

Preoperative Prediction of TACE Refractoriness in Hepatocellular Carcinoma Using CT-Based Radiomics Model

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Purpose: To develop an integrated predictive model that combines radiomics, and clinical risk factors to predict early refractoriness to transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC).

Methods: The study cohort comprised 180 HCC patients from Hospital A, while the external validation cohort included 42 patients from Hospital B. Optimal radiomic features extracted from computed tomography (CT) were selected using both LASSO regression and the Boruta algorithm. Eight machine learning models based on radiomics were developed. SHapley Additive Explanations (SHAP) were utilized to interpret the predictions and assess feature importance of the best model. Furthermore, independent clinical risk factors for TACE refractoriness were identified within the study cohort, leading to the construction of a combined model. The predictive performance of the model was evaluated using the area under the curve (AUC), calibration curve, and decision-curve analysis (DCA).

Results: The random forest (RF) model exhibited the superior performance, achieving an AUC of 0.841 (95% CI: 0.731–0.950) and 0.777 (95% CI: 0.624–0.929) in the testing and validation cohorts, respectively. SHAP analysis indicated that radiomic features significantly contributed to the RF model. Subsequently, Radscore was integrated with the clinically independent risk factor (tumor diameter) identified through univariate and multivariate logistic regression to develop the combined model. The combined model exhibited superior AUC performance compared with the clinic and radiomics models, with AUCs of 0.842 (95% CI: 0.736–0.948) and 0.847 (95% CI: 0.721–0.973) in the testing and validation cohorts, respectively. Calibration curve and decision curve analyses confirmed the utility of the combined model nomogram in clinical practice.

Conclusion: The combined model exhibits strong predictive performance for early TACE refractoriness, potentially offering improved guidance for decision-making regarding subsequent TACE treatments.

Keywords: HCC, radiomics, TACE refractoriness, machine learning, nomogram

Introduction

HCC ranks as the sixth most common malignancy globally and is the third leading cause of cancer-related mortality.¹ Approximately 80% of patients with HCC present with intermediate to advanced unresectable lesions.² The Barcelona Clinic Liver Cancer (BCLC) staging system advocates for TACE as the standard treatment for intermediate-stage HCC.³ However, Intermediate stage HCC is very heterogeneous in terms of tumor diameter, tumor counts, and liver function, and TACE is not beneficial for all patients.⁴ The Japan Society of Hepatology (JHS) first defined the concept of TACE failure/refractoriness in 2010,⁵ which was subsequently revised by the JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014⁶: 1) Intrahepatic lesion: Two or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE; two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure)

even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE; (2) Continuous elevation of tumor markers immediately after TACE even though a slight transient decrease is observed; (3) Appearance of vascular invasion; and (4) Appearance of extrahepatic spread.^{7,8} The assessment of viable lesion >50% was strictly performed in accordance with the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC,⁹ which is the gold standard for evaluating tumor response to anti-angiogenic and locoregional therapy in HCC. The viable tumor was defined as the enhancing portion of the tumor in the arterial phase of contrast-enhanced CT/MRI. Moreover, multiple courses of TACE are linked to heightened angiogenesis and liver damage related to embolization, potentially undermining the therapeutic benefits obtained in the tumor and adversely impacting overall survival (OS).^{10–12} Therefore, the early identification of critical factors that may predict TACE refractoriness is essential for the effective management of patients with HCC.

Recent research has shown that molecular biomarkers of HCC (eg, PD-L1 expression, ctDNA mutations, and angiogenesis-related genes) are closely associated with the response to TACE therapy.^{13,14} However, the detection of molecular biomarkers is often invasive and costly, limiting its clinical application. CT imaging is commonly employed in clinical practice for patients with HCC to identify tumors and assess their stage.¹⁵ Conventional imaging evaluations rely on semantic characteristics and provide limited metrics, thereby overlooking a significant amount of valuable information regarding tumor heterogeneity.^{16–18} Radiomics, an emerging approach to medical image analysis, facilitates the quantification of tumor phenotypic traits, thereby providing predictive insights.¹⁹ Recent advances that integrate radiomics with artificial intelligence have introduced innovative strategies to tackle this clinical challenge.²⁰ Radiomics exhibits enhanced predictive capabilities for treatment response and tumor recurrence in patients with HCC compared to traditional imaging techniques.²¹ However, achieving a complete response (CR) with a single session of TACE may be challenging in patients with a high tumor burden. Furthermore, the follow-up interval ranged from 1 to 3 months post-TACE, necessitating at least two sessions of TACE within a 6-month period to accurately evaluate the optimal response.^{22,23} This study aimed to identify independent risk factors associated with TACE refractoriness and to develop a radiomic-clinical model, along with a nomogram, for predicting TACE refractoriness in patients with HCC who underwent TACE monotherapy at least twice as their initial treatment.

Materials and Methods

Patient Characteristics

This retrospective study was approved by the Ethics Committee of NanFang Hospital of Southern Medical University (NFEC-2024-489). The need for written informed consent was waived due to the retrospective study design. All patient clinical and imaging data used in this study were de-identified and strictly confidential in accordance with the ethical guidelines and hospital data management regulations. No personal identifiable information was involved in the research and manuscript writing. Between January 2016 and December 2022, 1500 and 300 HCC patients receiving TACE therapy were screened from medical center A and medical center B, respectively. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) compensated liver function (Child-Pugh class A or B); (3) Eastern Cooperative Oncology Group (ECOG) scores = 0; (4) BCLC stage A or B; (5) received TACE twice consecutively treatment; and (6) underwent contrast-enhanced CT within a week prior to TACE. The exclusion criteria were: (1) extrahepatic metastasis or vascular invasion; (2) history of prior treatment for HCC (TACE, ablation, chemotherapy, etc); (3) an interval between the first and second TACE exceeding 6 months; (4) insufficient follow-up data; and (5) poor quality CT images used for analysis. After applying inclusion and exclusion criteria, 180 patients from medical center A were divided into training and testing cohorts with a 7:3 ratio using stratified random sampling to ensure the distribution balance of key variables between the two cohorts. 42 patients from medical center B were utilized as the external validation cohort. The patient selection process is illustrated in Figure 1.

