Prognostic effect and prognostic factors of TACE for the treatment of unresectable hepatocellular carcinoma: Propensity score matching analysis

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Received December 27, 2025; Accepted March 17, 2026

DOI: 10.3892/ol.2026.15603

Abstract. Hepatocellular carcinoma (HCC) remains a global challenge due to its high morbidity and mortality as well as its adverse response to treatment. Transcatheter arterial chemoembolization (TACE) is widely used in the treatment of unresectable (u)HCC. However, no consensus has been reached regarding the optimal number of TACE sessions for uHCC. The present study aimed to evaluate the prognostic value of TACE treatment frequency in patients with uHCC and identify factors affecting prognosis. Data were collected from patients with HCC treated with TACE in Hebei General Hospital (Shijiazhuang, China) between January 2017 and December 2023. Patients were divided into three groups based on number of TACE treatments: TACE 1 (one time), 2 (two times) and 3 (≥3 times). The outcomes assessed included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety profiles. The propensity score matching was used to decrease the influence of confounding factors on the outcomes. The best ORR in the TACE 1, 2 and 3 groups was 29.6, 77.8 and 44.4%, respectively (P=0.001); the best DCR was 66.7, 88.9 and 96.3% (P=0.016); median PFS was 5, 14 and 22 months (P=0.0034) and median OS was 8, 21 and 26 months (P=0.0028). No significant differences were observed between groups regarding grade 1/2 adverse events. Hypertension, number of TACE sessions, adverse reactions, targeted therapy/immunotherapy and Barcelona Clinic Liver Cancer (BCLC) stage were independent prognostic factors for PFS; similarly, carbohydrate antigen 199 levels, number of TACE sessions, adverse reactions and BCLC stage were independent prognostic factors for OS. Compared with a single TACE session, two or three TACE sessions were associated with significantly prolonged PFS and OS times; however, no further improvement was observed beyond three sessions. Within the range of one to three TACE sessions, an increased number of TACE sessions was associated with prolonged PFS and OS times, improved prognosis and a favorable safety profile.

Introduction

Liver cancer represents a notable global health burden, characterized by high morbidity and mortality rates. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for ~90% of all cases (1,2). Globally, HCC ranks as the sixth most common malignancy and the third leading cause of cancer-related death, with an estimated 830,200 deaths annually (3-5). The notable causes of liver cancer include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, non-alcoholic fatty liver disease, aflatoxin, alcoholism, obesity and hereditary factors (6). It is estimated that by 2030, >1,000,000 people will die annually from primary liver cancer worldwide (7).

Despite advances in surveillance programs for HCC, ~80% of patients are diagnosed at intermediate or advanced stages (8,9). Among the various treatment options for liver cancer, transcatheter arterial chemoembolization (TACE) has emerged as a primary modality for patients with unresectable (u)HCC, owing to its distinct therapeutic advantages, including the ability to deliver high concentrations of chemotherapeutic agents directly into the tumor via the hepatic artery while simultaneously inducing ischemic necrosis through embolization. This approach maximizes local antitumor efficacy while minimizing systemic toxicity, and can be repeated as needed based on tumor response. It is also one of the most frequently employed locoregional therapies for liver cancer (10,11).

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Key words: hepatocellular carcinoma, transcatheter arterial chemoembolization, propensity score matching, prognosis

The clinical efficacy of TACE has been demonstrated in multiple aspects; compared with traditional surgical resection, TACE is effective and associated with less physical trauma. According to a meta-analysis by Lencioni *et al* (12), the 1-, 3- and 5-year overall survival (OS) rates are 70.3, 40.4 and 32.4%, respectively, with a median survival time of 19.4 months. A meta-analysis encompassing 4,966 patients with HCC reported that those treated with TACE achieve improved survival outcomes, with a median OS time of 3.3 years and a 5-year OS rate of 34% (13).

The efficacy of TACE is influenced by multiple factors, including tumor vascularity, tumor size and number and liver function reserve (13). TACE is generally more effective in hypervascular tumors, whereas its therapeutic effect is relatively limited in hypovascular tumors (14). Moreover, current evidence indicates that TACE has inherent limitations (15). Factors such as tumor progression, unfavorable tumor location or size and incomplete embolization contribute to a low rate of complete necrosis and a high rate of local recurrence; studies (14,16) have reported a complete necrosis rate <20% following TACE. Furthermore, whether repeated TACE sessions consistently confer clinical benefit remains controversial (17). The present study aimed to evaluate the clinical efficacy of TACE frequencies in patients with uHCC and to identify factors influencing prognosis.

Materials and methods

Study design and patient selection. The present retrospective study was conducted in compliance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Hebei General Hospital (Shijiazhuang, China) (approval no. 2024-LW-0204). Medical records of 159 patients diagnosed with uHCC who were admitted to Hebei General Hospital between January 2017 and December 2023 were retrospectively reviewed. The patients had a median age of 62 years (range, 35-81 years) and included 125 males (78.6%) and 34 females (21.4%). Laboratory data obtained ≤3 days before the first TACE session were collected. Inclusion criteria were as follows: i) Histologically, cytologically or clinically confirmed HCC based on American Association for the Study of Liver Diseases criteria (18); ii) Child-Pugh class A or B (19); iii) Barcelona Clinic Liver Cancer (BCLC) stage B or C (20), or stage A with contraindications to surgery (severe cardiopulmonary insufficiency); iv) no prior TACE or systemic antitumor therapy for HCC; v) eligibility for TACE according to established indications (15); and vi) availability of complete follow-up data. Exclusion criteria were as follows: i) History or presence of other malignancies; ii) prior local or systemic therapy for HCC; iii) Child-Pugh class C; iv) pregnancy; v) coagulation disorders; and vi) missing or incomplete follow-up data. Liver function was assessed using the Child-Pugh classification, which allocates 1 to 3 points for each of five parameters (total bilirubin, serum albumin, prothrombin time, ascites and hepatic encephalopathy), with a total score ranging from 5 to 15 points. Scores were categorized as follows: Class A, 5-6 points; class B, 7-9 points; and class C, ≥10 points. Tumor staging was performed according to the BCLC system. Patient demographics, medical history, preoperative laboratory tests (including blood count, liver function and tumor markers), imaging findings and other relevant data, including body mass index, Child-Pugh class, HBV infection status, HCV infection status, hypertension, diabetes, α-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9, albumin, alanine aminotransferase and aspartate aminotransferase levels, white blood cell count, neutrophil-to-lymphocyte ratio, platelet count, cirrhosis, tumor number, portal vein tumor thrombus, extrahepatic metastasis, maximal tumor size and BCLC stage, were retrieved from the electronic medical record system.

Treatment. All patients were hospitalized to complete preoperative evaluations, which included comprehensive laboratory tests (blood count, liver and renal function, coagulation profile and tumor markers), contrast-enhanced imaging (CT or MRI) to assess tumor burden and vascular anatomy, and evaluation of liver function reserve using the Child-Pugh classification. Patients were then informed of the available treatment options, underwent TACE according to their wishes and tumor characteristics, and provided written informed consent. TACE was performed by an experienced interventional radiologist following clinical practice guidelines (15). Following routine disinfection, draping and local anesthesia, the femoral artery was punctured and the location, number and size of tumors were confirmed by hepatic arteriography. Based on the angiographic findings, the catheter was advanced into the tumor-feeding artery. Embolic agents (lipiodol, gelatin sponge, drug-eluting microspheres) were injected to occlude the tumor blood supply, followed by infusion of chemotherapeutic drugs (fluorouracil, cisplatin, epirubicin) to induce tumor cell death. The dosage was tailored based on tumor vascularity, patient body surface area, general condition, liver function and tolerance to the procedure. Following embolization, intraoperative digital subtraction angiography was performed to evaluate tumor devascularization. The procedure was considered successful when repeat imaging of the common hepatic artery confirmed near-complete absence of tumor staining. Following completion of the infusion, the catheter was removed and manual compression was applied at the puncture site for 15 min to achieve hemostasis. The patient was transferred to the Department of Hepatobiliary Surgery in stable condition, without any intraoperative complications. Postprocedural supportive care included hepatoprotective agents, gastric mucosal protection, antiemetics, analgesics and nutritional support; prophylactic antibiotics were administered as needed to prevent infection. Follow-up imaging was repeated 4-6 weeks after TACE using contrast-enhanced CT (Siemens SOMATOM Definition Flash; Siemens Healthineers) or contrast-enhanced MRI (Siemens MAGNETOM Skyra 3.0T; Siemens Healthineers). CT scanning parameters were as follows: Tube voltage, 120 kV; tube current, 200-250 mAsec; slice thickness, 5 mm; and intravenous injection of 80-100 ml of iodinated contrast agent (Omnipaque, 350 mg I/ml) at a rate of 3 ml/sec, with arterial, portal venous and delayed phase imaging. MRI parameters included axial T1-weighted, T2-weighted and diffusion-weighted sequences, with intravenous administration of 0.1 mmol/kg of gadolinium-based contrast agent (Gd-DTPA) for dynamic contrast-enhanced imaging. The necessity for additional TACE sessions was assessed based on imaging findings and tumor marker levels.

Patients were informed about the recommended and alternative treatment options, including the benefits and risks of each approach, potential treatment-related adverse effects (AEs) and tumor-related risk factors. To account for procedural heterogeneity, the specific embolic agents and chemotherapeutic regimens used in each TACE session were documented. The decision to repeat TACE was made by a multidisciplinary team according to standardized clinical criteria as follows: i) Presence of residual viable tumor or new intrahepatic lesions on follow-up contrast-enhanced CT/MRI performed 4-6 weeks after the previous TACE; ii) preserved liver function (Child-Pugh class A or B); iii) acceptable tolerance to prior TACE sessions (absence of grade ≥3 AEs); iv) absence of contraindications, including notable tumor progression with new extrahepatic metastases, main portal vein invasion or deterioration of performance status to Eastern Cooperative Oncology Group (ECOG) ≥3 (21); and v) patient preference following discussion of risks and benefits. TACE was not repeated in cases of disease progression with new extrahepatic metastases, notable deterioration of liver function (Child-Pugh class C) or patient refusal. Repeat TACE was performed at intervals of 4-8 weeks, as determined by the multidisciplinary team to allow sufficient time for tumor response assessment (typically 4-6 weeks post-TACE) and for patient recovery from any post-embolization syndrome (PES).

