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Multisequence MRI-Based Radiomic Features Combined with Inflammatory Indices for Predicting the Overall Survival of HCC Patients After TACE

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Objective: To develop a model for predicting the overall survival (OS) of hepatocellular carcinoma (HCC) patients after transarterial chemoembolization (TACE) on the basis of multisequence MRI radiomic features and clinical variables.

Methods: The DCE-MRI and clinical data of 116 HCC patients treated with TACE for the first time were retrospectively analyzed. The included patients were randomly divided into training and validation cohorts at a ratio of 7:3. Univariate and multivariate Cox proportional hazards regression models were used to identify independent risk factors that affect the OS of patients with HCC after TACE. Radiomic features were extracted from the sequences of FS-T2W images and arterial-phase (A) and portal venous-phase (P) axial DCE-MR images. The LASSO method was used to select the best radiomic features. Logistic regression was used to establish a radiomic model of each sequence, a joint model of MRI features (M model) combined the radiomic features of all the sequences, and a radiomic-clinical model (M-C model) that integrated the radiomic signatures and clinically independent predictors. The diagnostic performance of each model was evaluated as the area under the receiver operating characteristic (ROC) curve (AUC).

Results: The Child–Turcotte–Pugh (CTP) score and neutrophil-to-lymphocyte ratio (NLR) –platelet–to–lymphocyte ratio (PLR) were found to be independent risk factors that affect the OS of patients with HCC treated with TACE. The AUCs of the FS-T_2WI, A, P, M, and M-C models for predicting the OS of HCC patients after TACE treatment were 0.779, 0.803, 0.745, 0.858 and 0.893, respectively, in the training group and 0.635, 0.651, 0.644, 0.778 and 0.803, respectively, in the validation group. The M-C model had the best predictive performance.

Conclusion: Multiparameter MRI-based radiomic features may be helpful for predicting OS after TACE treatment in HCC patients. The inclusion of clinical indicators such as inflammation scores can improve the predictive performance.

Keywords: magnetic resonance imaging, radiomics, hepatocellular carcinoma, transcatheter arterial chemoembolization, inflammatory indices, overall survival

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor and the third leading cause of cancer death worldwide.[1] Owing to the insidious onset of HCC, most patients with HCC are already in the middle or advanced stages of this disease when they seek medical treatment and are thus outside the ideal window for surgical resection. Transarterial chemoembolization (TACE) plays an important role in the treatment of middle- and advanced-stage HCC.[2,3] However, due to tumor heterogeneity, among other reasons, not all patients can benefit from TACE.[4] Therefore, accurate preoperative prediction of the prognosis of HCC patients after TACE treatment is helpful for the development of individualized treatment strategies.

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Since its proposal as a field of study by Lambin et al in 2012, radiomics has been gradually applied to various clinical tasks, including tumor classification, detection and prediction.[5–13] Magnetic resonance imaging (MRI) plays an important role in staging HCC, making treatment decisions, and evaluating treatment responses and has thus been recommended as the preferred method for evaluating the effects of TACE in HCC patients.[14] MRI radiomic features have important value in predicting the response to TACE and the prognosis of HCC patients.[15–20] Recent studies have shown that inflammation is closely related to tumor development and progression and that inflammatory indices are correlated with the prognosis of HCC patients receiving TACE treatment.[21–34]

To date, no studies have employed a combination of multisequence MRI radiomic features and inflammatory markers to predict the prognosis of HCC patients who have undergone TACE. In this study, FS-T2WI and arterial-phase (phase A) and portal venous-phase (phase P) dynamic contrast-enhanced MR images of HCC patients before TACE were retrospectively analyzed, radiomic features were extracted and screened, and clinical data, such as inflammatory indicators, were assessed. A multisequence radiomic-clinical joint prediction model was constructed to investigate the value of combining multisequence MRI radiomic features and inflammatory indices to predict the prognosis of HCC patients treated with TACE.

Materials and Methods

Clinical Data

This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (No. 2022ER085-1) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study and the use of anonymous data collection without any risk to patients. The preoperative MRI and clinical data of patients with pathologically or clinically confirmed HCC treated in our hospital between December 2019 and July 2023 were retrospectively analyzed. The inclusion criteria were as follows: (1) a pathological or clinical diagnosis of HCC; (2) new TACE treatment with no other antitumor treatments, such as ablation, radiotherapy or chemotherapy; and (3) MRI of the upper abdomen performed within 4 weeks before surgery that yielded good image quality. The exclusion criteria were as follows: (1) incomplete clinical and imaging data; (2) insufficient lesion size; and (3) the presence of other tumors. A total of 116 patients who met the inclusion and exclusion criteria were screened. Owing to the relatively small sample size, patients were randomly assigned to the training group or the validation group at a ratio of 7:3 according to the literature.[13]

