%, 40.0%, and 15.4%, respectively. The median PFS was 11.0 months (95% CI: 9.2-12.8). These findings characterize the real-world outcomes of the study cohort. Because 90.58% of patients had BCLC stage B disease, the overall survival estimates and prognostic associations should be interpreted primarily in the context of BCLC stage B HCC. The relatively small number of patients with BCLC stage A disease precludes robust stage-specific conclusions for this subgroup.

In the prognostic factor analysis, univariable Cox regression identified AFP, BCLC stage, portal hypertension, and tumor number as factor significantly associated with OS. AFP level, BCLC stage, portal hypertension, tumor number, and maximum tumor diameter were significantly associated with PFS. Since both maximum tumor diameter and tumor number reflect tumor burden and may be correlated, only tumor number was retained in the multivariable regression analysis for PFS to reduce potential collinearity. This choice was also consistent with the OS analysis, in which maximum tumor diameter was not significantly associated with OS in the univariable analysis. The multivariable analyses subsequently identified AFP levels ≥ 200 ng/mL, portal hypertension, and ≥ 4 tumor lesions as factors associated with poorer OS and PFS after accounting for subsequent repeat TACE and systemic targeted therapy

and/or immunotherapy as time-dependent covariates.

In the multivariable regression analysis, AFP level ≥ 200 ng/mL, portal hypertension, and the ≥ 4 tumor lesions were independently associated with poorer OS following TACE. AFP is a well-known serum tumor marker for HCC, and elevated AFP level may reflect more aggressive tumor proliferation and higher potential for invasion and metastasis. Such patients are more likely to experience residual disease or tumor recurrence after TACE [31], potentially contributing to an increased risk of mortality. Portal hypertension reflects underlying portal hemodynamic abnormalities and is often associated with advanced hepatic fibrosis or cirrhosis, which not only reduces patients' tolerance to repeated TACE but also increases the risk of complication, including upper gastrointestinal bleeding and hepatic decompensation [32, 33]. Similarly, the presence of ≥ 4 tumor lesions indicates a higher tumor burden and may be associated with a higher likelihood of occult micrometastases, limited disease control with locoregional therapy, and an increased risk of intrahepatic recurrence and progression. In this cohort, sex and HCC etiology were not independently associated with OS. These findings suggest that tumor burden and hepatic functional status may be more informative prognostic factors than the underlying etiology of liver disease in this population. These findings further illustrate that, for HCC patients scheduled to undergo TACE, a comprehensive assessment combining serological markers, liver function, and tumor burden may help identify high-risk subgroups. However, this study was designed as an exploratory association analysis and did not construct or validate a comprehensive prognostic score or nomogram.

To assess the robustness of the observed associations to potential unmeasured confounding, E-values were calculated. The point-estimate E-values ranged from 2.70 to 3.65, indicating that an unmeasured confounder would need to be associated with both the exposure and the outcome by a risk ratio of roughly 2.7-3.7 to fully explain away the observed associations. However, the E-values for the lower confidence limits ranged from 1.28 to 1.90, indicating that more moderate unmeasured confounding could shift the confidence intervals to include the null. Given that detailed liver functional indices, quantitative TACE procedural parameters, cirrhosis severity, and esophagogastric varices were not uniformly available in this retrospective database, confounding of this magnitude cannot be excluded. Therefore, the E-value analyses reinforce, rather than replace, the interpretation of these findings as exploratory prognostic associations.

It should also be noted that cTACE and DEB-TACE were used in approximately equal proportions in this cohort; however, the present study was not designed or powered to compare the efficacy or safety of these two modalities. Baseline characteristics of the two groups are summarized in Supplementary Table 1, with standardized mean differences reported for descriptive purposes only. No formal hypothesis testing between modalities was performed. Furthermore, no subgroup survival analysis or interaction tests by treatment modality were performed. Given the limited statistical power for such comparisons, treatment modality was treated only as a potential confounder rather than as a comparative exposure. Therefore, no conclusion regarding the comparative efficacy of cTACE versus DEB-TACE can be drawn from this dataset.

