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ORIGINAL RESEARCH

Post-TACE ALBI-Score Trajectory in Intermediate and Advanced Hepatocellular Carcinoma: Prognostic Implications and Influencing Factors Analysis

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Objective: The long-term effects of transarterial chemoembolization (TACE) on liver function and their prognostic implications in hepatocellular carcinoma (HCC) have not been fully explored. The Albumin-Bilirubin (ALBI) score, an objective measure of liver function, is a validated prognostic tool in HCC. This study aims to characterize the longitudinal trajectories of ALBI-scores after TACE, evaluate their impact on clinical outcomes, and identify factors influencing these trajectories.

Materials and Methods: This retrospective study included patients with BCLC stage B/C HCC who underwent TACE, with baseline and at least two post-TACE ALBI-score measurements. Group-Based Trajectory Modeling (GBTM) was used to identify distinct ALBI-score trajectories. Clinical outcomes and patient characteristics were compared across trajectory groups. A CatBoost-based clinical prediction model was developed to identify factors influencing ALBI-score trajectories, with Shapley Additive Explanations (SHAP) values providing feature importance interpretation.

Results: Among 501 patients, three ALBI-score trajectories were identified: improve, stable, and decline. The improve group had better overall survival (OS) and progression-free survival (PFS) compared to the stable and decline groups. Multivariate analysis confirmed that ALBI-score trajectories were independent risk factors for OS. Subgroup analysis suggested that TACE plus systemic therapy reduced mortality risk in the stable and decline groups. The CatBoost model effectively distinguished distinct trajectory groups, with SHAP analysis highlighting ALBI-grade, Child-Pugh class, and tumor number as key predictors.

Conclusion: Post-TACE ALBI-score trajectories are closely linked to clinical outcomes, with improved liver function associated with better prognosis. Monitoring these trajectories could guide personalized treatment strategies for HCC patients undergoing TACE.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, group-based trajectory modeling, machine learning, shapley additive explanations

Key Points

Question: Does monitoring liver function trajectories after TACE provide guidance for prognostic predictions and personalized treatment strategies in HCC patients?

Findings: The study identified three distinct ALBI-score trajectories post-TACE: improve, stable, and decline; patients in the improve group showed better OS and FPS.

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Clinical relevance: ALBI-score trajectories post-TACE effectively predicts clinical outcomes and supports personalized treatment strategies for HCC. Improved post-TACE liver function correlates with enhanced survival, highlighting the importance of regular liver function assessments to help clinicians tailor treatments for better patient outcomes.

Introduction

Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related mortality and the sixth most prevalent malignant neoplasm globally, with projections indicating an annual incidence exceeding one million cases by 2025.[1,2] The primary etiological factors for HCC include hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, collectively accounting for approximately 70% of cases.[2] Metabolic dysfunction-associated steatotic liver disease (MASLD), often associated with metabolic syndrome or diabetes, is increasingly recognized as a significant risk factor, particularly in Western countries.[3,4]

While curative-intent therapies such as surgical resection, organ transplantation, and ablation are viable options for early-stage HCC, the majority of cases are diagnosed at intermediate and advanced stages, limiting the applicability of these treatments.[5,6] Consequently, there is an increasing reliance on non-curative therapies to manage disease progression and improve patient outcomes.[6] Transarterial chemoembolization (TACE) and systemic treatments have emerged as the cornerstone of therapy for intermediate and advanced HCC patients.[7] However, the marked heterogeneity within this patient population presents significant challenges in tailoring individualized therapies to further optimize the clinical outcome.

A distinctive characteristic of HCC is the close association between patient prognosis and two key factors: tumor burden and hepatic function.[8] This dual dependency differentiates HCC from many other solid malignancies. The Child-Pugh class has been widely utilized for decades to assess liver function in these patients.[9] However, this score is limited by its reliance on subjective evaluations of hepatic encephalopathy and ascites.[10,11] The Albumin-Bilirubin (ALBI) score, a novel prognostic tool developed to assess liver function in HCC patients, offers a more objective and quantifiable measure based solely on serum albumin and bilirubin levels.[11,12] Its utility as a prognostic indicator has been validated in previous studies, demonstrating predictive value for overall survival and treatment outcomes in HCC patients.[13–15] Furthermore, recent research has shown that changes in ALBI-grade (delta ALBI-grade) before and after TACE can effectively predict the prognosis of chronic hepatitis C-related HCC (CHC-HCC) patients.[16]

While the baseline ALBI-score reflects pre-treatment liver function reserve, and the delta ALBI-grade captures linear changes in liver function over a short period before and after treatment, previous studies have not extensively examined the longitudinal trajectory of ALBI-score changes throughout the entire treatment process. Clinical observations have revealed varying degrees of heterogeneity in ALBI-score change trajectories among HCC patients during treatment.[17] To date, no studies have confirmed whether this heterogeneity correlates with treatment response and long-term prognosis in patients receiving TACE.

This longitudinal cohort study aims to employ a group-based trajectory model (GBTM) to analyze variations in the ALBI-score among patients with intermediate and advanced stages of HCC undergoing TACE-based systemic therapies. By categorizing patients into distinct trajectory groups according to their ALBI-score trajectories, we intend to elucidate the clinical characteristics and prognostic distinctions among these groups, thereby providing a theoretical foundation for developing more personalized treatment strategies for patients with intermediate and advanced HCC.

Methods and Materials

This study was conducted in accordance with the Declaration of Helsinki (version 2013) and approved by the Bioethics Committee of Beijing Friendship Hospital (No. 2022-P2-282-01). With the approval of the Committee, written informed consent was waived for all patients, and informed consent was obtained through telephone.

