



Ki-67 expression correlates with hepatocellular carcinoma recurrence and is predictable using radiomics features

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Abstract

Objective This study aims to identify the optimal Ki-67 cutoff for predicting HCC recurrence and to develop a radiomics model based on CT arterial phase features for non-invasive preoperative Ki-67 assessment.

Methods A total of 180 HCC patients who underwent radical resection were enrolled. The prognostic value of Ki-67 was analyzed using multivariate Cox proportional hazards regression models, and the optimal Ki-67 expression threshold for recurrence prediction was determined by the area under the ROC curve (AUC). Radiomics features from both intratumoral and peritumoral regions were extracted from preoperative CT arterial-phase images. Key features were selected to develop a radiomics prediction model. The predictive performances of the radiomics, clinical, and combined models were compared, and key influencing features for the optimal model were identified through Shapley additive explanations (SHAP) analysis.

Results High Ki-67 expression ($\geq 25\%$) was identified as an independent risk factor for postoperative HCC recurrence (hazard ratio [HR]=9.923, 95% confidence interval [CI]: 3.383–29.108, $P<0.001$). The recurrence-free survival rate was significantly lower in the high Ki-67 expression group compared to the low expression group ($P=0.009$). In the testing set, the radiomics model utilizing random forest (RF) algorithm demonstrated superior predictive performance for Ki-67 expression (AUC=0.869, sensitivity=0.733, specificity=0.846). Its performance significantly exceeded that of the clinical model (AUC: 0.869 vs. 0.540, $P=0.005$), while the combined model showed no significant improvement compared to the radiomics model alone (AUC: 0.870 vs. 0.869, $P=0.979$). SHAP analysis revealed that the peritumoral texture heterogeneity feature (peri_wavelet_LLH_firstorder_Kurtosis) contributed most significantly to the radiomics model (SHAP value=+0.17).

Conclusion High Ki-67 expression ($\geq 25\%$) is a key prognostic factor for postoperative HCC recurrence. The CT arterial phase radiomics model allows non-invasive preoperative Ki-67 assessment, emphasizing the role of peritumoral heterogeneity.

Keywords Hepatocellular carcinoma · Ki-67 · Radiomics · Prognosis · Computed tomography

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Introduction

Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related mortality worldwide. According to 2020 global cancer burden data from the International Agency for Research on Cancer (IARC), a division of the World Health Organization, the five-year survival rate for HCC remains below 20%, with postoperative recurrence rates reaching 70% within five years, constituting a critical determinant of patient prognosis [1, 2]. Ki-67, a cell cycle-dependent nuclear protein, serves as a marker of proliferative activity during the G1/S/G2/M phases, directly reflecting tumor proliferative dynamics. Multiple studies have demonstrated that Ki-67 expression levels correlate closely with tumor cell proliferation, cell cycle regulation, and biological behaviors including growth patterns, recurrence, and metastasis [3–5]. Research has established that Ki-67 expression is significantly associated with HCC invasiveness and prognosis, making it a critical biomarker for prognostic assessment in HCC patients [3, 6–8]. However, the precise definition of the optimal Ki-67 threshold for HCC remains controversial, with current research suggesting a threshold range of 10–20% [3, 7, 9]. Some studies have directly adopted Ki-67 threshold standards from other malignancies, such as breast cancer [10, 11] and nasopharyngeal carcinoma [12], without specific biological validation for HCC. This heterogeneity in threshold definition introduces bias in clinical prognostic assessments, highlighting the urgent need for a standardized interpretation system based on large-sample cohorts and evidence-based medicine. Moreover, traditional Ki-67 detection relies on postoperative immunohistochemistry, which precludes preoperative risk stratification and dynamic monitoring of treatment response, thereby limiting the implementation of precision diagnostic and treatment strategies. In recent years, high-throughput extraction of deep features from CT and magnetic resonance imaging (MRI) has opened new avenues for non-invasive assessment of tumor heterogeneity. Preliminary studies have tentatively validated the feasibility of predicting Ki-67 expression [3, 9, 13]; however, these studies exhibit significant limitations: first, feature selection is often restricted to the intratumoral region, neglecting the prognostic value of the 2-mm peritumoral microenvironment; second, model construction lacks an interpretable framework, complicating the analysis of association mechanisms between key imaging features and biological phenotypes. This study integrates intratumoral and peritumoral dual-region CT arterial phase radiomics features, combined with the SHAP explainability algorithm, aiming to achieve three main objectives: first, determine the optimal Ki-67 expression threshold for HCC based on

recurrence/metastasis endpoint events; second, develop an interpretable preoperative non-invasive prediction model for Ki-67 expression; and third, assess the predictive performance of radiomics signatures for postoperative recurrence-free survival, providing imaging biomarkers for personalized monitoring and intervention in HCC.

Materials and methods

Patients

This study received approval from the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities (approval number: YYFY-LL-2024-038). In accordance with the Declaration of Helsinki, retrospective studies may be exempt from obtaining informed consent from participants. The study included 180 patients with pathologically confirmed HCC from the Affiliated Hospital of Youjiang Medical University between January 2022 and February 2025. Patients were randomly divided into a training set (126 cases) and a testing set (54 cases) at a 7:3 ratio. This study was retrospective in nature, with pathological data retrieved through querying pathology reports in the pathology information system. All reports were independently reviewed by two pathologists: the primary diagnostician, who possesses a minimum of 3 years of experience, and the reviewing pathologist, who has over 10 years of diagnostic expertise. This dual-review process ensured the accuracy and reliability of the pathological data. Inclusion criteria were as follows: (a) Patients with HCC staged according to the China Liver Cancer (CNLC) classification [14], those in stages Ia to IIa, with complete postoperative pathological data on Ki-67 expression, and a clear correspondence between the postoperative specimens and the imaging findings of the tumor lesions. (b) Non-contrast and triple-phase contrast-enhanced CT of the upper abdomen was performed within 14 days prior to surgery (median: 7 days, range: 1–14 days). (c) No history of preoperative anti-tumor therapy was reported. Exclusion criteria: (a) Artifacts in CT imaging can hinder the accurate delineation of regions of interest (ROIs); (b) Presence of other concurrent malignancies, such as prostate or breast cancer (Fig. 1).

