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Prognosis of Patients with Hepatocellular Carcinoma Treated with TACE: A New Score Combining Alpha-Fetoprotein and Des-γ-Carboxy Prothrombin

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Purpose: Hepatocellular carcinoma (HCC) represents a significant global health problem, requiring precise prognostic tools for optimal treatment stratification. This study aimed to develop a new risk prediction score, called AD score, based on the serum markers alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), to offer an objective and accurate preoperative assessment of HCC in patients undergoing transarterial chemoembolization (TACE).

Patients and Methods: This was a retrospective study that included 295 HCC patients who were subjected to TACE (training set, n=147; testing set, n=148). Serum AFP and DCP levels were log-transformed to construct the AD score. Multivariate Cox regression analysis on cirrhosis subgroups validated the objectivity of the model. Performance comparison of established models (Child Pugh, BCLC, ALBI, Up-to-seven, Six-and-twelve, Four and seven, HAP score, mHAP-II, FAIL-T score), was assessed through time-dependent receiver operating characteristic (ROC) curves and risk stratification.

Results: The AD score, incorporating lgAFP and lgDCP, demonstrated superior predictive accuracy than the existing models. Time-dependent ROC curve revealed the consistent superiority of the AD score over a 5-year period. The risk stratification into low, intermediate, and high group based on the AD score showed a significant survival difference in both training and testing set.

Conclusion: For HCC patients undergoing TACE, the AD score serves as an objective and straightforward prognostic tool, enhancing predictive accuracy and showcasing its clinical utility. It demonstrates potential significance as a crucial addition to preoperative risk assessment for TACE.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, prognostic model, risk assessment, AD score

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause of cancer-related death globally.[1,2] Transarterial chemoembolization (TACE) is widely recognized as one of the most commonly used treatments for HCC. According to the Barcelona Clinic Liver Cancer prognosis (BCLC) guidelines, surgical treatment is not suitable for patients with advanced HCC. For these patients, systemic therapy and TACE are the available treatment options.[3,4] However, the clinical practice revealed that not all individuals may equally benefit from TACE due to the difference in liver function and tumor burden.[5–7] Therefore, an accurate preoperative tumor staging is essential to identify the appropriate treatment and evaluate the prognosis in patients with HCC.[8,9]

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The main methods to evaluate the prognosis of TACE-treated patients in clinical practice are divided into two categories: those focusing on liver function, such as Child-Pugh and ALBI scores,[10] and those targeting tumor burden, including Up-to-seven and Six-and-twelve scores.[11,12] Although these staging methods predict the prognosis of HCC patients undergoing TACE to some extent, the discrepancy between liver function and tumor progression is evident. The complexity of tests also presents certain obstacles for clinical application. Therefore, an objective and simple method is needed to accurately predict the prognosis of patients undergoing TACE treatment. Currently, few reports are available on the combined use of common tumor markers in clinical practice for the preoperative assessment of HCC patients undergoing TACE.

In clinical, The two major tumor markers for the preoperative assessment of liver cancer are alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP).[13] They respectively reflect tumor burden and liver function status. Additionally, DCP is also associated with hepatic insufficiency. It is undeniable that a significant survival difference exists between patients with high and low expression of AFP and DCP. However, survival differences are difficult to evaluate using the existing models in patients with neither high nor low AFP levels.

The objective of this study is to develop and validate a new risk score by combining AFP and DCP, which considers both tumor burden and liver function. This score will be used for subsequent risk stratification to predict the prognosis of patients undergoing TACE.

Materials and Methods

Study Population

The medical records of a total of 1261 HCC patients treated with TACE at our department from December 2018 to November 2023 were retrospectively analyzed. HCC diagnosis was performed based on histology or imaging according to the European Association for the study of the liver criteria guidelines. The diagnosis of liver cirrhosis was based on the "2019 Chinese guidelines on the management of liver cirrhosis". According to the guidelines, high levels of AFP were defined as AFP greater than 400 ng/mL. And based on our previous research, high levels of DCP were defined as DCP great than 180 mAU/mL.[14] The inclusion criteria were the following: (1) patients with unresectable HCC undergoing TACE. (2) Pre-operative Child–Pugh class A or B. (3) age ≥ 18 years. The exclusion criteria were the following: (1) patients with incomplete preoperative AFP and DCP data or who were lost to follow-up. (2) A score of the Eastern Cooperative Oncology Group (ECOG) performance status>1. (3) Patients with extrahepatic metastases. (4) Patients who had other malignant tumors. (5) treatment with other systemic or loco-regional therapies. A total of 295 patients were ultimately enrolled in this study. All patients were monitored until death or the final date of the follow-up in November 2021. The patients were randomly divided into two groups: the training group (n=147), and the testing group (n=148). The flow chart of the present study is shown in Figure 1.

Clinical Data

The present retrospective study was approved by the ethics committee review board of the First Affiliated Hospital of Nanjing Medical University, (approval no. 2022-SR-249), due to the nature of retrospective studies, informed consent was waived. Baseline patient data were collected, including age, sex, combination of cirrhosis or hepatitis, imaging study results, ECOG score, Child-Pugh score, AFP, DCP, aspartate and alanine aminotransferase (ALT and AST) and other coagulation function parameters. (Detailed information on tumor markers can be found in the supplementary materials). Patients were followed up through telephone consultations to assess symptoms and overall health conditions, as well as through scheduled outpatient visits for detailed clinical evaluations during the first month after the TACE procedure. Overall survival (OS) was defined as the time from the date of TACE treatment to either the end of the follow-up period or death.

TACE Procedure

The procedure began with routine disinfection, followed by towel spreading and administration of local anesthesia with 2% lidocaine. A 5F sheath was introduced into each patient's femoral artery using the Seldinger technique. A 5-F RH catheter was then used, through which arteriography of the celiac trunk, superior mesenteric artery, and hepatic arteries