Patient Selection

We retrospectively included patients with a clinical diagnosis of Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC who received TACE at the Department of Interventional Radiology, Beijing Friendship Hospital, Capital Medical University, between January 2016 and December 2022. Inclusion criteria mandated that patients had baseline ALBI-score

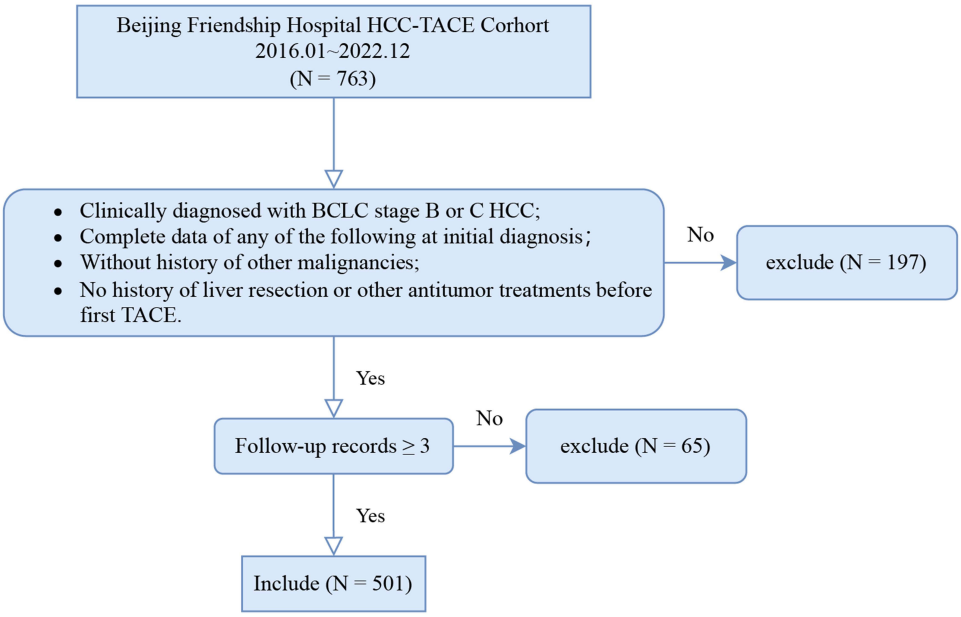

Figure 1 Flowchart for the patients with intermediate-stage HCC after TACE.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer.

measurements taken before the first TACE procedure and at least three additional measurements within 15 months postoperatively. Patients who had undergone hepatectomy or other anti-neoplastic therapies prior to their first TACE procedure were excluded. Detailed inclusion and exclusion criteria are presented in Figure 1.

TACE-Based Treatment Plan

Patients included in this study received conventional TACE (cTACE) or drug-eluting beads TACE (DEB-TACE). TACE procedures were performed by interventional radiologists with a minimum of ten years of experience according to TACE standardization.[18,19] Decisions regarding sequential TACE and systemic treatment were based on the patient's general condition, residual tumor activity, and preoperative BCLC stage. Upon imaging-confirmed progression under first-line treatment, patients underwent comprehensive evaluation and were transitioned to an appropriate second-line systemic therapy regimen.

Follow-up and Outcome Definitions

Imaging and laboratory tests were conducted one month after the initial TACE procedure to assess tumor response according to the m-RECIST guidelines.[20] Prior to achieving complete response (CR), patients were followed up every 2–3 months, and after CR, follow-ups occurred every 3–6 months. Each follow-up included a physical examination, imaging, and laboratory tests. The primary endpoint was overall survival (OS), defined as the time from initial TACE treatment to the date of death or last follow-up. The secondary endpoint was progression-free survival (PFS), defined as the duration from the start of therapy until the progression of the liver tumor, lymph node metastases, or the emergence of distant metastasis.

ALBI-Score Calculation

The ALBI-score was calculated using the formula: ALBI-score = (log10 bilirubin × 0.66) + (albumin × −0.085), where bilirubin is measured in μmol/L and albumin in g/L. ALBI-grades were defined as follows: grade 1 (≤−2.60), grade 2 (> −2.60 to ≤−1.39), and grade 3 (>−1.39).[12] Lower grades indicate better liver function. Baseline ALBI-grade was determined for all patients to establish a reference for liver function status prior to treatment.

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Statistical Analysis

Group-Based Trajectory Model

Group-Based Trajectory Modeling (GBTM) was employed to identify trajectory changes in ALBI-scores throughout the treatment process, utilizing the PROC TRAJ procedure implemented by Nagin et al in SAS.[21] Longitudinal measurements were modeled as linear or nonlinear functions of time (months from each measurement date to the TACE date), initially fitting linear, quadratic, and cubic models for 2 to 6 group trajectories. Key fit indices included Average Posterior Probability (Avep%), Proportions per Class, Bayesian Information Criterion (BIC), and Relative Entropy (Ek). The criteria for selecting the optimal group trajectory model were listed in Table S1.

Analysis of Patient Characteristics and Clinical Outcomes in Different Trajectory Groups

Characteristics across different groups were compared using Student's *t*-test or Kruskal−Wallis tests for continuous variables, and chi-square tests or Fisher's exact test for categorical variables. OS and PFS for each trajectory group were estimated using the Kaplan-Meier method, with inter-group differences evaluated via the Log rank test. Univariable and multivariable Cox proportional hazards models were employed to explore the association between ALBI-score trajectories and clinical outcomes. To identify potential sources of heterogeneity, subgroup analyses were conducted based on key clinical features (eg, age, sex, etiology, largest tumor diameter, number of tumors), with interaction tests performed using the Cox regression model.

Comparison of Post-TACE ALBI-Score Trajectories between cTACE and DEB-TACE Subgroups

To investigate potential heterogeneity in ALBI-score trajectories between cTACE and DEB-TACE cohorts, we conducted a comparative sub-analysis. ALBI-score trajectories for patients who underwent cTACE and those who underwent DEB-TACE. A Linear Mixed Effects Model (LMM) was employed to assess the differences in ALBI-score trajectories over time between the two treatment modalities. The model included fixed effects for TACE type (cTACE vs DEB-TACE), time (modeled as a 3-degree-of-freedom natural spline), and their interaction, with random intercepts for individual patients to account for repeated measurements. The statistical significance of trajectory differences was evaluated through likelihood ratio tests comparing nested models with and without treatment-time interaction terms.

Development and Interpretation of Clinical Prediction Model

To further investigate the factors influencing the trajectory of ALBI-score changes following TACE, we developed an interpretable clinical prediction model. Clinical characteristics significantly correlated with the ALBI trajectory group in univariate analyses were used to construct the model. Participants were randomly divided into two groups, with 80% of the data allocated to the training set and 20% to the validation set. Prediction modeling was conducted using Categorical Boosting (CatBoost).[22] Model performance was assessed using multiple metrics: the area under the receiver operating characteristic curve (AUC), accuracy, precision, recall, and F1-score. Additionally, a confusion matrix was employed to evaluate the model's predictive performance across specific categories. Finally, to interpret the contributions of individual features to the model's predictions, we employed the Shapley Additive Explanations (SHAP) approach, which is grounded in game theory's Shapley values.[23] This method quantifies the impact of each feature by calculating its average contribution across all possible feature combinations, represented by SHAP values.