Clinical data collection and follow-up

Baseline clinical parameters were collected, including age, gender, alcohol consumption history, hepatitis B surface antigen (HBsAg) status, alpha-fetoprotein (AFP) levels, aspartate aminotransferase (AST), alanine aminotransferase

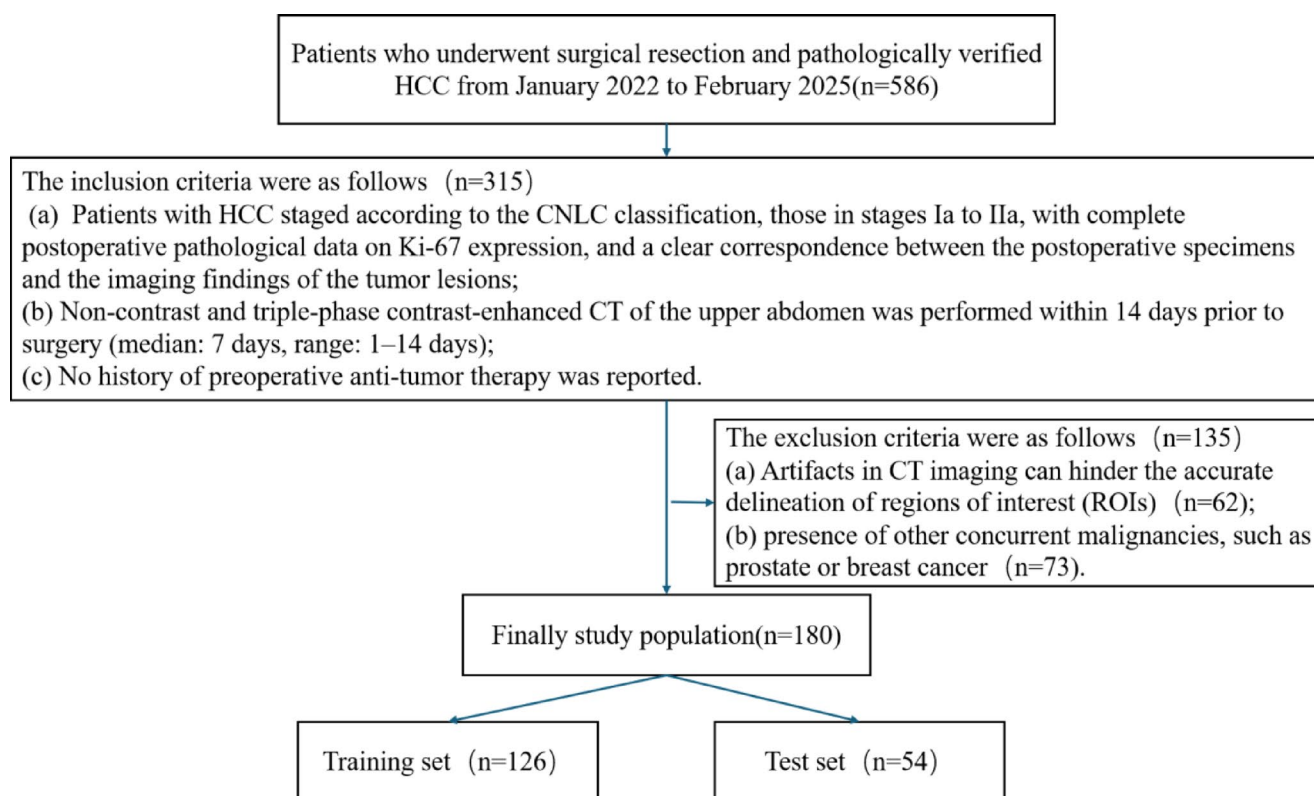


Fig. 1 Flow diagram of the study cohort selection process

(ALT), cirrhosis, metabolic-associated fatty liver disease (MASLD), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection status. Postoperative follow-up was performed every 3 months, involving serum AFP measurements and imaging assessments (including contrast-enhanced CT/MRI), with a total follow-up duration of 15 months. The primary endpoint was defined as tumor recurrence or metastasis, confirmed through enhanced CT or MRI imaging during follow-up. The criteria for postoperative HCC recurrence or local metastasis were as follows: the emergence of new tumor lesions within the surgical site during follow-up, exhibiting imaging characteristics consistent with HCC enhancement patterns. In cases where the enhancement patterns were atypical, tumor recurrence was considered if the lesion progressively enlarged during the follow-up period. Local metastasis was defined as the development of new lesions within the liver, with imaging features consistent with either HCC or metastatic tumors, and/or the presence of portal vein thrombosis. Postoperative distant metastasis was characterized by the appearance of extrahepatic metastatic lesions during follow-up, including metastases to lymph nodes, peritoneum, lungs, adrenal glands, or bones. All follow-up imaging studies were independently reviewed by two physicians with 5 and 8 years of experience in abdominal imaging, ensuring the accuracy and consistency of the diagnoses.

Ki-67 detection method

Postoperative tissue samples from the core region of HCC tumor underwent routine hematoxylin-eosin staining, paraffin embedding, and sectioning (3–5 μm). Immunohistochemical staining was performed using a mouse anti-human Ki-67 monoclonal antibody. Two pathologists independently evaluated the samples by selecting five random 400 $\times$ high-power fields and counting the number of positive cells with brown nuclear staining among 100 tumor cells. The average positivity rate was calculated as the Ki-67 expression index.

CT scan protocol

The CT scan protocol encompassed the region from the apex of the diaphragm to the inferior margin of the liver, utilizing iopromide as the contrast agent. The injection volume was calculated as 1.5 mL/kg with an infusion rate of 3.5 mL/s, followed by a saline flush of 40 mL at the same rate. The ROI was designated within the descending aorta, and arterial-phase scanning was initiated 8 s after the threshold was reached. The CT imaging protocols for various equipment are outlined in Table 1, with all arterial-phase CT images exported in Digital Imaging and Communications in Medicine (DICOM) format and subsequently converted

Table 1 CT scanning parameters for various devices

Devices	Revolution ACa (GE)	Ingenuity Core 64 (Philips)	Revolution(GE)
Slice thickness (mm)	5	5	5
Slice interval (mm)	5	5	5
Tube voltage (kV)	120	120	120
Tube current (mA)	50	30	50
Matrix size	512 × 512	512 × 512	512 × 512
Threshold of ROI(HU)	100	150	120

to Neuroimaging Informatics Technology Initiative (NIfTI) format.