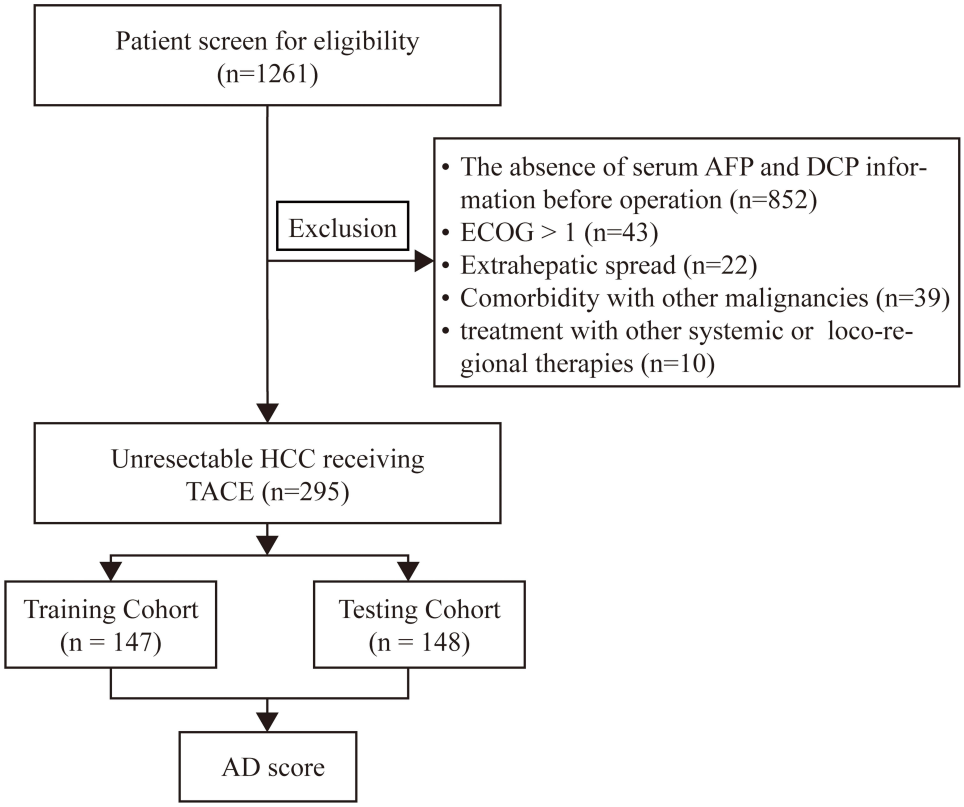

Figure 1 The Flowchart of this study.
Abbreviations: AFP, alpha-fetoprotein; DCP, des-γ-carboxyprothrombin; TACE, transcatheter arterial chemoembolization. ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma.

were successively performed to collect an overview of the hepatic arterial blood supply and evaluate tumor location, number, and size of HCC. The 2.7-F microcatheter was superselected into the blood supply artery, and angiography confirmed that the microcatheter was accurately positioned. After the target artery was catheterized, a 1:1 mixed suspension of iodized oil and epirubicin was infused into the artery through the catheter, depending on liver function and tumor size. Finally, gelatin sponge particles were infused to embolize the artery until no tumor staining was found after repeat angiography. Finally, the guidewire and catheters were removed, and the femoral artery was compressed for 10 min to secure hemostasis at the puncture site.

The Construction of lgAFP and lgDCP

In this study, the levels of AFP and DCP were log-transformed to create lgAFP and lgDCP, respectively. Log transformation was applied to normalize the distribution of these biomarkers and to linearize their relationship with overall survival, as non-linear variables can lead to instability in statistical modeling. By applying this transformation, we ensured that AFP and DCP could be appropriately incorporated into the Cox regression model for survival analysis. The formula for the AD score was subsequently derived based on these log-transformed variables.

Establishment and Validation of the Prognostic Model

Cox regression analysis (progressing through forward stepwise regression) was performed on cirrhosis subgroups of the training set to remove the impact of cirrhosis on the relevant indicators. A multivariate Cox regression analysis for lgAFP and lgDCP was performed on the training set to obtain their respective coefficients (coef values) and the formula for calculating the risk score was obtained. Subsequently, the risk score was calculated for each patient in the training set, using the X-tile software (version 3.6.1) to determine the optimal value to categorize individuals into high-risk, intermediate-risk, and low-risk group. The model was validated using the ROC curve and calibration curve in the testing set.

AD Score Model Compared with Other Models

The AD score and AD group were compared with other mainstream prognostic models. Firstly, the performance of the AD score and AD group was compared with that of models including Child Pugh, BCLC, ALBI, Up-to-seven, Six-and-twelve, Four and seven, HAP score, mHAP-II and FAIL-T score by the calculation of the area under the curve (AUC) in the survival prediction. Secondly, a time-dependent ROC curve analysis was performed to assess the predictive performance of the model at different time points.

Survival Prediction in Different Subgroups

Further evaluation was performed on subgroups of BCLC staging, tumor quantity, and maximum tumor diameter in the stratification of AD scores. The Kaplan-Meier curve was used to analyze the survival curve for the overall cohort as well as different subgroups in both the training and testing set. The objective was to explore the predictive performance of the AD score across different patient subgroups.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL) and R software (version 4.1; www.r-project.org/). Continuous data were expressed as mean ± standard deviation (SD) or median (interquartile range). Two groups with continuous variables that fit a normal distribution were compared using unpaired Student's *t*-test. Non-normally distributed data were compared using the Mann–Whitney *U*-test. Non-continuous and categorical data were compared using the chi-square test. The Kaplan–Meier method was used to perform the survival analysis, and the Log rank test was used to compare the survival between groups. The effectiveness of the models was assessed by the ROC curve. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline Demographics and Clinical Characteristics

After randomization, the training and testing set contained 147 and 148 patients, respectively. The median survival time in the total cohort was 34 months. There were no significant differences in all baseline clinicopathological characteristics and all of them are listed in Table 1. The median follow-up in the training and testing sets was 32.6 months and 32.1 months, respectively. Most patients were male (79.7%), and infection with hepatitis virus was the underlying cause in most patients (73.6%).

Prognostic Factors for Recommending TACE in Patients in the Training Set

The linear transformation of AFP and DCP was conspicuously evident after the logarithmic transformation (Figure 2). Factors associated with an increased risk of death included hepatitis, lgAFP, lgDCP, international normalized ratio (INR), ALT, AST, blood platelet (PLT), albumin and total bilirubin (Tbil), as revealed by the univariate analysis. Cirrhosis (HR = 0.511, 95% CI: 0.304–0.859, P = 0.011), Tbil (HR = 1.008, 95% CI: 1.001–1.014, P = 0.017), lgAFP (HR = 1.328, 95% CI:1.016–1.736, P = 0.038), and lgDCP (HR = 1.392, 95% CI: 1.008–1.922, P = 0.044) were independently associated with decreased survival (Table 2), as revealed by the multivariate Cox analysis.

Construction of the Risk Assessment Score

Both lgAFP (HR = 1.604, 95% CI: 1.104–2.332, P = 0.013) and lgDCP (HR = 1.692, 95% CI: 1.093–2.621, P = 0.018) significantly contributed to the prediction of the survival rate, as revealed by the multivariate Cox regression analyses on the cirrhosis subgroup of the training set. This removed the influence of cirrhosis on these variables (Table S1). Subsequently, the model was constructed based on lgAFP and lgDCP. The formula for the risk assessment score was the following (which was called the AD score):

AD score = 0.375 × lgAFP + 0.482 × lgDCP

(Where "lgAFP" and "lgDCP" are binary variables)

Table 1 Baseline Demographics and Clinical Characteristics

Baseline Characteristics	Number (%) / Median (IQR)			p
	Overall (n=295)	Train cohort (n=147)	Test cohort (n=148)	
Age (years)				0.322
≤60	147 (49.8)	78 (53.1)	69 (46.6)	
>60	148 (50.2)	69 (46.9)	79 (53.4)	
Sex				0.118
Male	60 (20.3)	24 (16.3)	36 (24.3)	
Female	235 (79.7)	123 (83.7)	112 (75.7)	
Hepatitis				0.666
No	78 (26.4)	41 (27.9)	37 (25.0)	
Yes	217 (73.6)	106 (72.1)	111 (75.0)	
Cirrhosis				1.000
No	148 (50.2)	74 (50.3)	74 (50.0)	
Yes	147 (49.8)	73 (49.7)	74 (50.0)	
ECOG				0.258
0	123 (41.7)	56 (38.1)	67 (45.3)	
1	172 (58.3)	91 (61.9)	81 (54.7)	
CP				0.342
A	244 (82.7)	118 (80.3)	126 (85.1)	
B	51 (17.3)	29 (19.7)	22 (14.9)	
Number				0.485
≤3	99 (33.6)	46 (31.3)	53 (35.8)	
>3	196 (66.4)	101 (68.7)	95 (64.2)	
Size (cm)				0.503
≤5	115 (39.0)	54 (36.7)	61 (41.2)	
>5	180 (61.0)	93 (63.3)	87 (58.8)	
lgAFP	1.81 [0.87, 2.89]	1.93 [0.97, 2.84]	1.75 [0.83, 2.91]	0.583
lgDCP	2.40 [1.78, 3.47]	2.29 [1.72, 3.23]	2.56 [1.82, 3.68]	0.051
ALT (U/L)	29.80 [20.15, 47.15]	29.80 [19.85, 45.50]	30.05 [20.85, 50.85]	0.578
AST (U/L)	38.80 [28.25, 62.10]	36.70 [28.10, 56.50]	39.95 [28.77, 62.65]	0.517
PLT (10^9/L)	116.10 [75.05, 165.00]	116.00 [76.50, 153.50]	119.05 [74.75, 187.78]	0.255
INR (median [IQR])	1.13 [1.07, 1.20]	1.12 [1.08, 1.20]	1.13 [1.07, 1.19]	0.775
Albumin (g/L)	37.00 [33.90, 40.30]	37.60 [33.60, 40.45]	37.00 [34.05, 39.80]	0.770
Tbil (mmol/L)	16.30 [12.00, 22.85]	16.60 [12.05, 22.75]	15.90 [12.00, 22.97]	0.533

Abbreviations: CP, Child-Pugh class; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; DCP, des-γ-carboxyprothrombin; AST, alanine; AST, aspartate aminotransferase; PLT, Platelet Count; INR, International Normalized Ratio; IQR, Interquartile Range.

The sum of points was used to predict the risk at 1, 2 and 3 years after TACE for each patient. The same scoring method was used on the testing set for subsequent validation. In the overall cohort, patients were categorized into three groups based on the AD score: low, intermediate and high- group, which were called AD groups.

Optimal Prediction of OS by the AD Score

Patients were divided into three groups in the training set using the third quartile of the AD score as the cutoff value. The cutoff point was as follows: low-AD group: AD score ≤ 1.63; intermediate-AD group: AD score > 1.63 and ≤ to 2.32; high-AD group: AD score > 2.32. The training set showed a significant difference in OS between the high, intermediate and low-AD group (Figure 3A, P < 0.0001). Comparisons within each group also revealed a significant difference. (Figure 3B–D). Similarly, a significant difference in OS was found among patients in the high, intermediate and low-AD group in the testing set (Figure 3E, P < 0.0001) and overall cohort (Figure 3I, P < 0.0001), as well as in comparisons within the groups (Figure 3F–H, *P* < 0.0001; Figure 3J-L, P < 0.0001).

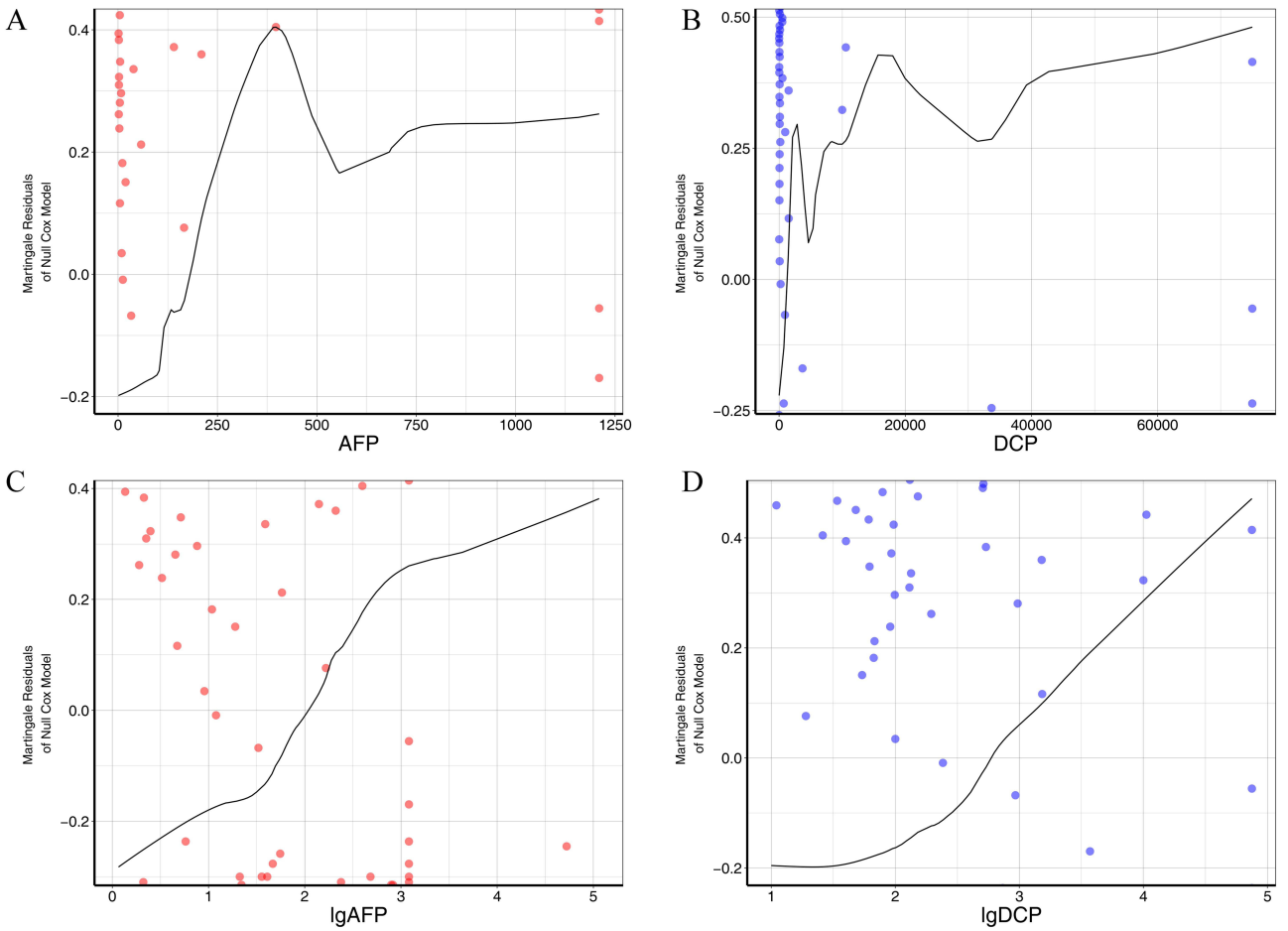

Figure 2 Linear Transformation of AFP and DCP (**A** and **B**), before transformation, (**C** and **D**), after transformation).
Abbreviations: AFP, alpha-fetoprotein; DCP, des-γ-carboxyprothrombin.

Predictive Performance of the AD Score Model

The calibration curve showed that the model had good calibration, further supporting the model's predictive ability and reliability (Figure S1). At a same time, comparative analysis with other established HCC prognostic models was performed, such as Child Pugh, BCLC, ALBI, Up-to-seven, Six-and-twelve, Four and seven, HAP score, mHAP-II and FAIL-T score by calculating the ROC curve. The results indicated that this model exhibits excellent predictive performance along with a simpler and more efficient testing method. (Figure 4A-B, AD score AUC= 0.656, AD group AUC= 0.637).

The time-dependent ROC curve for our model was calculated, and the results demonstrated its excellent predictive performance. The area under the ROC curve was the highest for the AD score (1-year: 0.824; 2-year: 0.756; 3-year: 0.769) and AD group (1-year: 0.779; 2-year: 0.734; 3-year: 0.770) in 3 years (Figure 5A-B). The time-dependent ROC curves were also computed for other models, and the 1- and 2-, and 3-year AUROC values of the AD score were higher than those of the other models (Table 3). The results in the form of a time-dependent AUC provided a more intuitive representation, clearly indicating that the predictive performance of the AD score within a 5-year period consistently surpassed that of other models (Figure 5C).

Effective Prediction of the Survival Outcome Among Different Subgroups by the AD Score

The survival analysis was performed separately for different subgroups within the overall cohort based on BCLC staging, tumor number, and tumor size. Figure 6 shows that in the three stratified subgroups, different AD groups also showed a significant statistical difference in OS, providing further evidence of the excellent predictive effect of the AD score.

Table 2 Cox Regression in Train Cohort

Characteristics	Univariate cox			Multivariate cox					
	HR	95% CI	p	HR	95% CI	SE	Z	P	Coef
Train Cohort (n=147)									
Sex	0.908	0.476–1.732	0.769						
Age	0.989	0.612–1.598	0.964						
Hepatitis	0.861	0.502–1.477	0.588						
Cirrhosis	0.514	0.316–0.837	0.008*	0.511	0.304–0.859	0.265	−2.534	0.011*	
ECOG	0.713	0.443–1.149	0.165						
CP	1.899	1.095–3.294	0.023*	1.612	0.875–2.969	0.312	1.532	0.126	
Number	2.234	1.373–3.634	0.001*	1.490	0.846–2.625	0.289	1.380	0.168	
Size	2.406	1.485–3.897	<0.001*	1.101	0.556–2.181	0.349	0.277	0.782	
lgAFP	1.611	1.259–2.062	<0.001*	1.328	1.016–1.736	0.137	2.078	0.038*	
lgDCP	1.776	1.403–2.248	<0.001*	1.392	1.008–1.922	0.165	2.011	0.044*	
ALT	1.009	1.004–1.014	<0.001*	1.007	0.994–1.019	0.006	1.056	0.291	
AST	1.007	1.004–1.010	<0.001*	1.001	0.992–1.009	0.004	0.128	0.898	
PLT	1.002	0.999–1.006	0.150						
INR	0.977	0.212–4.495	0.976						
Albumin	0.937	0.899–0.978	0.003*	0.972	0.928–1.018	0.023	−1.216	0.224	
Tbil	1.008	1.003–1.014	0.005*	1.008	1.001–1.014	0.003	2.392	0.017*	
Model Parameters in Train Cohort									
lgAFP				1.455	1.142–1.854	0.124	3.033	0.002*	0.375
lgDCP				1.619	1.282–2.043	0.119	4.057	<0.001*	0.482

Abbreviations: CP, Child-Pugh class; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; DCP, des-γ-carboxyprothrombin; AST, alanine; AST, aspartate aminotransferase; PLT, Platelet Count; INR, International Normalized Ratio; HR, hazard ratio.

Discussion

TACE is the primary treatment for unresectable HCC increasingly used in clinical practice to effectively prolong patient survival.[15] Accurately identifying which patients will benefit from TACE is important. Existing prognostic models for HCC patients are usually based on liver function or tumor burden in clinical practice. However, changes in liver function do not always correspond with tumor progression, meaning the predictive accuracy of this model for HCC patients undergoing TACE is not fully reliable.[16–18] Although several prognostic models have been developed to predict the effectiveness of TACE, the complexity of the tests also poses challenges for clinical application.

AFP and DCP are tumor markers commonly used to assess the prognosis of HCC patients undergoing TACE, they reflect tumor burden and liver function, respectively, and DCP is also associated with hepatic insufficiency.[19,20] AFP is not the most suitable prognostic indicator in clinical practice due to its low specificity and sensitivity (sensitivity of 39–64%, specificity of 76–91%).[21,22] Since Liebman et al first reported the correlation between DCP levels and the occurrence, metastasis, and recurrence of HCC in 1984, several studies demonstrated its value in the diagnosis and prognosis of HCC.[23–25] Our previous research demonstrated a correlation between increased serum DCP levels and poor prognosis in HCC patients who are AFP-negative and undergoing TACE.[14] Thus, the combination of AFP and DCP as a biomarker panel for the prognostic preoperative assessment of patients undergoing TACE may possess an increased diagnostic value. A meta-analysis evaluating the diagnostic value of serum markers in HCC demonstrated that the diagnostic performance of AFP and DCP combination is superior to that of AFP or DCP alone (AUC[AFP+DCP] = 0.90, AUC[AFP] = 0.75, AUC[DCP] = 0.88).[26] Lee et al also demonstrated that increased levels of AFP and DCP are important predictive factors for OS in patients undergoing TACE.[27] Indeed, they found a significant difference in OS between patients with high and low levels of AFP and DCP expression. However, it is difficult to make accurate

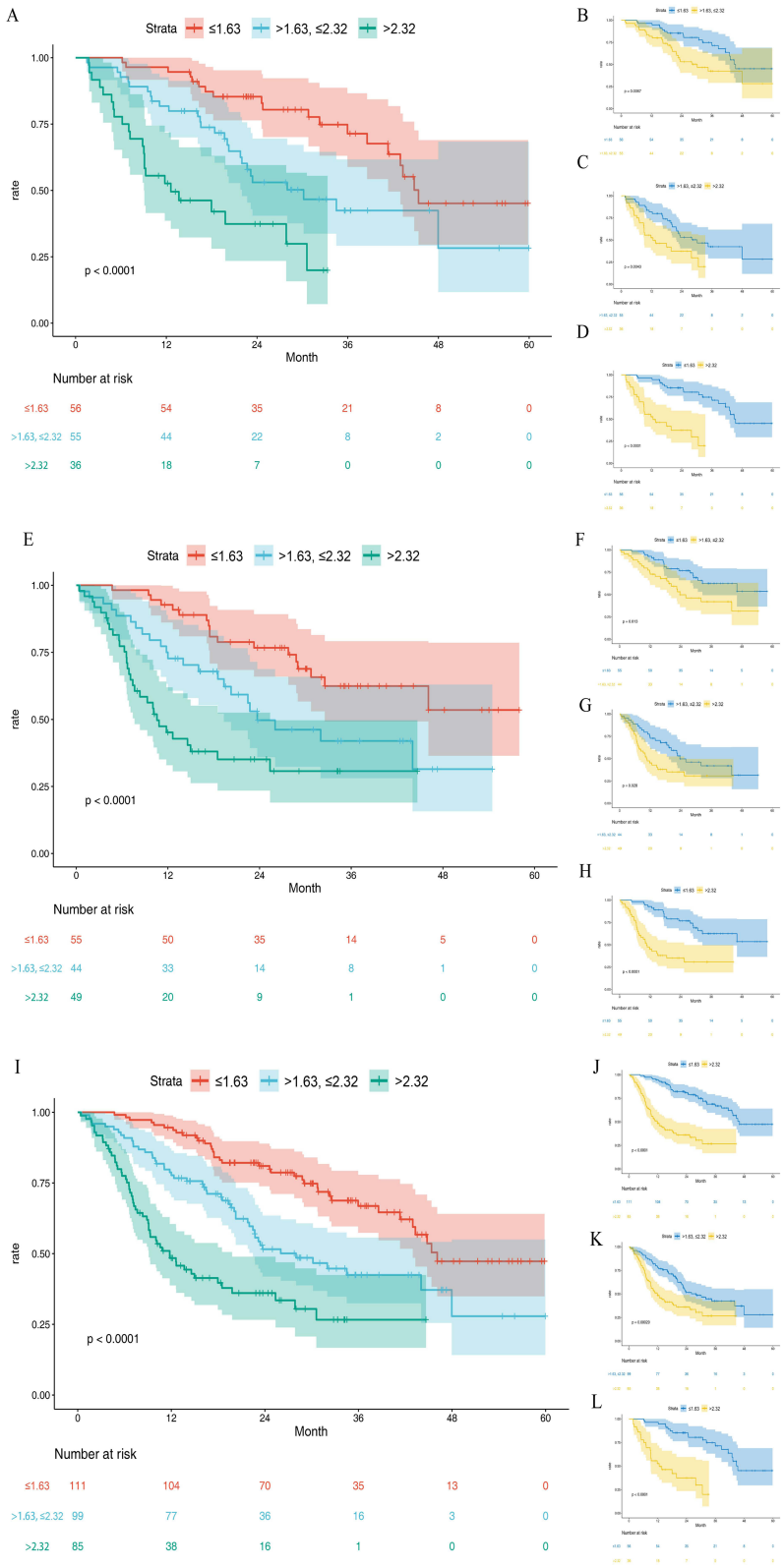

Figure 3 Kaplan-Meier survival curves after dividing patients into three groups based on the AD score. (**A**–**D**) The overall survival curves for the three groups in the training set, as well as the pairwise comparison survival curves between the three groups. (**E**–**H**) The overall survival curves for the three groups in the test set, as well as the pairwise comparison survival curves between the three groups. (**I**–**L**) The overall survival curves for the three groups in the entire cohort, as well as the pairwise comparison survival curves between the three groups.

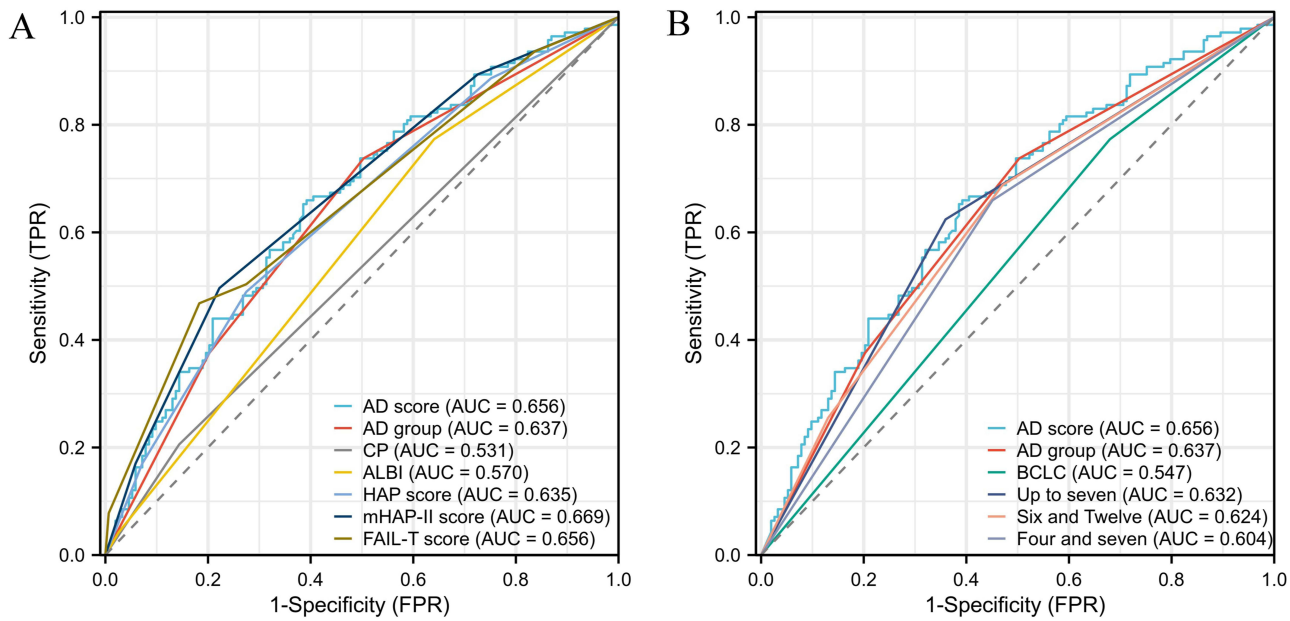

Figure 4 ROC curve in different Prognostic Models. (**A**) The ROC curve of AD score, AD group, Child-Pugh, ALBI, HAP score, mHAP-II and FAIL-T models. (**B**) The ROC curve of AD score, AD group, BCLC, Up-to-seven, Six-and-Twelve, and Four-and-seven models.

Abbreviations: CP, Child Pugh class, BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin. HAP score, hepatoma arterial-embolization prognostic score; mHAP-II score, modified hepatoma arterial-embolization prognostic-II score; FAIL-T, AFP, AST, tumor size, ALT, and Tumor number.

prognostic predictions using the existing assessment models for patients with levels of AFP and DCP that are neither high nor low. Therefore, an objective and simple model is necessary to accurately predict the prognosis of these patients.

Using Cox regression to build a model requires linear variables, while AFP and DCP are non-linear variables.[28–30]Although previous studies have explored the role of tumor markers in the prognosis of HCC patients,[31,32] these variables were not log-transformed in the model construction, which may have affected the predictive performance of the models. By log-transforming AFP and DCP into logAFP and logDCP, the transformed variables demonstrated a clear linear relationship, this helps to improve the performance of our model.

Thus, a serum-based scoring model (AD score) was constructed based on the logAFP and logDCP. The coefficients in the AD score were obtained through multivariate Cox regression analysis. After log-transforming, we applied Cox regression to determine the relationship between these variables and the hazard of death. The resulting coefficients reflect the relative contributions of each marker to the risk of death, and the AD score was constructed by combining these weighted contributions. The coefficients for lgAFP and lgDCP were derived by minimizing the residuals in the Cox model, ensuring the most accurate representation of their impact on prognosis. The scores of each individual were calculated and applied to the testing set and the total cohort. The AUC of the AD score at 1, 2, and 3 years indicated the best predictive performance compared with that of other models. The time-dependent AUC also visually demonstrated that the performance of the AD score was significantly superior to other existing models over a period of 5 years, suggesting that this score more accurately predicted the survival status of patients at various time points. As regards the six and twelve model, classical prognostic models of liver cancer, our results were compared with the original study, and both showed similar AUCs at 3 years (1-year: 0.703; 2-year: 0.643; 3-year: 633 vs 1-year: 0.72; 2-year: 0.69; 3-year: 0.65), further confirming the reliability of our data. Continuous prognostic tools predict outcomes more accurately, while risk-stratified models are more suitable for clinical use. Therefore, patients were divided into high, medium and low-AD group. The survival analysis showed significant differences in patient survival among the three groups. The high AD score group in the subgroup of BCLC staging showed a significantly poorer survival prognosis compared to that in the mid-low score group, emphasizing the differential prognostic value of the AD score at different disease stages. In the subgroup analysis based on tumor quantity and diameter, the high AD score group similarly showed a significant survival difference from the mid-low score group, providing support in the use of the AD score under different tumor burdens.

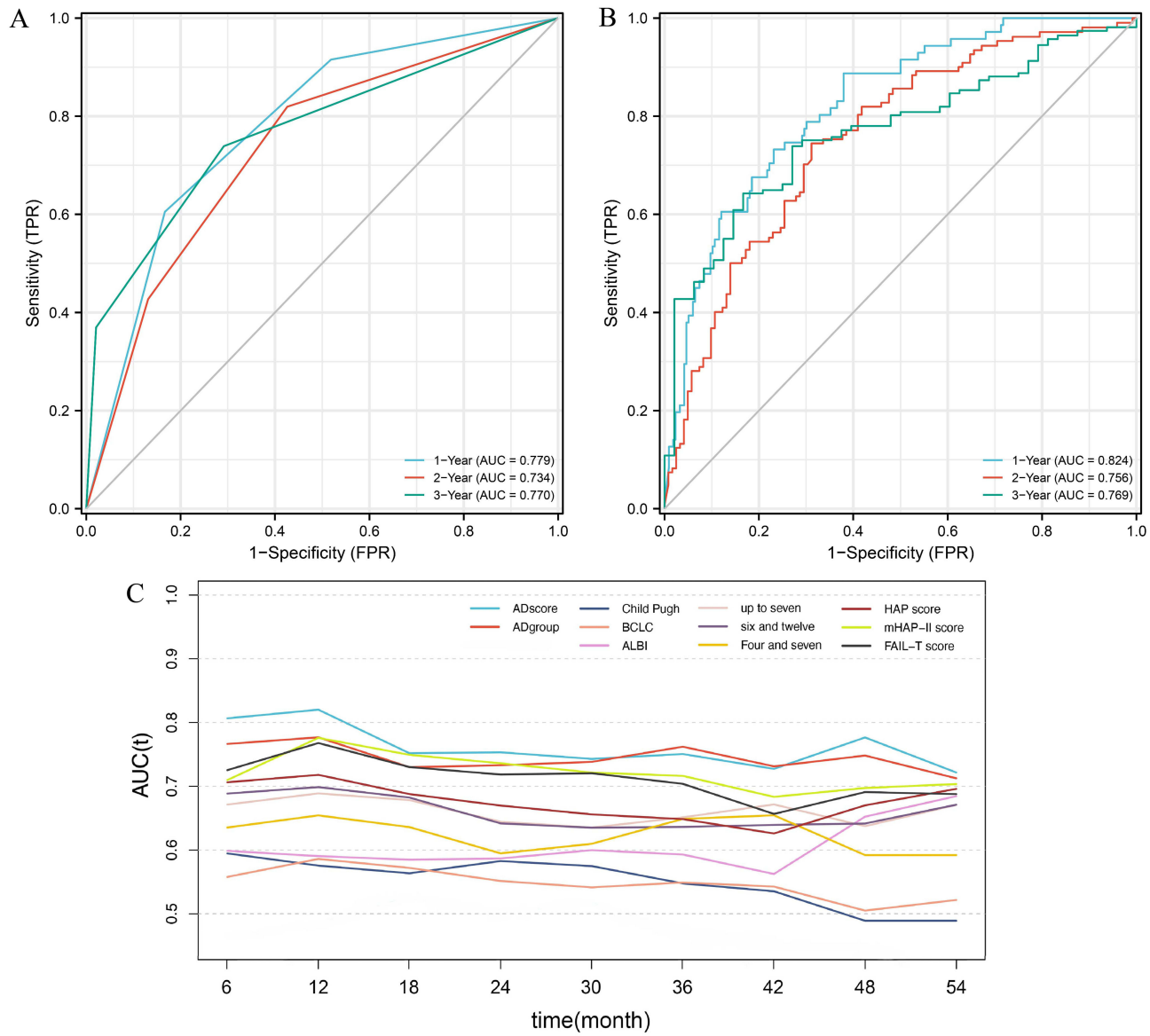

Figure 5 (**A**) Time-Dependent ROC of AD score. (**B**)Time-Dependent ROC of AD group. (**C**) Time-Dependent AUC in different Prognostic Models.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin. HAP score, hepatoma arterial-embolization prognostic score; mHAP-II score, modified hepatoma arterial-embolization prognostic-II score; FAIL-T, AFP, AST, tumor size, ALT, and Tumor number.

This suggested that the AD group model was a simple and feasible prognostic tool for predicting the survival of these patients. The survival distribution, discrimination, and mortality prediction of patients with an ideal TACE who relapsed were compared with Child Pugh, BCLC, ALBI, Up-to-seven, Six-and-twelve systems, Four and seven, HAP score, mHAP-II and FAIL-T score. The AD score and group had higher predictive efficacy and provided a simpler, more efficient testing method than the other models.

In our study, the median survival time of patients in the training set was 35 months, which was similar to that of the total cohort. lgAFP and lgDCP were independent prognostic predictors after TACE, which was consistent with previous studies where a greater tumor burden leads to shorter survival length. Increased serum AFP and DCP levels are an established biomarker of poor prognosis at all stages of HCC, reflecting the tumor's intrinsic properties, suggesting higher aggressiveness, higher proliferation and poor histological differentiation.[33] Our model integrates the tumor markers AFP and DCP, simplifying the diagnostic process by avoiding complex multi-parameter testing while maintaining strong predictive performance. Additionally, the model accounts for both tumor burden and liver function,

Table 3 Time-Dependent AUC in Different Prognostic Models

Model	1-yr AUROC (95% CI)	2-yr AUROC (95% CI)	3-yr AUROC (95% CI)
Training Cohort (n=147)			
AD score	0.838 (0.798–0.878)	0.775 (0.733–0.817)	0.818 (0.769–0.867)
AD group	0.787 (0.745–0.829)	0.737 (0.694–0.780)	0.813 (0.771–0.855)
Child Pugh	0.616 (0.568–0.664)	0.593 (0.557–0.629)	0.536 (0.491–0.581)
BCLC	0.658 (0.620–0.696)	0.586 (0.542–0.630)	0.572 (0.509–0.635)
ALBI	0.620 (0.576–0.664)	0.615 (0.572–0.658)	0.621 (0.565–0.677)
Up to seven	0.744 (0.702–0.786)	0.662 (0.617–0.707)	0.702 (0.650–0.754)
Six and twelve	0.732 (0.686–0.778)	0.623 (0.574–0.672)	0.667 (0.611–0.723)
HAP score	0.728 (0.677–0.779)	0.733 (0.688–0.778)	0.707 (0.65–0.764)
mHAP-II score	0.734 (0.686–0.782)	0.77 (0.725–0.815)	0.766 (0.718–0.814)
FAIL-T score	0.787 (0.748–0.826)	0.708 (0.665–0.751)	0.678 (0.617–0.739)
Four and seven	0.688 (0.648–0.728)	0.667 (0.623–0.711)	0.648 (0.59–0.706)
Testing Cohort (n=148)			
AD score	0.809 (0.772–0.846)	0.737 (0.691–0.783)	0.724 (0.666–0.782)
AD group	0.771 (0.732–0.810)	0.730 (0.686–0.774)	0.728 (0.677–0.779)
Child Pugh	0.565 (0.529–0.601)	0.578 (0.550–0.606)	0.557 (0.527–0.587)
BCLC	0.598 (0.555–0.641)	0.517 (0.473–0.561)	0.515 (0.467–0.563)
ALBI	0.573 (0.533–0.613)	0.558 (0.515–0.601)	0.547 (0.493–0.601)
Up to seven	0.634 (0.591–0.677)	0.619 (0.574–0.664)	0.608 (0.548–0.668)
Six and twelve	0.679 (0.629–0.729)	0.661 (0.614–0.708)	0.599 (0.54–0.658)
HAP score	0.723 (0.675–0.771)	0.61 (0.56–0.66)	0.577 (0.513–0.641)
mHAP-II score	0.822 (0.786–0.858)	0.702 (0.657–0.747)	0.668 (0.606–0.73)
FAIL-T score	0.787 (0.748–0.826)	0.708 (0.665–0.751)	0.678 (0.617–0.739)
Four and seven	0.63 (0.587–0.673)	0.525 (0.479–0.571)	0.66 (0.602–0.718)
Total Cohort (n=295)			
ADscore	0.824 (0.797–0.851)	0.756 (0.725–0.787)	0.769 (0.731–0.807)
ADgroup	0.779 (0.750–0.808)	0.734 (0.703–0.765)	0.770 (0.736–0.804)
Child Pugh	0.583 (0.554–0.612)	0.583 (0.56–0.606)	0.545 (0.517–0.573)
BCLC	0.624 (0.594–0.654)	0.552 (0.521–0.583)	0.543 (0.503–0.583)
ALBI	0.591 (0.562–0.620)	0.585 (0.555–0.615)	0.585 (0.546–0.624)
Up to seven	0.686 (0.656–0.716)	0.642 (0.611–0.673)	0.658 (0.618–0.698)
Six and twelve	0.703 (0.668–0.738)	0.643 (0.609–0.677)	0.633 (0.592–0.674)
HAP score	0.725 (0.69–0.76)	0.67 (0.636–0.704)	0.643 (0.6–0.686)
mHAP-II score	0.78 (0.75–0.81)	0.736 (0.704–0.768)	0.716 (0.677–0.755)
FAIL-T score	0.773 (0.743–0.803)	0.718 (0.687–0.749)	0.693 (0.655–0.731)
Four and seven	0.657 (0.627–0.687)	0.595 (0.563–0.627)	0.653 (0.612–0.694)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin; HAP score, hepatoma arterial-embolization prognostic score; mHAP-II score, modified hepatoma arterial-embolization prognostic-II score; FAIL-T, AFP, AST, tumor size, ALT, and Tumor number.