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated on the basis of blood neutrophil, platelet, and lymphocyte counts. Receiver operating characteristic (ROC) curves were drawn with the NLR, the PLR, the maximum tumor diameter, and patient survival as state variables. The cutoff value for each variable was the value that maximized Youden's index (Table 1). An NLR $\leq$ 3.465 and a PLR $\leq$ 63.500 were each scored as 0 points, and an NLR > 3.465 and a PLR > 63.500 were each scored as 1 point. The NLR and PLR scores were summed to obtain the NLR-PLR score, according to which the patients were divided into 3 groups: the 0-point group, the 1-point group, and the 2-point group. Univariate and multivariate Cox models were used to screen independent clinical predictors of overall survival (OS) in HCC patients treated with TACE. The follow-up date was December 31, 2023. OS was defined as the time from the day of TACE to the time of death or the final follow-up date.

Table 1 Optimal Cutoff Values for the NLR, PLR, and Maximum Tumor Diameter

Variable	AUC	Optimal threshold	Sensitivity	Specificity	Youden index	95% CI	
						Lower limit	Upper limit
NLR	0.645	3.465	0.638	0.638	0.276	0.544	0.747
PLR	0.594	63.500	0.915	0.275	0.190	0.489	0.699
Maximum tumor diameter (cm)	0.657	6.750	0.809	0.493	0.302	0.557	0.757

TACE Operation

Following routine disinfection, draping, and anesthesia administration, the right femoral artery was punctured, and a hepatic catheter was inserted to perform abdominal trunk and hepatic arteriography. Physiological saline (100 mL) containing fluorouracil (0.75 g) was slowly injected into the common hepatic artery for perfusion chemotherapy; after the feeding vessel to the tumor was selected using a 3F microcatheter, a mixture of lipiodol (5–20 mL) + epirubicin (20–30 mg) + lobaplatin (30–40 mg) and gelatin sponge particles was injected for chemoembolization. Doses were determined on the basis of liver function test results and the size of the lesion.

MRI Scanning

All study subjects underwent abdominal scanning using a Discovery 750 3.0 T superconducting MRI scanner (GE, USA) after fasting for 4 hours before the scan. To minimize the effects of motion artifacts, all patients performed breathing exercises. All patients underwent axial FS-T2WI and dynamic contrast-enhanced MR scanning. During the dynamic contrast-enhanced scan, 15–20 mL of contrast agent (Gd-DTPA) was injected through the dorsal vein of the hand using a high-pressure syringe at an injection speed of 2–2.5 mL/s. Arterial and portal venous-phase scanning was performed at 18–25 s and 45–60 s, respectively, after contrast agent injection.

Feature Extraction

The MR images of all included patients in DICOM format were imported into 3D-Slicer software for tumor segmentation. The volume of the entire tumor was manually delineated layer by layer along the edge of the lesion on the axial FS-T2W images, enhanced arterial-phase images, and enhanced portal venous-phase images (Figure 1), and radiomic features, including intensity, shape, texture, and filter features (including wavelet features), of the delineated areas were extracted.

Feature Selection

To evaluate the stability and consistency of the radiomic features, 46 patients were randomly selected for consistency analysis. Two radiologists participated in this analysis. For the same group of patients, Radiologist A delineated the tumors twice at least one week apart, whereas Radiologist B delineated them once. The interobserver repeatability of each feature was evaluated as the intraclass correlation coefficient (ICC), and the ICC value was interpreted with a threshold commonly used in ICC analysis, ie, an ICC greater than 0.75 was considered excellent.[13] Features with an ICC $\geq$ 0.75 were retained (Figure 2). Least absolute shrinkage and selection operator (LASSO) regression was used to reduce the dimensionality of the features and select the optimal features (Figure 3).

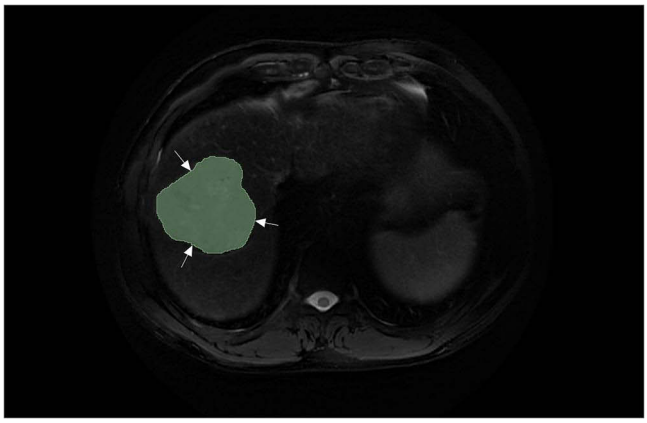

Figure 1 Layer-by-layer region of interest (green shading) delineation along the edge of the lesion (white arrows) on MRI.