CT image preprocessing and tumor segmentation

All arterial-phase CT images underwent standardized preprocessing, including: (1) voxel resampling ($1 \times 1 \times 1 \text{ mm}^3$); (2) uniform window width/window level settings (liver window: 150/40 HU). If HCC was multifocal, the primary lesion confirmed by pathology was selected for segmentation, corresponding to the largest lesion identified on CT images. Two radiologists with 5 (Nong Haiyang) and 8 years (Cen Yongyi) of experience in abdominal imaging diagnosis employed ITK-SNAP 3.8 software to perform layer-by-layer, three-dimensional delineation of the tumor core region, with each radiologist independently completing 90 tumor segmentations. From the tumor-internal ROI, a 2-mm automatic expansion was applied to generate the tumor-peripheral ROI, followed by manual correction for portions extending beyond the liver parenchyma. The delineation results were reviewed by a third radiologist with 22 years of abdominal imaging experience (Huang Deyou). In cases of disagreement, the three radiologists reached a consensus after collaborative review and mutual consultation. Figure 2 illustrates the schematic diagram of intratumoral and peritumoral ROI delineation.

Feature engineering and model construction

PyRadiomics3.0.1 was employed to extract 1,834 radiomics features from both intratumoral and peritumoral regions of HCC, including first-order, shape, and texture features. The feature selection process involved: (1) Z-score normalization; (2) t-test/Mann-Whitney U test ($P < 0.05$); (3) Pearson correlation coefficient to eliminate redundant features ($r > 0.9$); and (4) LASSO regression (10-fold cross-validation, $\lambda = 1\text{SE}$) for selecting key features. Clinical features were evaluated for differences using the Shapiro-Wilk normality test, and statistically significant clinical features ($P < 0.05$) were selected through t-test/Mann-Whitney U test or χ^2 test. Subsequently, these features were used to construct three common prediction models, including Logistic Regression (LR), Support Vector Machine (SVM), and Random Forest (RF). The Synthetic Minority Over-sampling Technique (SMOTE) was utilized to balance the data, and grid search was employed to optimize hyperparameters. Finally, logistic regression (LR) was applied to construct a nomogram based on the optimal radiomics and clinical model scores, referred to as the combined model. Model performance was assessed using ROC curves, and for the best predictive model, the SHAP algorithm was utilized to analyze feature contributions. The schematic of the overall design process is presented in Fig. 3.

Statistical analysis and sample size estimation

Cox regression analysis was conducted to examine the relationship between Ki-67 and RFS. The ROC curve was used to determine the optimal Ki-67 expression threshold using the Youden index, and the Kaplan-Meier method was employed to compare survival differences between high and low expression groups (GraphPad Prism 10.1.2). Dimensionality reduction of radiomics features, baseline clinical

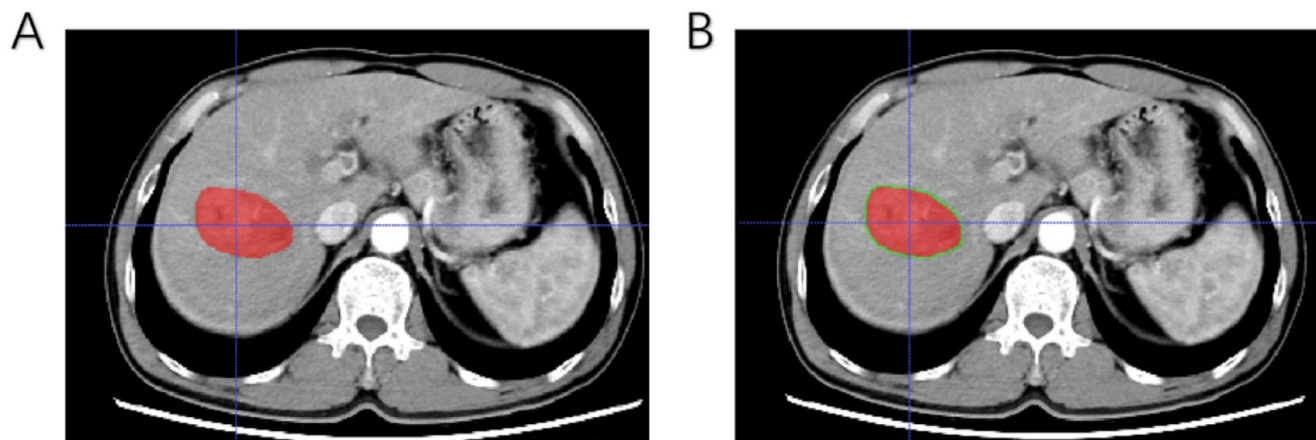


Fig. 2 Delineation of regions of interest (ROIs) in hepatocellular carcinoma. **A** Intratumoral ROI delineation. **B** Peritumoral ROI delineation extending 2 mm beyond the tumor boundary