All statistical analyses were performed using SAS (version 9.4), R (version 4.2.2) and Python (version 3.9.12), with a p value < 0.05 considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of patients meeting the study criteria was summarized in Table 1. The patient selection process is depicted in Figure 1. The final cohort comprised 501 patients, with a median of 6 serum albumin and bilirubin measurements per patient (range: 3–16). The median follow-up duration was 14.1 months. During this period, 305 patients (60.9%) succumbed to their illness. Viral hepatitis was the predominant etiology of HCC, accounting for 382 of 501 patients (76.25%), encompassing both HBV and HCV infections.

Table 1 Patient Baseline Characteristics of Three Trajectory Group

Characteristics*	Total (N=501)	Improve (N=144)	Stable (N=206)	Decline (N=151)	*P* value
Age, Median (IQR)	63.00 (55.00 to 70.00)	63.00 (53.00 to 70.00)	64.00 (56.00 to 71.00)	62.00 (55.00 to 69.00)	0.611
Gender					
Female	117 (23.35%)	35 (24.3%)	48 (23.3%)	34 (22.5%)	0.936
Male	384 (76.65%)	109 (75.7%)	158 (76.7%)	117 (77.5%)	
Cirrhosis					
Absent	178 (35.53%)	72 (50%)	80 (38.8%)	26 (17.2%)	<0.001
Present	323 (64.47%)	72 (50%)	126 (61.2%)	125 (82.8%)	
Viral hepatitis					
Absent	119 (23.75%)	23 (16%)	39 (18.9%)	57 (37.7%)	<0.001
Present	382 (76.25%)	121 (84%)	167 (81.1%)	94 (62.3%)	
AFP					
≤ 400 ng/mL	385 (76.85%)	128 (88.9%)	147 (71.4%)	110 (72.8%)	<0.001
> 400 ng/mL	116 (23.15%)	16 (11.1%)	59 (28.6%)	41 (27.2%)	
Largest tumor diameter					
≤ 5 cm	311 (62.08%)	93 (64.6%)	121 (58.7%)	97 (64.2%)	0.436
> 5 cm	190 (37.92%)	51 (35.4%)	85 (41.3%)	54 (35.8%)	
Number of tumor					
≤ 3	355 (70.86%)	121 (84%)	140 (68%)	94 (62.3%)	<0.001
> 3	146 (29.14%)	23 (16%)	66 (32%)	57 (37.7%)	
Macrovascular invasion					
Absent	404 (80.64%)	134 (93.1%)	164 (79.6%)	106 (70.2%)	<0.001
Present	97 (19.36%)	10 (6.9%)	42 (20.4%)	45 (29.8%)	
Extrahepatic spread					
Absent	385 (76.85%)	117 (81.2%)	158 (76.7%)	110 (72.8%)	0.231
Present	116 (23.15%)	27 (18.8%)	48 (23.3%)	41 (27.2%)	
BCLC stage					
B	277 (55.29%)	106 (73.6%)	105 (51%)	66 (43.7%)	<0.001
C	224 (44.71%)	38 (26.4%)	101 (49%)	85 (56.3%)	
Child-pugh class					
A	359 (71.66%)	125 (86.8%)	175 (85%)	59 (39.1%)	<0.001
B	142 (28.34%)	19 (13.2%)	31 (15%)	92 (60.9%)	
TACE times, Median (IQR)	4.00 (2.00 to 7.00)	5.00 (3.00 to 9.00)	5.00 (3.00 to 8.00)	3.00 (2.00 to 5.00)	<0.001
#Average interval time of TACE, Median (IQR)	66.00 (50.00 to 107.75)	84.18 (58.00 to 123.41)	62.47 (49.00 to 105.00)	57.00 (44.50 to 81.17)	<0.001
Systematic therapy					
None	305 (60.88%)	88 (61.1%)	120 (58.3%)	97 (64.2%)	0.646
TKI	152 (30.34%)	45 (31.2%)	68 (33%)	39 (25.8%)	
Anti-VEGF antibody/TKI + ICI	44 (8.78%)	11 (7.6%)	18 (8.7%)	15 (9.9%)	
ALBI-grade					
1	96 (19.16%)	56 (38.9%)	40 (19.4%)	0 (0%)	<0.001
2	370 (73.85%)	70 (61.1%)	184 (80.6%)	116 (76.8%)	
3	35 (6.99%)	0 (0%)	0 (0%)	35 (23.2%)	
TACE type					
cTACE	437 (87.23%)	120 (83.3%)	184 (89.3%)	133 (88.1%)	0.238
DEB-TACE	64 (12.77%)	24 (16.7%)	22 (10.7%)	18 (11.9%)	

Notes: *Except where indicated, data are number (%). Chi-squared test or Fisher exact test for categorical variables were applied. #Calculated only for patients with a number of TACEs ≥ 2 (N = 433).

Abbreviations: AFP, Alpha-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial cheoembolization; TKI, tyrosine kinase inhibitors; ICI: Immune Checkpoint Inhibitor; ALBI-grade: Albumin-Bilirubin Grade; cTACE, conventional TACE; DEB-TACE, drug-eluting beads TACE.

Identification of ALBI-Score Trajectory Groups

The fitting process for models with 2 through 6 groups using the group-based trajectory model is delineated in Table S1. Tables S2 and S3 present the parameter estimates and mathematical equations of the three trajectory models, respectively. Based on fit indices and trajectory shape interpretability, the optimal model was determined to comprise two quadratic trajectories and one linear trajectory. Three distinct ALBI-score trajectories were identified (Figure 2): improve (28.74%; n = 144), stable (41.12%; n = 206), and decline (30.14%; n = 151). Overall, the improve and stable groups exhibited smaller tumor burdens, better baseline liver function, and underwent more TACE procedures with longer mean intervals