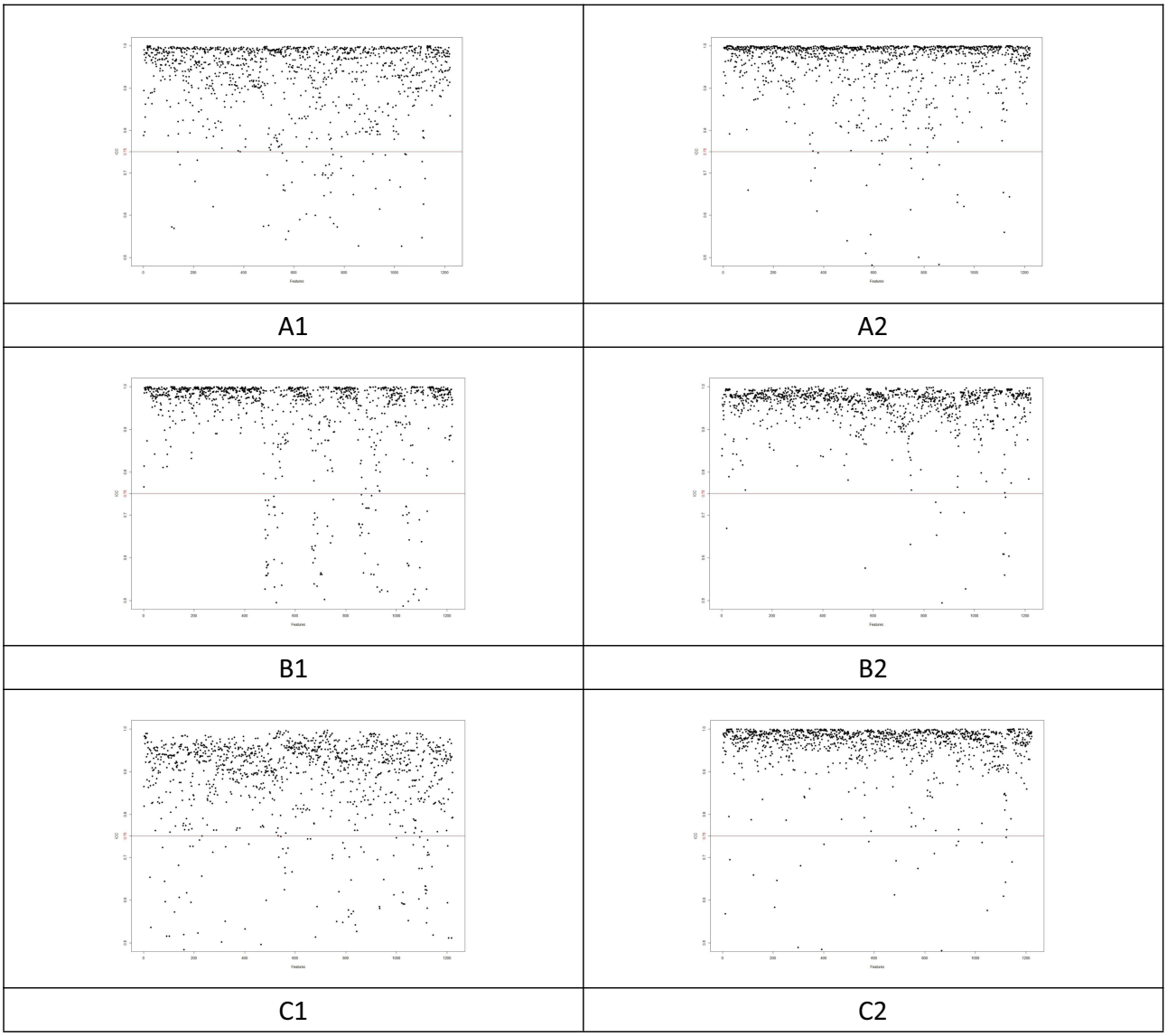

Figure 2 Consistency assessment of extracted MRI radiomic features by ICC. Assessments of interobserver and intraobserver agreement for FS-T2W images (A1-A2), arterial-phase images (B1-B2), and portal venous-phase images (C1-C2), respectively.

Model Construction and Evaluation

The optimal features screened for each image sequence were used to construct single-sequence radiomic models (the FS-T2WI, A, and P models) through logistic regression; a joint model (M model) that combined the optimal features of each sequence; and a joint imaging-clinical model (M-C model) that integrated the optimal features of the imaging sequences with clinical variables.

