

Predictive Efficacy of a Combined Triphasic CT Radiomics and Clinical Feature Model for Ki-67 Expression in Hepatocellular Carcinoma

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Objective: Ki-67 is a well-established biomarker for tumor aggressiveness and poor prognosis in hepatocellular carcinoma (HCC). A reliable non-invasive method for preoperative Ki-67 assessment is clinically needed for risk stratification and individualized treatment. This study aimed to develop and validate a prediction model integrating triphasic contrast-enhanced CT radiomics with clinical features for preoperative Ki-67 expression status in HCC.

Materials and Methods: This retrospective dual-center study enrolled 200 patients with 213 pathologically confirmed HCC lesions, Ki-67 expression was dichotomized as high (Ki-67 >20%) and low ($\leq$ 20%) based on established clinical criteria. Radiomic features were extracted from arterial, portal venous, and delayed phases. After rigorous feature selection, logistic regression was used to construct single-phase models, a multi-phase radiomics fusion model, a clinical model, and a combined clinical-radiomics fusion model. Performance was assessed by area under the curve, net reclassification index, integrated discrimination improvement, and decision curve analysis.

Results: The combined fusion model showed robust discrimination, with AUCs of 0.866 and 0.824 in the training and internal test sets, respectively. In independent external validation (n=64), it achieved an AUC of 0.829 (95% CI: 0.709–0.948), significantly outperforming the arterial phase model (AUC=0.713, $P=0.031$) and the radiomics-only fusion model (AUC=0.722, $P=0.031$). NRI and IDI confirmed significant incremental value (NRI=0.374, $P=0.005$; IDI=0.191, $P<0.001$), and DCA demonstrated superior clinical net benefit.

Conclusion: The fusion model integrating multi-phase CECT radiomic features with clinical indicators provides an effective, non-invasive tool for preoperative prediction of Ki-67 expression in HCC. It may facilitate risk stratification and inform individualized treatment planning in clinical practice.

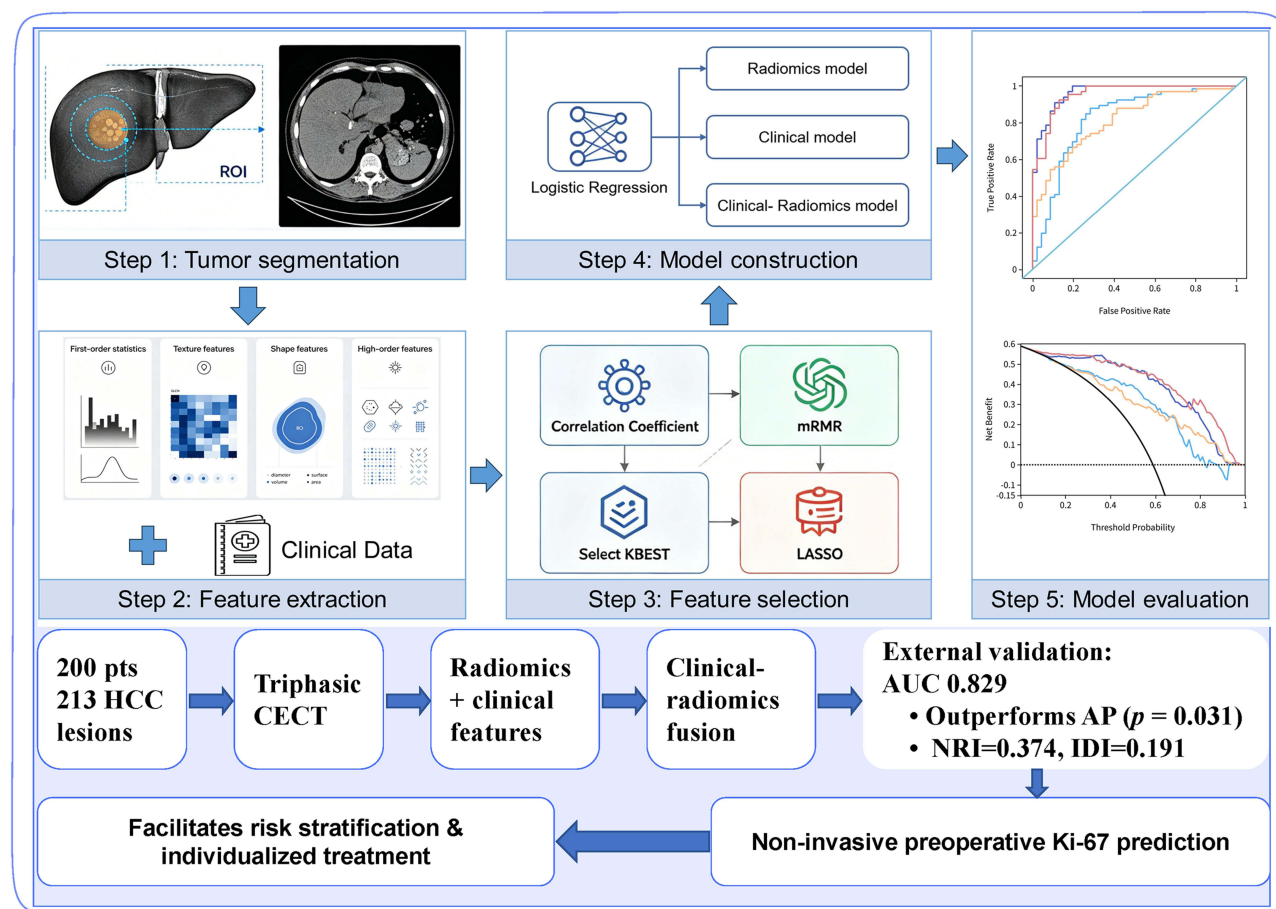
Plain Language Summary: Question: A reliable non-invasive method for preoperative Ki-67 assessment in HCC is needed for risk stratification and personalized treatment.