Follow-up and assessment. Enrolled patients were followed up regularly through review of clinical records or by telephone contact. Survival status was documented. The final follow-up date was October 2024. Contrast-enhanced CT/MRI and laboratory tests were performed 4-6 weeks after the first TACE session to assess treatment response. Thereafter, imaging and laboratory assessments were repeated every 3 months on an outpatient basis. Follow-up results were reviewed by the multidisciplinary team to determine tumor status (progression or non-progression). Overall survival (OS) was defined as the time from first TACE to death from any cause or the last follow-up (October 2024). PFS was defined as the interval from first TACE to the first documented disease progression [according to Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria] (22) or death from any cause, whichever occurred first. Patients without progression or death at the last follow-up were censored. For patients who underwent TACE for recurrent HCC following hepatectomy, the starting point was similarly the date of the first TACE session for the recurrence. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 5.0 (23). OS was the primary endpoint of the present study, while PFS and the incidence of AEs were secondary endpoints. Tumor response was assessed by two diagnostic radiologists, each with >10 years of experience, according to mRECIST (22). Efficacy was evaluated using mRECIST criteria as follows: i) Complete response (CR), disappearance of intratumoral arterial enhancement in all target lesions; ii) partial response (PR), ≥30% decrease in the sum of diameters of viable (enhancing) target lesions; iii) progressive disease (PD), increase of ≥20% in the sum of diameters of viable target lesions, or appearance of new lesions; iv) stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Best objective response rate (ORR) was defined as the proportion of patients achieving either CR or PR at any time during follow-up, according to mRECIST criteria. A total of two tumor response measures were reported: Response at the first assessment (4-6 weeks after the initial TACE), which enables unbiased comparison with uniform follow-up duration across groups, and cumulative best response over the entire follow-up period, reflecting the maximum response achieved at any time.

Statistical analysis. Statistical analyses were conducted using Microsoft Excel (version 2019; Microsoft Corp.), SPSS (version 26.0; IBM Corp.) and R software (version 4.3.3; R Foundation for Statistical Computing; https://www.R-project.org/). The propensity score model included the following baseline covariates measured before the first TACE session: Sex (male/female), age (<60 vs. ≥60 years), body mass index (BMI; <24 vs. ≥24 kg/m^2), Child-Pugh class (A vs. B), HBV infection (yes/no), HCV infection (yes/no), hypertension (yes/no), diabetes (yes/no), α-fetoprotein (AFP; <400 vs. ≥400 ng/ml), carcinoembryonic antigen (CEA; <5 vs. ≥5 ng/ml), carbohydrate antigen 19-9 (CA199; <37 vs. ≥37 U/ml), albumin (<35 vs. ≥35 g/l), alanine aminotransferase (ALT; <40 vs. ≥40 U/l), aspartate aminotransferase (AST; <40 vs. ≥40 U/l), white blood cell (WBC) count (<10 vs. ≥10x10^9/l), neutrophil-to-lymphocyte ratio (NLR; continuous), platelet (PLT) count (<100 vs. ≥100x10^9/l), cirrhosis (yes/no), tumor number (single vs. multiple), portal vein tumor thrombus (yes/no), extrahepatic metastasis (yes/no), maximal tumor size (<5 vs. ≥5 cm) and BCLC stage (A/B vs. C). The number of TACE sessions was excluded from the propensity score model, as it represented the treatment assignment. Matching was performed using a 1:1 nearest neighbor matching algorithm with a caliper width of 0.1 using the 'MatchIt' package [version 4.5.0) (24) in R software (https://cran.r-project.org/web/packages/MatchIt/]. For the three-group comparison, a sequential pairwise matching approach was employed. First, propensity scores were estimated using logistic regression based on the aforementioned baseline covariates. Second, patients in the TACE 2 group were matched 1:1 to those in the TACE 1 group using nearest neighbor matching with a caliper of 0.1. From the remaining unmatched patients, those in the TACE ≥3 group were matched 1:1 to patients in the TACE 1 group using the same caliper. Standardized mean differences (SMDs) were calculated to evaluate post-matching balance; all covariates exhibited SMD <0.1, indicating successful matching. Quantitative data are presented as frequencies, mean ± standard deviation or medians with 95% confidence intervals (CIs) before and after propensity score matching (PSM). Differences between groups were assessed using the χ^2 or Fisher's exact test, as appropriate. Survival curves for PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Uni- and multivariate analyses were conducted using Cox proportional hazards models to identify prognostic factors. All variables with P<0.05 in the univariate analysis were included in a multivariate Cox proportional hazards model to identify independent predictors. All statistical tests were two-tailed, and P<0.05 was considered to indicate a statistically significant difference. The proportional hazards assumption was assessed using Schoenfeld residuals. Receiver operating characteristic (ROC) curve analysis was performed to determine

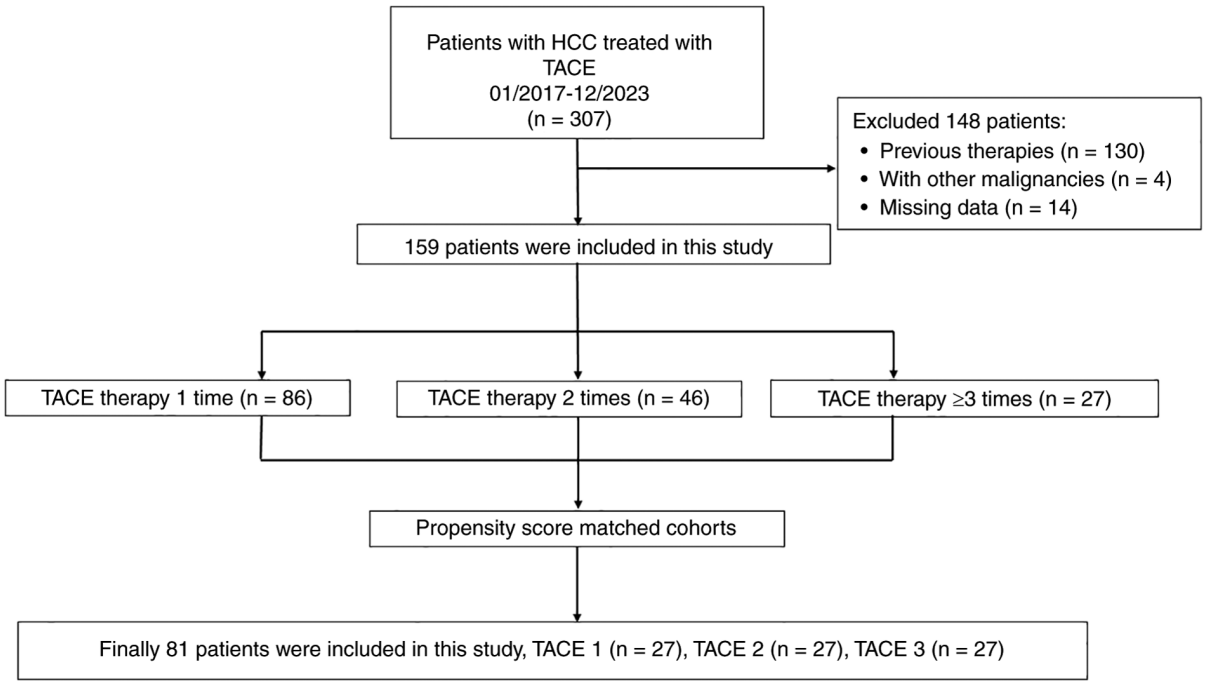

Figure 1. Patient selection process. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

the optimal cutoff value for the NLR. The optimal cutoff was defined as the value maximizing the Youden index (sensitivity + specificity - 1). Data on systemic therapy (targeted therapy and/or immunotherapy) were collected, including the timing of initiation relative to TACE sessions. Patients were categorized according to the timing of systemic therapy initiation (between TACE sessions) or after the completion of all TACE sessions. Patients who received systemic therapy prior to any TACE were excluded according to the inclusion criteria. In the Cox regression models, systemic therapy was included as a binary covariate (ever vs. never received). Sensitivity analyses were performed excluding patients who received systemic therapy between TACE sessions to assess potential confounding. To mitigate the risk of overfitting given the sample size of 81 patients following matching, a conservative modeling strategy was employed. Only variables with $P<0.10$ in the univariate analysis were considered for inclusion in the multivariate models. The final multivariate models included seven variables for PFS and six variables for OS.

Results

Patient characteristics. A total of 307 patients who underwent TACE for primary HCC during the study period were initially screened (Fig. 1). Based on the inclusion and exclusion criteria, 159 patients were enrolled, including 86 in the TACE 1 group, 46 in the TACE 2 group and 27 in the TACE ≥3 group. Before PSM, there was a significant difference among the three groups in the presence of portal vein tumor thrombus (all $P<0.05$), whereas no significant differences were observed for the remaining variables ($P>0.05$; Table I). Through a sequential pairwise matching process, 27 patients were successfully identified in each group, resulting in well-balanced baseline characteristics across all three groups (Table II). The absence of significant differences in all baseline covariates after matching (all $P>0.05$) confirmed that the three groups were well balanced, thereby supporting the validity of subsequent comparisons.

Procedural characteristics. To account for procedural heterogeneity, the specific embolic agents and chemotherapeutic regimens used in each TACE session were documented. The distribution of embolic agents was comparable across groups: Lipiodol alone (42%), lipiodol + gelatin sponge (38%) and drug-eluting microspheres (20%), with no significant intergroup differences ($P=0.45$). Chemotherapeutic regimens included epirubicin + cisplatin + fluorouracil (55%), epirubicin alone (25%) and other combinations (20%), with no significant differences between groups ($P=0.52$). The choice of regimen and dosage was at the discretion of the operator, guided by tumor characteristics, liver function and patient tolerance, reflecting real-world clinical practice.

Treatment characteristics. In the TACE ≥3 group, the number of sessions ranged from 3 to 6, with a median of 3 [interquartile range (IQR): 3-4). The median interval between the first and second TACE sessions was 6.2 weeks (IQR: 5.1-8.4), and between the second and third sessions was 7.8 weeks (IQR: 6.3-10.2). These intervals did not differ significantly between the TACE 2 and ≥3 groups for the first two sessions ($P=0.42$), indicating comparable initial treatment intensity.

Efficacy. According to mRECIST criteria, one patient in the TACE 1 group achieved CR and seven achieved PR. In the TACE 2 group, eight patients achieved CR and 13 achieved PR, while in the TACE 3 group, seven achieved CR and five achieved PR (Table III, Fig. 2). The ORR in the TACE 1, TACE 2, and TACE 3 groups was 29.6, 77.8 and 44.4%, respectively

Table I. Patient demographics and baseline characteristics before propensity score matching in the TACE 1 (n=86), TACE 2 (n=46) and TACE 3 (n=27) groups.