The area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and F1 score were obtained by calculating logistic regression confusion matrices to assess model performance.

Statistical Methods

R Studio 4.2.0 software was used for the statistical analysis. The R packages used included "psych", "glmnet", "pROC", "survival", and "survminer". For quantitative data, the independent-samples *t* test or Mann–Whitney *U*-test was used to

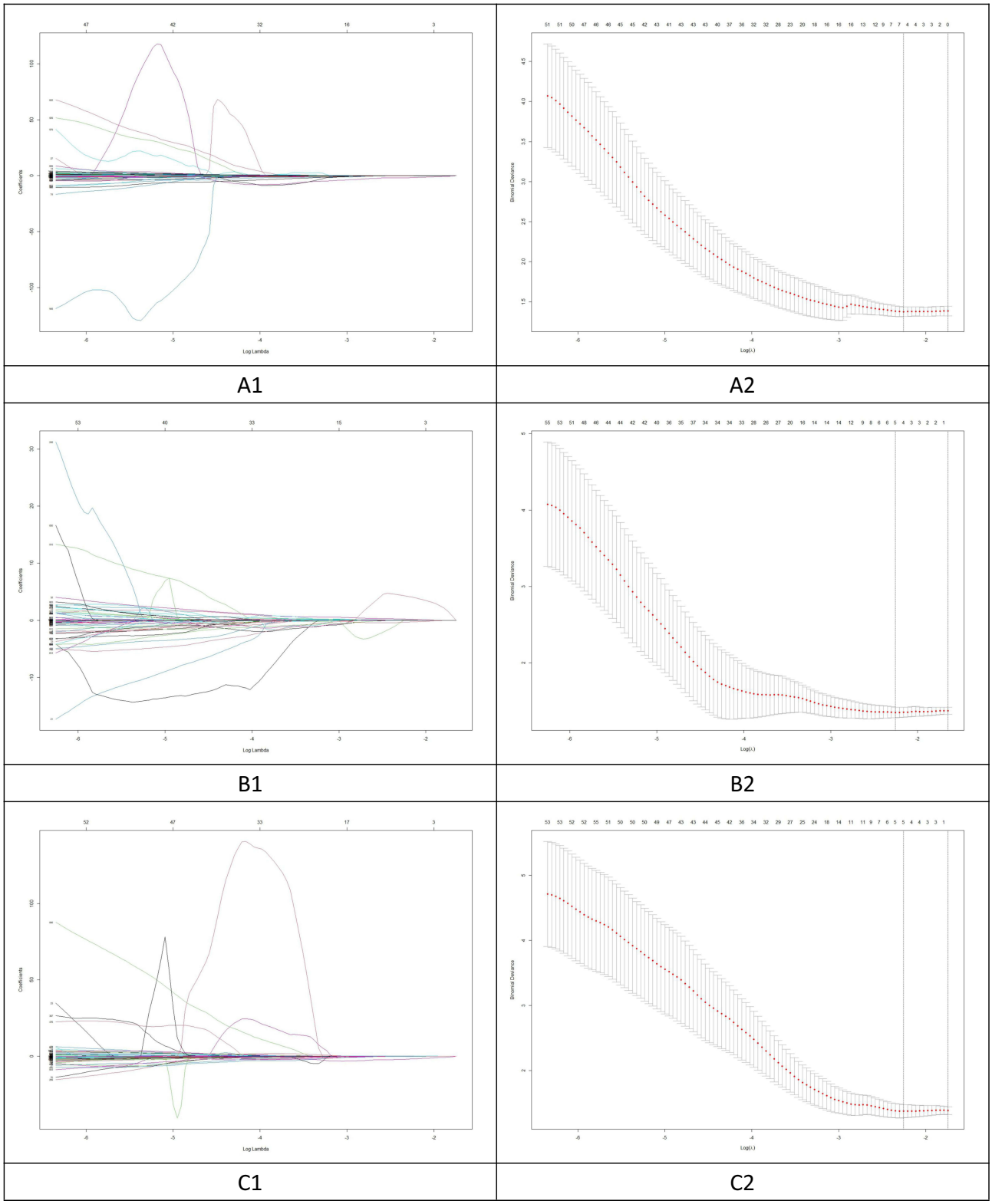

Figure 3 Optimal feature selection using LASSO regression for dimensionality reduction. (A1-A2) FS-T2WI features. (B1-B2) Arterial-phase image features. (C1-C2) Portal venous-phase image features.

compare groups. For categorical variables, the chi-square test was performed for intergroup comparisons. For all analyses, a two-sided P <0.05 was considered to indicate statistical significance.