Findings: A model combining triphasic CT radiomics and clinical features effectively predicted Ki-67 expression, showing robust performance (AUC=0.829) in external validation.

Clinical Relevance Statement: This CT-based model provides an accessible, non-invasive tool to preoperatively assess tumor proliferation, potentially aiding individualized treatment planning and improving prognosis in HCC patients.

Keywords: hepatocellular carcinoma, tomography, x-ray computed, radiomics, ki-67 antigen, predictive model, clinical features

Graphical Abstract



Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide.¹ Although surgical resection offers a curative option for early-stage disease, postoperative recurrence rate remains high, posing a significant clinical challenge.^{2,3} Ki-67, a nuclear protein associated with cell proliferation, is a well-established biomarker correlating with aggressive pathological features and unfavourable prognosis in HCC, serving as an important tool for risk stratification.⁴⁻⁶ Therefore, an accurate, non-invasive preoperative assessment of Ki-67 expression level holds significance value for formulating individualized treatment strategies.

Radiomics, by extracting high-throughput quantitative features from medical images, offers a promising approach for non-invasive assessment of tumor heterogeneity.⁷ While magnetic resonance imaging (MRI)-based radiomics has shown efficacy in predicting HCC biology,^{8,9} Contrast-enhanced CT (CECT) remains the more widely accessible and standardised imaging modality for preoperative HCC evaluation. Previous CT radiomics studies have primarily focused on single-phase analysis,¹⁰⁻¹² potentially underutilising the comprehensive haemodynamic and microenvironmental information inherent in multi-phase imaging.¹³ Furthermore, tumour aggressiveness arises from complex interactions between genomic, phenotypic, and host microenvironmental factors, which may not be fully captured by unimodal imaging or clinical data alone. The former may miss key macroscopic pathological features like satellite nodules,¹⁴ while the latter lacks detailed quantification of tumor micro-heterogeneity.¹⁵

Several CT-based radiomics models have been developed for Ki-67 prediction in HCC. Wu et al constructed a combined model integrating radiomics features and clinical indicators, achieving a C-index of 0.88 for Ki-67 prediction.¹⁶ Similarly, Cai

et al developed an enhanced CT-based predictive model for preoperative Ki-67 assessment in HCC.¹⁷ However, most existing studies rely on single-phase CT data and lack independent external validation, limiting their generalizability. To our knowledge, no study has developed a triphasic CT fusion model with dual-center validation for preoperative Ki-67 stratification in HCC.

This study hypothesises that integrating radiomic features from arterial, venous, and delayed phase CT images with key clinicopathological indicators can provide a more comprehensive characterisation of HCC, leading to improved preoperative prediction of Ki-67 expression status. We aimed to develop and rigorously validate such a clinical-radiomics fusion model through internal testing and independent external centre validation.

Materials and Methods

The overall study design and analytical workflow are illustrated in Figure 1.

Study Population

This retrospective dual-center study was conducted in accordance with the Declaration of Helsinki. Consecutive patients who underwent radical liver resection for solitary HCC between January 2018 and October 2025 at Nanning Second People's Hospital (Centre A) and Qinzhou First People's Hospital (Centre B) were screened.

The study was approved by the Ethics Committee of Nanning Second People's Hospital on December 12, 2025 (Approval No.: Y2025341), as a pre-specified sub-study of the approved project "Pathological characteristics of Hepatocellular Carcinoma: Correlation Analysis and Clinical prognostic Value". The research content of this manuscript, including the triphasic CT radiomics analysis and Ki-67 expression prediction, falls entirely within the scope of the initial ethical review, so no separate ethical approval was required for this sub-study. Informed consent was waived due to the retrospective nature of the study.

Inclusion Criteria Were

① Standard triphasic liver CECT performed within 4 weeks preoperatively with diagnostic image quality; ② Available postoperative Ki-67 immunohistochemistry results; ③ Complete clinicopathological data.