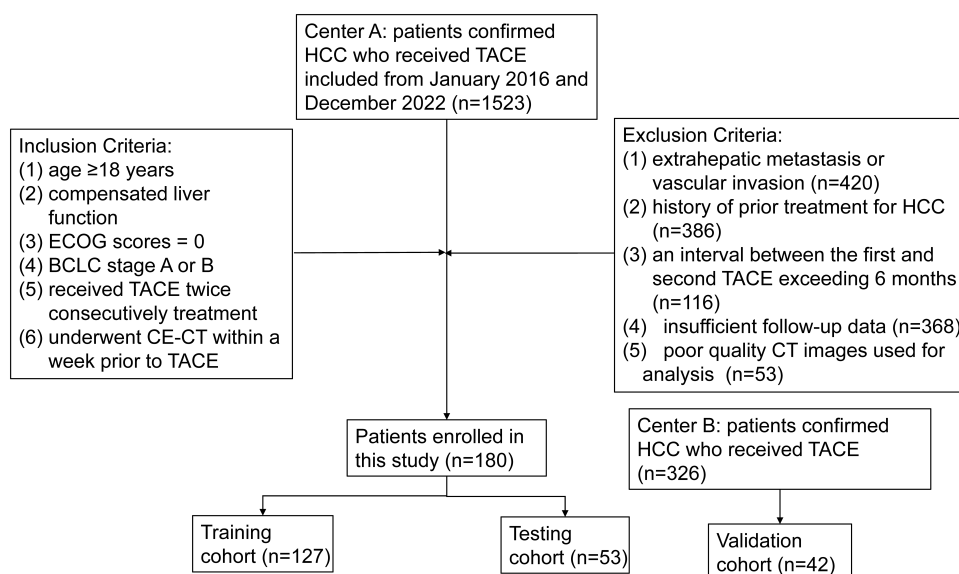


Figure 1 A flowchart of participant enrollment.

CT Data Acquisition

This study adhered to the abdominal CE-CT scanning protocol. Prior to scanning, patients received training on breath-holding techniques. The scans were conducted in the supine position with arms elevated, and patients were instructed to hold their breath at the end of deep inspiration. The scanning range extended from the diaphragmatic dome to the lower pole of the kidney. The Revolution Apex 256 (GE HealthCare), Somatom Definition (Siemens Medical Solutions), and Brilliance ICT (Philips HealthCare) were employed, with the following scanning parameters: tube voltage of 120 kV, tube current of 80 mAs, and automatic tube current modulation (noise index 12, GE). The reconstruction slice thickness was set to 5 mm. The dosage of Ultravist (Byer Schering Pharma) administered was 2 mL/kg, injected via the cubital vein at a flow rate of 3.0 mL/s. Three-phase scans were performed at 25–30 s (arterial phase), 50–60 s (portal venous phase), and 90–120 s (delayed phase) post-injection. The detailed operational procedure of TACE is provided in the Supplementary.

Tumor Segmentation and Extraction of Radiomics Features

Preoperative CT images, including non-enhanced, arterial, portal, and delayed phases, were exported in DICOM format and imported into the open-source software ITK-SNAP (v. 3.6.0, <https://www.itksnap.org/>), then were spatially registered using the rigid registration module. A radiologist (Observer A, with 7 years of experience in abdominal imaging) manually outlined the entire tumor volume on each axial slice. Feature extraction was conducted using the Pyradiomics package (<http://www.radiomics.io/pyradiomics.html>). The images were resampled to 1×1×1 mm voxels with a bin width of 25 to mitigate differences in image specifications. Following the Image Biomarker Standardization Initiative (IBSI) guidelines, 428 features were extracted from each tumor volume for the non-enhanced, arterial, portal, and delayed phase images. These features included first-order features, gray-level co-occurrence matrix (GLCM), gray-level dependence matrix (GLDM), gray-level run length matrix (GLRLM), gray-level size zone matrix (GLSZM), neighboring gray tone difference matrix (NGTDM), and shape features. The volume of interest (VOI) segmentation diagram is presented in Figure 2. To evaluate interobserver variability, a second radiologist (Observer B, with 10 years of experience in hepatobiliary imaging) independently segmented all VOIs in a randomly selected subset of 40 cases. The reproducibility of the features was quantified using intraclass correlation coefficients (ICCs), with an ICC of ≥ 0.8 considered indicative of excellent agreement.