Characteristic	TACE 1, n (%)	TACE 2, n (%)	TACE 3, n (%)	χ^2/Fisher's statistic	P-value
Sex				1.316	0.518
Female	17 (19.77)	9 (19.57)	8 (29.63)		
Male	69 (80.23)	37 (80.43)	19 (70.37)		
Age, years				0.041	0.980
<60	31 (36.05)	16 (34.78)	10 (37.04)		
≥60	55 (63.95)	30 (65.22)	17 (62.96)		
BMI, kg/m^2				1.154	0.562
<24	47 (54.65)	23 (50.00)	17 (62.96)		
≥24	39 (45.35)	23 (50.00)	10 (37.04)		
Child-Pugh				0.683	0.711
A	57 (66.28)	33 (71.74)	17 (62.96)		
B	29 (33.72)	13 (28.26)	10 (37.04)		
HBV				0.740	0.691
No	26 (39.53)	12 (26.09)	6 (22.22)		
Yes	60 (60.47)	34 (73.91)	21 (77.78)		
HCV				4.192	0.123
No	74 (86.05)	41 (89.13)	27 (100.00)		
Yes	12 (13.95)	5 (10.87)	0 (0.00)		
Hypertension				0.706	0.703
No	54 (62.79)	28 (60.87)	19 (70.37)		
Yes	32 (37.21)	18 (39.13)	8 (29.63)		
Diabetes				0.262	0.877
No	69 (80.23)	38 (82.61)	21 (77.78)		
Yes	17 (19.77)	8 (17.39)	6 (22.22)		
AFP, ng/ml				0.103	0.950
<400	51 (59.30)	26 (56.52)	16 (59.26)		
≥400	35 (40.70)	20 (43.48)	11 (40.74)		
CEA, ng/ml				0.952	0.621
<5	69 (80.23)	40 (86.96)	22 (81.48)		
≥5	17 (19.77)	6 (13.04)	5 (18.52)		
CA199, U/ml				0.693	0.707
<37	38 (44.19)	23 (50.00)	14 (51.85)		
≥37	48 (55.81)	23 (50.00)	13 (48.15)		
Albumin, g/l				1.235	0.539
<35	39 (45.35)	19 (41.30)	9 (33.33)		
≥35	47 (54.65)	27 (58.70)	18 (66.67)		
ALT, U/l				2.394	0.302
<40	46 (53.49)	31 (67.39)	16 (59.26)		
≥40	40 (46.51)	15 (32.61)	11 (40.74)		
AST, U/l				0.480	0.787
<40	25 (29.07)	16 (34.78)	8 (29.63)		
≥40	61 (70.93)	30 (65.22)	19 (70.37)		
WBC (x10^9/l)				2.954	0.228
<10	77 (89.53)	45 (97.83)	25 (92.59)		
≥10	9 (10.47)	1 (2.17)	2 (7.41)		
NLR				4.247	0.120
<1.82	15 (17.44)	15 (32.61)	5 (18.52)		
≥1.82	71 (82.56)	31 (67.39)	22 (81.48)		

Table I. Continued.

Characteristic	TACE 1, n (%)	TACE 2, n (%)	TACE 3, n (%)	χ^2/Fisher's statistic	P-value
PLT ($x10^9$/l)				2.474	0.290
<100	20 (23.26)	10 (21.74)	10 (37.04)		
≥100	66 (76.74)	36 (78.26)	17 (62.96)		
Cirrhosis				1.704	0.427
No	40 (46.51)	18 (39.13)	9 (33.33)		
Yes	46 (53.49)	28 (60.87)	18 (66.67)		
Tumor number				1.133	0.567
Single	33 (38.37)	21 (45.65)	13 (48.15)		
Multiple	53 (61.63)	25 (54.35)	14 (51.85)		
Portal vein tumor thrombus				7.700	0.021
No	52 (60.47)	32 (69.57)	24 (88.89)		
Yes	34 (39.53)	14 (30.43)	3 (11.11)		
Extrahepatic metastasis				2.031	0.362
No	64 (74.42)	38 (82.61)	23 (85.19)		
Yes	22 (25.58)	8 (17.39)	4 (14.81)		
Maximum tumor diameter, cm				0.056	0.973
<5	23 (26.74)	13 (28.26)	7 (25.93)		
≥5	63 (73.26)	33 (71.74)	20 (74.07)		
BCLC stage				4.385	0.356
A	20 (23.26)	13 (28.26)	10 (37.04)		
B	21 (24.42)	12 (26.09)	9 (33.33)		
C	45 (52.33)	21 (45.65)	8 (29.63)		

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization.

(P=0.001). The DCR in the TACE 1, TACE 2, and TACE 3 groups was 66.7, 88.9 and 96.3%, respectively (P=0.016). The differences in ORR and DCR among the three groups were significant (both P<0.05; Table III, Fig. 2). Pairwise comparisons revealed significant differences in both ORR and DCR between the TACE 1 and 2 groups (Table III; Fig. 2). The difference in DCR between the TACE 1 and 3 groups was significant (P≤0.05), whereas the difference in ORR was not (P>0.05). Conversely, the difference in ORR between the TACE 2 and 3 groups was significant (P=0.012), while the difference in DCR was not (P=0.61; Fig. 3).

Safety analysis. Treatment-related AEs occurred in 60/81 patients (74.1%). The majority were grade 1-2 in severity and were manageable with symptomatic treatment. No treatment-related deaths were observed. The incidence of AEs was 19 patients (70.4%) in the TACE 1 group, 23 (85.2%) in the TACE 2 group and 18 (66.7%) in the TACE 3 group, with no significant difference among groups (P=0.259). Furthermore, no significant differences were observed in the frequencies of specific AEs between groups (Table IV).

Survival analysis. Follow-up duration was calculated from the date of the first TACE to the date of death or last follow-up (October 2024). Adherence to the follow-up schedule was high: 91% of patients underwent imaging at 3 months, 84% at 6 months and 76% at 12 months. The frequency of imaging/unit time was similar across groups (every 3.2-3.8 months), indicating comparable follow-up intensity. The median number of follow-up imaging assessments was four (IQR: 2-7) in the TACE 1 group, six (IQR: 4-9) in the TACE 2 group and seven (IQR: 5-10) in the TACE 3 group, reflecting the longer total follow-up duration in the multi-session groups rather than a difference in follow-up intensity. The comparable frequency of assessments/unit time across groups suggested that surveillance bias was unlikely to account for the observed differences in outcomes (data not shown). The median overall follow-up duration for the entire cohort was 20 months (95% CI: 16.1-23.9). The TACE 3 group exhibited the longest median OS (26 months; 95% CI: 14.6-37.4), followed by the TACE 2 group (21 months; 95% CI: 16.4-25.6) and the TACE 1 group (8 months; 95% CI: 0-18.2; P=0.0028; Fig. 4). Compared with the TACE 1 group, OS was significantly prolonged in both the TACE 2 and 3 groups (P<0.05; Fig. 5A and B), whereas no significant difference was observed between the TACE 2 and 3 groups (Fig. 5C). Similarly, median PFS was longest in the TACE 3 group (22 months; 95% CI: 11.5-32.5), followed by the TACE 2 group (14 months; 95% CI: 6.9-21.1) and shortest in the TACE 1 group (5 months; 95% CI: 0.0-10.1; P=0.0034;

Table II. Patient demographics and baseline characteristics after propensity score matching in the TACE 1 (n=27), TACE 2 (n=27) and TACE 3 (n=27) groups.

Characteristic	TACE 1, n (%)	TACE 2, n (%)	TACE 3, n (%)	χ^2/Fisher's statistic	P-value
Sex				1.714	0.424
Female	4 (14.81)	6 (22.22)	8 (29.63)		
Male	23 (85.19)	21 (77.78)	19 (70.37)		
Age, years				0.453	0.797
<60	8 (29.63)	8 (29.63)	10 (37.04)		
≥60	19 (70.37)	19 (70.37)	17 (62.96)		
BMI, kg/m^2				1.884	0.390
<24	12 (44.44)	14 (51.85)	17 (62.96)		
≥24	15 (55.56)	13 (48.15)	10 (37.04)		
Child-Pugh				2.371	0.306
A	20 (74.07)	22 (81.48)	17 (62.96)		
B	7 (25.93)	5 (18.52)	10 (37.04)		
HBV				0.963	0.618
No	5 (18.52)	8 (29.63)	6 (22.22)		
Yes	22 (81.48)	19 (70.37)	21 (77.78)		
HCV				5.271	0.072
No	22 (81.48)	24 (88.89)	27 (100.00)		
Yes	5 (18.52)	3 (11.11)	0 (0.00)		
Hypertension				0.752	0.687
No	16 (59.26)	17 (62.96)	19 (70.37)		
Yes	11 (40.74)	10 (37.04)	8 (29.63)		
Diabetes				<0.001	>0.999
No	21 (77.78)	21 (77.78)	21 (77.78)		
Yes	6 (22.22)	6 (22.22)	6 (22.22)		
AFP, ng/ml				<0.001	>0.999
<400	16 (59.26)	16 (59.26)	16 (59.26)		
≥400	11 (40.74)	11 (40.74)	11 (40.74)		
CEA, ng/ml				2.382	0.304
<5	21 (77.78)	25 (92.59)	22 (81.48)		
≥5	6 (22.22)	2 (7.41)	5 (18.52)		
CA199, U/ml				0.100	0.951
<37	15 (55.56)	15 (55.56)	14 (51.85)		
≥37	12 (44.44)	12 (44.44)	13 (48.15)		
Albumin, g/l				0.418	0.811
<35	11 (40.74)	11 (40.74)	9 (33.33)		
≥35	16 (59.26)	16 (59.26)	18 (66.67)		
ALT, U/l (%)				0.723	0.697
<40	15 (55.56)	18 (66.67)	16 (59.26)		
≥40	12 (44.44)	9 (33.33)	11 (40.74)		
AST, U/l				0.437	0.804
<40	10 (37.04)	10 (37.04)	8 (29.63)		
≥40	17 (62.96)	17 (62.96)	19 (70.37)		
WBC (x10^9/l)				0.426	0.808
<10	25 (92.59)	26 (96.30)	25 (92.59)		
≥10	2 (7.41)	1 (3.70)	2 (7.41)		
NLR				5.222	0.073
<1.82	6 (22.22)	12 (44.44)	5 (18.52)		
≥1.82	21 (77.78)	15 (55.56)	22 (81.48)		

Table II. Continued.

Characteristic	TACE 1, n (%)	TACE 2, n (%)	TACE 3, n (%)	χ^2/Fisher's statistic	P-value
PLT (x10^9/l)				1.997	0.368
<100	6 (22.22)	6 (22.22)	10 (37.04)		
≥100	21 (77.78)	21 (77.78)	17 (62.96)		
Cirrhosis				0.418	0.811
No	11 (40.74)	11 (40.74)	9 (33.33)		
Yes	16 (59.26)	16 (59.26)	18 (66.67)		
Tumor number				0.297	0.862
Single	12 (44.44)	14 (51.85)	13 (48.15)		
Multiple	15 (55.56)	13 (48.15)	14 (51.85)		
Portal vein tumor thrombus				5.951	0.051
No	17 (62.96)	17 (62.96)	24 (88.89)		
Yes	10 (37.04)	10 (37.04)	3 (11.11)		
Extrahepatic metastasis				1.942	0.379
No	24 (88.89)	26 (96.30)	23 (85.19)		
Yes	3 (11.11)	1 (3.70)	4 (14.81)		
Maximum tumor diameter, cm				0.793	0.673
<5	9 (33.33)	10 (37.04)	7 (25.93)		
≥5	18 (66.67)	17 (62.96)	20 (74.07)		
BCLC stage				1.404	0.843
A	11 (40.74)	10 (37.04)	10 (37.04)		
B	6 (22.22)	6 (22.22)	9 (33.33)		
C	10 (37.04)	11 (40.74)	8 (29.63)		

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization.