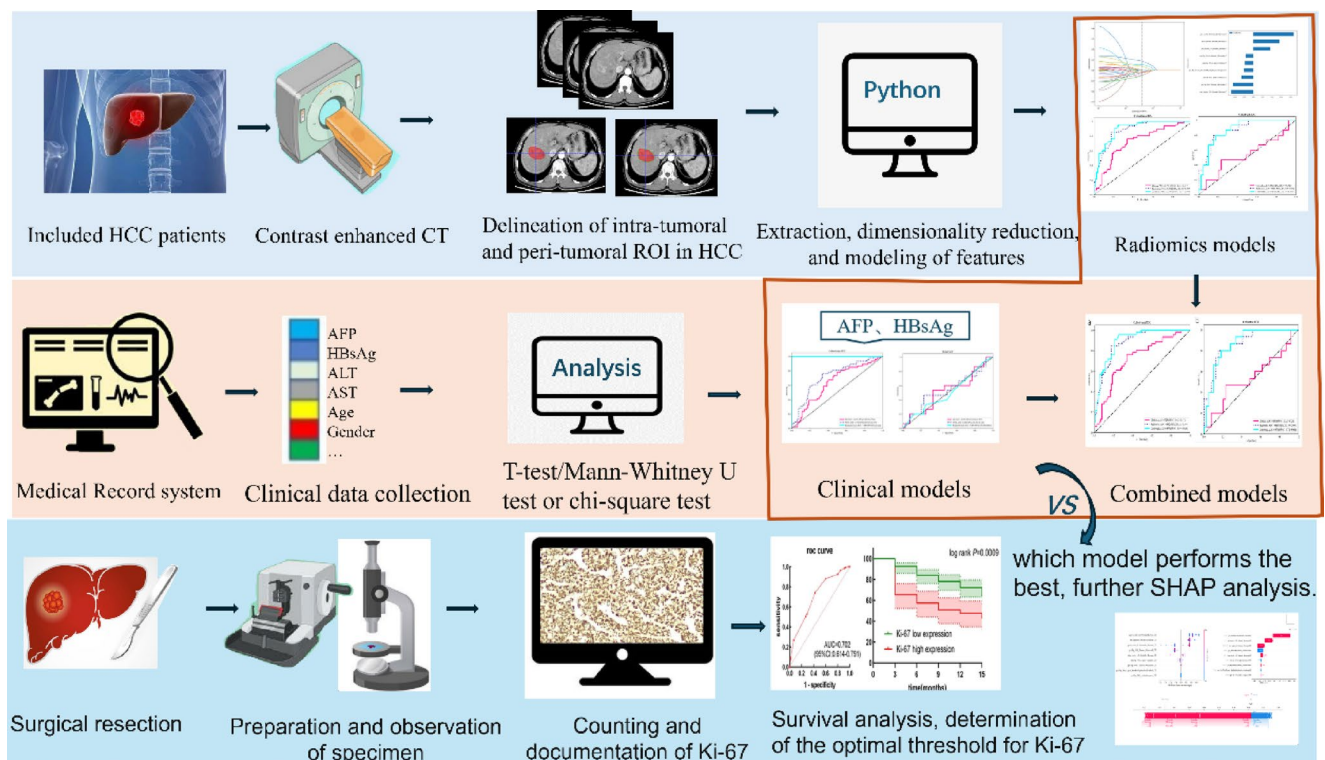


Fig. 3 Overall design flowchart illustrating the radiomics analysis pipeline from image acquisition to model construction and validation

feature analysis, and predictive model performance evaluation were conducted using Python 3.7. Sample size was validated using MedCalc23.0.1 (<https://www.medcalc.org>); the training set required at least 26 cases ($\alpha=0.05$, $\beta=0.2$, expected AUC=0.8), and a total of 126 cases (46 high expression/80 low expression) were included to meet statistical power requirements.

Results

Prognostic value of Ki-67 and validation of the critical threshold

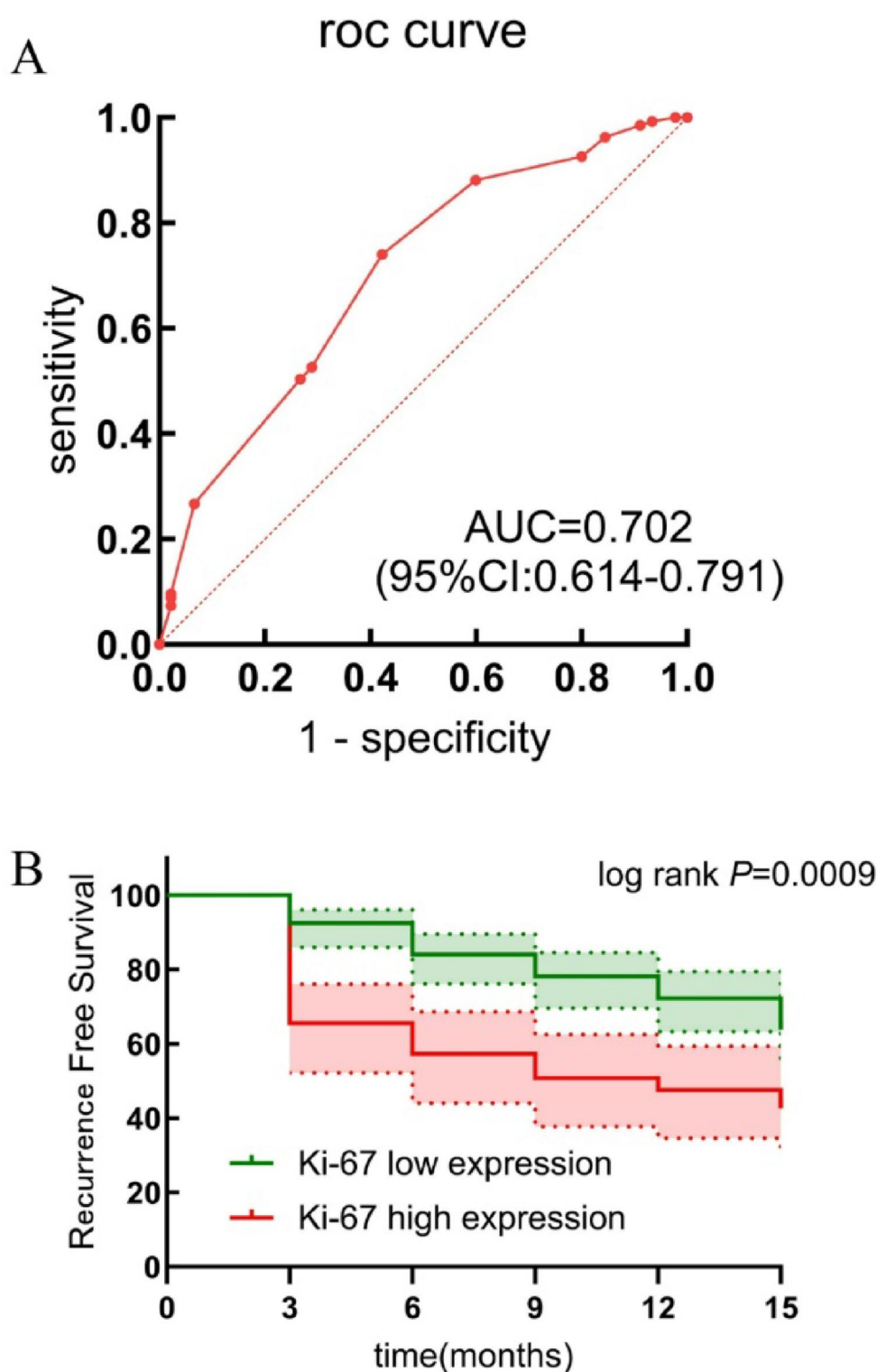
Among the 180 study participants, follow-up assessments were conducted every three months postoperatively, with a cumulative follow-up period of 15 months. During the follow-up, 75 patients developed postoperative recurrence or metastasis, comprising 56 cases of local recurrence and metastasis, and 19 cases of distant metastasis. The distant metastases included 5 cases of lymph node involvement, 5 cases of peritoneal or abdominal cavity metastasis, 1 case of abdominal wall metastasis, and 8 cases of lung and/or bone metastasis. The quartile values (25%, 50%, and 75%) for postoperative recurrence or metastasis were 6.75, 15.00, and 15.00 months, respectively. The time corresponding to the 25% quartile (6.75 months) was defined

as the recurrence threshold for HCC following surgery. Cox multivariate regression analysis demonstrated that elevated Ki-67 expression was an independent risk factor for HCC recurrence (HR=9.92, 95% CI: 3.38–29.11, $P<0.001$). ROC curve analysis identified the optimal Ki-67 expression threshold for predicting recurrence as 25% (AUC=0.702, sensitivity=58.0%, specificity=74.0%) (Fig. 4A). Kaplan-Meier analysis confirmed that the recurrence-free survival rate in the high Ki-67 expression group ($\geq 25\%$) was significantly lower compared to the low expression group (log-rank $P=0.0009$) (Fig. 4B).