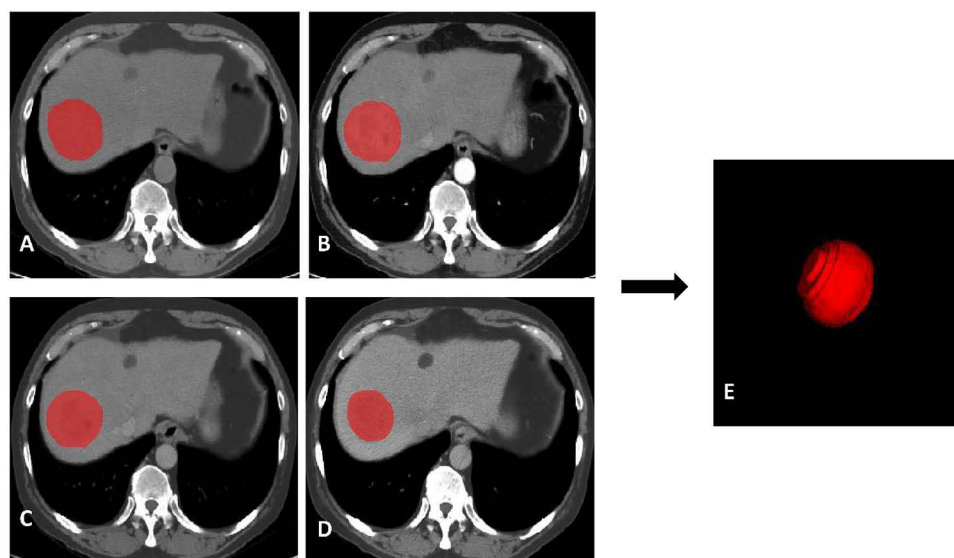


Figure 2 An exemplary diagram of VOI segmentation illustrates the delineation of VOIs across different phases of CT images: non-enhanced phase (A), arterial phase (B), portal venous phase (C), and delayed phase (D). The VOI is represented in panel (E).

Feature Selection and Model Construction

All features preprocessing underwent Z-score normalization for standardization. Initially, radiomics features exhibiting zero variance and near-zero variance were excluded. Subsequently, key features were identified through both least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation and the Boruta algorithm.

The dataset was randomly divided into a training cohort (70%) and a testing cohort (30%) using stratified sampling to maintain distributional balance. All predictive models were developed using R (version 4.5.1), including logistic regression (LR), support vector machine (SVM), random forest (RF), extreme gradient boosting (XGBoost), k-nearest neighbors (KNN), adaptive boosting (AdaBoost), light gradient boosting machine (LightGBM), and categorical boosting (CatBoost). The clinical model was developed using LR. To enhance model performance, Combined model was created by integrating clinical predictors and Radscore through logistic regression. The performance of all constructed models was validated across the training, testing, and validation cohorts. Model efficacy was assessed using multiple metrics, including AUC, accuracy, precision, sensitivity, specificity, and F1 score.

Statistical Analysis

Continuous variables that followed a normal distribution were expressed as mean $\pm$ standard deviation and analyzed using the Student's *t*-test. Non-normally distributed variables were reported as median (interquartile range) and assessed with the Wilcoxon rank-sum test. Categorical variables were presented as counts (percentages) and compared using either the Chi-squared test or Fisher's exact test. All statistical analyses were conducted using R (version 4.5.1; <https://www.r-project.org>). A two-sided *p* value < 0.05 was deemed statistically significant for all analyses.

Results

Patient Characteristics

A total of 222 patients (median age, 53 years; range, 46–63 years) were enrolled, consisting of 10% females (24/222) and 90% males (198/222). These patients were categorized into training, testing, and validation cohorts. The training cohort included 127 patients with a median age of 52 years, comprising 9% (11/127) females and 91% (116/127) males. The testing cohort consisted of 53 patients with a median age of 55 years, including 10% (7/53) females and 90% (46/53) males. The validation cohort comprised 42 patients with a median age of 55 years, consisting of 10% (6/42) females and 90% (36/42) males. Within the entire study population, 129 patients exhibited early TACE refractoriness (129/222, 58.1%). The detailed demographic, radiological, and laboratory characteristics are summarized in Table 1.

Table 1 Baseline Characteristics

Characteristic	Training (n=127)	Testing (n=53)	Validation (n=42)
Age (y)	53.40 ±10.91	56.83±10.82	53.93 ±11.89
Gender			
Male	116 (91.3%)	46 (86.8%)	36 (85.7%)
Female	9(8.7%)	7(13.2%)	6(14.3%)
Hepatitis			
With	119 (93.7%)	52 (98.1%)	40 (95.2%)
Without	8(6.3%)	1(1.9%)	2(4.8%)
Ascites			
With	16 (12.6%)	10 (18.9%)	12 (28.6%)
Without	111(87.4%)	43(81.1%)	30(71.4%)
Number of tumor			
Solitary	78(61.4%)	34(64.2%)	29(69.0%)
≥2	49 (38.6%)	19 (35.8%)	13 (31.0%)
Capsule			
With	57 (44.9%)	31 (58.5%)	36 (85.7%)
Without	72(55.1%)	22(41.5%)	6(14.3%)
Vessel			
With	101 (79.5%)	47 (88.7%)	40 (95.2%)
Without	26(20.5%)	6(11.3%)	2(4.8%)
Cirrhosis			
With	68 (53.5%)	26 (49.1%)	32 (76.2%)
Without	59(46.5%)	27(50.9%)	10(23.8)
Tumor distribution			
Left lobe	8 (6.3%)	4 (7.5%)	6 (14.3%)
Right lobe	99 (78.0%)	40 (75.5%)	23 (54.8%)
Both lobes	20 (15.7%)	9 (17.0%)	13 (31.0%)
Diameter	64.41 ±34.79	65.81±38.98	60.90 ±36.66
TBIL	17.16±10.14	18.00 ±10.49	24.57 ±29.40
ALB	37.81 ±5.10	37.42 ±5.61	36.40±5.41
PT	12.91±1.88	12.72 ±1.38	14.42 ±2.48
AST	49.25±30.00	49.51±28.72	58.22 ±54.62
ALT	44.57±32.52	48.88 ±36.73	46.24 ±30.72
CPR	63.15 ±533.56	17.13 ±32.12	22.57 ±37.89
AFP	4602.04 ±12,138.35	4929.85±14,271.39	4568.03±13,477.25
TACE refractoriness			
Presence	73(57.4%)	30(56.6%)	26(61.9%)
Absence	54(42.6%)	23(43.4%)	16(38.1%)

Abbreviations: TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPR, C-reactive protein; AFP, α -fetoprotein.