Fig. 6). Pairwise comparisons revealed significant differences in PFS between TACE 1 and 2 (P=0.035; Fig. 7A) and between TACE 1 and 3 (P=0.0019; Fig. 7B), but not between TACE 2 and 3 (P=0.16; Fig. 7C). In summary, both the TACE 2 and 3 groups achieved significantly longer PFS and OS compared with the TACE 1 group, however, no significant difference was observed between the TACE 2 and 3 groups. Notably, the survival benefit in the TACE 2 and 3 groups became evident within the first 6 months of follow-up (Figs. 4-7) and persisted throughout the observation period. The early divergence of the survival curves, before notable immortal time could accumulate, supports the interpretation that the benefits reflect genuine treatment effects rather than bias.

Risk factor analysis. ROC curve analysis was performed to determine the optimal cutoff value for NLR. The area under the curve was 0.673, and the optimal cutoff value was 1.82 (P=0.003; Fig. 8). Uni- and multivariate Cox regression analyses were performed to identify factors associated with PFS and OS. In the matched cohort, univariate analysis revealed that hypertension, CA199 levels, portal vein tumor thrombus, number of TACE sessions, AEs, targeted therapy/immunotherapy and BCLC stage were significantly associated with PFS (all P<0.05) (Table V; Fig. 9). Among the 81 patients following PSM, 38 (46.9%) received targeted therapy and/or immunotherapy during follow-up (Table II). Of these, eight patients (21.1%) received systemic therapy between TACE sessions (typically following documented progression following the first TACE), whereas 30 (78.9%) initiated systemic therapy after completing all TACE sessions. The median time from the first TACE to initiation of systemic therapy was 9.2 months (IQR: 5.8-14.3) (data not shown). Sensitivity analysis excluding the eight patients who received systemic therapy between TACE sessions yielded similar results for the association between the number of TACE sessions and survival outcomes (data not shown), suggesting minimal confounding by the timing of systemic therapy. Multivariate analysis identified hypertension, number of TACE sessions, adverse reactions, targeted therapy/immunotherapy and BCLC stage as independent prognostic factors for PFS (Table V; Fig. 9). Univariate analysis showed that hypertension, CA199 levels, NLR, portal vein tumor thrombus, maximal tumor size, number of TACE sessions, adverse reactions and BCLC stage were associated with OS (all P<0.05) (Table VI; Fig. 10). Multivariate analysis revealed that CA199 levels, number of TACE sessions, adverse reactions and BCLC stage were independent prognostic factors for OS (Table VI; Fig. 10). No significant violations were detected for any covariate in the final models (P=0.38 for OS and P=0.31 for PFS). Visual inspection of log-minus-log

Table III. Therapeutic efficacy.

Variable (%)	TACE 1 (n=27)	TACE 2 (n=27)	TACE 3 (n=27)	P-value
CR	1 (3.7)	8 (29.6)	7 (25.9)	0.027
PR	7 (25.9)	13 (48.1)	5 (18.5)	0.067
SD	10 (37.0)	3 (11.1)	14 (51.9)	0.002
PD	9 (33.3)	3 (11.1)	1 (3.7)	0.003
Objective response rate	8 (29.6)	21 (77.8)	12 (44.4)	0.001
Disease control rate	18 (66.7)	24 (88.9)	26 (96.3)	0.016

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TACE, transcatheter arterial chemoembolization.

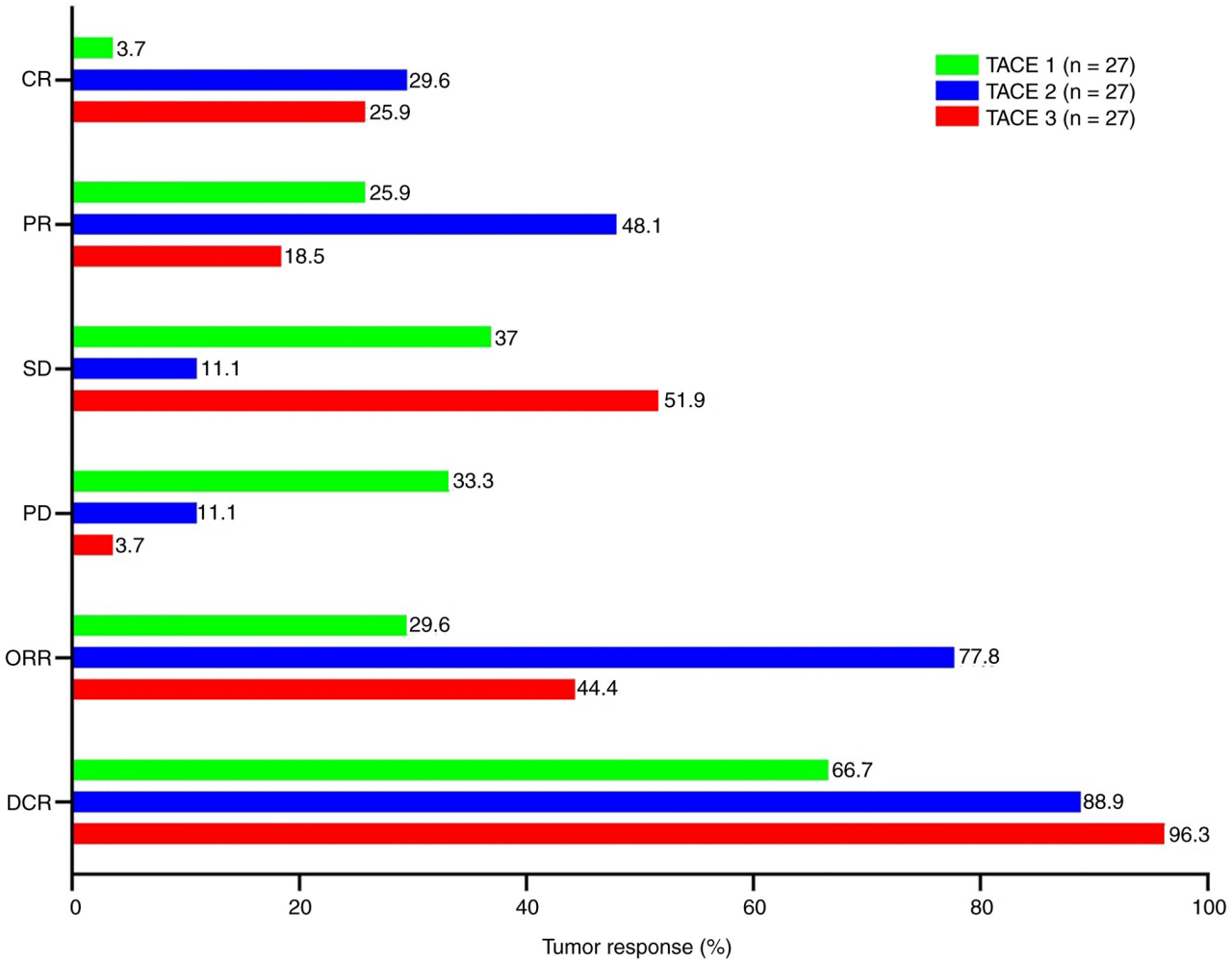

Figure 2. Overall tumor response according to Modified Response Evaluation Criteria in Solid Tumors (based on all target lesions). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TACE, transcatheter arterial chemoembolization.

survival plots confirmed parallel curves for categorical variables, supporting the validity of the Cox proportional hazards models (data not shown).

Discussion

By contrast with normal liver tissue, which receives ~75% of its blood supply from the portal vein and 25% from the hepatic artery, HCC derives 85-90% of its blood supply from the hepatic artery. This unique vascularization forms the basis for TACE, which achieves its antitumor effect by occluding the tumor main feeding artery (25). According to the BCLC staging system, first-line treatment options for intermediate and advanced HCC include TACE, transarterial radioembolization and systemic therapy (17). Among these, TACE is the most commonly used and preferred treatment for uHCC,

Table IV. Treatment emergent adverse events.

Adverse events (%)	TACE 1 (n=27)	TACE 2 (n=27)	TACE 3 (n=27)	P-value
Total	19 (70.4)	23 (85.2)	18 (66.7)	0.259
Fever	8 (29.6)	7 (25.9)	8 (29.6)	0.941
Abdominal pain	9 (33.3)	12 (44.4)	9 (33.3)	0.621
Vomiting or nausea	1 (3.7)	7 (25.9)	2 (7.4)	0.068
Elevated ALT or AST	3 (11.1)	4 (14.8)	0 (0.0)	0.152
Decreased appetite	2 (7.4)	7 (25.9)	2 (7.4)	0.097
Rash	0 (0.0)	3 (11.1)	0 (0.0)	0.103
Hypertension	0 (0.0)	0 (0.0)	1 (3.7)	>0.999
Hand-foot syndrome	0 (0.0)	3 (11.1)	0 (0.0)	0.103
Diarrhea	0 (0.0)	2 (7.4)	0 (0.0)	0.325
Hypoalbuminemia	1 (3.7)	0 (0.0)	0 (0.0)	>0.999
Hypothyroidism	0 (0.0)	0 (0.0)	2 (7.4)	0.325
WBC decrease	1 (3.7)	0 (0.0)	1 (3.7)	>0.999

AST, aspartate aminotransferase; ALT, alanine transaminase; WBC, white blood cell; TACE, transcatheter arterial chemoembolization.