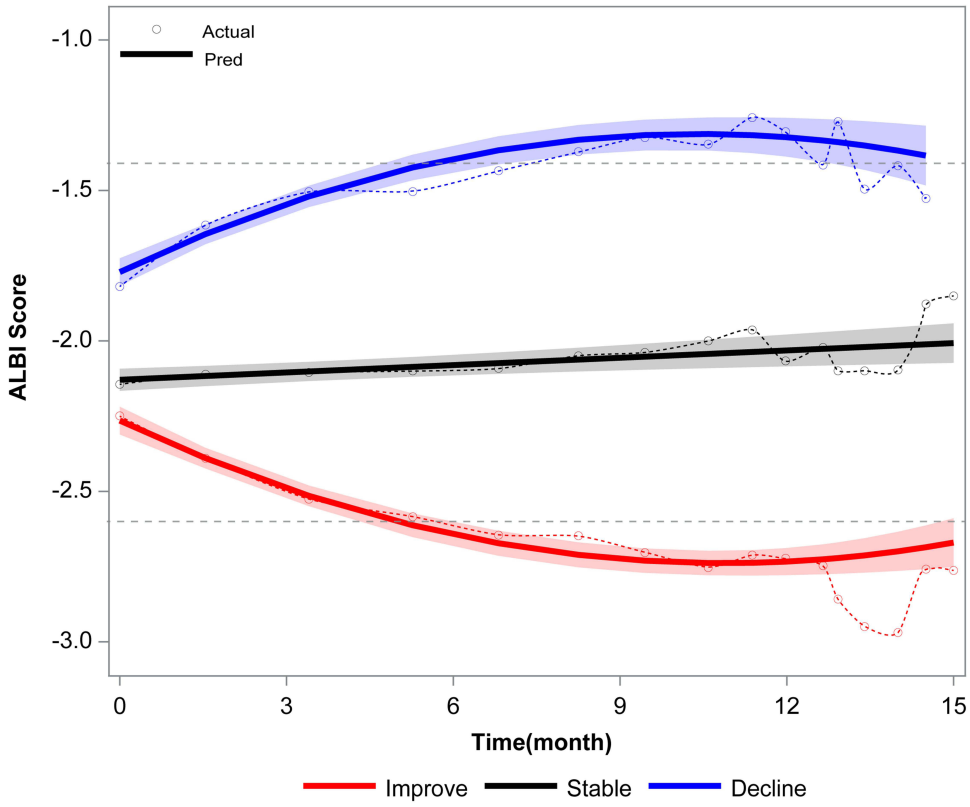

Figure 2 ALBI-score trajectory over time Post-TACE in intermediate and advanced HCC patients. This figure illustrates the actual (dotted lines with open circles) versus predicted (solid lines) trajectories of ALBI-score in patients with HCC over 15 months following TACE. Shaded areas represent the 95% confidence intervals for the predicted ALBI-score in each group.
Abbreviations: TACE, transarterial chemoembolization; ALBI-score, albumin-bilirubin score; HCC, hepatocellular carcinoma.

between TACE sessions compared to the decline group. No significant inter-group differences were observed in age, gender, or treatment plan. Intriguingly, a higher incidence of viral hepatitis was observed in the stable and improve groups compared to the decline group (84.0% and 81.1% vs 62.3%, $p < 0.001$).

Clinical Outcomes of Different Trajectory Groups

Figure 3 depicts the Kaplan-Meier curves for OS and PFS across the three trajectory groups. Patients exhibiting an improving ALBI-score trajectory demonstrated significantly prolonged OS and PFS compared to those with stable or declining trajectories. As illustrated in Figure 3A, the median OS was 43.1 months (95% CI, 39.6–51.0) for the improve group, 22.1 months (95% CI, 18.9–27.8) for the stable group, and 10.4 months (95% CI, 9.0–13.0) for the decline group ($p < 0.0001$). Figure 3B presents the median PFS: 25.3 months (95% CI, 20.2–30.2) for the improve group, 11.8 months (95% CI, 10.2–14.6) for the stable group, and 5.9 months (95% CI, 5.0–7.6) for the decline group ($p < 0.0001$).

Cox proportional hazards model analysis indicated that, compared to the improve group, both the stable and decline groups exhibited a higher risk of mortality, as detailed in Table 2. After adjusting for other risk factors in the multivariate model, the hazard ratio (HR) was 2.51 (95% CI 1.81–3.48) for the stable group and 4.03 (95% CI 2.80–5.81) for the decline group. Subgroup analyses revealed a consistent trend where the trajectory of ALBI-score changes positively correlated with mortality risk (Table 3). Notably, the differential mortality risk was exacerbated in patients with higher tumor burdens. However, TACE combined with systemic therapy mitigated the increased mortality risk associated with unfavorable ALBI-score trajectories (Table 3). Subgroup analysis also indicated that patients in the stable and decline groups who received TACE combined with systemic therapy had a lower mortality risk compared to those who received TACE alone (Table 3). The results presented in Figure 4 indicate that in the improve group, there was no significant