Radiomic Feature Selection and Model Construction

A total of 428 radiomic features were extracted from NP, AP, VP, and DP for the original images. Subsequently, 292 features met the criterion of $ICC \geq 0.8$, 292 features remained. The LASSO and Boruta algorithms identified seven features, as illustrated in [Figure 3A](#) and [B](#): NP_original_shape_Maximum2DDiameterColumn, NP_original_firstorder_Skewness, NP_original_firstorder_Variance, AP_original_shape_Sphericity, AP_original_shape_Maximum3DDiameter, VP_original_shape_Sphericity, and VP_original_firstorder_Maximum. ICC of seven radiomic features showed as [Supplementary Table S1](#). The SHAP algorithm was employed to interpret feature importance and evaluate the contribution of individual variables, as shown in [Figure 3C](#) and [D](#).

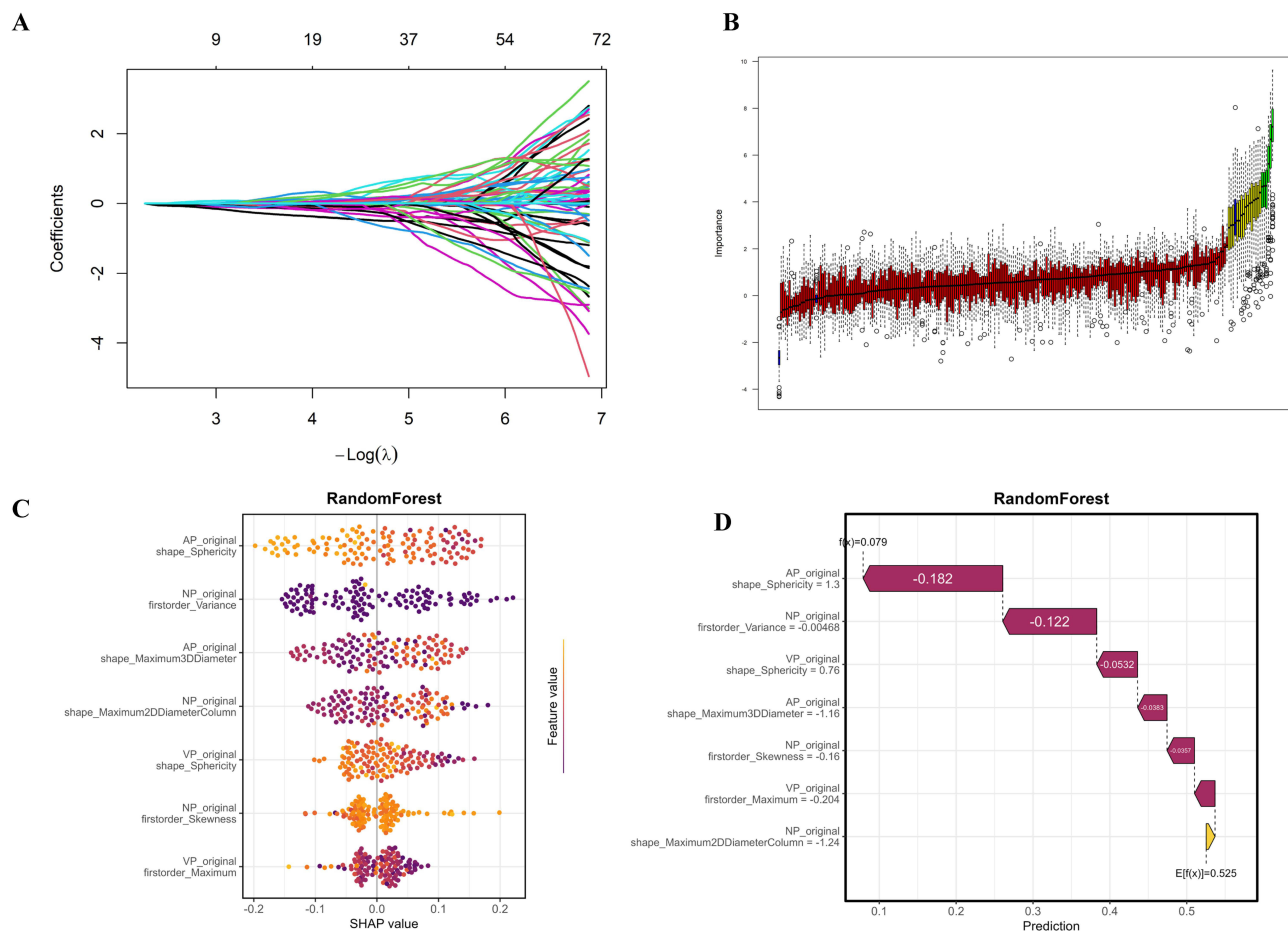


Figure 3 Radiomics feature selection using the LASSO (A) and Boruta algorithm (B). (C) The SHAP summary plot. SHAP values of each feature in the RF model. The different colors (yellow and red) represent different levels of effect on the output of the model. (D) Local model explanation by the SHAP method. The SHAP waterfall plots illustrate the contribution of each feature to individual predictions.

Model Construction and Evaluation for the Prediction of TACE Refractoriness

For all machine learning models, hyperparameter tuning was performed using grid search with 10-fold cross-validation on the training cohort. Eight machine learning algorithms (LR, SVM, RF, Xgboost, KNN, Adaboost, LightGBM, CatBoost) were employed to develop predictive models. The optimal hyperparameters for each model are detailed in [Supplementary Table S2](#). The performance of the ML models in the training, testing and validation cohorts were shown in [Table 2](#). The optimal probability thresholds for each model are listed in [Supplementary Table S4](#). Additionally, the receiver operating characteristic (ROC) curves were demonstrated in [Figure 4](#). The RF-based model demonstrated a good discrimination for predicting early TACE refractoriness. The AUCs for the RF model in training, testing, and validation cohorts were 1.000 (95% CI: 1.000–1.000), 0.841 (95% CI: 0.731–0.950) and 0.777 (95% CI: 0.624–0.929), respectively. In the testing cohort, although RF model achieved the highest AUC (0.841), its accuracy (0.811), sensitivity (0.794), specificity (0.842), precision (0.9), and F1 score (0.844) were comparable to Adaboost. In the validation cohort, the AUCs of RF and Adaboost were nearly identical (0.777 vs. 0.779). The RF showed a slightly higher specificity (0.8), precision (0.87), but lower sensitivity (0.741) and F1 score (0.8) compared to Adaboost. Consequently, RF was selected as the final radiomics model.