Construction and performance evaluation of the Ki-67 predictive model

We conducted an analysis of the baseline clinical characteristics of the study cohort (Table 2). The results indicated that, in the training set, statistically significant differences were observed in the levels of HBsAg and AFP between the high and low Ki-67 expression groups ($P<0.05$). However, no significant differences were found between the test and training sets for other clinical variables, including gender, age, AST, ALT, alcohol consumption, cirrhosis, MASLD, and HBV and HCV infection status. In the clinical model developed using HBsAg and AFP, the SVM model demonstrated optimal performance. The area under the curve (AUC) values for the training and test sets were 0.725 and

Fig. 4 Prognostic value of Ki-67 expression in hepatocellular carcinoma. **A** Receiver operating characteristic (ROC) curve for determining the optimal Ki-67 threshold, with AUC=0.702 (95% CI: 0.614–0.791). **B** Kaplan-Meier survival curves comparing recurrence-free survival between patients with low (<25%) and high ($\geq 25\%$) Ki-67 expression (log-rank $P=0.0009$)



0.540, respectively (Supplementary Material 1). Feature selection identified nine key radiomics features from CT arterial phase images, including three intratumoral and six peritumoral radiomics features (Figs. 5A, B). The radiomics model utilizing the RF algorithm performed optimally in

the testing set, with an AUC of 0.869 (sensitivity=73.3%, specificity=84.6%), significantly outperforming the clinical model (AUC=0.540, $P<0.05$) (Tables 3 and 4; Figs. 5C, D). The AUC of the combined model in the testing set was 0.870 (sensitivity=40.0%, specificity=89.7%). The

Table 2 Analysis of the baseline clinical characteristics

Feature	Training set (<i>n</i> = 126)		pvalue	Validation set(<i>n</i> = 54)		p value
	Ki-67 low expression group	Ki-67 high expression group		Ki-67 low expression group	Ki-67 high expression group	
Age	52.44 ± 9.60	51.57 ± 12.00	0.655	52.08 ± 11.09	51.00 ± 11.44	0.753
HBsAg	1023.13 ± 946.87	1256.67 ± 739.79	0.035	1003.65 ± 876.29	641.37 ± 486.59	0.206
AFP	382.70 ± 498.93	587.88 ± 532.47	0.003	427.32 ± 512.16	587.15 ± 514.12	0.243
AST	68.25 ± 77.93	61.52 ± 51.62	0.693	82.84 ± 168.94	65.97 ± 53.92	0.706
ALT	68.49 ± 89.32	54.92 ± 58.66	0.865	76.66 ± 133.46	73.00 ± 83.34	0.699
Sex			0.685			0.537
Female	14 (17.50%)	6 (13.04%)		7 (17.95%)	1 (6.67%)	
Male	66 (82.50%)	40 (86.96%)		32(82.05%)	14 (93.33%)	
Drinking			0.786			1
No	52 (65.00%)	28 (60.87%)		26(66.67%)	10 (66.67%)	
Yes	28 (35.00%)	18 (39.13%)		13(33.33%)	5 (33.33%)	
Cirrhosis			0.096			0.835
No	45 (56.25%)	18 (39.13%)		16 (41.03%)	5 (33.33%)	
Yes	35 (43.75%)	28 (60.87%)		23 (58.97%)	10 (66.67%)	
HBV infection			0.273			0.872
No	14 (17.50%)	4 (8.70%)		5 (12.82%)	1 (6.67%)	
Yes	66 (82.50%)	42 (91.30%)		34 (87.18%)	14 (93.33%)	
HCV infection			0.778			1.0
No	80 (100%)	45 (97.83%)		38 (97.44%)	15 (100%)	
Yes	0 (0%)	1 (2.17%)		1 (2.56%)	0 (0%)	
MASLD			1.0			0.617
No	79 (98.75%)	45 (97.83%)		39 (100%)	14 (93.33%)	
Yes	1 (1.25%)	1 (2.17%)		0 (0%)	1 (6.67%)	

DeLong test revealed that the AUCs of the radiomics and combined models were significantly higher than that of the clinical model in the testing set ($P=0.005$ and 0.001 , respectively). Additionally, the combined model showed no significant performance improvement over the radiomics-only model ($P=0.979$), suggesting that clinical features contributed limitedly to prediction effectiveness (Figs. 6A, B).

SHAP explainability analysis for radiomics models

SHAP explainability analysis further confirmed that the peritumoral texture heterogeneity feature (peri_wavelet_LLH_firstorder_Kurtosis) was the most influential predictor of high Ki-67 expression, exerting a positive driving effect (SHAP value = +0.17) (Figs. 7A-C).