The safety evaluation results showed that among the 138 patients, PES occurred in 96 cases (69.57%), including fever alone in 18 cases (13.04%), abdominal pain alone in 12 cases (8.70%), and vomiting alone in 9 cases (6.52%); concurrent occurrence of multiple symptoms also accounted for a certain proportion. Grade 3-4 treatment-related adverse events occurred in 21 cases (15.22%), whereas 117 cases (84.78%) experienced no grade 3-4 adverse events. PES is a relatively common treatment-related inflammatory reaction after TACE, potentially mediated by inflammatory factors released during tumor ischemia and necrosis, and is primarily characterized by fever, abdominal pain, nausea, and vomiting [34]. These symptoms can generally be managed by symptomatic treatment, including antipyretics, analgesics, antiemetics, and fluid replacement, and are not necessarily classified as severe adverse events. In clinical practice, patients with impaired liver function and portal hypertension warrant particular attention because of their potential vulnerability to treatment-related com-

plications. Careful pretreatment risk assessment, close monitoring of liver function and vital signs after TACE, and prompt recognition and management of severe complications are therefore essential.

Limitations

Several limitations should be acknowledged. First, this was a single-center retrospective study, which is susceptible to potential selection and information bias. The cohort was predominantly composed of patients with BCLC stage A-B HCC who underwent initial TACE, with BCLC stage A patients accounted for only 9.42%. This imbalance limits the generalizability of the findings to patients with early-stage HCC and raises concerns about the representativeness of treatment protocols, etiological spectra, and follow-up practices observed at this center. The findings also cannot be extrapolated to patients receiving repeated TACE, those with severe ascites, or Child-Pugh C.

Second, residual confounding and incomplete variable availability remain important concerns. Some patients received targeted therapy and/or immunotherapy after TACE, and these treatments were modeled as time-dependent covariates. However, subsequent treatment are generally influenced by tumor response, liver function, and tumor burden. Therefore, confounding by indication may persist despite adjustment using time-dependent Cox regression, and unmeasured confounding cannot be fully excluded. Several clinically relevant variables were not uniformly recorded, including granular liver functional indices and scores (albumin, bilirubin, INR/PT, ALBI, MELD), quantitative TACE procedural parameters (embolization degree, chemotherapy dose, agent type, lipiodol dose, completeness of embolization), baseline cirrhosis severity, portal hypertension-related complications such as esophagogastric varices, systemic inflammatory and immune indicators, detailed portal vein tumor thrombus stratification, and post-TACE dynamic liver function changes. Because these factors could not be incorporated into the multivariable models, residual confounding may have affected the estimated hazard ratios. Accordingly, the observed associations should be regarded as exploratory associations rather than validated independent effects.

Third, the robustness of the analyses remains incompletely established. E-values were calculated for the three key associations. The point-estimate E-values ranged from 2.70 to 3.65, whereas CI-limit E-values ranged from 1.28 to 1.90, indicating that although the point estimates would require strong unmeasured confounding to be explained away, moderate confounding could shift the lower confidence bounds toward the null. A sensitivity analysis excluding BCLC stage A patients was not performed, because of the small number of BCLC stage A patients (n = 13; none of them had ≥ 4 tumor lesions) and substantial difference from BCLC stage B patients in the distribution of AFP ≥ 200 ng/mL (53.8% vs 74.4%) and portal hypertension (30.8% vs 76.8%). Excluding these patients would therefore change both the exposure distribution and the overall event rate, making it difficult to distinguish the effects of cohort composition from those associated with disease stage. In addition, the small subgroup size would limit the precision of stage-specific or stage-restricted estimates. Other sensitivity analyses, including alternative variable-selection methods (e.g., LASSO, bootstrap, or forced entry of all candidates), alternative tumor-burden cutoffs, and multiple imputation for missing data (complete-case analysis was used), were not performed because the candidate variable pool was deliberately limited to uniformly collected variables and because the non-recorded confounders were unavailable rather than missing at random. The Cox modeling was also exploratory: candidate variables were selected based on univariable results, and only tumor number was retained to avoid collinearity with maximum tumor diameter, which may introduce model selection bias. Therefore, the reported hazard ratios should be interpreted as associative findings only and should not be used directly as externally validated coefficients for individualized risk prediction.

Finally, established TACE-related prognostic tools such as HAP, ART, and STATE could not be reconstructed or compared, because several constituent variables were not uniformly available. Consequently, comparisons of discrimination, calibration, or net clinical benefit could not be performed, and no conclusion can be drawn regarding the relative performance of the identified factors versus these established scoring

systems. Coupled with the absence of an external validation cohort, these limitations preclude broad generalization of the findings to patients with BCLC stage A disease, centers with different TACE protocols or etiological profiles, or patients receiving treatment pathways that differ from those observed in this cohort, including repeated TACE or combined systemic therapy. Independent, multicenter cohorts with comprehensive and standardized data collection are needed to validate these exploratory associations and to determine whether they can contribute to the development or validation of a clinically useful prognostic score, with direct benchmarking against HAP, ART, and STATE.