Univariate and multivariate analyses revealed that tumor diameter (HR = 1.01; 95% CI: 1.00–1.02; $p=0.028$) was independently correlated with TACE refractoriness, as outlined in [Supplementary Table S3](#). Tumor diameter, both with and without the Radscore, was incorporated into the Clinic model and the Combined model, which are ultimately presented through nomograms ([Figure 5A](#)).

Table 2 Comparison of the Performance of ML Models in Training, Testing and Validation Cohorts

Cohort	Model	Accuracy	Sensitivity	Specificity	Precision	FI Score
Training	Logistic	0.661	0.479	0.907	0.875	0.619
	SVM	0.756	0.726	0.796	0.828	0.774
	RandomForest	1	1	1	1	1
	Xgboost	0.835	0.808	0.87	0.894	0.849
	KNN	0.953	0.918	1	1	0.957
	Adaboost	0.921	0.973	0.852	0.899	0.934
	LightGBM	1	1	1	1	1
	CatBoost	0.74	0.795	0.667	0.763	0.779
Testing	Logistic	0.755	0.735	0.789	0.862	0.794
	SVM	0.755	0.735	0.789	0.862	0.794
	RandomForest	0.811	0.794	0.842	0.9	0.844
	Xgboost	0.792	0.765	0.842	0.897	0.825
	KNN	0.736	0.706	0.789	0.857	0.774
	Adaboost	0.811	0.794	0.842	0.9	0.844
	LightGBM	0.755	0.706	0.842	0.889	0.787
	CatBoost	0.642	0.618	0.684	0.778	0.689
Validation	Logistic	0.452	0.481	0.4	0.591	0.531
	SVM	0.619	0.63	0.6	0.739	0.68
	RandomForest	0.762	0.741	0.8	0.87	0.8
	Xgboost	0.69	0.704	0.667	0.792	0.745
	KNN	0.786	0.963	0.467	0.765	0.852
	Adaboost	0.762	0.778	0.733	0.84	0.808
	LightGBM	0.69	0.63	0.8	0.85	0.723
	CatBoost	0.643	0.63	0.667	0.773	0.694

In the testing cohort, the Combined model yielded a slightly higher AUC (0.842) than both the clinic model (0.761) and the radiomic model (0.841). However, these differences did not reach statistical significance (combined vs. clinic: $p=0.361$; combined vs. radiomic: $p=0.952$). In the validation cohort, the combined model again demonstrated a numerically superior AUC (0.847) relative to the clinic model (0.680) and radiomic model (0.777), yet no statistically significant differences were detected (combined vs. clinic: $p=0.119$; combined vs. radiomic: $p=0.295$). Nonetheless, the

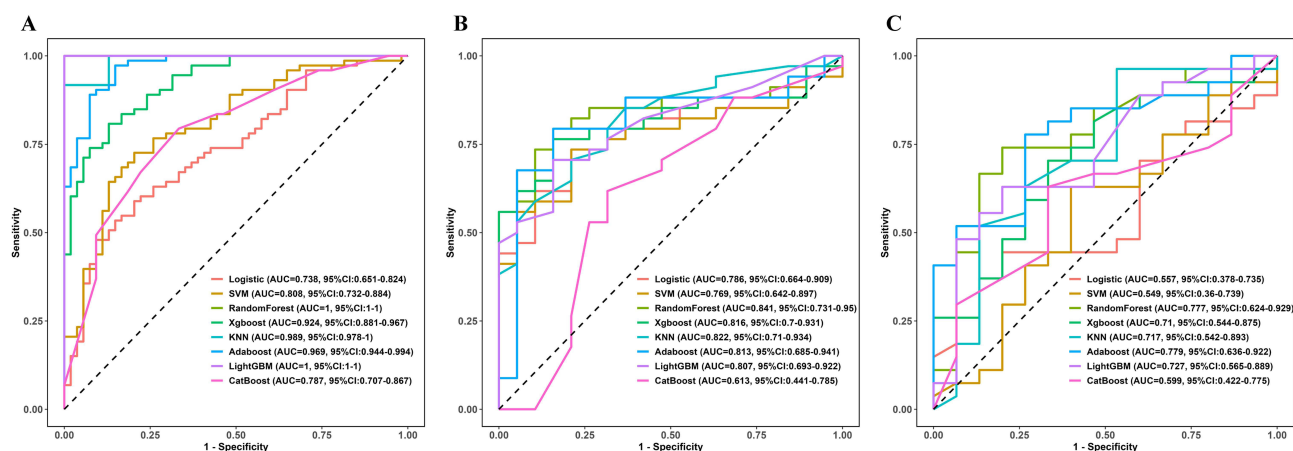


Figure 4 ROC curves of the different cohorts of eight ML models. (A) ROC curves of the training cohort. (B) ROC curves of the testing cohort. (C) ROC curves of the validation cohort.