Results

Clinical Data

This study enrolled 116 patients, including 104 males and 12 females. The ages of the participants ranged from 26 to 82 years (mean: 58.5 years) (Table 2). No patient was lost to follow-up until the final follow-up date. Among the patients, 69 survived, and 47 died. The median survival time was 670 days.

The univariate Cox proportional hazards model revealed no significant differences in sex, age, NLR, PLR, albumin–bilirubin index (ALBI), abnormal prothrombin (APT), alpha-fetoprotein (AFP), the number of tumors, liver cirrhosis, venous tumor thrombus, alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), or prothrombin time (PT) (P>0.05). The NLR-PLR score, maximum tumor diameter, and Child–Turcotte–Pugh (CTP) score were significantly associated with the OS of HCC patients (P <0.05). Multivariate Cox regression revealed that the NLR-PLR score and the CTP score were independent predictors of OS in HCC patients treated with TACE (Table 3).

Feature Extraction and Selection

Using 3D-Slicer software, 1223 features were extracted from the FS-T2WI, A, and P datasets. After the consistency test was carried out and features with intragroup and intergroup ICC values lower than 0.75 were excluded,[13] the remaining features were included in the LASSO regression analysis. Finally, 6, 5, and 3 optimal features were retained from the FS-T2WI, A, and P sequences, respectively (Table 4). Among the 14 optimal features, texture features accounted for 71.4% (10/14).

Model Construction and Evaluation

The AUC values of the FS-T2WI, A, P, M, and M-C models were 0.779, 0.803, 0.745, 0.858, and 0.893, respectively, in the training dataset and 0.635, 0.651, 0.644, 0.778, and 0.803, respectively, in the validation dataset. Among all the models, the M-C model had the best predictive performance (Table 5, Figure 4).

The optimal features of the M model were included in the LASSO regression analysis to calculate a Rad score. The Rad score, NLR-PLR score and CTP score were combined to create a radiomic nomogram using logistic regression to predict OS (Figure 5).

Discussion

Recent studies have demonstrated the application value of radiomics in the identification of HCC and the prediction of its histological grade, microvascular invasion (MVI) status, treatment response, and prognosis.[5,6,15–20,35–38] Kong et al[18] enrolled 99 advanced HCC patients receiving TACE treatment and extracted radiomic features from their T2W images to establish a model to predict the response to TACE treatment. In the training and validation cohorts, the area under the Rad score-based ROC curve was 0.812 and 0.866, respectively. The Rad score and relevant clinical indicators were integrated to construct a novel predictive nomogram. In the training and validation cohorts, the AUC of the nomogram increased to 0.861 and 0.884, respectively. Liu et al[16] developed a machine learning model for predicting the response to TACE and survival in HCC patients by integrating clinical and imaging modalities. A total of 140 HCC patients receiving TACE treatment were included in the study. During training and testing, for the logistic regression model that combined the Rad score derived from T2W images with the BCLC stage and ALBI, the AUCs for predicting the tumor response were 0.813 and 0.781, respectively. Survival analysis revealed that progression-free survival (PFS) and OS were significantly different between responders and nonresponders. The logistic regression-predicted response, ALBI, satellite node status and BCLC stage were found to be independent predictors of OS. These findings suggest that the model combining MRI radiomic features and clinical factors performed well in predicting the tumor response and clinical outcomes and could thus be helpful for developing personalized clinical management plans.

Table 2 Clinical Information

Variable	Training group	Validation group
Sex		
Male	71	33
Women	9	3
Age (years)		
≤60	46	20
>60	34	16
Number of tumors		
Single	36	12
Multiple	44	24
Maximum tumor diameter (cm)		
≤6.75	22	7
>6.75	58	29
Liver cirrhosis		
Yes	34	18
No	46	18
Portal vein tumor thrombus		
Yes	19	11
No	61	25
NLR		
≤3.47	41	20
>3.47	39	16
PLR		
≤63.50	28	9
>63.50	50	27
NLR-PLR score		
0	22	8
1	28	13
2	30	15
ALBI		
Grade 1	44	14
Grade 2	36	22
Grade 3	0	0
CTP		
Grade A	62	30
Grade B	18	6
APT (mAU/mL)		
≤40	3	6
>40	77	30
AFP (ng/mL)		
<20	20	16
20–400	31	7
>400	29	13
ALT (u/l)		
≤60	49	20
>60	31	16
AST (u/L)		
≤40	23	9
>40	57	27
ALB (g/L)		
≤40	45	17
>40	35	19

(*Continued*)

Table 2 (Continued).