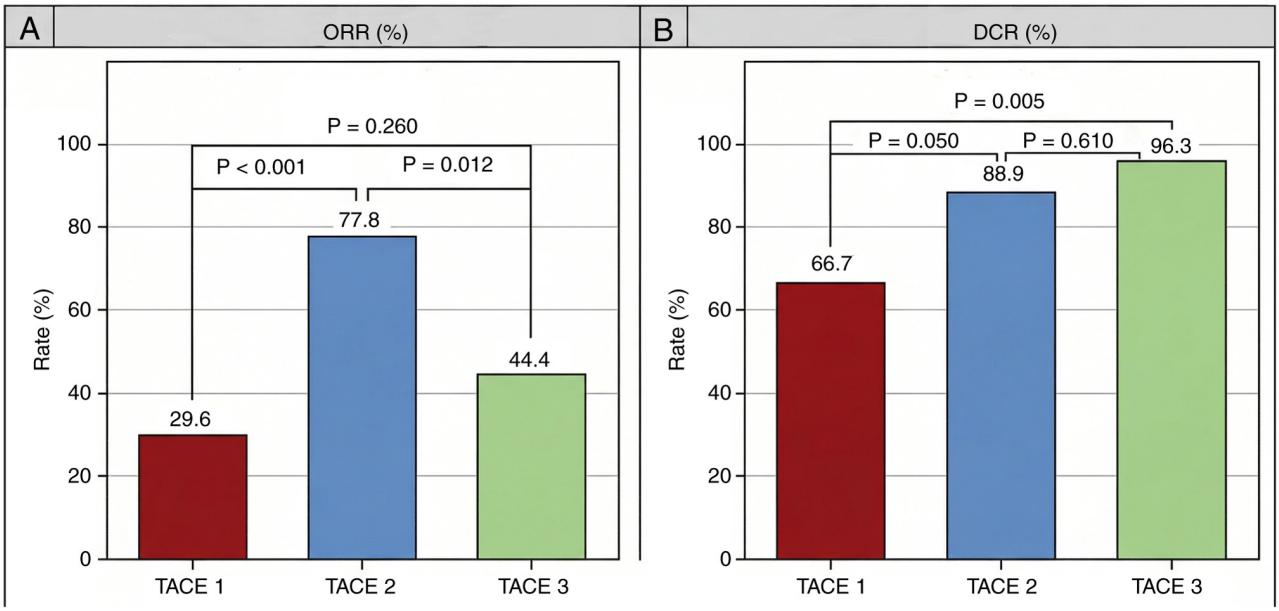

Figure 3. Patient responses. (A) ORR and (B) DCR. TACE, transcatheter arterial chemoembolization; ORR, objective response rate; DCR, disease control rate.

offering the advantages of decreasing tumor burden and alleviating symptoms (17).

In China, TACE is primarily employed as a palliative treatment for HCC (11,26). In particular, it provides a key therapeutic option for patients with intermediate or advanced HCC who are not candidates for surgical resection or local ablation. TACE can achieve curative outcomes in selected patients with HCC with small tumor burden, a relatively simple blood supply and feasible superselective catheterization (27,28).

The clinical practice of administering multiple TACE sessions is based on an on-demand approach (17). However, the association between the number of TACE sessions and long-term patient prognosis has become a notable focus of clinical research (29).

In the present study, a significant association was observed between the number of TACE sessions and treatment efficacy in patients with primary liver cancer. Specifically, the short-term efficacy of a single TACE session was inferior to that of multiple sessions. However, increasing the number of sessions beyond two did not further improve outcomes; ORR was lower in patients receiving ≥3 sessions compared with those receiving two sessions. This may be attributable to the multifaceted effects of TACE, which exerts its therapeutic action through the intra-arterial infusion of chemotherapeutic agents and embolic materials into the tumor-feeding hepatic artery (17). In this process, chemotherapeutic drugs directly target tumor cells, while embolic agents occlude the tumor vascular supply, inducing ischemia and hypoxia within the tumor tissue and

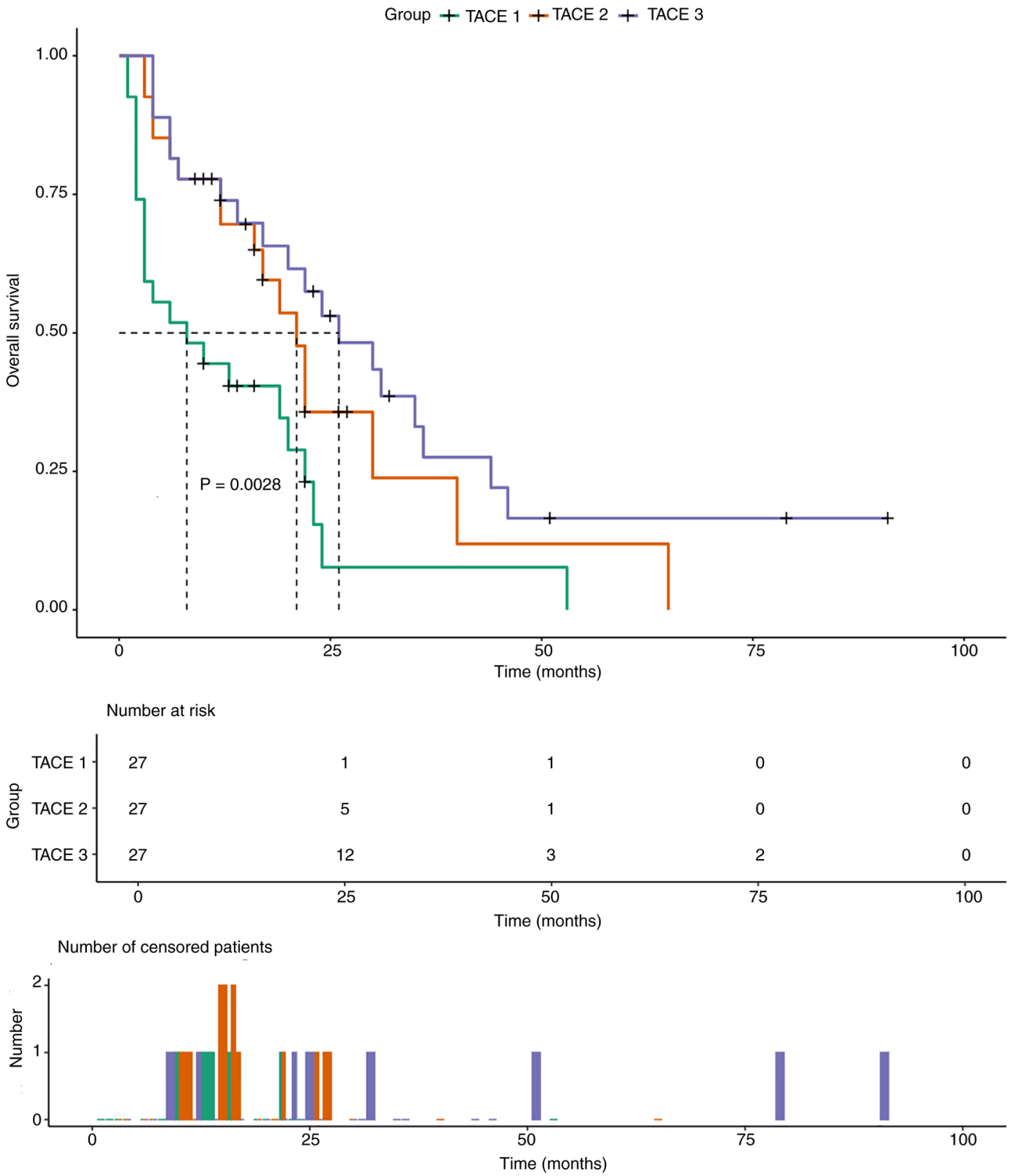

Figure 4. Kaplan-Meier survival curves showing overall survival stratified by treatment options in patients with unresectable hepatocellular carcinoma. TACE, transcatheter arterial chemoembolization.

leading to necrosis. However, repeated TACE sessions may also damage normal liver parenchyma, particularly when the number of sessions is high, potentially exacerbating liver function impairment (17). Multiple TACE sessions may induce alterations in the peritumoral microenvironment, including hypoxia-induced angiogenesis, upregulation of pro-angiogenic factors such as vascular endothelial growth factor, recruitment of immunosuppressive cells (for example, myeloid-derived suppressor cells and tumor-associated macrophages) and epithelial-mesenchymal transition, potentially promoting tumor recurrence and metastasis (30,31). Furthermore, repeated TACE may lead to a decline in hepatic functional reserve, adversely affecting patient overall health and quality of life (32). In the present study, two measures of tumor response were assessed: Response at the first assessment, which enables unbiased comparison with uniform follow-up duration across

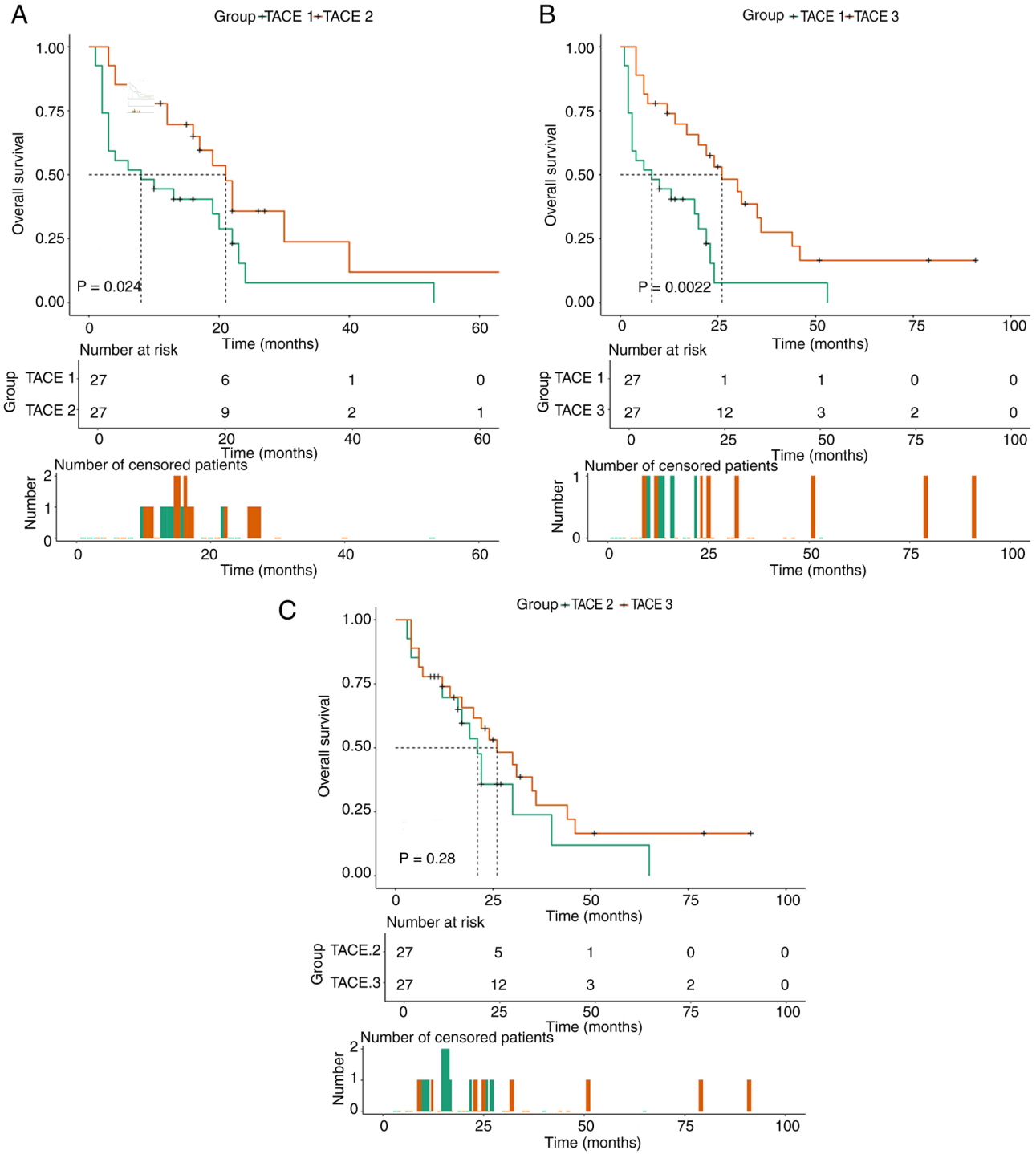

Figure 5. Kaplan-Meier survival curves showing overall survival stratified by treatment options in patients with unresectable hepatocellular carcinoma. Overall survival between TACE (A) 1 and 2, (B) 1 and 3 and (C) 2 and 3. TACE, transcatheter arterial chemoembolization.

groups, and cumulative best response over the entire follow-up period, which reflects the maximum response achieved at any time. The latter measure is clinically meaningful, as it captures the benefit of additional treatments in patients who respond to subsequent TACE sessions; however, it may be influenced by differences in follow-up duration.