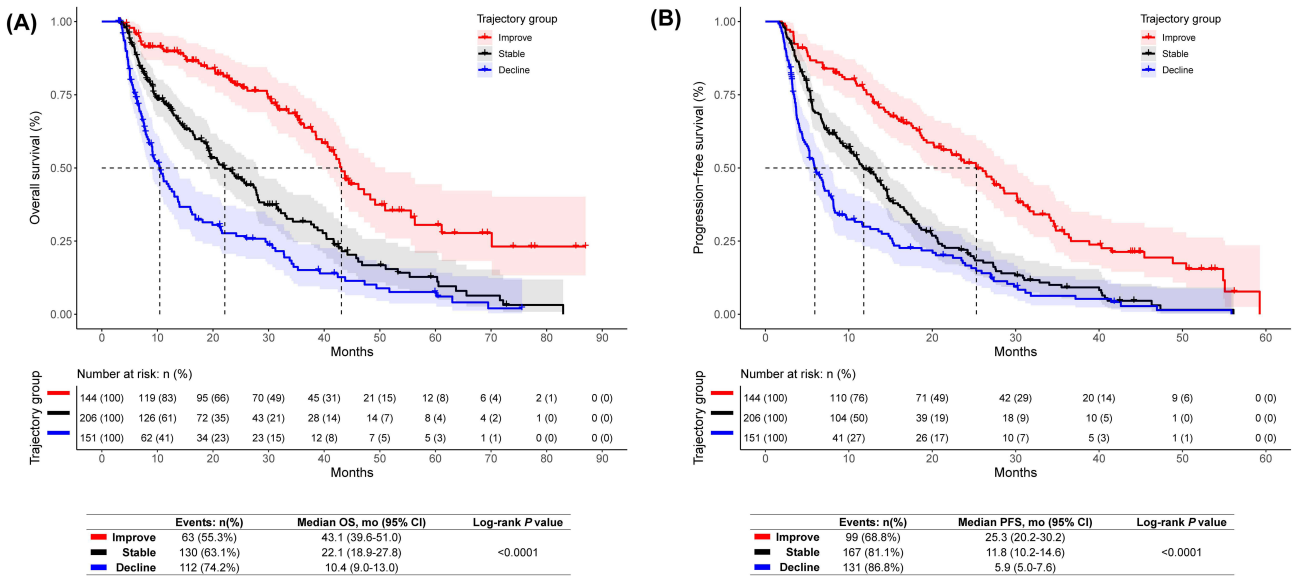

Figure 3 Kaplan-Meier curves of OS and PFS stratified by post-TACE ALBI-score trajectories in intermediate and advanced HCC Patients. This figure displays Kaplan-Meier curves illustrating (**A**) Overall Survival (OS) and (**B**) Progression-Free Survival (PFS) in patients with HCC stratified by post-TACE ALBI-score trajectories. Shaded areas represent the 95% confidence intervals. Log-rank p-values are provided for each comparison, indicating the statistical significance of the differences in OS and PFS between the different trajectory group.
Abbreviations: TACE, transarterial chemoembolization; ALBI-score, albumin-bilirubin score; HCC, hepatocellular carcinoma.

difference in OS between TACE alone and combination therapy. However, in the stable and decline trajectory groups, patients who received combined therapy demonstrated a longer OS.

Subgroup Analysis: Post-TACE ALBI-Score Trajectories by TACE Types

Linear mixed-effects modeling revealed no statistically significant interaction between TACE type and time (interaction $p = 0.072$), indicating comparable overall ALBI trajectories between cTACE and DEB-TACE groups (Figure S1). Individual trajectories within each subgroup exhibited limited heterogeneity, with most patients following the group-averaged trend. Post hoc comparisons at predefined postoperative timepoints (1, 3, 6, and 12 months) further confirmed the absence of significant differences between groups after Bonferroni correction (all $p > 0.05$; Table S4).

Clinical Prediction Model and SHAP Analysis

A clinical prediction model was developed using variables identified through univariate analysis. The Catboost-based model demonstrated efficacy in distinguishing between different ALBI-score trajectories post-TACE (Table S5, Figure 5A). Figure S2 shows the confusion matrix of the model's performance in predicting ALBI-score trajectory groups for the training set and test set.The model demonstrated efficacy in distinguishing between different ALBI-score trajectories post-TACE, with micro/macro-AUC of 0.96 and 0.84 on the training and test sets, respectively. Overall, the model exhibited optimal performance in predicting the decline trajectory group, with F1-scores of 0.89 and 0.79 on the training and test sets, respectively. However, the model's performance on the test set showed a decrease compared to the training set, particularly when predicting the stable trajectory group.

SHAP analysis provided quantitative explanations for the Catboost model. Baseline ALBI-grade, Child-Pugh class, and tumor number as the top influential factors in the model's decision process (Figure 5B). Key predictive features for each trajectory group are visualized in Figure 5C. For the improve trajectory group, ALBI-grade 1/2, lower tumor number, and absence of cirrhosis were the most significant features (Figure 5C). In the stable trajectory group, Child-Pugh class A, higher baseline AFP level, and greater tumor diameter were predominant (Figure 5C). For the decline trajectory group, Child-Pugh class B, ALBI-grade 2/3, and presence of cirrhosis were the key predictive features (Figure 5C).

Table 2 Trajectory Groups of ALBI-Score and Multivariate Hazard Ratios of Overall Survival with 95% Confidence Intervals

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Group						
Stale vs Improve	2.33	1.72–3.15	<0.001	2.51	1.81–3.48	<0.001
Decline vs Improve	3.90	2.85–5.33	<0.001	4.03	2.80–5.81	<0.001
Age	1.01	1.00–1.02	0.049	1.01	1.00–1.02	0.051
Gender (male vs female)	1.30	1.00–1.70	0.051			
Cirrhosis (present vs absent)	1.08	0.85–1.36	0.543			
Viral hepatitis (present vs absent)	0.88	0.68–1.13	0.317			
AFP (> 400 ng/m vs ≤ 400 ng/mL)	1.74	1.34–2.26	<0.001	1.26	0.95–1.67	0.106
Largest tumor diameter (> 50mm vs ≤ 50mm)	1.44	1.14–1.83	0.002	1.29	1.00–1.66	0.052
Number of tumor (> 3 vs ≤ 3)	2.26	1.77–2.88	<0.001	1.87	1.42–2.45	<0.001
Macrovascular invasion (present vs absent)	2.28	1.72–3.02	<0.001	0.91	0.62–1.35	0.643
Extrahepatic spread (present vs absent)	1.74	1.34–2.27	<0.001	1.35	0.97–1.89	0.077
BCLC stage (C vs B)	2.95	2.33–3.73	<0.001	2.44	1.69–3.52	<0.001
Child-pugh class (B vs A)	2.38	1.86–3.04	<0.001	1.49	1.09–2.04	0.012
TACE times	0.90	0.88–0.93	<0.001	0.91	0.88–0.95	<0.001
Systematic therapy						
TKI vs None	0.66	0.51–0.85	<0.001	0.72	0.55–0.95	0.020
Anti-VEGF antibody/TKI + ICI vs None	0.52	0.27–0.98	0.042	0.34	0.18–0.68	0.002
ALBI-grade						
2 vs 1	1.76	1.29–2.39	<0.001	0.97	0.70–1.35	0.858
3 vs 1	1.94	1.17–3.20	0.009	0.68	0.37–1.24	0.204
TACE type (DEB-TACE vs cTACE)	0.64	0.44–0.95	0.027	0.65	0.43–0.97	0.035

Abbreviations: HR, Hazard Ratio; AFP, Alpha-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial cheoembolization; TKI, tyrosine kinase inhibitors; ICI, Immune Checkpoint Inhibitor; ALBI-grade, Albumin-Bilirubin Grade; cTACE, conventional TACE; DEB-TACE, drug-eluting beads TACE.

Discussion

This retrospective longitudinal cohort study identified three distinct ALBI-score trajectories—improve, stable, and decline—following TACE in patients with intermediate and advanced HCC. These trajectories were significantly associated with clinical outcomes, independent of baseline liver function and tumor burden. A Catboost-based clinical prediction model showed strong efficacy in predicting ALBI-score trajectories, with baseline ALBI-grade, Child-Pugh class, and tumor number as the most influential predictors.