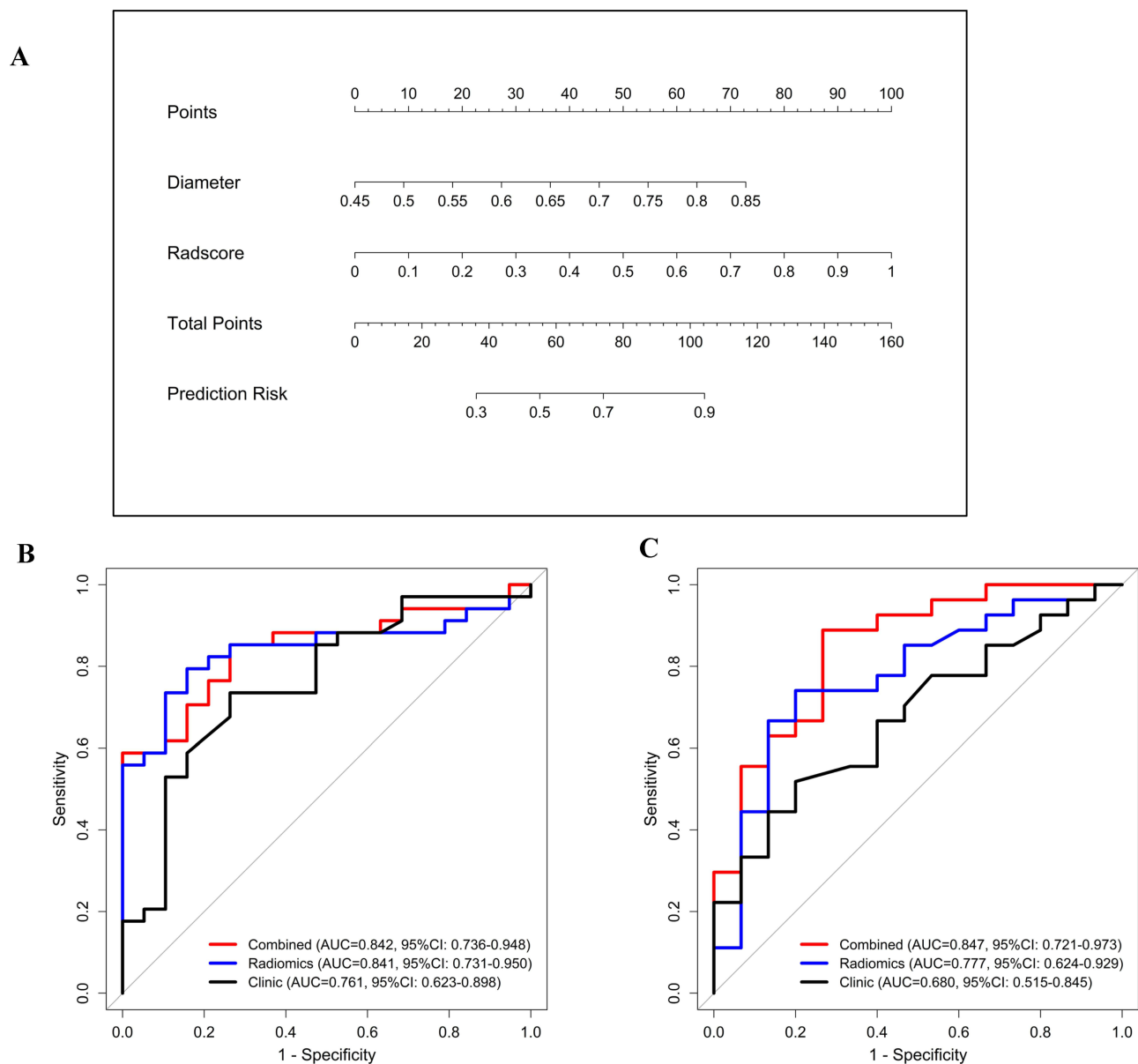


Figure 5 The combined nomogram incorporating tumor diameter, and Radscore to individually predict the risk of TACE refractoriness (A). ROC curves of the testing and validation cohorts of Clinic, Radiomics, and Combined models. ROC curves of the testing cohort (B). ROC curves of the validation cohort (C).

combined model showed clear numerical superiority over both the clinic and radiomic models used in isolation (Figure 5B and C). Model performance comparisons were performed using DeLong's test, as summarized in Supplementary Table S5.

In the testing cohort, the Combined model achieved a sensitivity of 85.3% and an overall accuracy of 81.1%; corresponding values in the validation cohort were 88.9% and 83.3%, respectively (Table 3). Decision curve analysis (DCA) confirmed the clinical utility of the Combined model, indicating substantial net benefits across a range of probability thresholds (Figure 6A and B). Calibration curves indicated excellent agreement between the combined model-predicted probabilities and the observed rates of TACE refractoriness (Figure 6C and D). Furthermore, satisfactory calibration was confirmed by the Hosmer-Lemeshow test, with p values of 0.586 and 0.491 in the testing and validation cohort, respectively.

Table 3 Comparison of the Performance of Clinic, Radiomics and Combined Models in Training, Testing and Validation Cohorts

	Model	Accuracy	Sensitivity	Specificity	PPV	NPV
Training	Clinic	0.606299	0.506849	0.740741	0.72549	0.526316
	Radiomics	1	1	1	1	1
	Combined	1	1	1	1	1
Testing	Clinic	0.735849	0.735294	0.736842	0.833333	0.608696
	Radiomics	0.811321	0.794118	0.842105	0.9	0.695652
	Combined	0.811321	0.852941	0.736842	0.852941	0.736842
Validation	Clinic	0.619048	0.518519	0.8	0.823529	0.48
	Radiomics	0.761905	0.740741	0.8	0.869565	0.631579
	Combined	0.833333	0.888889	0.733333	0.857143	0.785714