Discussion

Biological and clinical significance of Ki-67 thresholds

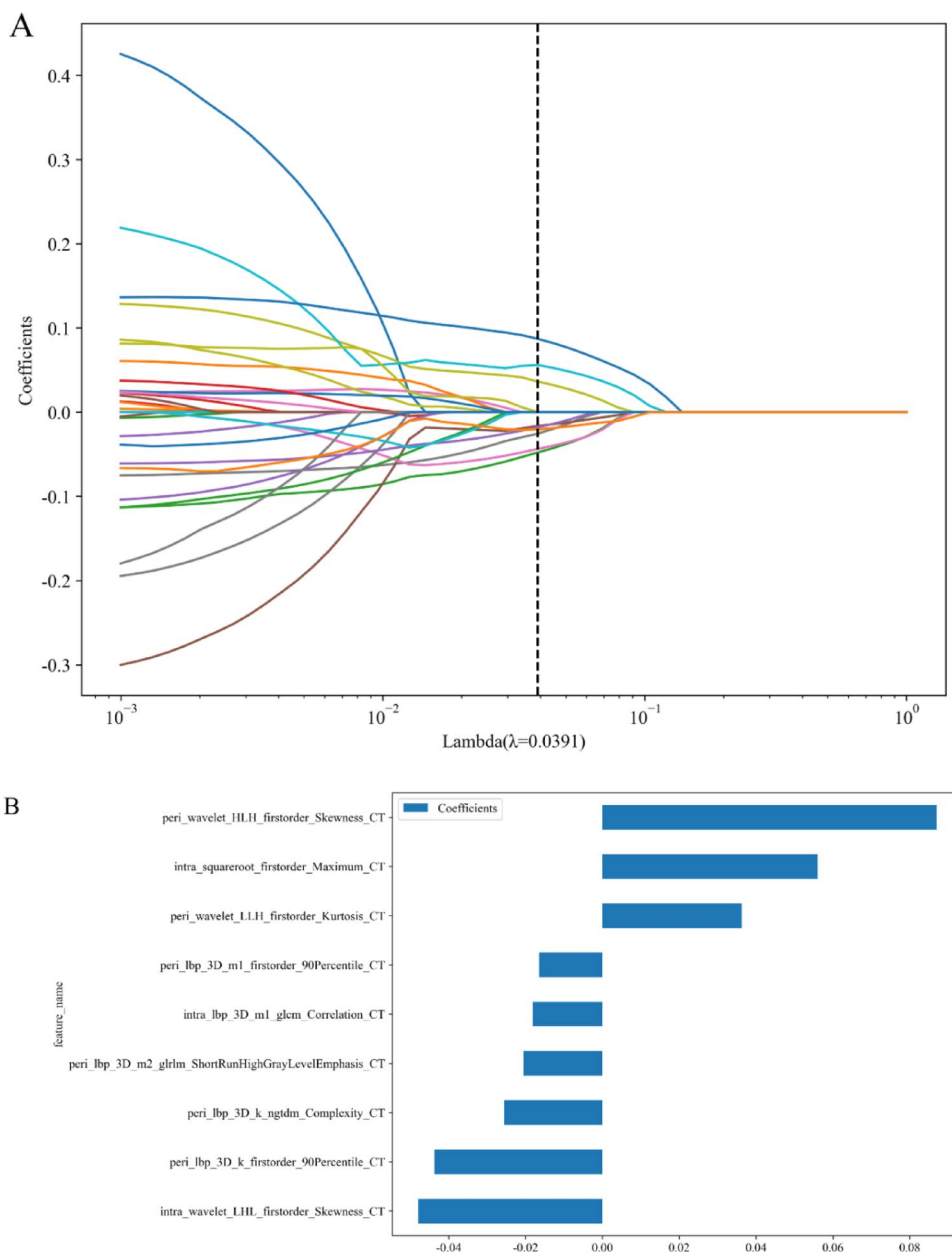
In this study, data from a cohort of 180 HCC cases identified 25% as the optimal threshold for predicting recurrence (AUC = 0.702), offering superior prognostic stratification

capabilities compared to previously established thresholds (10%–20%) [3, 7, 9]. This threshold was independently validated through Cox multivariate regression analysis (HR = 9.92, $P < 0.001$) and survival analysis (log-rank $P = 0.0009$), and may offer valuable insights for clinical practice. These findings suggest that tumors with $\text{Ki-67} \geq 25\%$ may exhibit enhanced proliferative invasiveness, potentially linked to the upregulation of angiogenesis factors such as vascular endothelial growth factor (VEGF) and the remodeling of an immunosuppressive microenvironment.

Innovative value of the arterial phase radiomics model

HCC is predominantly supplied by the hepatic artery, and during the arterial phase, contrast agents rapidly enhance tumor tissue, creating a clear density difference with surrounding normal liver tissue. This contrast distinctly outlines tumor boundaries and accentuates internal heterogeneity [3, 15]. Compared to the portal venous and equilibrium phases, the CT arterial phase increases the contrast between tumor and liver parenchyma, enhancing sensitivity for detecting tumor neovascularization and microinvasive foci [16]. This study selected three intratumoral and six peritumoral radiomics features, consistent with findings by Qian et al. [17], who developed a radiomics model based on

Fig. 5 Feature selection and model performance evaluation. **A** LASSO regularization path for radiomics feature selection. **B** Feature importance ranking based on model coefficients. **C** ROC curves comparing different machine learning algorithms (LR, SVM, RF) for the intratumoral and peritumoral radiomics model in the training set. **D** ROC curves comparing different machine learning algorithms in the testing set

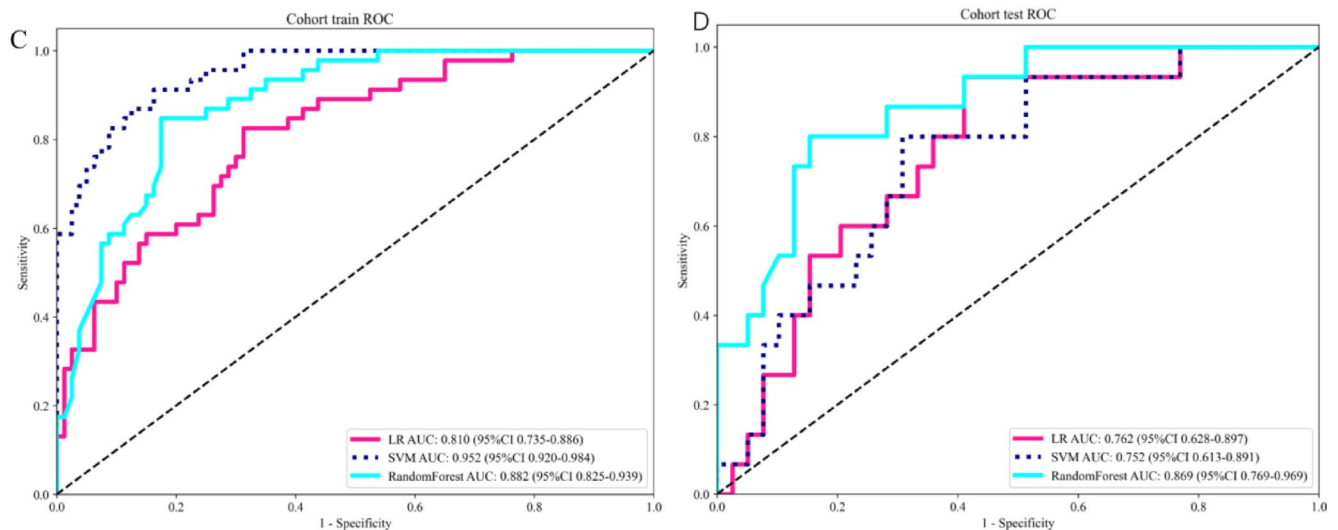


abdominal ultrasound to predict Ki-67 expression in HCC patients. SHAP analysis demonstrated that the peritumoral radiomics feature `peri_wavelet_LLH_firstorder_Kurtosis` made the largest positive contribution to the model. This feature reflects asymmetry in grayscale distribution within the peritumoral region, potentially corresponding to heterogeneity in inflammatory cell infiltration or fibrous matrix remodeling within the microenvironment. Comprehensive analysis of both intratumoral and peritumoral features provides a more accurate reflection of tumor biological behavior. Regarding HCC Ki-67 prediction performance, the radiomics model achieved an AUC of 0.869 in the testing set, significantly outperforming the traditional clinical model (AUC=0.540, $P=0.005$). This performance

improvement can be attributed to radiomics features from both intratumoral and peritumoral regions, which effectively capture the biological behavior characteristics of the tumor and surrounding host tissue, validating the hypothesis that “tumor edges drive biological behavior” [18].