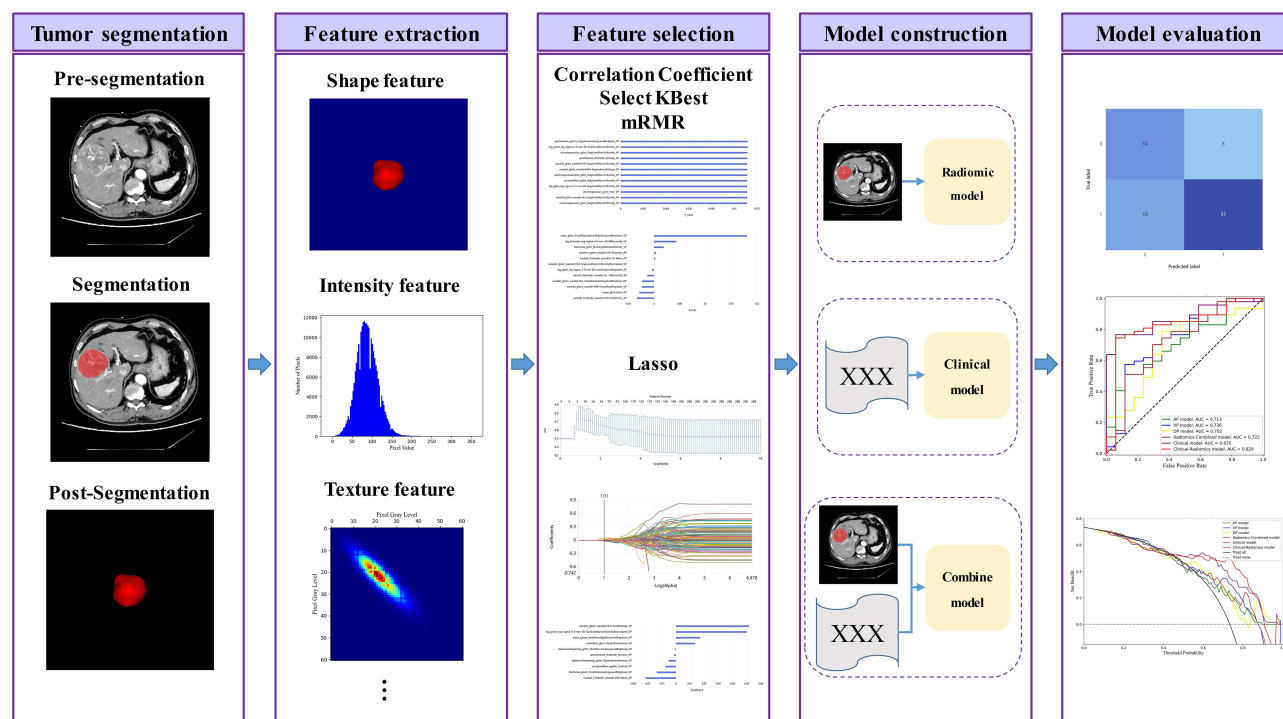


Figure 1 Study flowchart.

Exclusion Criteria Were

① Any prior antitumor therapy; ② Severe image artifacts or indistinct lesion borders; ③ Pathological diagnosis other than HCC (eg, mixed hepatocellular-cholangiocarcinoma); ④ Infiltrative HCC.

A total of 200 patients with 213 lesions were finally enrolled (comprising 149 lesions from Center A and 64 lesions from Center B). Lesions from Center A were randomly split into a training set ($n=104$ lesions) and an internal test set ($n=45$ lesions) in a 7:3 ratio. All lesions from Center B constituted an independent external validation set ($n=64$). The patient screening and enrollment process is summarized in Figure 2. The sample size was deemed adequate based on the events-per-variable criterion >10 in the training set to mitigate overfitting.¹⁸

Clinical Data and Pathological Reference Standard

Preoperative clinical data (age, gender, hepatitis B/C virus history, cirrhosis, serum alpha-fetoprotein [AFP]) were retrieved from electronic medical records. Surgical specimens were evaluated by two senior pathologists blinded to imaging data, recording Edmondson-Steiner grade, microvascular invasion (MVI) grade (M0: none; M1: ≤ 5 MVIs within ≤ 1 cm of tumor; M2: >5 MVIs or >1 cm from tumor),^{17,19} and satellite nodules presence (defined as microscopic/macroscopic nodules ≤ 2 cm from main tumor). Ki-67 expression index was determined by immunohistochemistry. Based on relevant guidelines and consensus,^{5,20} a Ki-67 index $>20\%$ defined the high-expression group, and $\leq 20\%$ the low-expression group. The 20% threshold for Ki-67 stratification was selected based on its widespread use in previous imaging-based prediction studies of HCC, where it has demonstrated robust prognostic discrimination.

CT Image Acquisition, Preprocessing, and Feature Extraction

Both centers used CT scanners (GE Discovery CT 750HD; Siemens SOMATOM Definition Flash) for standard liver triphasic enhanced scanning. Thin-slice images (≤ 1.5 mm) in DICOM format were imported into the United Imaging uAI Research Portal for standardised preprocessing: window width/level normalization (width 300 HU, level 40 HU) and isotropic voxel resampling ($1 \times 1 \times 1$ mm³). Two radiologists blinded to pathology, independently manually delineated three-dimensional volume of interest (VOI) encompassing the entire tumor on each phase, avoiding large vessels, necrosis, and hemorrhage areas. Inter-observer consistency was excellent (Dice=0.945). Using the PyRadiomics engine, 2264 radiomic features (first-order, shape, texture [GLCM, GLDM, GLRLM, GLSZM, NGTDM]), and wavelet-filtered features) were extracted from each phase VOI per reader. Feature stability was assessed via intraclass correlation coefficient (ICC); features with ICC > 0.75 (92.0% of features) were retained for subsequent analysis.

Feature Selection and Model Construction

All modeling steps were performed within the training set ($n=104$ lesions).

Radiomics Feature Selection for Single-Phase Models

For features from each phase (arterial [AP], portal venous [PVP], delayed [DP]), Z-score normalization was applied. Dimensionality reduction was performed in a strict, stepwise manner: (a) initial screening using Pearson correlation analysis (retaining features with $P < 0.05$); (b) selection of the top 100 most relevant features using the SelectKBest algorithm; (c) further refinement to 50 features with maximum relevance and minimum redundancy using the minimum Redundancy Maximum Relevance (mRMR) algorithm; (d) final selection of the most parsimonious and predictive feature subset via LASSO regression with 10-fold cross-validation.

Multi-Phase Feature Fusion Model

Radiomic features from all three phases were merged into an initial multi-phase feature pool. Feature selection was then performed following the same sequential procedure described above (Pearson correlation $\rightarrow$ SelectKBest $\rightarrow$ mRMR $\rightarrow$ LASSO with 10-fold cross-validation). The selected features were used to construct the multi-phase radiomics fusion model.