To our knowledge, this is the first clinical study to explore the heterogeneous trajectories of ALBI-score following TACE and their prognostic significance in HCC patients. While previous studies have established that baseline liver function is a robust predictor of clinical outcomes post-TACE, and demonstrated that dynamic changes in ALBI-score after treatment are highly predictive of survival outcomes in HCC patients undergoing systemic therapy,[16,17,24–26] our findings further extend this knowledge to the TACE setting.

The results of this study emphatically demonstrate that dynamic changes in liver function post-TACE significantly influence patient prognosis. Patients maintaining stable or improved liver function during treatment exhibit markedly favorable outcomes, underscoring the critical importance of liver function preservation throughout the TACE treatment continuum for HCC patients. Meanwhile, subgroup analysis results showed that in the stable and decline ALBI-score groups, the combination of TACE with systemic therapy, compared to TACE alone, could reduce the risk of death and prolong OS, suggesting that incorporating systemic therapy into the treatment plan may offer a significant survival advantage for patients whose liver function does not improve or deteriorates following TACE. Subgroup analysis comparing cTACE and DEB-TACE modalities revealed no significant difference in post-TACE ALBI-score trajectories (interaction $p = 0.072$). Post hoc comparisons at 1, 3, 6, and 12 months post-TACE

Table 3 Subgroup Analysis of Overall Survival for ALBI-Score Trajectories Stratified by Clinical Features

Characteristics	Events/N (%)	Stale vs Improve			Decline vs Improve		
		HR	(95% CI)	P value	HR	(95% CI)	P value
All patients	305/501 (60.8%)	2.33	1.72–3.15	<0.001	3.90	2.85–5.33	<0.001
Age							
≤ 60	117/198 (59.1%)	2.29	1.38–3.80	0.001	3.54	2.10–5.99	<0.001
> 60	188/303 (62.0%)	2.60	1.77–3.83	<0.001	4.72	3.17–7.03	<0.001
Gender							
Female	72/117 (61.5%)	2.25	1.21–4.16	0.010	4.42	2.28–8.55	<0.001
Male	233/384 (60.7%)	2.34	1.65–3.32	<0.001	3.71	2.60–5.29	<0.001
Cirrhosis							
Absent	106/178 (59.6%)	2.73	1.74–4.28	<0.001	8.31	4.65–14.83	<0.001
Present	199/323 (61.6%)	2.10	1.38–3.20	<0.001	3.47	2.30–5.23	<0.001
Viral hepatitis							
Absent	78/119 (65.5%)	1.71	0.83–3.54	0.147	2.83	1.46–5.49	0.002
Present	227/382 (59.4%)	2.49	1.78–3.47	<0.001	4.68	3.23–6.78	<0.001
AFP							
≤ 400 ng/mL	230/385 (59.7%)	2.02	1.45–2.81	<0.001	3.32	2.36–4.65	<0.001
> 400 ng/mL	75/116 (64.7%)	3.87	1.52–9.88	0.005	7.96	3.04–20.84	<0.001
Largest tumor diameter							
≤ 5	194/311 (62.4%)	2.04	1.41–2.95	<0.001	3.16	2.17–4.59	<0.001
> 5	111/190 (58.4%)	2.98	1.74–5.12	<0.001	7.42	4.16–13.22	<0.001
Number of tumor							
≤ 3	205/355 (57.7%)	2.15	1.53–3.03	<0.001	2.93	2.03–4.23	<0.001
> 3	100/146 (68.5%)	2.64	1.32–5.30	0.006	6.52	3.19–13.32	<0.001
Macrovascular invasion							
Absent	241/404 (59.7%)	2.26	1.63–3.13	<0.001	3.41	2.43–4.78	<0.001
Present	64/97 (66.0%)	2.05	0.77–5.45	0.148	5.54	2.01–15.24	<0.001
Extrahepatic spread							
Absent	231/385 (60.0%)	2.22	1.58–3.14	<0.001	3.76	2.64–5.37	<0.001
Present	74/116 (63.8%)	2.62	1.36–5.05	0.004	4.25	2.15–8.40	<0.001
BCLC stage							
B	163/277 (58.8%)	2.10	1.44–3.07	<0.001	2.88	1.93–4.30	<0.001
C	142/224 (63.4%)	2.10	1.22–3.61	0.007	4.83	2.74–8.50	<0.001
Child-pugh class							
A	213/359 (59.3%)	2.42	1.75–3.36	<0.001	2.96	1.99–4.39	<0.001
B	92/142 (64.8%)	2.01	0.89–4.56	0.093	3.09	1.52–6.25	0.002
Treatment plan							
TACE alone	209/305 (68.5%)	2.60	1.79–3.78	<0.001	4.26	2.91–6.22	<0.001
TACE+systematic therapy	96/196 (49.0%)	1.88	1.11–3.17	0.019	2.95	1.69–5.16	<0.001
TACE type							
cTACE	277/437 (63.4%)	2.31	1.68–3.18	<0.001	3.60	2.59–4.99	<0.001
DEB-TACE	28/64 (43.8%)	2.05	0.75–5.62	0.164	8.24	2.68–25.33	<0.001

Abbreviations: HR, Hazard Ratio; AFP, Alpha-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial cheoembolization; TKI, tyrosine kinase inhibitors; ICI, Immune Checkpoint Inhibitor; ALBI-grade, Albumin-Bilirubin Grade; cTACE, conventional TACE; DEB-TACE, drug-eluting beads TACE.

demonstrated overlapping confidence intervals (all $p > 0.05$), suggesting similar hepatic tolerability profiles between the two TACE types. However, the smaller sample size of the DEB-TACE subgroup (n=64 vs n=437 for cTACE) limits the statistical power to detect subtle differences. Further studies with balanced enrollment are required to confirm these observations. Notably, we observed that among patients who underwent more than two sessions of TACE, a longer interval between sessions was associated with more favorable changes in liver function. This aligns with previous studies reporting improved overall survival in patients with longer inter-TACE intervals.[27–29] These