Analysis of limitations of the combined model

Although the combined model incorporated the clinical indicators AFP and HBsAg, its AUC (0.870) did not significantly surpass that of the radiomics model ($P=0.979$). This finding contrasts with conclusions by Zhang et al. [19], who reported that the combined model offered certain advantages in predicting Ki-67 expression in breast cancer. On one

**Fig. 5** (continued)**Table 3** Predictive performance of various machine learning methods in the radiomics model

Dataset	Model	Accuracy	AUC (95% CI)	Sensitivity	Specificity
Training	LR	0.73	0.810 (0.735–0.886)	0.804	0.687
Testing	LR	0.667	0.762 (0.628–0.897)	0.867	0.59
Training	SVM	0.857	0.952 (0.920–0.984)	0.891	0.837
Testing	SVM	0.704	0.752 (0.613–0.891)	0.733	0.692
Training	RF	0.825	0.882 (0.825–0.939)	0.826	0.825
Testing	RF	0.815	0.869 (0.769–0.969)	0.733	0.846

Table 4 Performance of different models in predicting Ki-67 expression

Dataset	Model	Accuracy	AUC (95% CI)	Sensitivity	Specificity
Training	Clinical	0.69	0.725 (0.633–0.817)	0.739	0.662
Testing	Clinical	0.667	0.540 (0.353–0.728)	0.400	0.769
Training	Radiomics	0.825	0.882 (0.825–0.939)	0.826	0.825
Testing	Radiomics	0.815	0.869 (0.769–0.969)	0.733	0.846
Training	Combined	0.817	0.897 (0.844–0.950)	0.935	0.75
Testing	Combined	0.759	0.870 (0.775–0.965)	0.400	0.897

hand, while serum AFP levels can serve as a predictor of high Ki-67 expression in HCC [20, 21], and HBsAg shows statistical significance between high and low Ki-67 expression groups, these clinical indicators primarily reflect macro characteristics of the disease and do not precisely capture

the proliferative activity and biological behavior of tumor cells. Consequently, the combined model's performance improvement remains limited. On the other hand, significant disparity exists in feature space and information dimensions between clinical data and radiomics data. Radiomics already

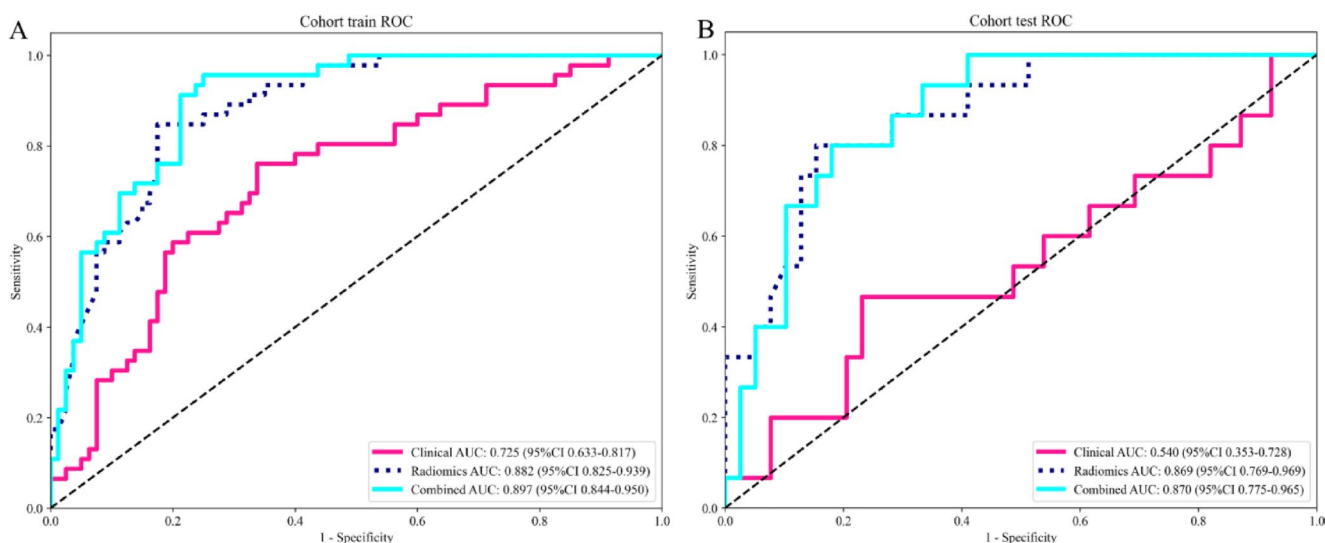
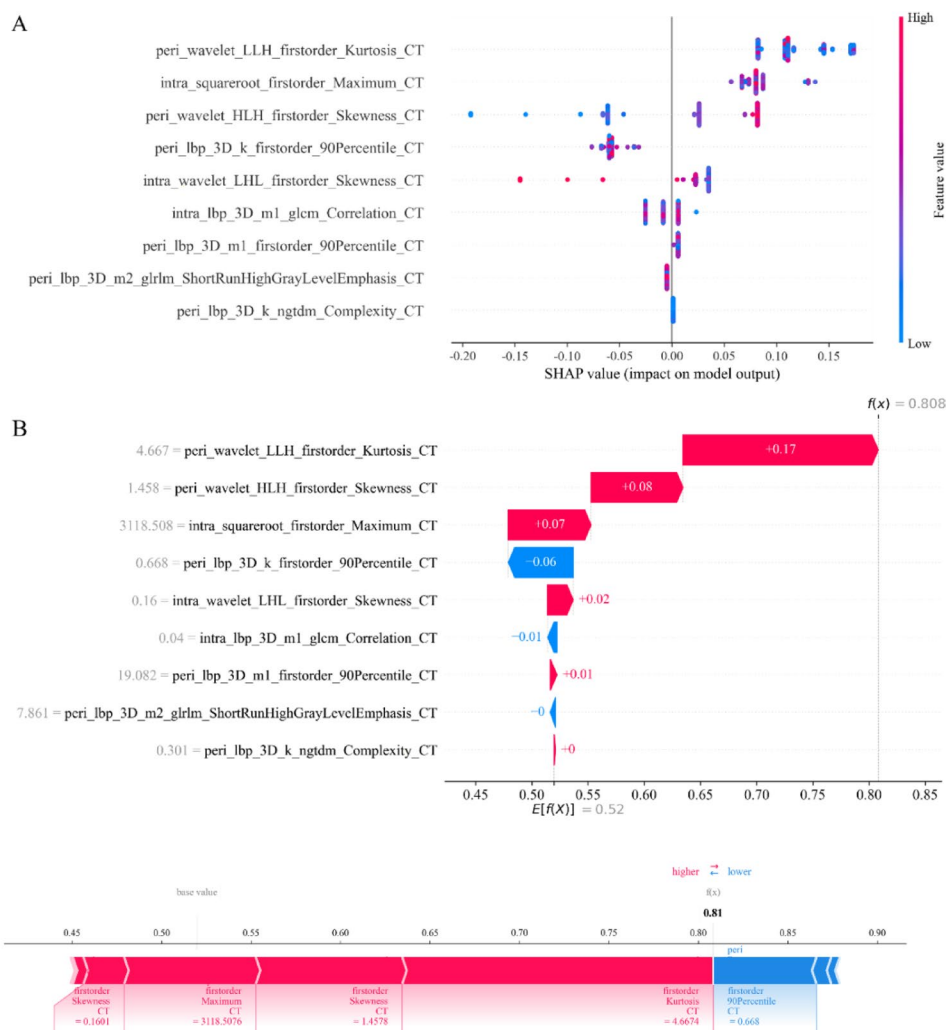