Discussion

In the present study, the RF model demonstrated superior performance in both the training, testing, and validation cohorts, confirming that the RF model not only fits well on the study set but also exhibits strong generalization ability when facing new data. We developed an integrated prediction model that combines radiomic features with clinical risk factors, achieving an AUC of 0.842 (95% CI: 0.736–0.948) in the testing cohort and 0.847 (95% CI: 0.721–0.973) in the external validation cohort. While the combined model exhibited numerically superior predictive performance relative to the clinic-only and radiomic-only models, the between-group differences did not achieve statistical significance. Several factors may account for this observation. First, the sample sizes of the testing and validation cohorts were relatively modest, which likely reduced statistical power and increased the likelihood of type II error, particularly when comparing AUCs of already high-performing models. Second, the radiomic model itself already demonstrated favorable discriminative ability, leaving only a narrow margin for further improvement by integration with clinical parameters. Nevertheless, the combined model achieved consistently higher AUC, sensitivity, and accuracy across both cohorts, alongside excellent calibration and favorable clinical utility in DCA. Taken together, these findings suggest a trend toward improved performance with the combined approach, even if formal statistical significance was not attained in the present study. Decision curve analysis (DCA) indicates that the net benefit of the Combined model is maximized when the threshold probability ranges from 20% to 70%.

The SHAP summary chart indicates that NP_original_firstorder_Variance and AP_original_shape_Sphericity are the top two contributors, respectively. Variance reflects the gray-scale heterogeneity within the tumor and exhibits a significant correlation with intratumoral hemorrhage, necrosis, and steatosis on a pathological level. A low Sphericity value suggests that the tumor exhibits an infiltrative growth pattern characterized by “multi-nodule fusion”, which aligns precisely with the subtype “tumor number increases”²⁴ The Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE) 2019 proposed that HCC “beyond up-to-7 criteria” was “likely to develop TACE failure/refractoriness”.²⁵ Tumor size is widely recognized as a crucial predictive factor for the response to TACE. HCC predominantly derives its blood supply from the hepatic artery. Larger tumors generally demonstrate increased vascularity, accelerated growth, a heightened ability to breach the capsule, and a greater tendency to infiltrate adjacent liver tissue. Furthermore, larger tumors exhibit a higher likelihood of portal vein invasion, which increases the risk of intrahepatic recurrence after TACE.^{26,27} In our study, tumor diameter emerged as a significant independent risk factor (OR=1.01, $p=0.028$), with a coefficient approximating 1, limiting its clinical interpretability. Integration of Radscore substantially improved the AUC in the validation cohort from 0.680 (Clinics model) to 0.847 (Combined model), underscoring the added value of radiomics beyond tumor diameter alone. The Combined model exhibited enhanced sensitivity (0.889) and NPV (0.786) in the validation cohort, suggesting its potential utility in identifying candidates for prompt systemic therapy. This finding validates the biological rationale of the feature from an image-pathological perspective and elucidates why a single clinical indicator, such as diameter, is inadequate for fully capturing spatial