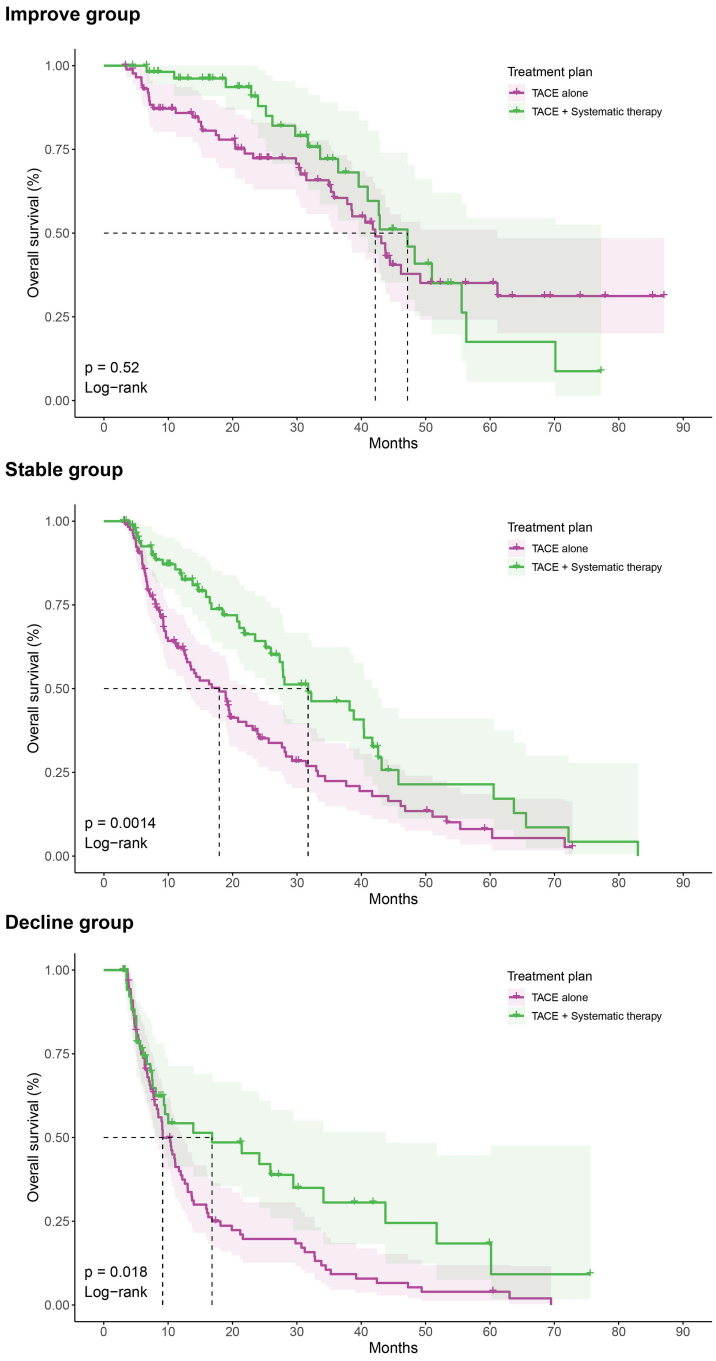

Figure 4 Kaplan-Meier curves of OS stratified by treatment plans in different post-TACE ALBI-score trajectories HCC patients. This figure presents Kaplan-Meier survival curves for overall survival (OS) stratified by treatment plan within each post-TACE ALBI-score trajectory group. Improve group: Patients with improving ALBI scores post-TACE (top panel). Stable group: Patients with stable ALBI scores post-TACE (middle panel). Decline group: Patients with declining ALBI scores post-TACE (bottom panel). Each panel compares survival outcomes between two treatment plans: TACE alone (Purple line); TACE combined with systemic therapy (Green line). Shaded areas represent the 95% confidence intervals. Log-rank p-values are provided for each comparison, indicating the statistical significance of the differences in survival between the treatment plans within each trajectory group.
Abbreviations: TACE, transarterial chemoembolization; ALBI-score, albumin-bilirubin score.

findings collectively suggest that judiciously prolonging the time between TACE sessions may contribute to liver function preservation, potentially enhancing patient prognosis. Furthermore, we found that compared to the ALBI-score decline trajectory group, the stable and improvement groups had a higher prevalence of viral hepatitis and a lower incidence of cirrhosis. The SHAP analysis further supports this finding, identifying cirrhosis and viral hepatitis as key predictors in our clinical prediction model. We posit that this phenomenon may be attributed to the