Fig. 6 Comparative performance of predictive models. **A** ROC curves for radiomics, clinical, and combined models in the training set. **B** ROC curves for radiomics, clinical, and combined models in the testing set, demonstrating superior performance of the radiomics model

Fig. 7 SHAP (Shapley Additive Explanations) analysis of the radiomics model. **A** SHAP summary plot showing the impact of each feature on model predictions. **B** SHAP feature importance ranking for intratumoral and peritumoral radiomics features. **C** SHAP force plot illustrating feature contributions for individual predictions, highlighting the dominant role of *peri_wavelet_LLH_firstorder_Kurtosis*



incorporates spatial heterogeneity information related to tumor biological behavior, and simple linear fusion struggles to achieve synergistic gains from multimodal data. Instead, it may introduce noise that disrupts the model's predictive ability. Future research may explore proposed "multimodal artificial intelligence (AI) systems" [22] that integrate multidimensional imaging features from both CT and MRI, alongside radiomics [10, 16]. Moreover, by incorporating liquid biopsy indicators, comprehensive predictive models could be developed. These models are anticipated to address the limitations of conventional single-modality imaging analysis, facilitating more accurate assessment of tumor proliferative activity and presenting new avenues for precise diagnosis and prognostic prediction of HCC.

Clinical translational significance and future prospects

The intratumoral and peritumoral radiomics model developed in this study elucidates the predictive importance of peritumoral texture features (such as `peri_wavelet_LLH_firstorder_Kurtosis`) on recurrence risk through SHAP analysis. This finding aligns with recent studies on pathological mechanisms, which suggest that the fibrotic stroma and pro-inflammatory microenvironment in the peritumoral region can elevate metastasis risk by facilitating epithelial-mesenchymal transition (EMT) [23]. Additionally, tumor-associated macrophages (TAMs) have been shown to influence HCC glycolysis and progression through regulation of `circMRCKα` [24]. These mechanisms underscore the pivotal role of the tumor microenvironment in HCC progression. By combining radiomics, SHAP analysis, and research on pathological mechanisms, this study offers novel insights for risk prediction and personalized treatment of HCC. Future research directions include: first, further validating the relationship between radiomics features and specific molecular pathways; second, exploring the integration of radiomics models with liquid biopsy and other biomarkers to enhance predictive accuracy; and third, developing AI-driven decision support systems to assist clinicians in formulating optimized treatment strategies.

Advantages and limitations of this study

The innovations of this study are as follows: first, in the investigation of Ki-67 thresholds, 25% was established as the optimal critical value. This threshold enables precise stratification of recurrence risk in patients and provides a quantifiable benchmark for clinical prognostic assessment; Second, in radiomics research, we integrated intratumoral and peritumoral imaging features, transcending the traditional focus on intratumoral features alone and exploring

imaging information from the tumor microenvironment more comprehensively; Third, through SHAP analysis, we performed interpretability analysis of the model, clarified key contributing features and their association with Ki-67 expression, thereby enhancing the model's scientific reliability. However, this study has several limitations: first, the single-center retrospective design limits sample diversity in terms of region, ethnicity, and treatment protocols, potentially leading to selection bias and affecting result generalizability; Second, this study constructs the model exclusively using CT arterial phase imaging, without incorporating multimodal imaging modalities such as MRI, PET-CT, or the intrinsic imaging characteristics of the tumor, which may limit the model's capacity to comprehensively capture the tumor's full spectrum of features. Third, the absence of co-expression analysis of Ki-67 with immune microenvironment markers such as programmed death-ligand 1 (PD-L1) and CD8⁺ T cells. Future research should prioritize multi-center prospective studies that integrate multi-omics technologies to explore the regulatory mechanisms of imaging features and molecular pathways.

In conclusion, this study identifies high Ki-67 expression ($\geq 25\%$) as a significant prognostic marker for postoperative HCC recurrence. The radiomics model, utilizing CT arterial phase intratumoral and peritumoral imaging, facilitates non-invasive preoperative assessment of Ki-67 expression in HCC. This model highlights the pivotal role of peritumoral heterogeneity features in predicting Ki-67 expression, offering quantifiable imaging biomarkers for HCC recurrence risk stratification.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00261-025-05191-5>.

Author contributions Haiyang Nong#, Yongyi Cen#, Deyou Huang, and Ke Ding designed the study, collected data, and drafted the manuscript. Haiyang Nong, Yongyi Cen, and Ke Ding performed statistical analyses and participated in study design. Zaolin Pan evaluated hepatocellular carcinoma (HCC) recurrence status. Yin Huang performed pathological assessments. Haiyang Nong and Jiaxin Chen assisted with manuscript preparation. All authors reviewed and approved the final manuscript.# These authors contributed equally to this work. Conflict of interest: The authors declare no conflicts of interest.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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