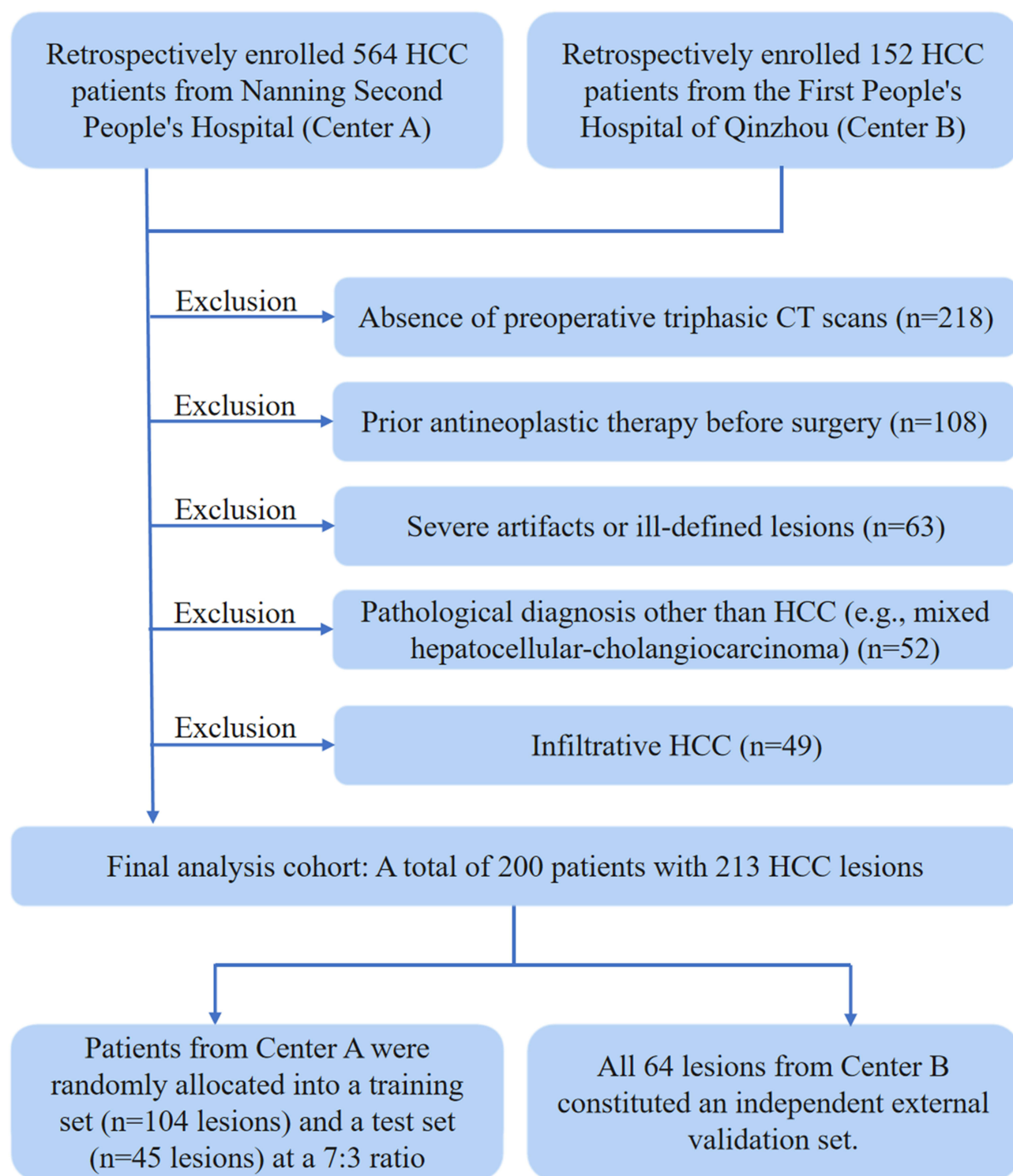


Figure 2 Cohort of patients.

Clinical Feature Selection

Clinicopathological variables were first evaluated by univariate analysis ($P < 0.1$). Variables with statistical significance were subsequently entered into multivariate logistic regression using a forward stepwise method ($P < 0.05$ for entry) to identify independent predictors, which were then used to build the clinical model.

Clinical-Radiomics Fusion Model

The features selected for the multi-phase radiomics fusion model (*ie.*, the LASSO-selected subset) were combined with the independent clinical predictors identified in step (3). The mRMR algorithm was reapplied to this combined feature set to select the most discriminative features. These features were used to build the final clinical-radiomics fusion model via logistic regression.

Statistical Analysis

Statistical analysis was performed using R (version 4.2.0) and the uAI Research Portal. Continuous variables are presented as mean $\pm$ SD or median (interquartile range); categorical variables as frequency (percentage). Inter-group comparisons used ANOVA, Kruskal–Wallis *H*-test, chi-square test, or Fisher's exact test. Model performance was evaluated by AUC, sensitivity, specificity, accuracy, and F1-score. DeLong's test compared AUCs in the external validation set. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) assessed incremental value. Decision curve analysis (DCA) evaluated clinical net benefit. A two-sided $P < 0.05$ considered statistical significance.

Results

Patient Baseline Characteristics

Baseline characteristics were balanced across the training, internal test, and external validation sets ($P > 0.05$ for all comparisons), including age, gender, aetiology, Edmondson-Steiner grade, MVI grade, satellite nodule status, serum AFP, and liver function markers (Table 1). The proportion of patients with high Ki-67 expression was relatively high in the overall cohort.

Table 1 Baseline Demographic and Clinicopathological Characteristics of Patients

Characteristics		Training Cohort (n=104)	Testing Cohort (n=45)	Validation Cohort (n=64)	p-value
Age (Mean $\pm$ SD)		57.769 $\pm$ 12.274	56.556 $\pm$ 12.827	53.844 $\pm$ 10.256	0.114
Gender (%)					0.605
	Male	89 (85.577)	40 (88.889)	58 (90.625)	
	Female	15 (14.423)	5 (11.111)	6 (9.375)	
Edmondson-Steiner Grading (%)	Grade I / Grade II	55 (52.885)	30 (66.667)	33 (51.562)	0.228
	Grade III / Grade IV	49 (47.115)	15 (33.333)	31 (48.438)	
Microvascular invasion Grading (%)	M0	28 (26.923)	14 (31.111)	24 (37.500)	0.382
	M1	37 (35.577)	19 (42.222)	24 (37.500)	
	M2	39 (37.500)	12 (26.667)	16 (25.000)	
Satellite Cancer Lesions (%)	Negative	51 (49.038)	29 (64.444)	34 (53.125)	0.223
	Positive	53 (50.962)	16 (35.556)	30 (46.875)	
Etiology (%)	Other / None	11 (10.577)	6 (13.333)	3 (4.688)	0.265
	HBV / HCV	93 (89.423)	39 (86.667)	61 (95.312)	
Serum AFP (%)	Normal	30 (28.846)	13 (28.889)	22 (34.375)	0.725
	Abnormal	74 (71.154)	32 (71.111)	42 (65.625)	
Total Bilirubin (Median[Q1,Q3])		13.650 [10.075,20.200]	14.600 [11.100,22.900]	15.050 [10.125,18.250]	0.861
Albumin (Median[Q1,Q3])		36.900 [33.100,39.500]	36.000 [33.600,37.800]	37.400 [33.800,40.775]	0.287
CA199 (Median[Q1,Q3])		15.700 [7.350,30.850]	22.100 [12.100,43.400]	13.680 [5.933,25.600]	0.052
CEA (Median[Q1,Q3])		2.200 [1.475,3.005]	2.600 [1.500,3.800]	2.255 [1.562,3.522]	0.505

Abbreviations: AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MVI, microvascular invasion; SD, standard deviation.

Comparison of Model Predictive Performance

Performance metrics are summarised in Table 2, and the corresponding ROC curves are shown in Figure 3. In the external validation set, the clinical model achieved the highest AUC (0.867), followed by the clinical-radiomics fusion model (AUC=0.829, 95% CI: 0.709–0.948). The AUCs for AP, PVP, and DP multi-phase radiomics fusion model were 0.713, 0.736, 0.702 and 0.722, respectively. DeLong's test (Table 3) showed the fusion's AUC was significantly higher than that of the AP model ($P=0.031$) and the multi-phase radiomics fusion model ($P=0.031$). The differences in AUC between the fusion model and the PVP, DP and clinical models were not statistically significant ($P>0.05$). The fusion models also showed robust performance in the training (AUC=0.866) and internal test (AUC=0.824) sets.

Incremental Predictive Value of the Models

NRI and IDI analysis (Table 4) confirmed the significant incremental value of the fusion model. For example, compared to the AP model at a risk threshold of 0.6, the categorical NRI was 0.374 ($P=0.005$), continuous NRI was 0.774 ($P=0.003$), and IDI was 0.191 ($P<0.001$). Decision curve analysis (Figure 4) demonstrated that within a threshold probability range of 0.1 to 0.7, the clinical-radiomics fusion model provided a higher net benefit than both the treat all and “treat none” strategies, as well as the single-phase and the radiomics-only fusion model.

Analysis of Key Features

Key features selected by LASSO regression for each model are shown in Figure 5. In the final clinical-radiomics fusion model, features with higher weights included venous-phase texture features (eg., mean_glszm_SmallAreaHighGrayLevelEmphasis) and the clinical feature “Satellite Nodule (Positive).” Some arterial-phase texture features (eg., wavelet-HHL_glcmm_Correlation) had negative weights.

Discussion

This study developed and validated a clinical-radiomics fusion model integrating triphasic CT radiomics and clinical features for preoperative prediction of Ki-67 expression in HCC. The model demonstrated robust performance in independent external validation (AUC 0.829), confirming the hypothesis that multi-dimensional information enables a more comprehensive assessment of tumor proliferative activity than single-dimension approaches.

Innovation and Advantages of Multidimensional Fusion

Previous prediction models mostly relied on a single information dimension—either radiomics²¹ or clinicopathological indicators alone.¹⁵ However, the biological behavior of HCC is highly complex, and a single dimension hardly captures its full aggressiveness and proliferative nature. Radiomic features can quantify intratumoral heterogeneity, potentially reflecting microstructures such as cellular density, necrosis, and fibrosis;²² clinicopathological features (eg., satellite nodules) are macroscopic manifestations of tumor invasiveness. This study is among the first to organically integrate these two complementary information on a conventional CT platform. The fusion model's performance significantly exceeded that of some single-dimension models (eg., arterial-phase model), aligning with the core concept of multimodal integrated analysis in precision medicine.²³

Biological Plausibility of Key Radiomic and Clinical Features

The key features selected for the fusion model have clear biological rationale. The high weight of PVP texture features (eg., wavelet-LHL_glszm_SmallAreaHighGrayLevelEmphasis) corresponds to the dense microvascular structures frequently observed in highly proliferative tumors, reflecting uniform perfusion in the portal venous stage.⁶ This imaging phenotype may mirror the pathophysiological basis of highly proliferative HCCs, which often exhibit dense sinusoidal microvasculature and more homogeneous perfusion. Conversely, the negative weights of some arterial-phase features (eg., wavelet-HHL_glcmm_Correlation) may indicate disorganized patterns of abnormal neovascularization, mirroring the angiogenic dysregulation associated with tumor proliferation.⁶ The extraction and interpretation of these quantitative imaging phenotypes are underpinned by standardized radiomics methodologies.²⁴ Together, these complementary

Table 2 Performance of Logistic Regression-Based Prediction Models Across Different Datasets

Models	AUC (95% CI)			Sensitivity			Specificity			Accuracy			F1 value		
	Train	Test	Validation	Train	Test	Validation	Train	Test	Validation	Train	Test	Validation	Train	Test	Validation
AP	0.774 (0.679–0.868)	0.647 (0.464–0.829)	0.713 (0.576–0.851)	0.928	0.833	0.872	0.429	0.467	0.235	0.760	0.711	0.703	0.837	0.794	0.812
VP	0.829 (0.745–0.912)	0.727 (0.555–0.898)	0.736 (0.586–0.886)	0.884	0.867	0.787	0.571	0.533	0.471	0.779	0.756	0.703	0.841	0.825	0.796
DP	0.765 (0.670–0.859)	0.642 (0.446–0.839)	0.702 (0.552–0.852)	0.870	0.900	0.894	0.429	0.400	0.294	0.721	0.733	0.734	0.805	0.818	0.832
AP+VP+DP	0.844 (0.765–0.922)	0.716 (0.534–0.897)	0.722 (0.569–0.876)	0.942	0.767	0.851	0.600	0.533	0.353	0.827	0.689	0.719	0.878	0.767	0.816
Clinical	0.791 (0.701–0.882)	0.771 (0.613–0.929)	0.867 (0.785–0.955)	0.841	0.767	0.766	0.571	0.667	0.824	0.750	0.733	0.781	0.817	0.793	0.837
Rad-Clinical	0.866 (0.794–0.938)	0.824 (0.684–0.965)	0.829 (0.709–0.948)	0.826	0.800	0.787	0.743	0.667	0.824	0.798	0.756	0.797	0.844	0.814	0.851

Abbreviations: AP, arterial phase; AUC, area under the curve; CI, confidence interval; DP, delayed phase; VP, venous phase.

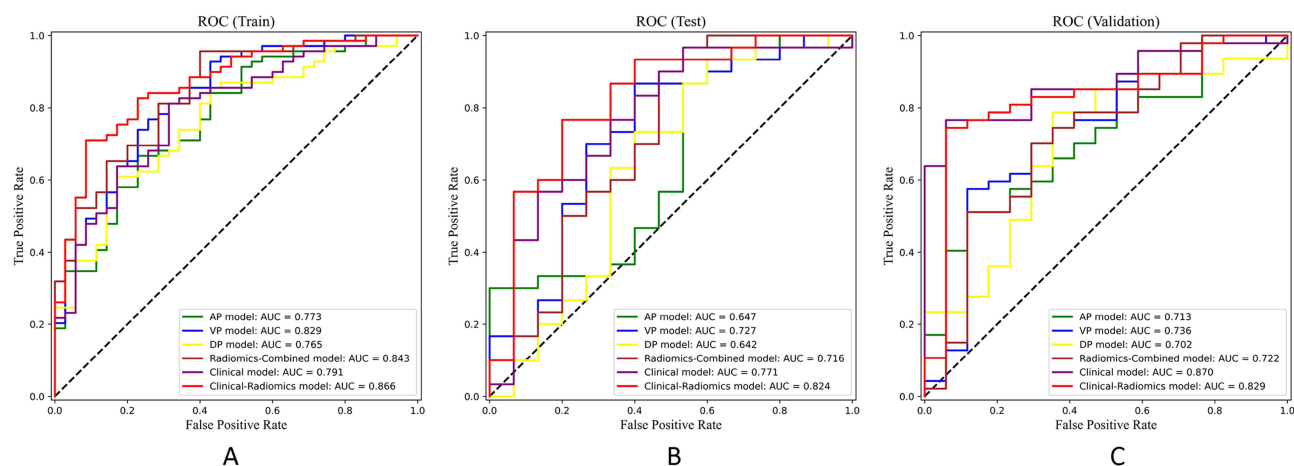


Figure 3 ROC curves in different predictive models in the (A) training set, (B) internal test set, and (C) external validation set.

features map key pathophysiological processes—from aberrant arterial supply to the proliferative microenvironment—thereby enhancing the model’s characterization of tumor biology.

Furthermore, the inclusion of the clinical feature “Satellite nodule (Positive)” adds a direct macroscopic dimension. As a direct radiological sign of intrahepatic metastasis,¹⁴ its strong predictive power biologically complements the cellular proliferation information conveyed by the Ki-67 index, providing a multi-scale assessment of tumor aggressiveness. Consequently, our model establishes a biologically interpretable framework by synthesizing information across vascular, micro-environmental, and macro-invasive scales.

Table 3 Comparison of Model AUCs in the External Validation Set Using DeLong’s Test

Model Comparison	Z-score	p-value	95% CI of AUC
Clinical-Radiomics Model vs AP Model	2.1524	0.0314	(0.0103, 0.2200)
Clinical-Radiomics Model vs VP Model	1.9237	0.0544	(−0.0017, 0.1870)
Clinical-Radiomics Model vs DP Model	1.4403	0.1498	(−0.0456, 0.2984)
Clinical-Radiomics Model vs Radiomics-Combined Model	2.1582	0.0309	(0.0098, 0.2030)
Clinical-Radiomics Model vs Clinical Model	−0.7631	0.4454	(−0.1474, 0.0648)

Abbreviations: AUC, area under the curve; CI, confidence interval.

Table 4 NRI and IDI Test (External Validation Set, Categorical Threshold Set to 0.6)

Model Comparison	NRI(Categorical) [95% CI]	NRI(Continuous) [95% CI]	IDI [95% CI]
Clinical-Radiomics Model vs AP Model	0.3742[0.1149, 0.6335]; p=0.0047	0.7735[0.2648, 1.2821]; p=0.0029	0.1906[0.0863, 0.2948]; p=0.0003
Clinical-Radiomics Model vs VP Model	0.2028[−0.0347, 0.4403]; p=0.0943	0.7635[0.2737, 1.2532]; p=0.0023	0.1062[0.0318, 0.1807]; p=0.0051
Clinical-Radiomics Model vs DP Model	0.2728[−0.0257, 0.5714]; p=0.0732	0.5932[0.0992, 1.0872]; p=0.0186	0.1918[0.0688, 0.3149]; p=0.0023
Clinical-Radiomics Model vs Radiomics-Combined Model	0.2941[0.0105, 0.5778]; p=0.04212	0.2728[−0.2639, 0.8096]; p=0.3191	0.0960[0.0124, 0.1797]; p=0.0244
Clinical-Radiomics Model vs Clinical Model	−0.0964[−0.2756, 0.0828]; p=0.2919	0.1952[−0.323, 0.7135]; p=0.4603	−0.0267[−0.1443, 0.0909]; p=0.6561

Abbreviations: NRI, Net reclassification improvement; IDI, integrated discrimination improvement.

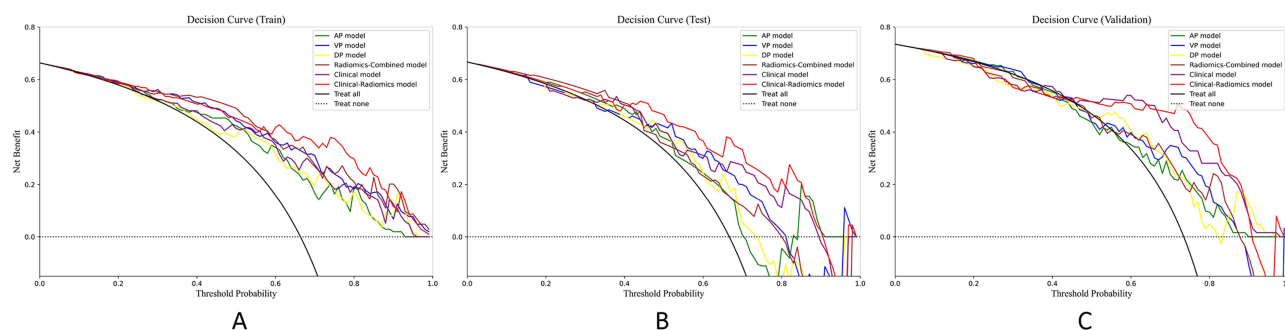


Figure 4 DCA for the clinical-radiomics fusion model and other models in the (A) training set, (B) internal test set, and (C) external validation set.

Biological Interpretability of Radiomic Features

Although our study is a purely diagnostic radiomics investigation without direct molecular correlates, it is worth speculating on potential biological links between our radiomic features and underlying molecular pathways in HCC. Emerging evidence has revealed that metabolic reprogramming—particularly lactylation modifications—plays a critical role in HCC malignant progression. For instance, ABCF1-K430 lactylation was shown to promote HCC growth and metastasis via transcriptional activation of the HIF1 signaling pathway.²⁵ Similarly, ASH2L-K312 lactylation stimulates tumor angiogenesis and accelerates HCC progression through VEGFA-mediated mechanisms.²⁶ Furthermore, ferritinophagy-related gene FTH1 has been identified as a key regulator linking tryptophan metabolism to redox homeostasis and ferroptosis, with prognostic implications in HCC.²⁷

Our venous-phase texture features, which may reflect microvascular heterogeneity and perfusion abnormalities, could indirectly capture the hemodynamic consequences of HIF1 pathway activation or lactylation-driven microenvironment remodeling. The inclusion of satellite nodules as a clinical predictor in our model aligns with their known association with aggressive angiogenic phenotypes, which may be driven by ASH2L-mediated VEGFA upregulation. While these connections remain speculative, they provide a foundation for future studies to directly correlate radiomic features with tissue-based molecular markers (eg, ABCF1/ASH2L expression, FTH1 activity, or lactate levels).

Comparison with Existing Literature

The external validation efficacy of our model (AUC=0.829) is comparable to recent studies based on advanced imaging techniques like spectral CT⁹ and MRI (AUC=0.80–0.90).^{8,10} However, spectral CT is not yet widely available, and MRI has cost and accessibility limitations. In contrast, by fusing triphasic features with clinical indicators on the ubiquitous conventional CECT platform, we constructed a high-performance and more universally applicable predictive tool. This success corroborates recent similar research; for example, a 2025 study based on CT radiomics and clinical features also achieved a high AUC in external validation for predicting HCC microvascular invasion.²⁸

It is noteworthy that in external validation, although the clinical-radiomics fusion model achieved the highest AUC (0.829), its performance did not show a statistically significant difference compared to the PVP model (AUC=0.736), the DP model (AUC=0.702), or the clinical-only model (AUC=0.867) ($P > 0.05$). Several reasons may account for this. First, PVP and DP images inherently capture pathophysiological features such as tumor microvascular structure, fibrosis, and extracellular space, which are intrinsically linked to Ki-67 expression, thereby endowing the single-phase models with substantial discriminative power. Second, during multi-phase feature fusion, some key predictive information might already be encapsulated within features from these two phases, resulting in a statistically non-significant incremental gain. Third, the limited sample size of the validation set may have reduced statistical power. Regarding the clinical-only model, its strong performance stems from the inclusion of powerful predictors like “satellite nodule”, a well-established marker of tumor aggressiveness. That our fusion model did not significantly surpass it statistically underscores the substantial predictive value of these conventional clinical indicators. However, the key advantage of the fusion model lies in its sole reliance on preoperative, non-invasive data, achieving predictive efficacy comparable to clinical model that