Conclusion

In this single-center retrospective cohort of patients with BCLC stage A-B HCC who underwent initial TACE, the median OS was 20.0 months and the median PFS was 11.0 months, with an ORR of 57.97% and a DCR of 86.23%. Elevated AFP (≥ 200 ng/mL), concomitant portal hypertension, and ≥ 4 tumor lesions were independently associated with poorer OS and PFS. Post-embolization syndrome was common, whereas grade 3-4 treatment-related adverse events occurred in a subset of patients and were manageable, and no treatment-related death occurred. These findings suggest that pre-TACE AFP levels, portal hypertension status, and tumor burden may help identify patients at increased risk of adverse outcomes and could inform preoperative risk stratification and follow-up planning. However, given the single-center retrospective design, the potential for residual confounding, and the exploratory nature of the Cox models, these associations should be regarded as hypothesis-generating rather than as validated predictors. Independent multicenter studies with comprehensive and standardized data collection are warranted to validate these findings before being applied to individualized risk prediction or clinical decision-making.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline characteristics of patients receiving cTACE versus DEB-TACE as initial TACE

Variable		Total (n = 138)	cTACE (n = 70)	DEB-TACE (n = 68)	P	SMD
Age (years), M (Q_1, Q_3)		59.00 (55.00, 64.00)	59.50 (57.00, 64.00)	59.00 (55.00, 64.00)	0.384	0.106
Sex, n (%)	Male	123 (89.13)	65 (92.86)	58 (85.29)	0.154	0.244
	Female	15 (10.87)	5 (7.14)	10 (14.71)		
Etiology, n (%)	HBV	94 (68.12)	47 (67.14)	47 (69.12)	0.832	0.094
	HCV	10 (7.25)	5 (7.14)	5 (7.35)		
	Alcoholic liver disease	12 (8.70)	7 (10.00)	5 (7.35)		
	Others	22 (15.94)	11 (15.71)	11 (16.18)		
Child-Pugh, n (%)	A	78 (56.52)	40 (57.14)	38 (55.88)	0.881	0.025
	B	60 (43.48)	30 (42.86)	30 (44.12)		
AFP, n (%)	< 200 ng/mL	38 (27.54)	20 (28.57)	18 (26.47)	0.782	0.047
	≥ 200 ng/mL	100 (72.46)	50 (71.43)	50 (73.53)		
BCLC, n (%)	A	13 (9.42)	8 (11.43)	5 (7.35)	0.413	0.140
	B	125 (90.58)	62 (88.57)	63 (92.65)		
Portal hypertension, n (%)	Yes	100 (72.46)	53 (75.71)	47 (69.12)	0.386	0.148
	No	38 (27.54)	17 (24.29)	21 (30.88)		
The number of tumors, n (%)	< 4	51 (36.96)	25 (35.71)	26 (38.24)	0.759	0.052
	≥ 4	87 (63.04)	45 (64.29)	42 (61.76)		
Maximum tumor diameter (cm), n (%)	≤ 5	80 (57.97)	49 (70.00)	31 (45.59)	0.004	0.510
	> 5	58 (42.03)	21 (30.00)	37 (54.41)		

Notes: HBV, Hepatitis B virus; HCV, Hepatitis C virus; AFP, Alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, Transcatheter Arterial Chemoembolization; cTACE, Conventional TACE; DEB-TACE, Drug-Eluting Bead TACE.

Supplementary Table 2. E-values for the key prognostic associations with OS and PFS

Association	Outcome	HR (95% CI)	E-value (estimate)	E-value (CI limit)
AFP ≥ 200 ng/mL	OS	2.113 (1.274-3.505)	3.65	1.90
Portal hypertension	OS	1.853 (1.111-3.091)	3.10	1.56
≥ 4 tumor lesions	OS	1.660 (1.045-2.637)	2.70	1.28
AFP ≥ 200 ng/mL	PFS	1.789 (1.143-2.804)	2.97	1.57
Portal hypertension	PFS	1.677 (1.071-2.625)	2.74	1.34
≥ 4 tumor lesions	PFS	2.030 (1.320-3.122)	3.46	1.74

Notes: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein.