ORIGINAL RESEARCH

A Machine Learning Model for Predicting Prognosis in HCC Patients With Diabetes After TACE

Linxia Wu [ID][1−3],*, Lei Chen [ID][1−3],*, Lijie Zhang [ID][1,4],*, Yiming Liu[1,5],*, Die Ouyang[1], Wenlong Wu[5,6], Yu Lei[5,6], Ping Han[1], Huangxuan Zhao[1−3], Chuansheng Zheng[1−3]

[1]Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430022, People's Republic of China; [2]Department of Interventional Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430022, People's Republic of China; [3]Hubei Provincial Clinical Research Center for Precision Radiology & Interventional Medicine, Wuhan, Hubei Province, 430022, People's Republic of China; [4]Department of Interventional Radiology, The Fifth Medical Center of Chinese, PLA General Hospital, Beijing, 100039, People's Republic of China; [5]Department of Interventional Radiology, Auto Valley Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430056, People's Republic of China; [6]Department of Interventional Radiology, Jinyinhu Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430048, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chuansheng Zheng; Huangxuan Zhao, Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430022, People's Republic of China, Email hqzcsxh@sina.com; zhao_huangxuan@sina.com

Purpose: Type II diabetes mellitus (T2DM) has been found to increase the mortality of patients with hepatocellular carcinoma (HCC). Therefore, this study aimed to establish and validate a machine learning-based explainable prediction model of prognosis in patients with HCC and T2DM undergoing transarterial chemoembolization (TACE).

Patients and Methods: The prediction model was developed using data from the derivation cohort comprising patients from three medical centers, followed by external validation utilizing patient data extracted from another center. Further, five predictive models were employed to establish prognosis models for 1-, 2-, and 3-year survival, respectively. Prediction performance was assessed by the receiver operating characteristic (ROC), calibration, and decision curve analysis curves. Lastly, the SHapley Additive exPlanations (SHAP) method was used to interpret the final ML model.

Results: A total of 636 patients were included. Thirteen variables were selected for the model development. The final random survival forest (RSF) model exhibited excellent performance in the internal validation cohort, with areas under the ROC curve (AUCs) of 0.824, 0.853, and 0.810 in the 1-, 2-, and 3-year survival groups, respectively. This model also demonstrated remarkable discrimination in the external validation cohort, achieving AUCs of 0.862, 0.815, and 0.798 in the 1-, 2-, and 3-year survival groups, respectively. SHAP summary plots were also created to interpret the RSF model.

Conclusion: An RSF model with good predictive performance was developed by incorporating simple parameters. This prognostic prediction model may assist physicians in early clinical intervention and improve prognosis outcomes in patients with HCC and comorbid T2DM after TACE.

Keywords: hepatocellular carcinoma, type II diabetes mellitus, transarterial chemoembolization, overall survival, SHapley Additive exPlanations

Introduction

Liver cancer is among the cancers with the highest morbidity and mortality rates worldwide.[1] Hepatocellular carcinoma (HCC) is the most prevalent pathological subtype of liver cancer, accounting for over 75% of all liver cancers.[2] Although the incidence of HCC has decreased in several Asian countries, its prognosis remains poor. In terms of therapeutic interventions, transarterial chemoembolization (TACE) is one of the crucial treatment modalities for HCC. Several guidelines recommend TACE as the first-line treatment for patients unsuitable for resection, including early-stage patients who cannot undergo hepatic resection, liver transplantation, or radiofrequency ablation (RFA).[3−5] However, patients who undergo TACE are prone to tumor recurrence or metastasis, with one of the primary reasons being that incomplete embolization can induce a hypoxic

microenvironment in the tumor, which in turn promotes tumor neovascularization and consequently tumor progression.[6] Similar findings of hypoxic microenvironment and accelerated tumor progression have been observed in patients with HCC and type II diabetes mellitus (T2DM), thereby leading to poor prognosis in this population.[7,8]

Diabetes mellitus is a relatively common condition in population.[9] Previous studies have shown that diabetes can result in increased cancer morbidity and worsened survival in patients with HCC.[8,10] Moreover, diabetes-induced hyperglycemia in patients undergoing TACE for HCC can augment the metabolism of the Wnt/β-signaling pathway. Subsequently, this alteration may induce tumor development in hypoxic tumor cells, ultimately fostering tumor growth, proliferation, and progression.[11,12] Therefore, survival prognosis remains a concern in patients with combined HCC and T2DM and treated with TACE, with multiple factors suggested to influence prognosis in this specific population. Several prior studies have utilized preoperative limiting factors to explore the prognosis of patients with HCC undergoing TACE to provide better clinical treatment.[13–16] However, these investigations employed preoperative limited factors of TACE for survival prediction, which might not fully capture the efficacy of TACE in the patients. Therefore, identifying more comprehensive predictive modalities is essential to predict patient outcomes following TACE therapy.

Machine learning (ML) offers significant advantages in predicting post-treatment outcomes for cancer patients. ML models can handle large, complex, and heterogeneous datasets, incorporating a wide range of variables, including clinical, pathological, and imaging features, to provide more comprehensive and personalized prognosis predictions.[17,18] Li J et al included 288 patients with HCC to develop and validate a nomogram for prediction of acute liver function deterioration (ALFD) after drug-eluting beads TACE. In the validation cohorts, the nomogram demonstrated promising prediction for ALFD with AUC of 0.878.[19] Zhang MQ et al used radiomics features and clinical information by four machine learning algorithms to predict the prognosis of patients with HCC who have been treated with TACE. They found that extreme gradient boosting (XGBoost) exhibited the best performance in combined models, achieving an AUC of 0.979 in the training set and 0.750 in the testing set, demonstrating its strong prognostic prediction capability.[20] Another study using radiomics and clinicoradiomics features to create machine learning models and evaluate the ability of the models to predict local response of patients with HCC after TACE. They found machine learning models created with clinical and MRI radiomics features, may have promise in predicting local response after TACE.[21] However, most ML models function as "black boxes" that fail to explain the specific steps involved in their survival prediction among patients with tumors, thereby hindering the targeting of precise features for the analysis and guidance of specific medication.[22] Recently, the SHapley Additive exPlanations (SHAP) method has emerged as an interpretable ML model that can elucidate model output by decomposing the prediction results into the effects of individual features.[23] In the case of survival prediction in patients with tumors, this approach can determine the weight of each predictive variable on patient prognosis. Consequently, the SHAP method enables clinicians to focus on the strong-weighted variables, thus resulting in a more rational treatment strategy for these patients. Although several researchers have employed the SHAP model to predict the outcomes of patients with HCC after receiving TACE,[24,25] no studies utilizing the SHAP model have been conducted to evaluate prognosis prediction in patients with combined HCC and T2DM following TACE therapy.

In this study, we retrospectively enrolled 636 patients with HCC and comorbid T2DM who underwent TACE treatment at four medical centers. Furthermore, five prediction models, including random survival forest (RSF), extreme gradient boosting (XGBoost), gradient boosting machine (GBM), ML techniques-extended Cox proportional hazards (CoxPH), and recursive partitioning and regression trees (Rpart), were used to determine the factors affecting patient survival at 1, 2, and 3 years after TACE according to the preoperative biochemical and imaging characteristics of the patients. Subsequently, the SHAP method was applied to the best predictive mode to provide transparent predictions for its clinical application. Moreover, we developed a web application to allow healthcare professionals to generate survival probabilities for individual patients at 1, 2, and 3 years post-TACE treatment based on the preoperative profile of each patient.

Materials and Methods
Study Population
This retrospective study included 636 patients with HCC and T2DM who underwent TACE at four medical centers between January 2014 and June 2023. Two independent patient cohorts were used in this study. The first cohort was

a primary derivation cohort comprising patients from three medical centers in China, which was further split into a training and internal validation set and utilized for hyperparameter optimization and model selection, respectively. The primary derivation cohort consisted of 542 patients with combined HCC and T2DM who received TACE at centers 1, 2, and 3. The second cohort was an external validation cohort solely employed to evaluate the final model. The data of this cohort were obtained from center 4, with information collected from 97 patients with HCC and comorbid T2DM who underwent TACE between January 2014 and June 2023. The patient inclusion and exclusion criteria were identical between the primary derivation and external validation cohorts. This study protocol was reviewed and approved by the Ethical Committee of the Hospital. Patient consent was waived owing to the retrospective design of this study. The data was anonymized or maintained with confidentiality. The study was conducted in compliance with the Declaration of Helsinki.[26]

The patient inclusion criteria were as follows: (1) HCC diagnosis according to pathological biopsy or imaging (CT/ MRI/ultrasound) results;[5,27] (2) T2DM diagnosis verified via medical records and based on fasting plasma glucose level or A1C criteria in accordance with the American Diabetes Association guidelines;[28] (3) underwent initial TACE therapy; (4) classification into Child–Pugh class A or B; and (5) achievement of Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1. The patients were excluded if they met any of the following criteria: (1) diagnosed with type I or other forms of diabetes; (2) presence of pre-existing concurrent cancers; (3) underwent systemic treatments before inclusion in this study; or (4) lost to follow-up (Figure 1).

Treatment

The decision to perform TACE for the patients was deliberated by a multidisciplinary committee of experts (radiologists, interventional radiologists, hepatobiliary surgeons, and gastroenterologists). Ultimately, the committee recommended that patients diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage A HCC and who were not suitable for liver resection or transplantation or RFA should undergo TACE. Three highly experienced interventional radiologists, each with over 10 years of expertise in interventional therapy, conducted the TACE procedures in all patients. The TACE treatment performed in this study has been extensively described in our previous research.[29] Briefly, percutaneous arterial puncture was conducted using the Seldinger method, followed by
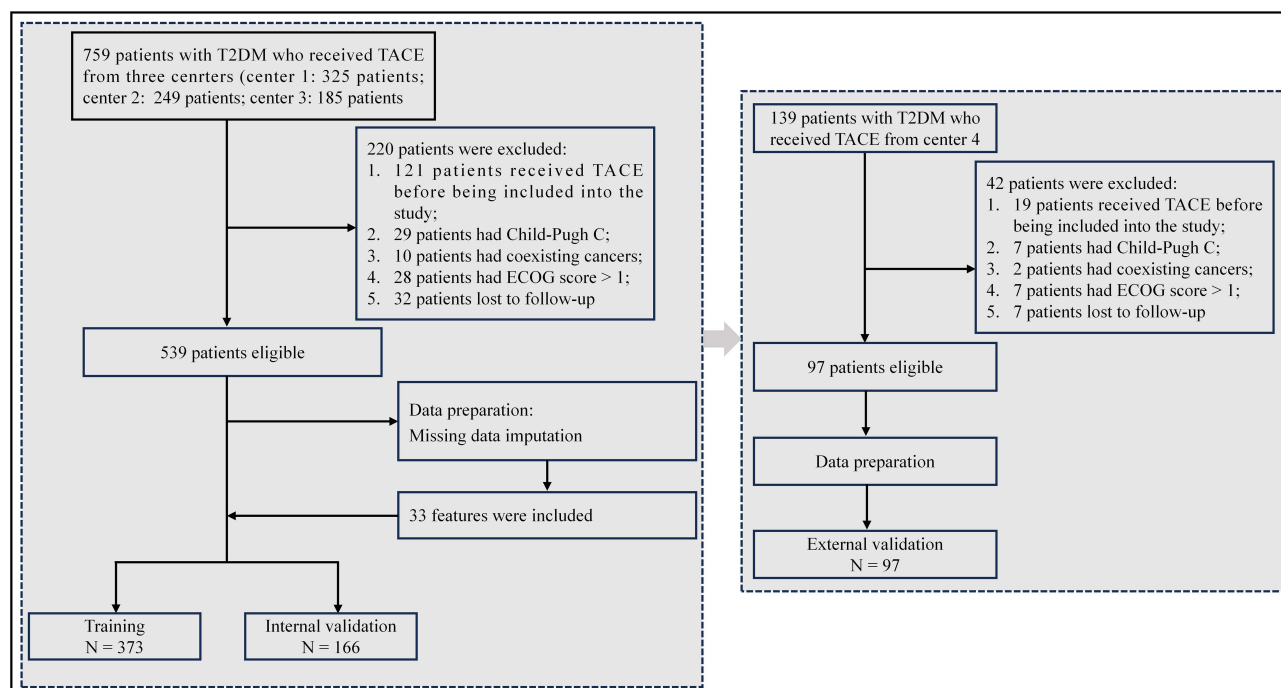

Figure 1 Flow chart of the patient selection process in this study.

introducing a 5F catheter (Cook, Bloomington, IN, USA) into the hepatic artery. Arteriography was then performed to visualize the tumor-feeding arteries, and a 3F microcatheter (Progreat, Terumo, Tokyo, Japan) was inserted into the tumor-feeding arteries through the 5F catheter. Subsequently, a mixture of lipiodol (Lipiodol Ultrafluido, Guerbet, Villepinte, France) and doxorubicin hydrochloride was emulsified at a ratio of 1 mL:2 mg. Considering the tumor size and liver function, 5–20 mL of the emulsion was slowly injected into the tumor-feeding arteries until stasis occurred. Supplemental embolization with gelatin sponge particles (300–700 μm, Cook, USA) was conducted if required.

Image Acquisition and Evaluation

All patients underwent enhanced CT or MRI scans before TACE. The features of tumor size, tumor number, liver cirrhosis, ascites, portal vein thrombus, and extrahepatic metastases were evaluated in a blinded manner by two radiologists having 8 and 10 years of experience. In the case of inconsistent results between the two radiologists, a third radiologist with 25 years of experience was asked to re-evaluate the results.

Study Predictors and Outcome

This study encompassed clinically pertinent characteristics of patients with HCC and T2DM collected before TACE surgery. Among the eligible patients, 32 predictors, including the clinical characteristics, laboratory parameters, and image findings, were retrospectively collected from the patients' medical records. The predicted outcome was overall survival (OS), which was defined as the duration from the surgery date to the date of death or last follow-up. The predictive ability of the model was assessed at 1, 2, and 3 years.

Feature Selection and Model Development

First, eligible patients from the primary derivation cohort were randomly divided into a training (n = 373) and an internal validation set (n = 166) at a 7:3 ratio. Second, Spearman correlation tests were performed in the training set to avoid significant multicollinearity among all variables before feature selection ([Figure S1](#)). Third, Boruta algorithm with 1000 bootstrap repetitions was applied in the training set to identify features important to the prediction target by comparing the original features with randomly generated shadow features.[30] Fourth, variance inflation factor (VIF) tests were conducted on the selected features to assess multicollinearity among the variables within the model. Fifth, the selected important features were entered into five commonly used ML models (including XGBoost, GBM, CoxPH, and Rpart) for modeling in the training cohort. Optimal hyperparameters for each ML model were obtained through random search and manual fine-tuning with 5-fold cross-validation.

The models were then evaluated using the concordance index (C-index), area under curve (AUC), and Brier score of the internal validation cohort, with the best-performing model selected for further analysis. The C-index represented the proportion of correctly distinguished pairs out of all possible pairs. The Brier score was employed to evaluate model calibration. This metric demonstrates the difference between the actual survival status and the predicted survival probability of a patient, with a lower score signifying better calibration performance. Lastly, calibration and decision curve analysis curves were plotted to assess the clinical utility of the optimal model.

Model Explanation

Model transparency is crucial for its application in the medical field. Therefore, we enhanced the transparency of the optimal model by implementing SHAP, a model-agnostic post-hoc interpretability algorithm widely used to explain ML models.[23] In this method, the SHAP values were calculated for each feature, and the features were ranked according to their importance.

Patient Assessment and Follow-up

All patients underwent clinical evaluation, liver function test, and abdominal CT or MRI scan (or both) at baseline, every 2 months in the first 6 months following initial TACE, and every 3–4 months after that.

Statistical Methods

The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared utilizing the independent samples *t*-test. Continuous variables with non-normal distribution were described as median (interquartile range) and compared with the Mann–Whitney *U*-test. Categorical variables were presented as number (n) and percentage (%), and group differences were assessed by conducting the chi-square test. All statistical analyses were performed using R software 4.1.3 (https://www.r-project.org/), with a two-sided p-value of <0.05 considered statistically significant.

Results

Clinicopathological Characteristics of the Study Patients

A total of 636 patients with HCC and T2DM who underwent TACE were enrolled after applying the study inclusion and exclusion criteria (Figure 1). The baseline characteristics of the training (n = 373), internal validation (n = 166), and external validation cohorts (n = 97) are presented in Table 1. In the training cohort, the median age was 59.0 years, and the median body mass index (BMI) was 24.1 kg/m^2. Further, 82.3% were male, and the diabetes duration was 46.0 months. The patients in the internal validation cohort had a median age of 60.0 years and a median BMI of 23.5 kg/m^2, while 83.1% were male and their diabetes duration was 48.0 months. In the case of the external validation cohort, the mean age was 61.0 years, and the median BMI was 23.8 kg/m^2. Additionally, the proportion of male patients was 76.3%, and the diabetes duration was 43.0 months. The median follow-up time of OS in the training, internal validation, and external validation cohorts was 27, 27, and 28 months,

Table 1 Baseline Characteristics of the Patients in the Training, Internal Validation, and External Validation Cohorts

Variables	Training Cohort (n = 373)	Internal Validation Cohort (n = 166)	External Validation Cohort (n = 97)
Demographics			
Age (years)	59 (53, 66)	60 (54, 66)	61 (53, 67)
Gender (n, %)			
Male	307 (82.3)	138 (83.1)	74 (76.3)
Female	66 (17.7)	28 (16.9)	23 (23.7)
BMI (kg/m^2)	24.1 (21.5, 25.9)	23.5 (21.5, 25.62)	23.8 (21.4, 26.6)
Past history			
Diabetes duration (months)	46.0 (32.0, 61.0)	48.0 (30.3, 65.8)	43.0 (29.0, 57.0)
Metformin use (n, %)	203 (54.4)	99 (59.6)	53 (54.6)
Hypertension (n, %)	88 (23.6)	41 (24.7)	24 (24.7)
Hyperlipemia (n, %)	46 (12.3)	18 (10.8)	11 (11.3)
CHD (n, %)	17 (4.6)	3 (1.8)	3 (3.1)
PSE or splenectomy (n, %)			
None	316 (84.7)	140 (84.34)	85 (87.63)
PSE	38 (10.2)	17 (10.24)	9 (9.28)
Splenectomy	19 (5.1)	9 (5.42)	3 (3.09)
Hepatitis (n, %)	301 (80.7)	141 (84.9)	72 (74.2)
ECOG (n, %)			
0	346 (92.8)	153 (92.17)	84 (86.6)
1	27 (7.2)	13 (7.83)	13 (13.4)
Imaging findings			
Liver cirrhosis (n, %)	260 (69.7)	119 (71.7)	65 (67.0)
Tumor number (n, %)			
1	157 (42.1)	61 (36.75)	44 (45.36)
≥2	216 (57.9)	105 (63.25)	53 (54.64)

(*Continued*)

Table 1 (Continued).

Variables	Training Cohort (n = 373)	Internal Validation Cohort (n = 166)	External Validation Cohort (n = 97)
Tumor size (cm)	4.0 (2.6, 6.0)	3.9 (2.9, 6.5)	4.2 (2.6, 6.5)
CHILD (n, %)			
A	261 (70.0)	119 (71.69)	67 (69.07)
B	112 (30.0)	47 (28.31)	30 (30.93)
BCLC stage (n, %)			
A	108 (29.0)	45 (27.11)	29 (29.9)
B	176 (47.2)	83 (50)	37 (38.1)
C	89 (23.8)	38 (22.89)	31 (31.9)
PVTT (n, %)	58 (15.5)	25 (15.1)	17 (17.5)
Extrahepatic metastases (n, %)	40 (10.7)	15 (9.0)	14 (14.4)
Laboratory parameters			
AFP (n, %)			
<200 μg/L	257 (68.9)	113 (68.07)	62 (63.92)
≥200 μg/L	116 (31.1)	53 (31.93)	35 (36.08)
HbA1c (%)	7.8 (7.5, 8.3)	7.9 (7.5, 8.4)	7.9 (7.5, 8.5)
FPG (mmol/L)	7.9 (7.5, 8.3)	7.9 (7.5, 8.4)	7.9 (7.6, 8.4)
Two-hour FGC (mmol/L)	9.8 (9.3, 10.6)	9.8 (9.2, 10.7)	9.7 (9.2, 10.6)
Albumin (g/L)	36.1 (31.0, 40.0)	36.0 (30.0, 39.5)	36.0 (29.7, 39.6)
ALT (U/L)	32.0 (21.0, 50.0)	29.0 (18.3, 47.0)	26.0 (18.0, 41.0)
AST (U/L)	36.0 (25.0, 58.0)	33.5 (25.0, 56.8)	31.0 (23.0, 51.0)
Creatinine (μmol/L)	67.0 (58.0, 81.0)	66.0 (55.5, 77.7)	66.4 (57.0, 79.4)
Bilirubin (μmol/L)	17.9 (10.7, 26.7)	18.7 (10.9, 29.9)	13.8 (7.9, 24.7)
Hemoglobin (g/L)	130 (116, 141)	128.5 (116.3, 143.0)	128 (115, 141)
PLR	100 (70.3, 151.9)	100.9 (75.2, 135.9)	95.6 (77.2, 131.0)
NLR	2.6 (1.8, 4.4)	2.5 (1.7, 4.1)	2.5 (1.7, 4.2)
Leukocyte, Median (10^9/L)	4.6 (3.4, 6.5)	4.9 (3.4, 6.4)	4.7 (3.7, 5.8)
PT (s)	13.4 (12.3, 14.5)	13.3 (12.2, 14.7)	13.8 (12.4, 14.7)

Abbreviations: AFP, Alpha-Fetoprotein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI =Body mass index; CHD, Coronary heart disease; CHILD, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group performance status; FPG, Fasting plasma glucose; HbA1c, Glycosylated hemoglobin; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; PSE, partial splenic embolization; PT, Prothrombin time. PVTT, Portal Vein Tumor Thrombosis.

respectively. Lastly, the median OS was 31, 29, and 28 months in the training, internal validation, and external validation cohorts, respectively.

Data Preprocessing, Feature Selection, and Collinearity Tests

Features with more than 30% missing data were excluded[31] because they provided limited information, whereas the missForest method was used to impute the remaining missing values of the continuous and categorical variable datasets.[32] Finally, 31 variables were identified as candidate predictors, and further analysis was performed using the following three steps. First, the correlations between different variables were examined by applying the Spearman correlation analysis to prevent overfitting or uncertainty in the model before its development stage (Figure S1). In this analysis, high collinearity was observed between alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and the feature exhibiting comparatively lower correlation with the outcome (ie, AST) was eliminated. Second, the Boruta algorithm was employed for feature screening. As depicted in the feature selection results in Figure 2 and Table S1, the variables in the orange region are considered important features, and those in the blue area represent unimportant features in the Boruta algorithm. Ultimately, 13 features were selected for predicting OS of the patients, including BCLC stage, portal vein tumor thrombosis (PVTT), tumor size, extrahepatic metastases, metformin use, liver cirrhosis, alpha-fetoprotein (AFP) level, platelet-to-
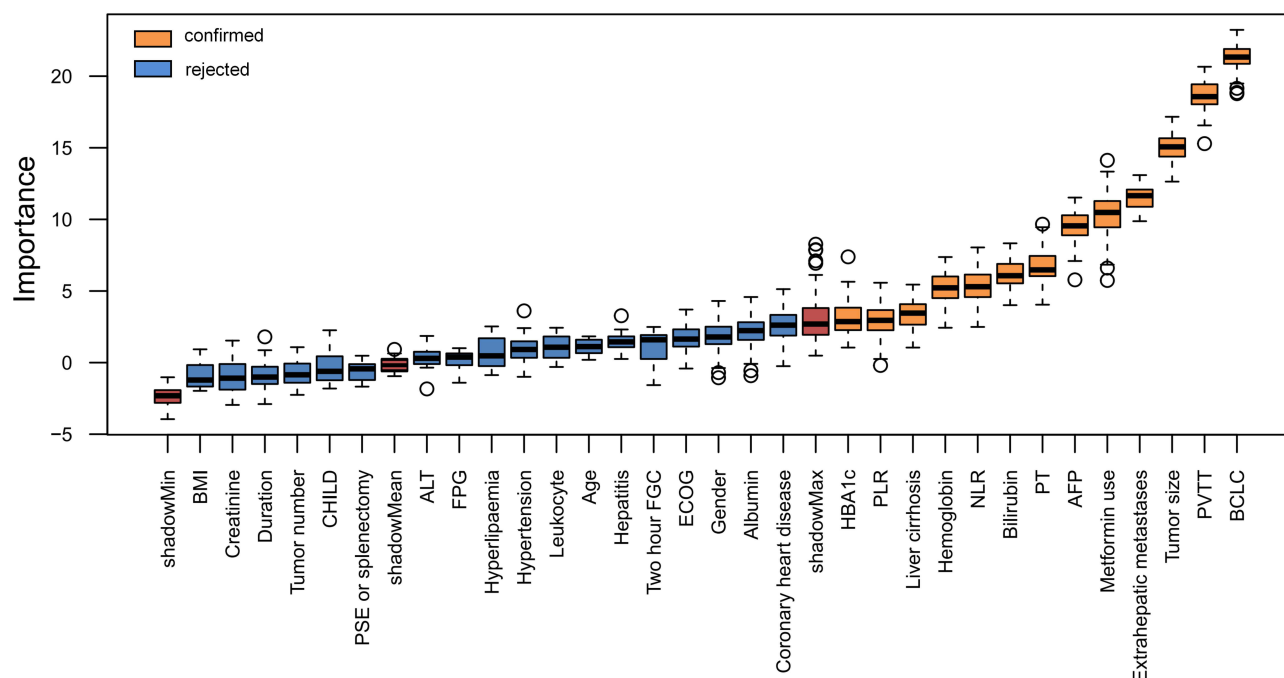
Boruta Algorithm

Figure 2 Feature selection results based on the Boruta algorithm. The horizontal axis represents the name of each variable, and the vertical axis indicates the importance value of each variable. The box plot illustrates the distribution of importance values for each variable during model calculation. The Orange boxes denote important variables, whereas blue boxes signify unimportant variables.

lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), glycosylated hemoglobin (HbA1c) level, hemoglobin level, bilirubin level, and prothrombin time (PT). Third, VIF tests demonstrated no strong correlation or multicollinearity between the selected features (Table S2), and all 13 variables were utilized for subsequent model development.

Model Development and Optimal Model Selection

Five survival analysis algorithms (ie, RSF, XGBoost, GBM, CoxPH, and Rpart) were used for model development in the training set. The hyperparametric search space and tuning results are presented in Table S3. The C-index values of the RSF, XGBoost, GBM, CoxPH, and Rpart models were 0.797, 0.841, 0.828, 0.770, and 0.758, respectively, in the training set, while these values were 0.754, 0.734, 0.743, 0.746, and 0.707, respectively, in the internal validation cohort and 0.759, 0.752, 0.758, 0.736, and 0.711, respectively, in the external validation cohort (Table 2 and Figure S2). The AUCs of the five final ML models (RSF, XGBoost, GBM, CoxPH, and Rpart) at 1, 2, and 3 years ranged from 0.832 to 0.918 in

Table 2 C-Index Values of the Five Machine Learning-Based Prognostic Models in the Training, Internal Validation, and External Validation Cohorts

Models	C-Index, Mean (95% CI)		
	Training Cohort	**Internal Validation**	**External Validation**
RSF	0.797 (0.773–0.821)	0.754 (0.706–0.797)	0.759 (0.703–0.817)
XGBoost	0.841 (0.821–0.863)	0.734 (0.688–0.779)	0.752 (0.704–0.812)
GBM	0.828 (0.805–0.850)	0.743 (0.696–0.787)	0.758 (0.712–0.816)
Coxph	0.770 (0.741–0.795)	0.746 (0.700–0.790)	0.736 (0.679–0.794)
Rpart	0.758 (0.729–0.786)	0.707 (0.654–0.757)	0.711 (0.641–0.770)

Abbreviations: RSF, random survival forest; XGBoost, extreme gradient boosting; GBM, gradient boost machine; Coxph, Cox Proportional Hazards Model; Rpart, recursive partitioning and regression trees.

the training cohort. Similarly, the AUCs of the final models in the internal validation and external validation cohorts ranged from 0.746 to 0.853 and from 0.746 to 0.862, respectively (Table 3). The Brier scores of the five final ML models across 1, 2, and 3 years spanned from 0.098 to 0.308 in the training cohort, 0.130 to 0.325 in the internal validation, and 0.142 to 0.343 in the external validation cohort (Table 4).

The C-index, AUC, and Brier score of the internal cohort were used to evaluate the discriminative performance of the developed models. As illustrated in Figure S3, the RSF model exhibited the best performance with a C-index of 0.754 (Figure S3A and Table 2) in the internal validation cohort. Moreover, the RSF model exhibited the highest AUC (Figure S3B and Table 3) and the lowest Brier score (Figure S3C and Table 4) among all models. Therefore, the RSF model demonstrated superior discriminative ability and calibration performance compared to the other four models. The RSF model also provided the best clinical benefits (Figure S4). Based on all these findings, the RSF model was further investigated.

Performance of the Final RSF Model

The RSF model showed good performance in the training cohort, achieving AUC values of 0.912, 0.895, and 0.893 for 1-, 2-, and 3-year OS, respectively (Figure 3A). Furthermore, the AUC values for 1-, 2-, and 3-year OS in the internal and external validation cohorts were 0.824, 0.853, and 0.810 (Figure 3B) and 0.862, 0.815, and 0.798 (Figure 3C), respectively.

Additionally, the calibration curves of the RSF model displayed good consistency between the actual observations and model predictions for 1-, 2-, and 3-year OS in the training, internal validation, and external validation cohorts (Figure 4A–C; respectively). Correspondingly, the decision curve analysis curves of the RSF model for 1-, 2-, and 3-year OS in the internal (Figure 5A–C; respectively) and external validation cohorts (Figure 5D–F; respectively) also exhibited good clinical utility, indicating a favorable positive net benefit.

Feature Importance Assessment of the Final RSF Model

Next, the SHAP method was applied to examine the impact of input features on the survival of patients with HCC and T2DM after undergoing TACE. Figure 6A illustrates the ranking of feature importance according to their SHAP values,

Table 3 AUCs of the Five Machine Learning-Based Prognostic Models in the Training, Internal Validation, and External Validation Cohorts

AUC	1-Year Survival	2-Year Survival	3-Year Survival
Training cohort			
RSF	0.912 (0.883–0.942)	0.895 (0.863–0.927)	0.893 (0.860–0.926)
XGBoost	0.918 (0.887–0.950)	0.912 (0.882–0.941)	0.917 (0.889–0.946)
GBM	0.892 (0.855–0.929)	0.878 (0.842–0.913)	0.877 (0.842–0.913)
Coxph	0.860 (0.817–0.904)	0.858 (0.818–0.897)	0.839 (0.797–0.880)
Rpart	0.832 (0.782–0.881)	0.848 (0.808–0.887)	0.833 (0.791–0.874)
Internal validation cohort			
RSF	0.824 (0.749–0.899)	0.853 (0.794–0.912)	0.810 (0.742–0.879)
Xgboost	0.818 (0.738–0.897)	0.829 (0.765–0.892)	0.774 (0.701–0.847)
GBM	0.822 (0.742–0.903)	0.839 (0.775–0.902)	0.794 (0.723–0.866)
Coxph	0.817 (0.732–0.903)	0.849 (0.787–0.912)	0.787 (0.713–0.861)
Rpart	0.768 (0.673–0.862)	0.771 (0.698–0.845)	0.746 (0.670–0.822)
External validation cohort			
RSF	0.862 (0.784–0.940)	0.815 (0.726–0.903)	0.798 (0.707–0.889)
Xgboost	0.850 (0.772–0.929)	0.816 (0.700–0.891)	0.793 (0.700–0.886)
GBM	0.842 (0.756–0.929)	0.807 (0.723–0.902)	0.814 (0.734–0.906)
Coxph	0.816 (0.715–0.916)	0.793 (0.698–0.887)	0.773 (0.680–0.868)
Rpart	0.785 (0.677–0.893)	0.748 (0.646–0.850)	0.746 (0.646–0.845)

Abbreviations: ROC, receiver operating characteristic curve; XGBoost, extreme gradient boosting; RSF, random survival forest; GBM, gradient boost machine; Coxph, Cox Proportional Hazards Model; Rpart, recursive partitioning and regression trees.

Table 4 Brier Score of Prognostic Models Built by Machine Learning Algorithms

Brier Score	1-Year Survival	2-Year Survival	3-Year Survival
Training cohort			
RSF	0.108 (0.092–0.126)	0.139 (0.123–0.156)	0.149 (0.135–0.163)
XGBoost	0.098 (0.080–0.116)	0.119 (0.103–0.135)	0.128 (0.113–0.143)
GBM	0.113 (0.094–0.132)	0.141 (0.123–0.158)	0.148 (0.132–0.163)
Coxph	0.116 (0.094–0.138)	0.148 (0.128–0.167)	0.161 (0.145–0.179)
Rpart	0.261 (0.236–0.285)	0.308 (0.278–0.337)	0.295 (0.259–0.332)
Internal validation cohort			
RSF	0.130 (0.099–0.163)	0.161 (0.134–0.189)	0.181 (0.157–0.205)
XGBoost	0.143 (0.108–0.179)	0.166 (0.136–0.197)	0.193 (0.161–0.224)
GBM	0.132 (0.099–0.164)	0.162 (0.134–0.189)	0.183 (0.156–0.211)
Coxph	0.135 (0.098–0.173)	0.162 (0.130–0.193)	0.186 (0.157–0.216)
Rpart	0.278 (0.241–0.315)	0.325 (0.279–0.370)	0.285 (0.229–0.340)
External validation cohort			
RSF	0.142 (0.103–0.180)	0.182 (0.139 −0.223)	0.179 (0.144–0.214)
Xoost	0.160 (0.109–0.211)	0.189 (0.139 −0.239)	0.183 (0.139–0.226)
GBM	0.146 (0.100–0.193)	0.180 (0.129 −0.230)	0.182 (0.137–0.228)
Coxph	0.142 (0.094–0.189)	0.176 (0.132–0.219)	0.185 (0.146–0.225)
Rpart	0.291 (0.237–0.346)	0.343 (0.303 −0.378)	0.294 (0.216–0.363)

Abbreviations: RSF, random survival forest; XGBoost, extreme gradient boosting; GBM, gradient boost machine; Coxph, Cox Proportional Hazards Model; Rpart, recursive partitioning and regression trees.

with features arranged from top to bottom in decreasing order of importance. In particular, a greater mean absolute SHAP value for a feature implies greater feature importance. The top five features ranked according to their importance included BCLC stage, PVTT, tumor size, metformin use, and extrahepatic metastases. The SHAP summary plot depicts the full distribution of each feature's impact on the model output. The colors of the dots denote the actual SHAP values of the features for each patient, where blue corresponds to a higher feature value and red represents a lower feature value. Additionally, the greater the distance of a point from the baseline SHAP value of 0, the stronger the effect of the corresponding feature on the output. As demonstrated in the SHAP summary dot plot in Figure 6B, higher BCLC stage, the presence of PVTT, larger tumor size, the absence of metformin use, and extrahepatic metastases were related to higher mortality risk.
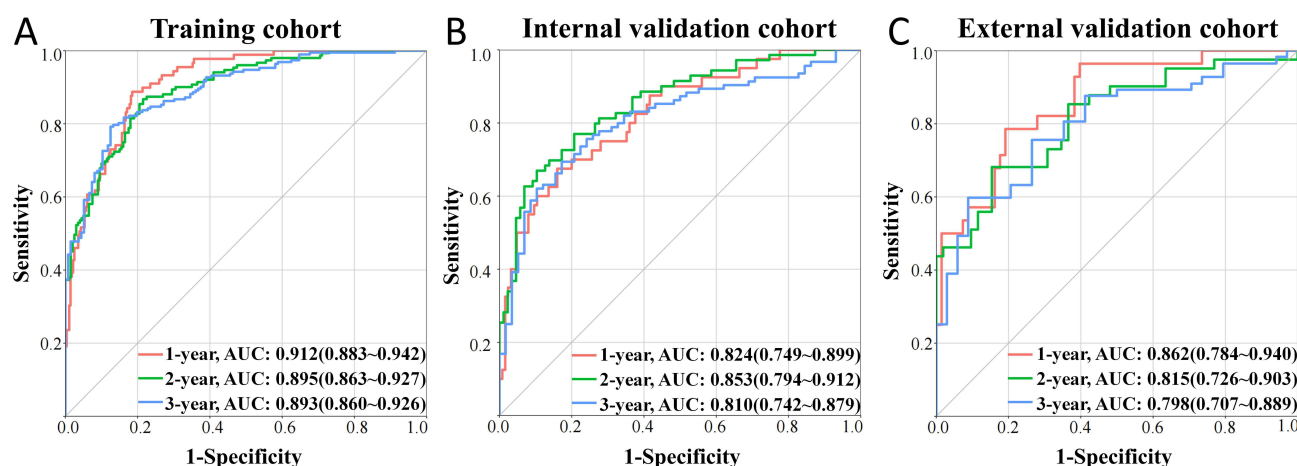

Figure 3 ROC curves of the final RSF model for 1-, 2-, and 3-year prognostic prediction in the (**A**) training, (**B**) internal validation, and (**C**) external validation cohorts.
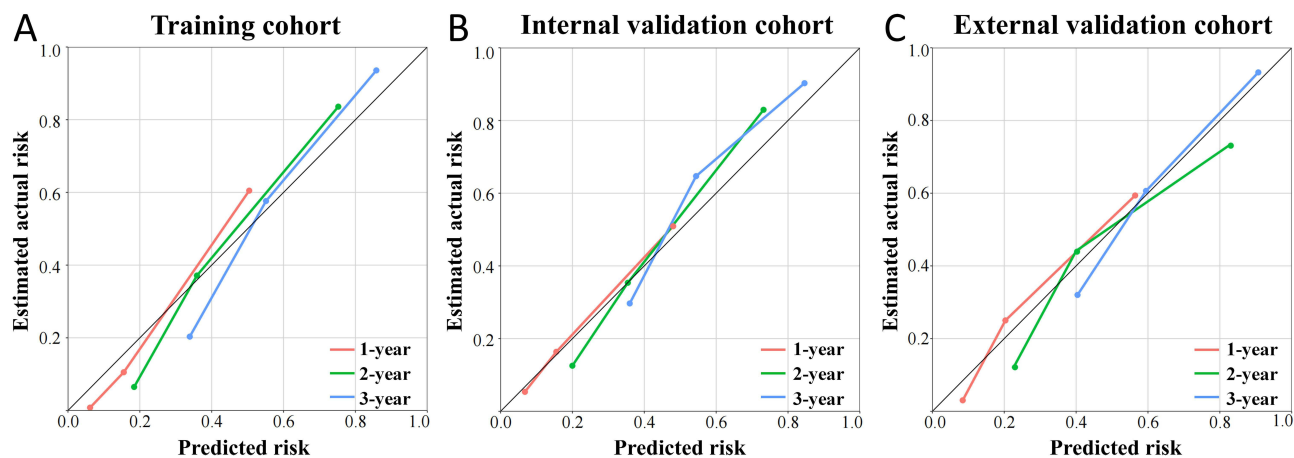**Abbreviations**: ROC, receiver operating characteristic; RSF, random survival forest.

Figure 4 Calibration curves of the final RSF model for 1-, 2-, and 3-year prognostic prediction in the (**A**) training, (**B**) internal validation, and (**C**) external validation cohorts.
Abbreviation: RSF, random survival forest.

Development of a Web Application for the Final RSF Model

The clinical application of the RSF model was facilitated by developing a user-friendly web application based on the Shiny platform. The final predictive model was implemented into the web application, as shown in Figure S5. After entering the values of the 13 required features, the web application can automatically predict the 1-, 2-, and 3-year survival probability of individual patients with HCC and T2DM following TACE based on their feature information. If the probability is greater than 0.5, the patient is predicted to survive; if it is less than 0.5, the patient is predicted to die. For instance, in the case shown in Figure S5A, the model predicted survival probabilities of 0.35, 0.132, and 0.063 for 1-, 2-, and 3-year survival, respectively, for a patient with 7-month survival. In another case shown in Figure S5B, for a patient with 42-month survival, the model predicted survival probabilities of 0.959, 0.854, and 0.734 for the same time points. The web application is accessible online at https://osprediction.shinyapps.io/survival_1y_2y_3y_prediction/, and detailed instructions for use are provided in the Table S4.

Discussion

Survival prediction in patients with tumors can lead to the selection of better treatment strategies by clinicians. Several studies have established that diabetes can result in a poorer prognosis in patients with various tumors.[33–35] In line with these findings, diabetes in patients with liver cancer who were treated with TACE was found to be associated with a poorer survival prognosis.[36,37] However, no studies have explored the survival factors affecting patients with HCC and comorbid T2DM following TACE therapy. In this study, we developed an ML-based model for predicting the survival of patients with HCC accompanied by T2DM who underwent TACE by incorporating preoperative demographics, biochemical test results, and imaging markers of this population.

Several prior studies have focused on the survival prediction in patients with HCC after receiving TACE.[38–40] However, the population heterogeneity of this patient group has made it difficult for a single sub-predictor to fully reflect the survival prognosis. Moreover, diabetes-related factors have been suggested to affect survival prognosis in patients with combined HCC and T2DM. Therefore, utilizing a single indicator for survival prediction in such patients may be relatively more challenging. ML is a powerful computational method that can manage complex and large amounts of data due to its capability of processing highly variable datasets and deciphering complex relationships between variables in a flexible and trainable manner. Therefore, combining multimodal data (demographics, biochemical test results, and imaging features) with sophisticated ML algorithms can facilitate the development of valuable clinical predictive models.[41] Among the five ML models evaluated in this study, the RSF model exhibited the best survival prediction at 1, 2, and 3 years after TACE therapy in terms of the AUC values of the internal and validation cohort. Numerous studies have demonstrated that the RSF method has excellent predictive value in patients with cancer.[42–44] In contras t to traditional scoring systems, such as the Child-Pugh score or the BCLC staging system,[27,45] which rely on relatively
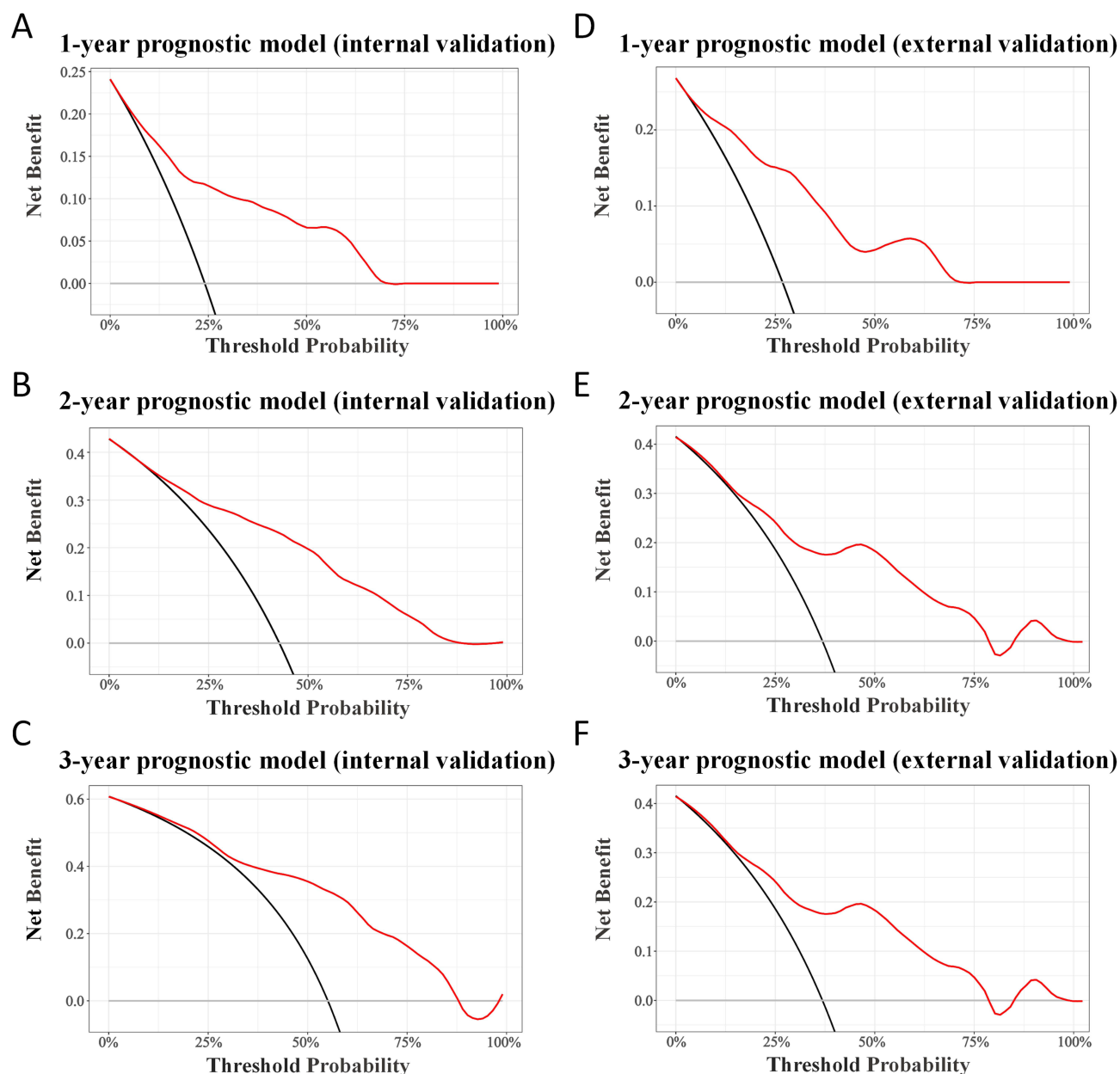
Figure 5 Decision curve analysis curves of the final RSF model for (**A**) 1-year, (**B**) 2-year, and (**C**) 3-year prognostic prediction in the internal validation cohort and for (**D**) 1-year, (**E**) 2-year, and (**F**) 3-year prognostic prediction in the external validation cohort.
Abbreviation: RSF: random survival forest.

limited clinical parameters (eg, liver function, tumor stage, and patient performance), the RSF model incorporates 13 features, representing a broader spectrum of factors. These features can be easily assessed at the time of patient admission, which makes the RSF model both a promising and practical tool for survival prediction in patients with combined HCC and T2DM undergoing TACE. Furthermore, while the traditional predictive models, such as Cox proportional hazards model, are widely used in cancer prognosis, they may struggle with non-linear relationships and complex interactions between multiple factors.[46] The RSF model, with its ensemble approach, handles these complexities more effectively, making it particularly well-suited for real-world clinical applications. The development of the 13-feature RSF model not only highlights its predictive power but also introduces a novel approach for personalizing clinical decision-making for patients with the dual burden of HCC and T2DM.
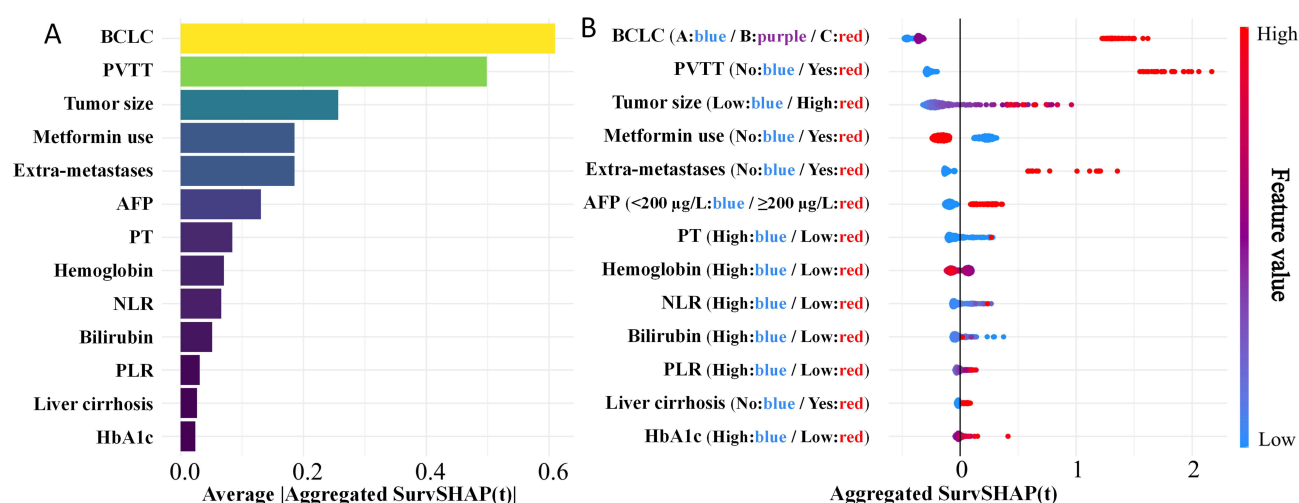
Figure 6 Feature importance analysis of the final RSF model using the SHAP method. (**A**) SHAP summary bar plot and (**B**) SHAP summary dot plot of the selected 13 features of the RSF model.
Abbreviations: RSF, random survival forest; SHAP, SHapley Additive explanation exPlanations.

Given the lack of studies on generative prediction models for patients with combined HCC and T2DM who are treated with TACE, no relevant guidelines or consensus are available on the selection of specific diagnostic features for prediction models. Thus, determining the number of features to be incorporated in the survival prediction model is challenging. Although including more modalities and baseline characteristics of patients may provide additional information for the prediction model, integrating a large number of features, particularly those with strong correlations, can cause model overfitting and produce unreliable model results. Moreover, combining an excessive number of specific diagnostic features in the prediction model may limit its clinical use, while including non-causal features may diminish prediction accuracy. In this study, the Spearman correlation analysis and the Boruta algorithm were applied to screen the diagnostic features, ultimately identifying 13 variables. Furthermore, the randomized forest (missForest) method was implemented to impute the missing values of the relevant variables of the patients to establish a simple and convenient ML prediction model. The final model can be used for survival prediction in patients with HCC and comorbid T2DM following TACE treatment, thereby aiding in the clinical decision-making process for this patient group.

Previous studies have reported that factors such as preoperative BCLC grade, tumor size, tumor number, and AFP level can influence the survival of patients with HCC who have undergone TACE.[27,47,48] In this study, the 13 variables that influenced patient survival included non-diabetes-related variables similar to those identified in previous studies. Nevertheless, diabetes-associated variables, such as metformin use and HbA1c level, also had a high weightage on the prediction of survival prognosis, suggesting the significance of these variables in patients with combined HCC and T2DM. Correspondingly, earlier research has demonstrated that metformin use in patients with HCC and T2DM who received TACE may lead to improved prognosis.[49,50] The current study revealed consistent results, indicating that a preoperative intervention for T2DM using metformin therapy may enhance survival prognosis in this patient population. Furthermore, this study employed the SHAP method to attach different weights to each variable affecting the survival prognosis of the patients. The results showed that BCLC stage, PVTT, tumor size, extrahepatic metastases, liver cirrhosis, AFP level, PLR, NLR, hemoglobin level, bilirubin level, and PT influenced patient survival prognosis. Along with their use for predicting patient survival, these factors may also guide clinicians in administering more appropriate treatments. Thus, clinicians can potentially extend patient survival by effectively managing these pre-TACE variables.

The ML model developed in this study and its corresponding web application provide quantitative and personalized survival probability predictions for patients with HCC and comorbid T2DM after TACE treatment. This study model marks a remarkable advancement from the traditional approach that generalizes risks based on heterogeneous population averages. The predictive model can also assist clinicians in determining a patient's risk for adverse survival outcomes, prioritizing treatments, and developing treatment strategies. For example, the model can provide early predictions of

potential survival probabilities at specified intervals, aiding in future care planning. Therefore, this study model can support the development of policies and procedures for enhancing survival outcomes, optimizing resource utilization, and improving prognosis for patients at varied risk levels.

However, our study has several limitations that should be considered. This study was a retrospective investigation; thus, selective bias may be inevitably present. Moreover, considering that a few enrolled patients underwent surgical resection treatment, this study did not assess pathological examination results or genetic testing data. Third, machine learning models typically require large sample sizes to achieve robust performance. Therefore, we plan to expand the sample size in future studies to further validate the stability and generalizability of the model. Finally, future studies should incorporate these variables to extend the survival prediction research in patients with HCC and T2DM receiving TACE.

Conclusion

In this study, we successfully developed an interpretable ML model that predicts 1-, 2-, and 3-year survival probabilities of patients undergoing TACE based on their pre-TACE-related information. The final RSF model exhibited excellent predictive ability in both the internal and external validation cohorts. Furthermore, our study results may provide clinicians with valuable guidance in selecting appropriate treatment modalities for patients with combined HCC and T2DM undergoing TACE. Future larger prospective studies are essential to further validate the clinical applicability and robustness of the model across diverse patient populations.

Abbreviations

HCC, hepatocellular carcinoma; T2DM, Type II diabetes mellitus; ML, machine learning; SHAP, SHapley Additive exPlanations; RSF, random survival forest; TACE, transarterial chemoembolization; OS, overall survival; C-index, concordance index; PVTT, portal vein tumor thrombosis; HbA1c, glycosylated hemoglobin.

Data Sharing Statement

The data used in the study can be available from the correspondence author (Chuansheng Zheng, hqzcsxh@sina.com).

Ethics Approval and Informed Consent

This study protocol was reviewed and approved by the Ethical Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, approval number UHCT-IEC-SOP-016-03-03. Patient consent was waived owing to the retrospective design of this study.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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