Variable	Training group	Validation group
PT(s)		
≤14	60	26
>14	20	10
Surviving	48	21
Deceased	32	15

Table 3 Univariate and Multivariate Cox Regression Risk Table

Variable	Univariate cox				Multivariate cox			
	P	HR	HR value 95.0% CI		P	HR	HR value 95.0% CI	
			Lower limit	Upper limit			Lower limit	Upper limit
Sex	0.377	1.907	0.455	7.99				
Age	0.619	1.195	0.593	2.405				
Maximum tumor diameter	0.024	2.64	1.138	6.121	0.207	1.76	0.731	4.24
Number of tumors	0.114	0.568	0.282	1.146				
Liver cirrhosis	0.424	0.746	0.364	1.529				
Portal vein tumor thrombus	0.526	1.3	0.578	2.923				
NLR	0.078	1.906	0.929	3.911				
PLR	0.054	4.119	0.978	17.344				
NLR-PLR score	0.013				0.033			
NLR-PLR 1	0.036	4.964	1.109	22.212	0.031	5.294	1.169	23.975
NLR-PLR 2	0.005	8.243	1.909	35.589	0.009	7.255	1.628	32.331
ALBI	0.23							
ALBI 1	0.474	1.294	0.639	2.623				
ALBI 2	0.098	5.685	0.727	44.477				
CTP score	0.017	2.445	1.176	5.085	0.01	2.635	1.259	5.516
APT	0.916	0.898	0.121	6.639				
AFP	0.655							
AFP 1	0.49	1.406	0.534	3.703				
AFP 2	0.36	1.574	0.596	4.157				
ALT	0.49	1.283	0.632	2.603				
AST	0.421	1.392	0.622	3.112				
ALB	0.318	1.424	0.711	2.849				
PT	0.412	0.703	0.303	1.631				

Manual delineation is the most common method for segmenting the region of interest (ROI) or volume of interest (VOI) related to the target lesion.[39] We also used manual segmentation to extract radiomic features from the preoperative FS-T2W and enhanced arterial-phase and portal venous-phase MR images of HCC patients scheduled to undergo TACE to establish models. As a result, with the training and validation sets, the AUC value of the M model was greater than that of the individual-sequence models, and the M-C model performed the best. Among the optimal radiomic features selected in this study, texture features account for the vast majority. These classes can be used to quantify tumor heterogeneity by reflecting the relationships between adjacent voxels/pixels.[40]

Univariate Cox regression revealed that the maximum tumor diameter, CTP score, and NLR-PLR score were risk factors that affect patient survival; further multivariate Cox regression revealed that the CTP score and NLR-PLR score were independent factors for predicting patient survival. The CTP score is widely used as an independent predictor of

Table 4 Optimal Radiomic Features Selected by LASSO

Cohort	Feature Type	Feature Name
FS-T2WI	Shape	Maximum 3D Diameter
	GLDM	Low Gray Level Emphasis
	First-order	Skewness
	GLRLM	Short Run Emphasis
	GLSZM	Small Area Low Gray Level Emphasis
		Large Area High Gray Level Emphasis
	First-order	Kurtosis
Arterial-phase images	GLSZM	Size Zone Non Uniformity
	GLDM	Small Dependence Low Gray Level Emphasis
		Dependence Entropy
	GLCM	Idn
Portal venous-phase images	Shape	Maximum 3D Diameter
	GLDM	Low Gray Level Emphasis
	GLRLM	Short Run Emphasis

Table 5 Predictive Performance of Each Model

Dataset	Model	AUC	Sen	Spe	PPV	NPV	ACC	F1 score
Training	FS-T2WI model	0.779	0.469	0.813	0.625	0.696	0.675	0.536
	A model	0.803	0.531	0.896	0.773	0.741	0.750	0.630
	P model	0.745	0.562	0.854	0.720	0.745	0.738	0.632
	M model	0.858	0.688	0.875	0.786	0.808	0.800	0.733
	MC model	0.893	0.750	0.875	0.800	0.840	0.825	0.774
Validation	FS-T2WI model	0.635	0.266	0.857	0.571	0.621	0.611	0.363
	A model	0.651	0.200	0.857	0.500	0.600	0.583	0.286
	P model	0.644	0.267	0.905	0.667	0.633	0.639	0.380
	M model	0.778	0.333	0.857	0.625	0.643	0.639	0.434
	MC model	0.803	0.600	0.810	0.692	0.739	0.722	0.643