enhancing its validity and making it more clinically valuable. Notably, parameters predictive of liver function, including Child–Pugh grade, were not significant after the multifactorial Cox analysis. This might be because the liver function parameters in recommended TACE patients were at relatively good levels, thus potentially introducing a certain degree of bias into the results.

It is essential to remove the influence of liver function factors from the model to achieve the most accurate and objective predictive performance. ALBI and BALAD are classical models for the assessment of HCC patient prognosis based on serum markers and are widely used in clinical practice.[10,34,35] Therefore, the modeling approach of ALBI was used in this study and COX regression analysis was performed on patients in the cirrhosis subgroup of the training set. The results indicated that lgAFP and lgDCP were both significant in distinguishing patients with or without cirrhosis, thus confirming that our model remains effective in predicting prognosis even in patients with cirrhosis. However, lgAFP

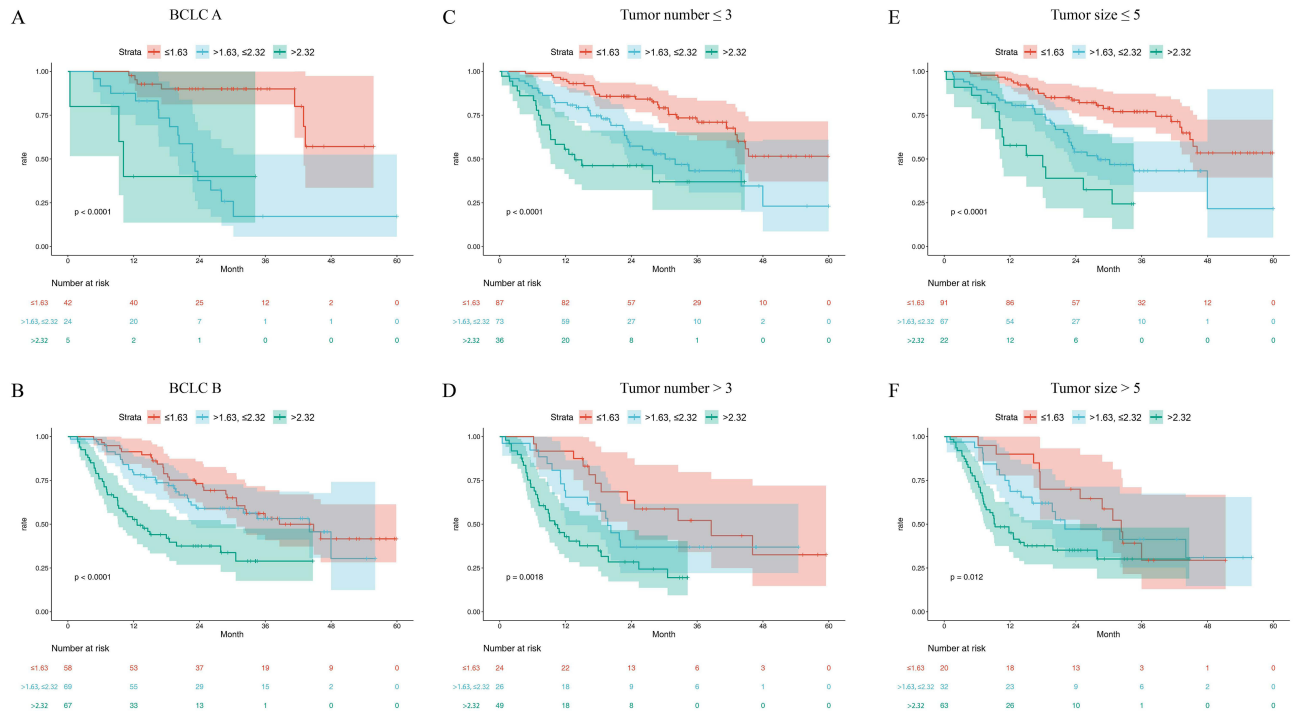

Figure 6 K-M Curves between AD groups in Subgroups. (**A**) Patients in BCLC A stage. (**B**) Patients in BCLC B stage. (**C**) Patients with a tumor count greater than or equal to three. (**D**) Patients with a tumor count less than three. (**E**) Patients with a maximum tumor diameter less than or equal to 5. (**F**) Patients with a maximum tumor diameter more than 5.

and lgDCP did not show simultaneous significance in two subgroups. This might be due to the subgroup regression being performed in the training set, where the number of cases was limited, leading to a certain degree of bias.

This study has some limitations. First, the included patients were selected in a single center, and selection bias could not be entirely avoided in this retrospective study. In addition, the method of categorizing continuous variables using optimal cutoff values might lead to a decrease in accuracy.[36] Finally, the sample size of the cohort was not large enough, which might have influenced the results.

Conclusion

The AD score constructed from the recommended TACE patient cohort predicted the prognosis of patients better than other traditional models. It has more accurate predictive efficacy and more simple testing approach than other traditional models, which might be of help in clinical decision-making.

Ethics Approval and Informed Consent

The present retrospective study was approved by the ethics committee review board of the First Affiliated Hospital of Nanjing Medical University.(Nanjing, China), which waived the requirement for informed patient consent (approval no. 2022-SR-249). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. All patient data used in this study has been anonymized or kept confidential in compliance with ethical guidelines and relevant privacy regulations.

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Disclosure

The authors report no conflicts of interest in this work.

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