Based on previous studies (15,32), following ≥3 consecutive standardized TACE sessions, patients underwent contrast-enhanced CT/MRI within 1-3 months of the last procedure to assess treatment response using mRECIST criteria. If the intrahepatic target lesion shows progressive disease compared with the pre-treatment status, TACE failure/refractoriness is considered to have occurred, which negatively impacts patient outcomes (15).

The most common complication following TACE is PES, characterized by hepatic pain, nausea, vomiting and fever. Some studies (33-35) have reported that PES may increase the risk of mortality in patients with primary liver cancer by nearly twofold and may serve as an early predictor of long-term survival. The incidence and severity of AEs in

Table V. Univariate and multivariate predictors of progression-free survival.

	Univariate Cox analysis			Multivariate Cox analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male/female)	0.960	0.712-1.294	0.787			
Age (<60/≥60 years)	0.945	0.722-1.238	0.683			
BMI (<24/≥24 kg/m^2)	1.515	0.901-2.548	0.117			
Child-Pugh class (A/B)	0.967	0.736-1.269	0.808			
HBV (yes/no)	0.845	0.477-1.499	0.565			
HCV (yes/no)	1.559	0.700-3.471	0.277			
Hypertension (yes/no)	2.515	1.473-4.296	0.001	1.933	1.107~3.376	0.020
Diabetes (yes/no)	1.289	0.705-2.357	0.409			
AFP (<400/≥400 ng/ml)	1.273	0.772-2.100	0.344			
CEA (<5/≥5 ng/ml)	1.504	0.779-2.906	0.224			
CA199 (<37/≥37 U/ml)	1.703	1.007-2.880	0.047	1.410	0.802-2.481	0.233
Albumin (<35/≥35 g/l)	0.920	0.547-1.547	0.753			
ALT (<40/≥40 U/l)	0.725	0.430-1.222	0.227			
AST (<40/≥40 U/l)	0.994	0.586-1.688	0.983			
WBC (<10/≥10x10^9/l)	0.963	0.346-2.684	0.943			
NLR (<1.82/≥1.82)	1.599	0.880-2.907	0.124			
PLT (<100/≥100x10^9/l)	1.624	0.907-2.908	0.103			
Cirrhosis (yes/no)	0.805	0.487-1.330	0.396			
Tumor number (single/multiple)	1.243	0.757-2.042	0.390			
Portal vein tumor thrombus (yes/no)	2.499	1.446-4.320	0.001	1.150	0.581-2.277	0.687
Extrahepatic metastasis (yes/no)	1.842	0.830-4.091	0.133			
Maximal tumor size (<5/≥5 cm)	1.716	0.966-3.049	0.066			
Number of TACE	0.728	0.589-0.899	0.003	0.679	0.523-0.880	0.003
Adverse reaction (yes/no)	2.119	1.113-4.037	0.022	2.588	1.301-5.147	0.007
Targeted therapy and immunotherapy (yes/no)	0.593	0.354-0.993	0.047	0.370	0.204-0.674	0.001
BCLC (A + B/C)	2.342	1.364-4.022	0.002	3.833	1.841-7.982	<0.001

Proportional hazards assumption was tested and confirmed for all variables in the final multivariate models. Number of TACE was analyzed as a continuous variable; the HR represents the change in risk per additional TACE session. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization.

the present study were consistent with those reported in the literature (17,34). Grade 1-2 AEs were predominant in all three groups and generally well tolerated. Symptoms gradually resolved with appropriate supportive care and no treatment-related deaths occurred. The incidence of adverse reactions did not differ significantly between the groups, which may be attributable to the limited sample size and warrants validation in larger studies. The present study has several limitations. First, as a single-center retrospective study, it is susceptible to inherent selection bias despite the application of PSM. The treatment protocols, patient selection criteria and follow-up practices reflect the experience of a single institution, potentially limiting the generalizability of findings to other settings with different patient populations or treatment approaches. Second, the sample size after PSM (81 patients) was modest, which may have limited the statistical power to detect smaller differences between the TACE 2 and 3 groups, a comparison that showed no significant differences in PFS (P=0.16) or OS (P=0.34) despite both groups outperforming the TACE 1 group, and to conduct more extensive subgroup analyses. Third, the observational design precluded definitive causal inferences regarding the optimal number of TACE sessions. Fourth, the heterogeneity in TACE techniques, embolic agents and chemotherapeutic regimens, although reflective of real-world practice, introduces potential confounding factors. Fifth, the follow-up duration, while adequate for assessing early-to-intermediate outcomes, may not capture long-term survival beyond 3-5 years. To address these limitations, future research should include multicenter prospective cohort studies with larger and more diverse patient populations, as well as standardized treatment protocols. Randomized controlled trials comparing different TACE strategies (on-demand vs. scheduled TACE, fixed number of sessions vs. response-adapted approach) would provide the highest level of evidence. Furthermore, studies incorporating

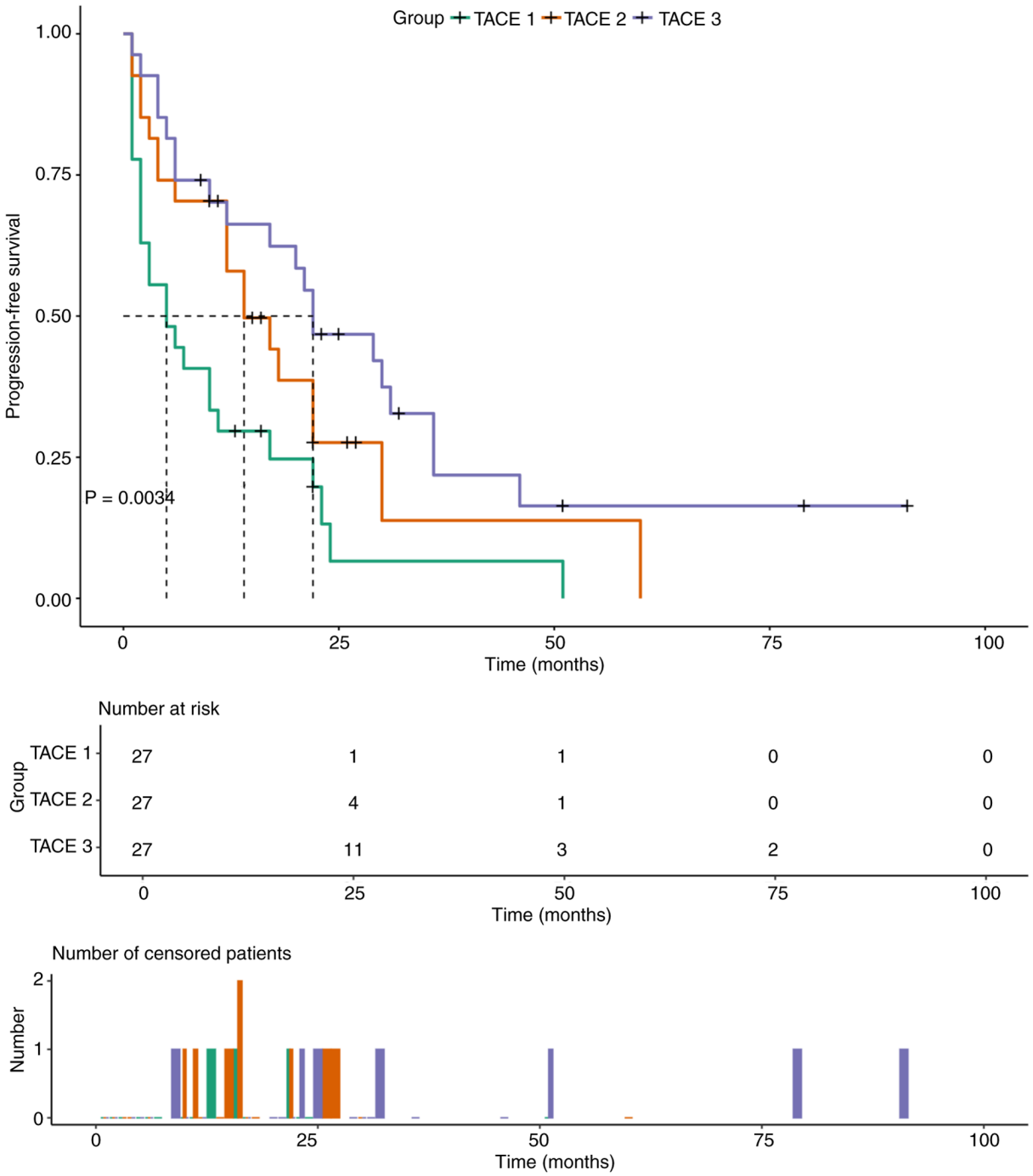

Figure 6. Kaplan-Meier survival curves showing progression-free survival stratified by treatment options in patients with unresectable hepatocellular carcinoma. TACE, transcatheter arterial chemoembolization.

quality-of-life assessment and cost-effectiveness analyses would provide more comprehensive information to guide clinical decision-making. With 62 progression events and 53 death events in the cohort, the models achieved events per variable (EPV) ratios of ~8.9 and 8.8, respectively, which are within acceptable limits to avoid overfitting (the commonly accepted threshold is EPV ≥10). Sensitivity analyses using stepwise selection and penalized Cox regression (ridge regression) yielded similar hazard ratio estimates, supporting the robustness of the findings.

The comparable distribution of these technical factors across groups suggests that procedural heterogeneity was unlikely to confound the comparison of outcomes among TACE frequency groups.