survival in HCC patients after TACE treatment. Akarapatima et al[41] retrospectively analyzed 158 HCC patients receiving TACE and evaluated the ability of the CTP score to predict patient prognosis. The results revealed that the OS of CTP A patients was greater than that of CTP B patients; in other words, a higher CTP score was negatively correlated with OS, suggesting that the CTP staging system is a powerful tool for predicting the prognosis of HCC patients receiving TACE. Our results are consistent with theirs. Other studies have shown that neutrophils, platelets, and lymphocytes participate in inflammatory and immune processes in the body and are associated with tumor progression and prognosis.[21–34,42,43] Neutrophils induce DNA damage and promote angiogenesis and immunosuppression, enhancing the biological behavior of tumors by producing genotoxic DNA fragments, whereas lymphopenia reduces the antitumor effect on the body.[42,43] Among the possible mechanisms by which platelets induce tumor progression are the following: (1) platelets promote the development of tumor-associated vasculature and enhance tumor growth and invasion; and (2) during metastasis, platelets form a barrier that protects tumor cells from high-velocity forces and immunosurveillance while ensuring establishment of the premetastatic niche before metastasis.[25–27,44] Schobert et al[29] investigated the value of quantitative imaging findings and inflammatory biomarkers in HCC patients for predicting the clinical outcome of drug-eluting bead (DEB)-TACE. A total of 46 early HCC patients receiving DEB-ACE treatment were included in this study. The results revealed that a high baseline NLR and PLR could predict a poor tumor response and a short PFS; additionally, a high NLR and PLR were associated with nonspherical tumor growth. Nicolini et al[45] reported that the radiological response and inflammatory markers predict tumor recurrence after TACE and are thus conducive to the

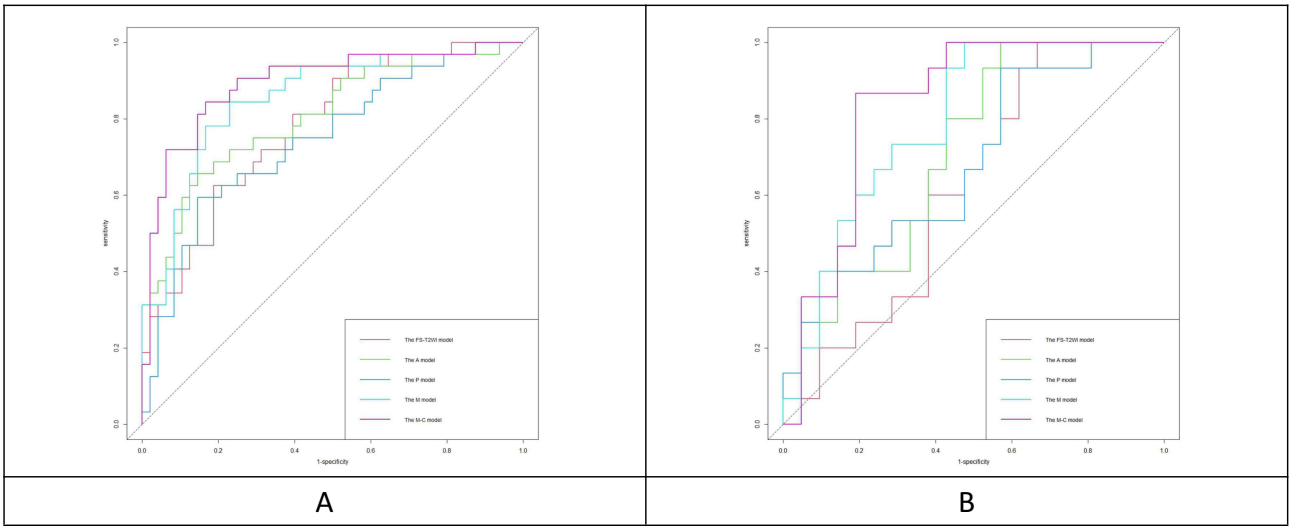

Figure 4 ROC curves of the FS-T2WI model, A model, P model, M model, and M-C model in the training group (**A**) and validation group (**B**).