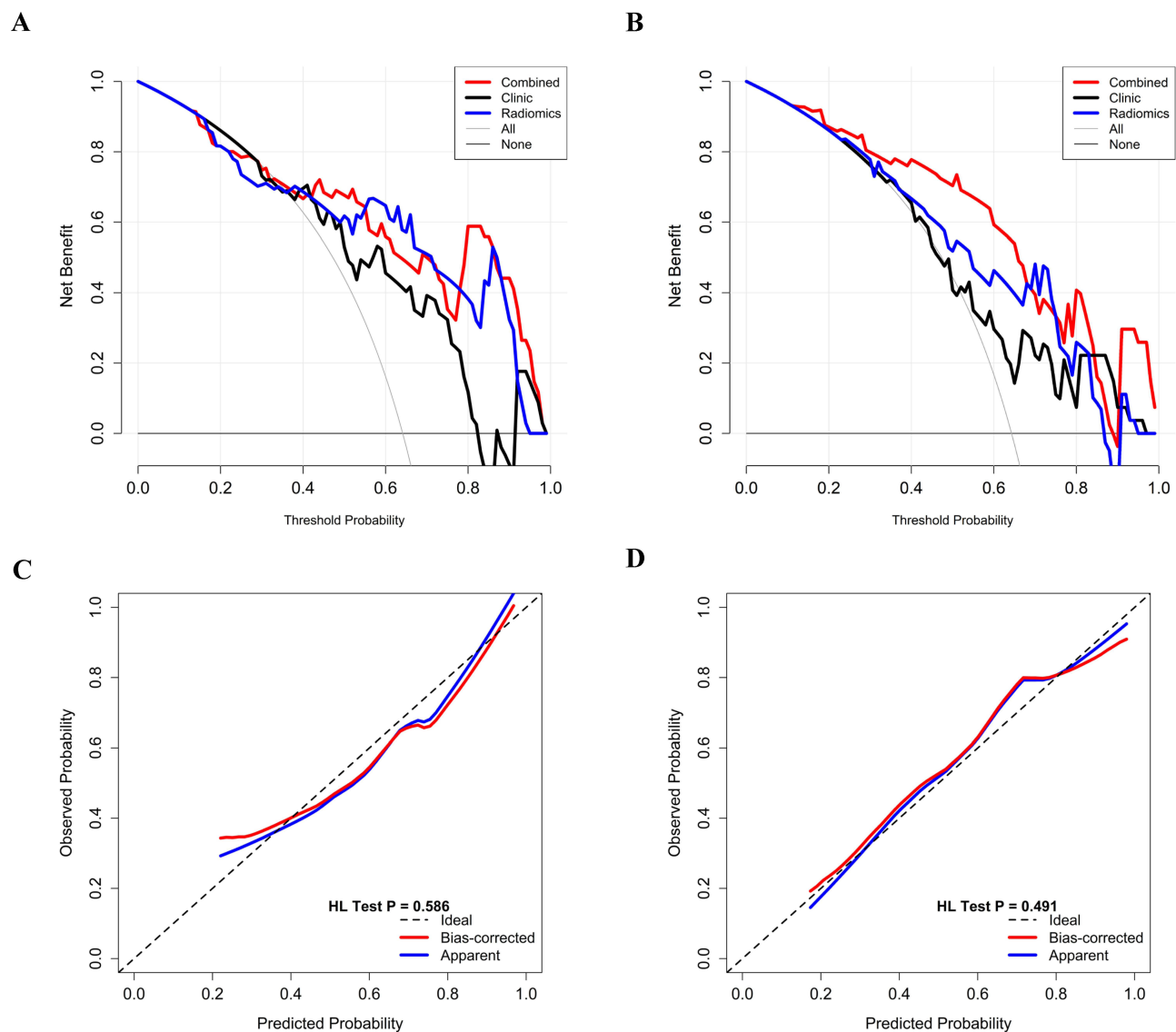


Figure 6 DCA of the testing cohort (A) and validation cohort (B) comparing clinical net benefit among three prediction models. The calibration curves of the Combined model demonstrated excellent agreement between the predicted and observed values in both the testing cohort (C) and validation cohort (D).

heterogeneity. Previous studies have identified the number of tumors and bilateral hepatic invasion as factors associated with TACE refractoriness.^{28,29} However, in our study, the correlation between these two factors was not significant, potentially due to the limited sample size. Zou et al³⁰ developed an RF model for predicting early TACE refractoriness in HCC patients. Their RF model achieved an AUC of 0.767 (95% CI: 0.650–0.861) and a sensitivity of 67.9% in the testing cohort. In comparison, our RF model attained an AUC of 0.841 (95% CI: 0.731–0.950) and a sensitivity of 79.4% in testing cohort. External validation of our model revealed an AUC of 0.778 (95% CI: 0.624–0.929) and a sensitivity of 74.1%. Additionally, researches have focused on intratumoral and peritumoral radiomics in relation to predicting resistance to TACE and treatment outcomes.^{15,31} Findings indicate that peritumoral radiomics provides distinct insights into the tumor microenvironment that extend beyond conventional intratumoral evaluations.^{22,32} Prior studies mainly relied on enhanced CT or MRI images,^{26,33,34} overlooking the importance of non-enhanced phases. Remarkably, three (NP_original_shape_Maximum2DDiameterColumn, NP_original_firstorder_Skewness, NP_original_firstorder_Variance) out of the seven crucial features identified in our research were obtained from non-enhanced phase, and the model was validated in an independent external cohort. Non-enhanced phase CT can reflect the intrinsic density and structural

heterogeneity of tumor tissue (eg, intratumoral hemorrhage, necrosis, and fibrosis) without the interference of contrast agents, which provides complementary information for evaluating tumor biological behavior and treatment response.³⁵ Our finding that three of the seven key features were derived from the non-enhanced phase is consistent with the latest research indicating that non-enhanced phase radiomics features can improve the predictive performance of models.³⁶ Jiao et al³⁷ find combining TACE programmed cell death ligand 1 [PD-L1] inhibitors and molecular targeted therapies (MTT) may prevent TACE refractoriness. Therefore, it is important to predict TACE refractoriness in advance and change the treatment approach.

This study has several limitations. First, the application of highly stringent inclusion criteria resulted in a relatively low proportion of patients included in the analysis. Although this approach facilitated cohort homogeneity during the initial model development phase, it may also restrict the generalizability of the findings to some extent. Secondly, variations in TACE surgical procedures may be present among the different hospital. Thirdly, this is a retrospective study, which may lead to selection bias. A major limitation of this study is the relatively small sample size of the single external validation center (n=42). In future research, we plan to launch a prospective multicenter clinical trial involving at least three external validation centers from different geographical regions and medical levels in China. Future research should focus on increasing the sample size and using a prospective methodology for model validation.

Conclusion

In conclusion, the RF-based integrated model demonstrated predictive capability for the prognosis of HCC patients who continued TACE treatment after developing TACE refractoriness. The Radscore, tumor diameter may serve as potential prognostic indicators in this patient population. Collectively, these findings provide insights into personalized clinical decision-making in this patient cohort, thereby minimizing unnecessary multiple TACE procedures and associated liver injuries.

Abbreviations

TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; CT, computed tomography; LASSO, least absolute shrinkage and selection operator; SHAP, SHapley Additive Explanations; AUC, area under the curve; DCA, decision-curve analysis; VOI, volume of interest; LR, logistic regression; SVM, support vector machine; RF, random forest; XGBoost, extreme gradient boosting; KNN, k-nearest neighbors; AdaBoost, adaptive boosting; LightGBM, light gradient boosting machine; CatBoost, categorical boosting; BCLC, Barcelona Clinic Liver Cancer; JHS, Japan Society of Hepatology; LCSGJ, JSH-Liver Cancer Study Group of Japan; OS, overall survival; CR, complete response; ECOG, Eastern Cooperative Oncology Group; CE-CT, Contrast-Enhanced Computed Tomography; IBSI, Image Biomarker Standardization Initiative; NP, non-enhanced phase; AP, arterial phase; VP, portal venous phase; DP, delayed phase; GLCM, gray-level co-occurrence matrix; GLDM, gray-level dependence matrix; GLRLM, gray-level run length matrix; GLSZM, gray-level size zone matrix; NGTDM, neighboring gray tone difference matrix; ICCs, intraclass correlation coefficients; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPR, C-reactive protein; AFP, α -fetoprotein; APPLE, Asia-Pacific Primary Liver Cancer Expert Meeting; PD-L1, programmed cell death ligand 1; MTT, molecular targeted therapies.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of NanFang Hospital of Southern Medical University (NFEC-2024-489) which waived the requirement for written informed consent. The protocol of this retrospective study conformed to the Declaration of Helsinki.

Acknowledgments

We sincerely appreciate the support and contributions of all the authors to this research and manuscript.

Funding

The authors state that this work has not received any funding.

Disclosure

The authors declare no competing interests.

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