Numerous factors influence the prognosis of liver cancer. Tumor stage and diameter are significantly associated with survival outcomes in HCC (36). Studies (20,37,38) have identified advanced tumor stage as an independent risk factor for poor prognosis in HCC. In the present study, hypertension, number of TACE sessions, adverse reactions, targeted therapy/immunotherapy and BCLC stage were identified as independent prognostic factors for PFS, while CA199 levels, number of TACE sessions, adverse reactions and BCLC stage were independent prognostic factors for OS. The BCLC staging system

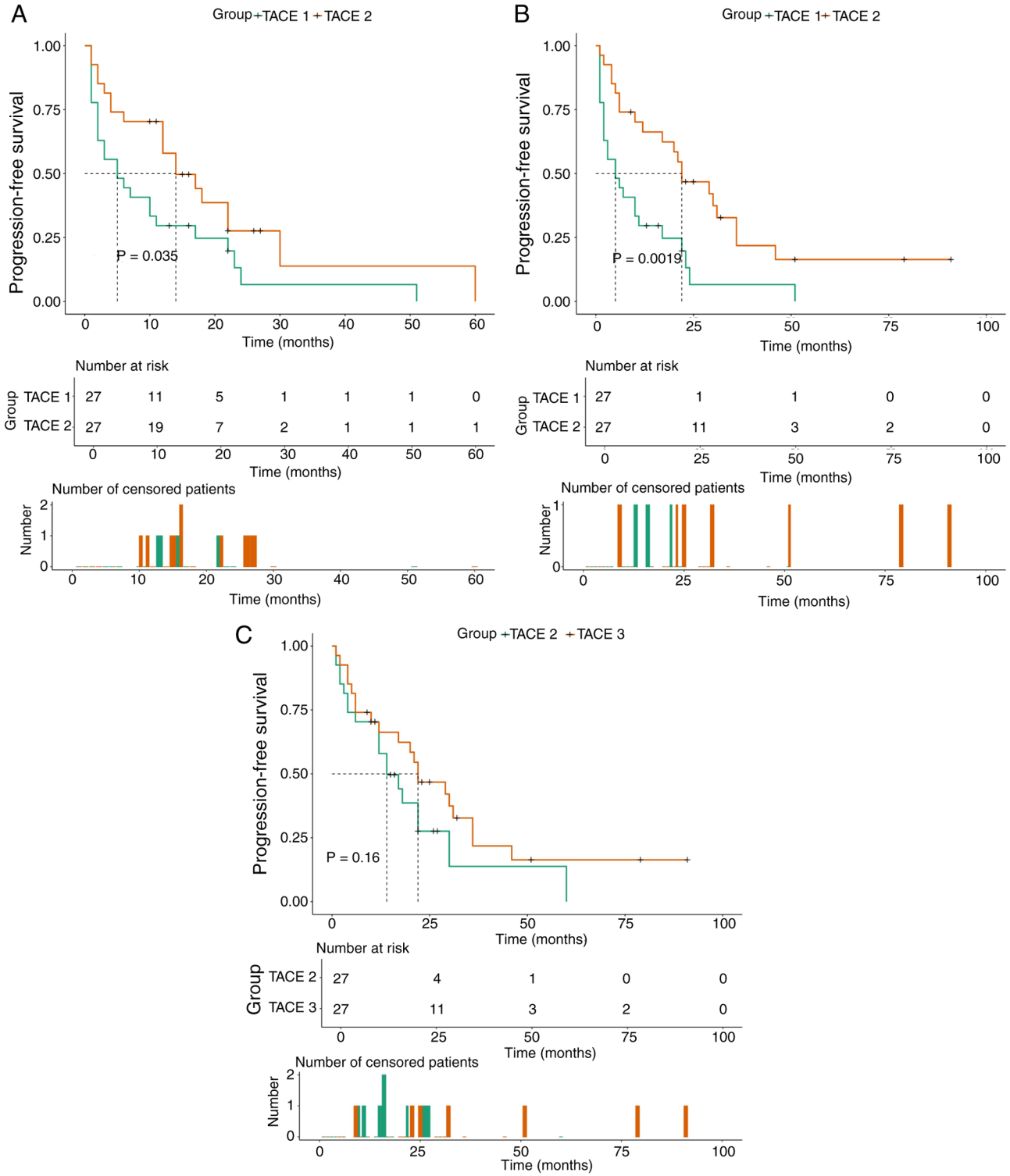

Figure 7. Kaplan-Meier survival curves showing progression-free survival stratified by treatment options in patients with unresectable hepatocellular carcinoma. Progression-free survival comparison between TACE (A) 1 and 2, (B) 1 and 3 and (C) 2 and 3. TACE, transcatheter arterial chemoembolization.

is one of the most widely used staging classifications for HCC; it integrates multiple variables, including tumor burden, liver functional reserve and tumor aggressiveness and is essential for both prognostic stratification and treatment selection. The BCLC system is widely accepted in clinical practice (38,39).

In the present study, both uni- and multivariate Cox regression analyses confirmed that BCLC stage and the occurrence of adverse reactions were independent prognostic factors for PFS and OS. Emerging evidence suggests that combining TACE with targeted therapy and immunotherapy significantly improves PFS, OS and ORR in patients with advanced HCC, with an acceptable safety profile, compared with TACE alone (40). However, in the present cohort, targeted therapy/immunotherapy was associated with PFS but not with OS, and hypertension was an independent predictor for PFS only, whereas CA199 level was independently

Table VI. Uni- and multivariate predictors of overall survival.

	Univariate Cox analysis			Multivariate Cox analysis		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male/female)	1.017	0.751-1.376	0.914			
Age (<60/≥60 years)	1.034	0.786-1.362	0.809			
BMI (<24/≥24 kg/m^2)	1.425	0.830-2.445	0.199			
Child-Pugh class (A/B)	0.943	0.711-1.250	0.682			
HBV (yes/no)	0.883	0.481-1.623	0.689			
HCV (yes/no)	1.678	0.748-3.762	0.209			
Hypertension (yes/no)	1.910	1.092-3.340	0.023	1.424	0.791-2.561	0.239
Diabetes (yes/no)	1.164	0.610-2.223	0.644			
AFP (<400/≥400 ng/ml)	1.174	0.696-1.978	0.548			
CEA (<5/≥5 ng/ml)	1.655	0.848-3.228	0.139			
CA199 (<37/≥37 U/ml)	2.259	1.282-3.981	0.005	2.211	1.211-4.037	0.010
Albumin (<35/≥35 g/l)	0.802	0.468-1.374	0.422			
ALT (<40/≥40 U/l)	0.897	0.524-1.534	0.690			
AST (<40/≥40 U/l)	1.394	0.787-2.467	0.254			
WBC (<10/≥10x10^9/l)	1.116	0.400-3.114	0.834			
NLR (<1.82/≥1.82)	1.946	1.026-3.690	0.042	1.572	0.803-3.078	0.187
PLT (<100/≥100x10^9/l)	1.421	0.786-2.569	0.245			
Cirrhosis (yes/no)	0.754	0.447-1.275	0.292			
Tumor number (single/multiple)	1.307	0.778-2.196	0.311			
Portal vein tumor thrombus (yes/no)	2.854	1.595-5.104	<0.001	1.049	0.524-2.099	0.894
Extrahepatic metastasis (yes/no)	1.833	0.775-4.335	0.167			
Maximal tumor size (<5/≥5 cm)	2.027	1.098-3.740	0.024	1.147	0.560-2.347	0.708
Number of TACE	0.729	0.585-0.908	0.005	0.628	0.477-0.826	0.001
Adverse reaction (yes/no)	2.264	1.132-4.527	0.021	2.209	1.063-4.593	0.034
Targeted therapy and immunotherapy (yes/no)	0.654	0.383-1.117	0.120			
BCLC (A + B/C)	2.343	1.337-4.104	0.003	3.161	1.497-6.673	0.003

Proportional hazards assumption was tested and confirmed for all variables in the final multivariate models. Number of TACE was analyzed as a continuous variable; the HR represents the change in risk per additional TACE session. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization.

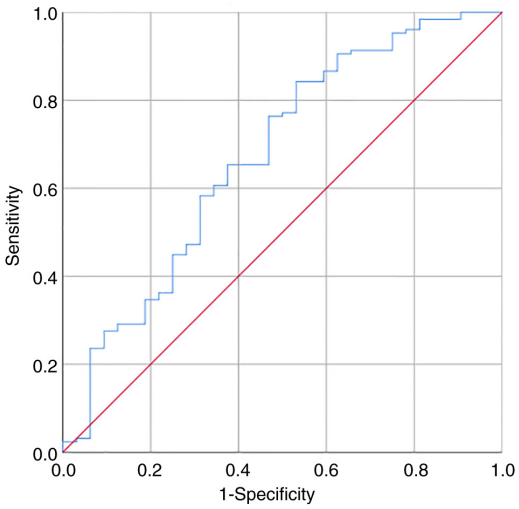

Figure 8. Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio.

associated with OS only. These findings may be attributable to the limited sample size. The potential confounding effect of subsequent systemic therapy warrants careful consideration. In the present cohort, the majority of patients (78.9%) received systemic therapy after completing all TACE sessions, typically following disease progression. This suggests that systemic therapy was more often a consequence of disease progression rather than a confounder of the association between TACE frequency and survival. Sensitivity analyses excluding patients who received systemic therapy between TACE sessions did not notably alter the findings. Nevertheless, the present study cannot exclude the possibility that the timing of systemic therapy influenced outcomes; future studies should collect detailed timing data to enable time-dependent covariate analysis. The identification of hypertension as an independent risk factor for PFS, but not for OS, warrants exploration of potential underlying mechanisms. Hypertension may affect hepatic microcirculation and