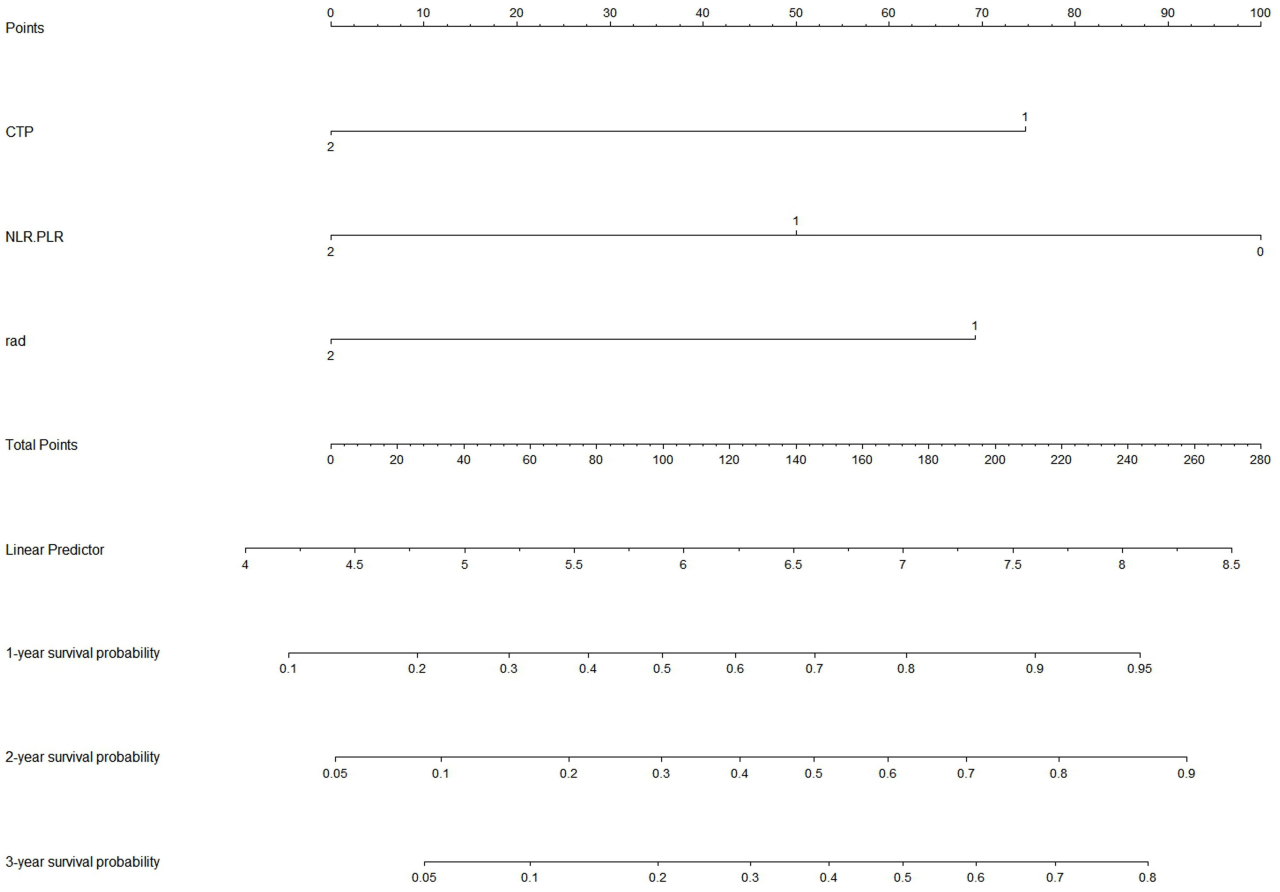

Figure 5 Nomogram for survival probabilities predicted by the multivariate Cox proportional hazards regression model.

selection of TACE-treated candidates for liver transplantation (LT) after TACE. Taussig et al[46] retrospectively analyzed the data of 86 HCC patients who received chemoembolization or radioembolization. Patients with an NLR>3 had significantly greater baseline CTP scores and poorer disease control. Logistic regression analysis of the tumor response revealed that an NLR>3 was the best predictor of early progression. These findings suggest that the NLR may serve as a serological biomarker for early progressive disease in HCC patients after intra-arterial treatment.

The above studies revealed the value of radiomic features from MR images and inflammatory cytokines in evaluating the prognosis of HCC patients after TACE treatment. There are no reports of the ability of MRI radiomic features combined with the NLR-PLR to predict the prognosis of HCC patients treated with TACE. This study integrated the optimal radiomic features from multisequence MRI and clinical factors, such as the NLR-PLR, to construct a joint model that could satisfactorily predict the prognosis of HCC patients receiving TACE treatment. The quantitative nomogram based on the Rad score and clinical factors may provide highly informative data for developing individualized treatment strategies.

This study has the following limitations. (1) This study was retrospective in nature. (2) Because of patient heterogeneity, there may be selection bias in the current study. (3) This study included data from a single center, and the sample size was small. In future studies, multicenter data should be collected from more patients to validate the findings of the current study. (4) The follow-up time was short; future studies should consider analyzing data from longer follow-up times.

Conclusions

A multisequence MRI radiomic model showed good performance in predicting the OS of HCC patients treated with TACE, and the inclusion of clinical indicators such as inflammation scores improved its predictive performance. The present study provides a new strategy for the personalized management of patients with HCC.

Author Contributions

All authors made a significant contribution to the reported work, whether 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 have agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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