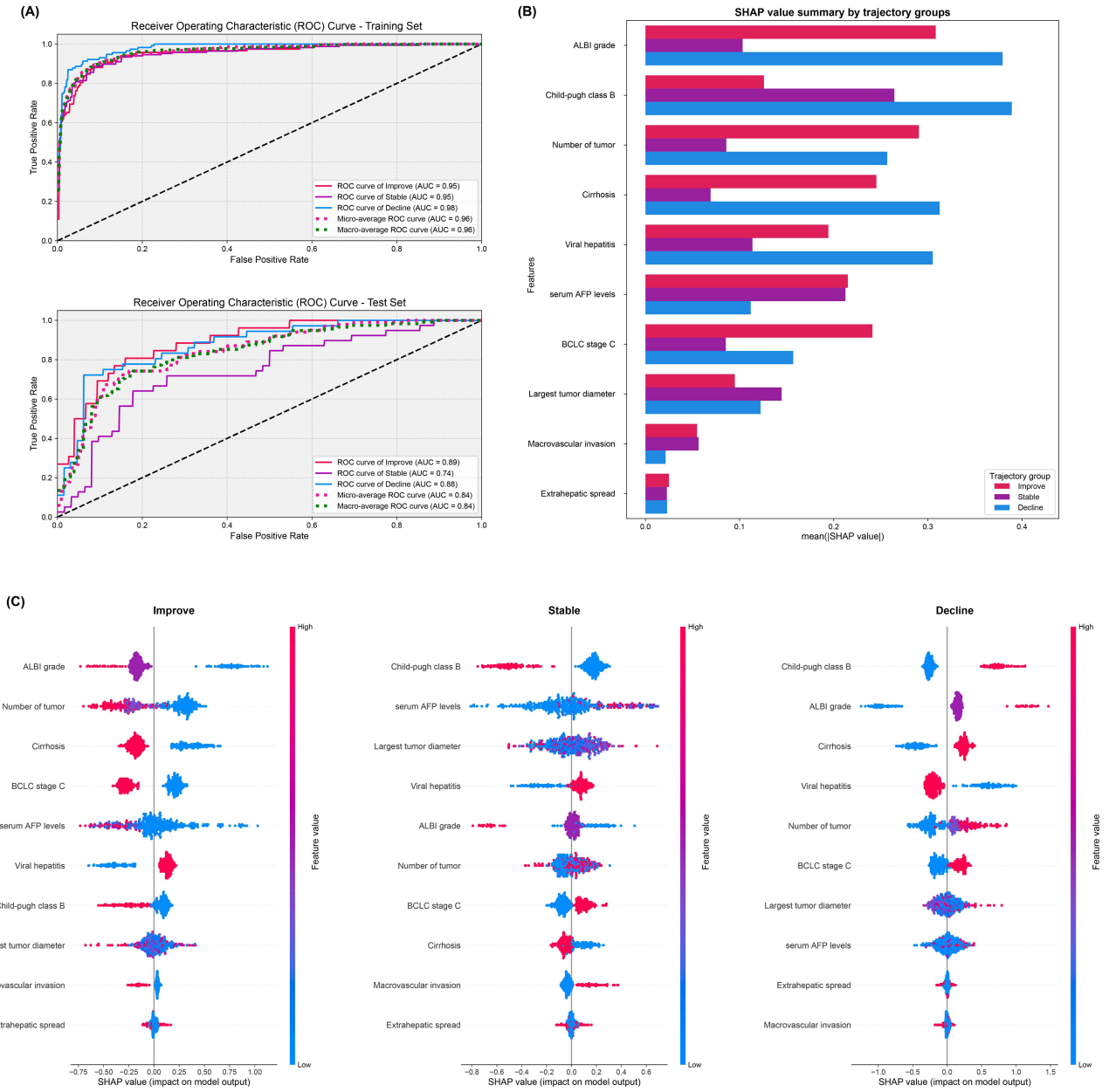

Figure 5 Performance and feature importance interpretation of the CatBoost model in predicting ALBI-score trajectories post-TACE. (**A**) ROC curves for the CatBoost model predicting ALBI-score trajectory groups (Improve, Stable, Decline) in both the training set (top panel) and test set (bottom panel). The AUC values for each trajectory group and the macro-average are provided, indicating the model's discriminatory power. (**B**) SHAP value summary plot showing the mean absolute SHAP value for each feature, indicating its overall importance in distinguishing ALBI-score trajectories. Features are listed in order of decreasing global importance from top to bottom. The length of each bar represents the average magnitude of the feature's impact on the model's output across all instances, with colors indicating the distribution of SHAP values for each trajectory group (Improve, Stable, Decline). Specifically, longer bars indicate features that, on average, have a larger influence on the model's predictions. (**C**) SHAP value beeswarm plots depicting the distribution of individual feature contributions (SHAP values) to the model's output for each trajectory group (Improve, Stable, Decline). Each point represents a patient, and its horizontal position shows the SHAP value for that feature for that patient's prediction. Features are listed in order of importance within each trajectory group (descending from top to bottom, although importance order can vary slightly across groups). The color of each point indicates the feature value (red = high, blue = low for continuous features; you might need to specify for categorical features if applicable). Positive SHAP values (to the right of zero) indicate that the feature pushes the prediction towards that specific trajectory group, while negative SHAP values (to the left of zero) push the prediction away from that group. The spread of points horizontally shows the variability of the feature's impact. For example, in the "Improve" plot, if "ALBI grade" has mostly negative SHAP values, it suggests that lower ALBI grades (better liver function) contribute to predicting an "Improve" trajectory.

Abbreviations: TACE, transarterial chemoembolization; ALBI-score, albumin-bilirubin score; AUC, Area Under the Curve; SHAP, Shapley Additive Explanations; ALBI grade, albumin-bilirubin grade; AFP, Alpha-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

concurrent initiation of antiviral therapy with TACE in HCC patients with viral etiology, effectively controlling the underlying disease, safeguarding liver function, and impeding progression to cirrhosis.[30–32] This observation highlights the importance of controlling the primary disease in HCC caused by viral hepatitis.

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The SHAP analysis of our Catboost-based clinical prediction model yielded additional insights. Baseline liver function metrics, particularly ALBI-grade and Child-Pugh class, emerged as the most influential predictors. This suggests that patients with better baseline liver function are more likely to experience favorable changes in liver function following TACE, corroborating previous findings that cumulative liver injury from repeat TACE is more pronounced in patients with cirrhosis and impaired liver function.[33] Interestingly, among the tumor burden metrics, the number of tumors (ranked 3rd for overall mean SHAP value) emerged as a more significant predictor than largest tumor diameter (8th) or serum AFP level (6th). This was particularly evident in predicting the improvement of the trajectory group, where tumor number ranked 2nd, with lower tumor numbers associated with improved post-TACE liver function (Figure 5C). Our clinical observations offer a potential explanation for this finding. Unlike the increase in feeding arteries caused by increased tumor volume, the feeding arteries of multiple tumors are often randomly distributed across different hepatic lobes or segments. In contrast, the increase in feeding arteries due to tumor volume enlargement is typically confined to a single hepatic lobe or adjacent segments (Figure S3A). Consequently, the presence of multiple tumors necessitates the treatment of a greater number of feeding arteries during chemoembolization, potentially leading to more extensive liver damage and complicating the achievement of precise TACE (Figure S3B).

The limitations of this study include its retrospective design, single-center nature, and predominance of viral hepatitis etiology. The clinical prediction model showed potential overfitting to the training set, particularly for the stable trajectory group. Further research is necessary to validate these findings in diverse patient populations and to refine the prediction model with additional influential features.

Conclusion

This study has provided valuable insights into the prognostic significance of ALBI-score trajectories in patients with intermediate and advanced HCC undergoing TACE. The identification of distinct ALBI-score trajectory and their association with survival outcomes underscores the importance of dynamic liver function assessment and protection of liver function during treatment in this patient population. While the findings have immediate clinical implications, particularly in guiding treatment decisions and follow-up strategies, further research is needed to validate and extend these results in broader contexts. The integration of ALBI-score trajectories into comprehensive prognostic models holds promise for enhancing personalized care in HCC, ultimately improving patient outcomes in this challenging disease.

Abbreviations

TACE, Transarterial chemoembolization; HCC, Hepatocellular carcinoma; ALBI-score, Albumin-Bilirubin score; GBTM, Group-Based Trajectory Modeling; SHAP, Shapley Additive Explanations; OS, Overall survival; PFS, Progression-free survival; cTACE, Conventional TACE; DEB-TACE, Drug-eluting beads TACE; CI, Confidence interval; CR, Complete response; AUC, Area under the receiver operating characteristic curve; Avep%, Average Posterior Probability Proportions per Class; BIC, Bayesian Information Criterion; Ek, Relative Entropy.

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Disclosure

The authors report no conflicts of interest in this work.

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