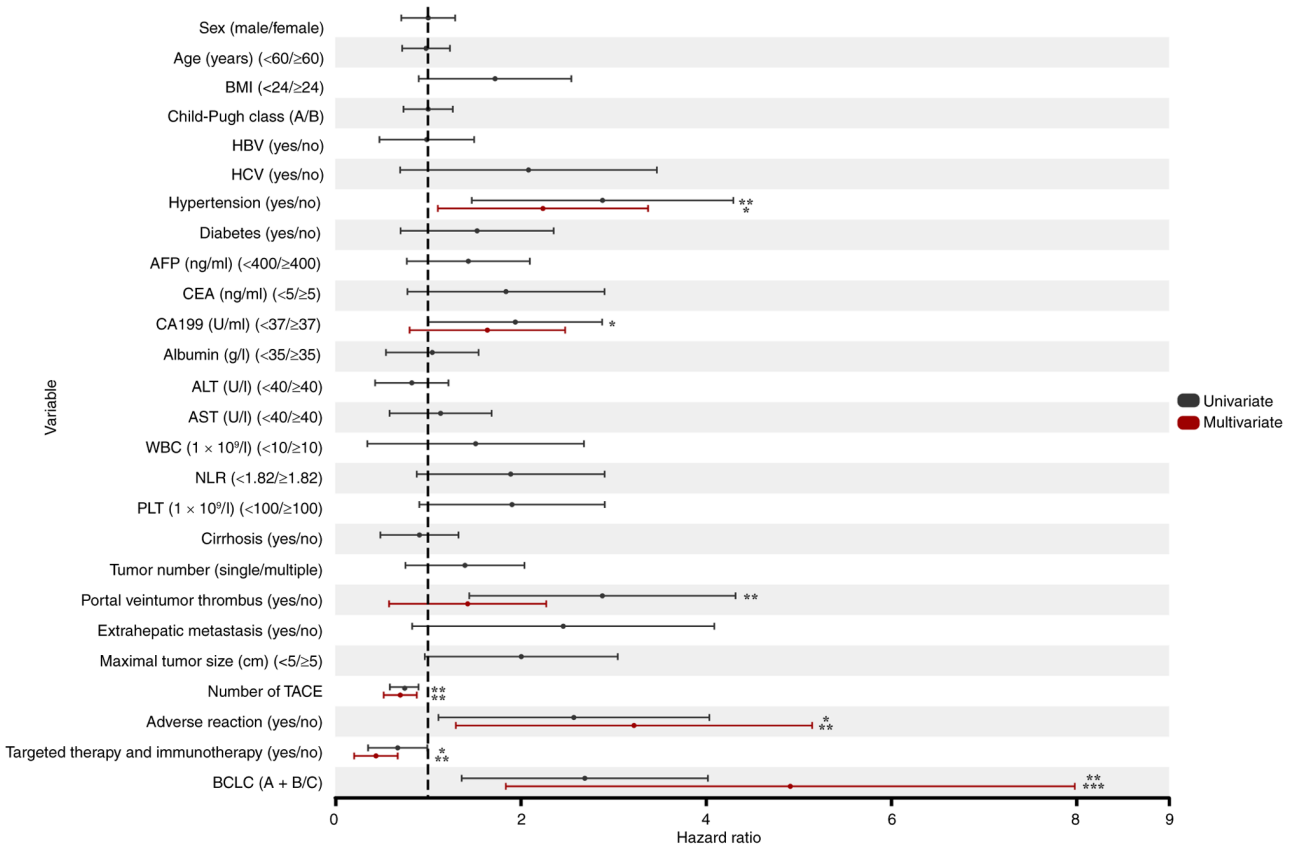

Figure 9. Forest plots of univariate and multivariate predictors of progression-free survival. *P<0.05, **P<0.01, ***P<0.001 vs. the reference category. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; TACE, transcatheter arterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer.

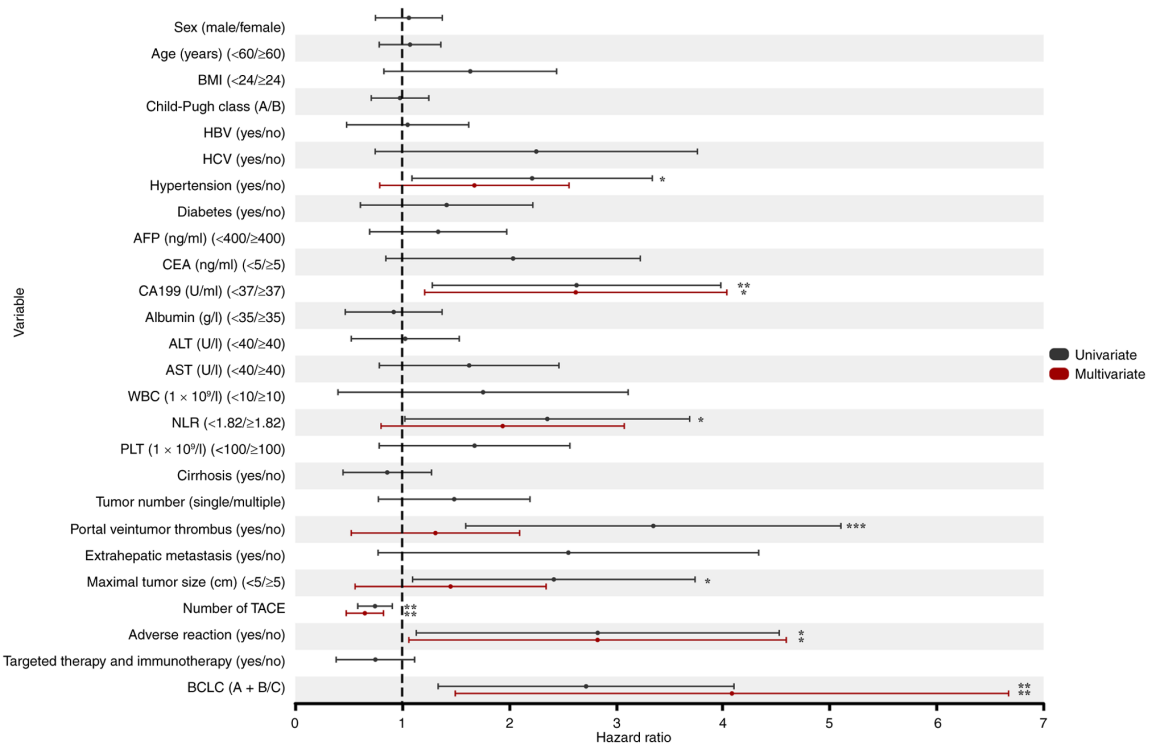

Figure 10. Forest plots of univariate and multivariate predictors of overall survival. *P<0.05, **P<0.01, ***P<0.001 vs. the reference category. BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; TACE, transcatheter arterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer.

sinusoidal pressure, potentially influencing drug delivery and distribution during TACE (41). Additionally, antihypertensive medications, particularly β-blockers, have been implicated in altered tumor angiogenesis and progression in some studies (42). Chronic hypertension may also reflect underlying endothelial dysfunction and systemic inflammation, which may promote tumor progression (43). However, these hypotheses require further investigation. Although CA199 is not a classical HCC biomarker, elevated levels may indicate several underlying conditions, such as undetected combined hepatocellular-cholangiocarcinoma components, which are associated with a poorer prognosis (44), biliary obstruction or cholangitis, which may complicate the clinical course and limit treatment options (45), or advanced liver disease with cholestasis, reflecting more severe underlying liver dysfunction (46). Additionally, tumor expression of CA199 may serve as a marker of more aggressive biological behavior (47). The specificity of CA199 for OS, rather than PFS, suggests that it may be more closely associated with overall disease progression and hepatic functional deterioration than early tumor response. Future studies incorporating histological confirmation and detailed biliary imaging would help elucidate this association. Immortal time bias is a theoretical concern in studies evaluating treatment frequency, as patients must survive long enough to receive multiple treatments. The present study evaluated treatment strategies (single vs. multiple TACE) rather than the time-dependent effect of each additional session. PSM balanced baseline prognostic factors that may influence both treatment receipt and survival, decreasing confounding by indication. All survival analyses were calculated from the date of first TACE, ensuring identical starting points for all groups. The relatively short intervals between TACE sessions (median, 6-8 weeks) minimized the immortal time window and the early divergence of survival curves (within the first 6 months) suggested that the observed benefits are unlikely to be solely attributable to immortal time bias. Nevertheless, the present study cannot entirely exclude residual confounding factors; future prospective studies employing landmark analyses or time-dependent covariate approaches are required to validate the present findings.

Previous studies (48,49) have demonstrated that the number of TACE sessions is a protective factor for prognosis in patients with HCC. The present study indicated that repeated TACE for HCC has clinical value. Within the range of one to three TACE sessions, an increased number of TACE sessions was associated with prolonged PFS and OS times. However, the indications for repeat TACE should be strictly applied; blind expansion of its use is not advocated, as preserving liver function, maintaining quality of life and minimizing unnecessary procedures are of paramount clinical importance. Furthermore, greater emphasis should be placed on comprehensive treatment strategies, such as TACE combined with targeted therapy and immunotherapy, to improve prognosis in patients with liver cancer.

The number of TACE sessions significantly influences the prognosis of patients with HCC. Prior to TACE, Child-Pugh class and the presence of cirrhosis should be assessed to evaluate hepatic functional reserve. During the procedure, superselective segmental embolization should be performed when possible to minimize damage to the peritumoral liver parenchyma. Following TACE, active hepatoprotective therapy should be administered to mitigate the occurrence of AEs. Additionally, the interval between TACE sessions should be appropriately managed and other therapeutic modalities, such as targeted therapy and immunotherapy, may be considered in combination. In clinical practice, treatment plans should be tailored to individual tumor characteristics and liver function, while avoiding indiscriminate repeat treatment that may compromise liver function and decrease survival.

In conclusion, the present study evaluated the efficacy and safety of different numbers of TACE sessions in patients with uHCC, with control for confounding factors through the use of PSM. While previous studies (50,51) have examined TACE refractoriness and repeated TACE, the present study specifically compares outcomes across three distinct treatment frequency groups (1, 2 and ≥3 sessions) in a well-balanced cohort following PSM. The present findings complement previous studies (17,52) and provide additional evidence to inform clinical decision-making regarding the optimal number of TACE sessions. However, indiscriminate repeat prophylactic TACE does not necessarily enhance treatment efficacy; treatment should be tailored to the individual clinical situation, integrating appropriate comprehensive strategies to optimize survival outcomes. For patients with uHCC and preserved liver function (Child-Pugh class A or B) who demonstrate initial response to TACE, ≥2 TACE sessions should be considered to optimize tumor response and survival outcomes. The present data suggest that a second planned TACE session, even in patients with an apparent good initial response, may confer additional benefit through more complete tumor necrosis and treatment of satellite lesions. Routine prophylactic TACE beyond three sessions should be avoided in the absence of clear evidence of ongoing benefit. The decision to proceed with a third or subsequent TACE session should be individualized, considering objective evidence of residual viable tumor on imaging, sustained adequate liver function (Child-Pugh class A or B with minimal decompensation), absence of TACE refractoriness (progressive disease despite two consecutive TACE sessions) and patient performance status and preferences. For patients with treatment-related adverse reactions, enhanced prognostic monitoring is warranted, as these patients exhibited significantly worse PFS and OS in the present study. Close attention to preserving liver function, aggressive supportive care and early consideration of alternative or combination therapies (targeted therapy, immunotherapy) may be beneficial in this subgroup. Patients with hypertension may require more intensive monitoring for early progression and optimal blood pressure control should be maintained throughout the treatment course. For patients with elevated CA199 at baseline, clinicians should consider the possibility of combined hepatocellular-cholangiocarcinoma or biliary pathology (53) and appropriate diagnostic workup may be warranted. These patients may benefit from closer surveillance and consideration of more aggressive treatment strategies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study are not publicly available due to patient privacy and ethical restrictions associated with the institutional review board approval, but may be requested from the corresponding author.

Authors' contributions

The study was conceptualized by LZ and XX. Formal analysis and data interpretation were performed by LZ, XX, CL, HG, XZ and WL. Data acquisition and clinical management were carried out by WL, CL and HG. Literature analysis was conducted by XX, CL and HG. Writing of the original draft was conducted by XX, LZ and CL. Reviewing and editing of the manuscript was performed by XX, LZ, CL, HG, XZ and WL. Supervision was provided by LZ, XZ, HG and WL. Project administration was conducted by CL, HG and WL. All authors have read and approved the final version of the manuscript. LZ, XX and CL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Hebei General Hospital (Shijiazhuang, China; approval no. 2024-LW-0204). Written informed consent was obtained from all patients for the TACE procedure prior to treatment. For the retrospective analysis of medical records, the requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study. The study was performed in accordance with The Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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