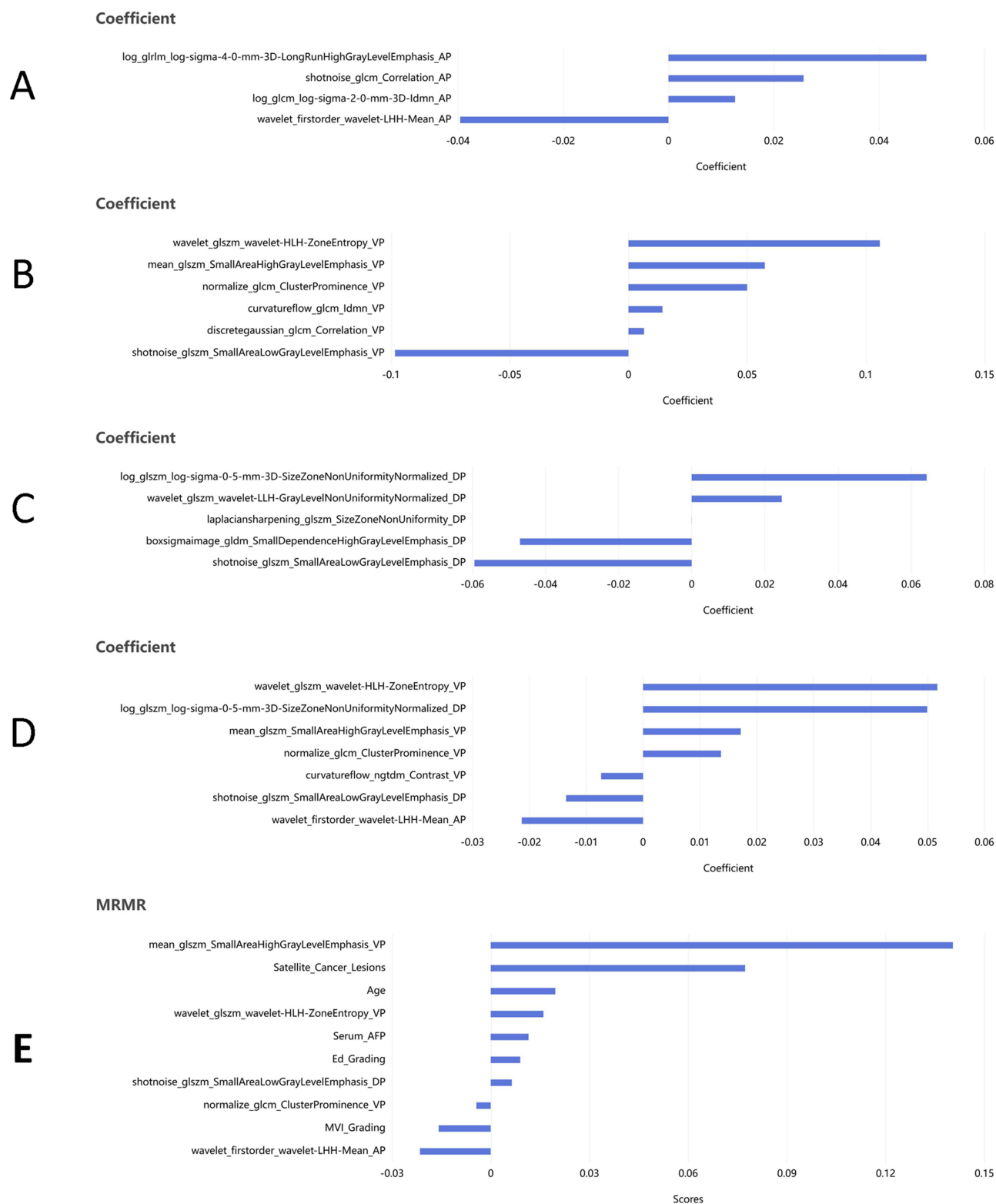


Figure 5 LASSO feature importance analysis. **(A)** Key features selected by LASSO regression for the arterial phase model. **(B)** Key features selected by LASSO regression for the venous phase model. **(C)** Key features selected by LASSO regression for the delayed phase model. **(D)** Key features selected by LASSO regression for the multi-phase radiomics fusion model. **(E)** Key features for the clinical-radiomics fusion model selected via mRMR optimization and LASSO regression.

incorporates some postoperative pathological factors. This makes the fusion model a novel and comprehensive tool for preoperative decision-making.

Incremental Value: NRI and IDI Analyses

Beyond conventional AUC comparison, the NRI and IDI metrics were employed to quantify the incremental clinical utility of the fusion model.^{29,30} Compared to the AP model, the fusion model yielded a continuous NRI of 0.774 ($P=0.003$) and a categorical NRI (threshold 0.6) of 0.374 ($P=0.005$), indicates a substantial overall improvement in risk stratification and a net correct reclassification of approximately 37.4% of patients at a clinically relevant threshold.

IDI was also significant (0.191, $P<0.001$). These metrics quantitatively prove the fusion model's significant incremental predictive value over single-phase and radiomics-only models. Notably, a recent CECT-based study³¹ found that its fusion model did not show significant incremental value, a discrepancy that may stem from methodological differences: our study employed a rigorous phase-wise selection-then-fusion strategy and included potent clinical predictors like satellite nodules. Importantly, NRI and IDI compared to the clinical model alone did not reach statistical significance. This observation, combined with their comparable AUCs, underscores a critical finding: our clinical-radiomics fusion model, using exclusively preoperative and non-invasive data, achieved predictive performance on par with a clinical model that incorporated powerful postoperative pathological features. This parity highlights the self-contained strength of the fusion model and its unique value as a preoperative decision-support tool.

We acknowledge that more sophisticated interpretability methods, such as SHapley Additive exPlanations (SHAP) analysis or permutation-based interaction tests, would provide deeper insights into feature contributions and interactions. These approaches should be prioritized in future studies to enhance model transparency and clinical trust.

Clinical Translation Pathway and Prospects

The model is based on logistic regression, and is computationally lightweight, and can be readily integrated into existing hospital infrastructures such as PACS or radiology reporting platforms. It can be embedded into the preoperative CECT workflow as an auxiliary diagnostic module, providing a quantitative risk score for Ki-67 expression to aid preoperative risk stratification, inform treatment decisions (*eg.*, surgical planning, adjuvant therapy), and personalize follow-up strategies. The next step requires prospective, multi-center studies to validate the model's efficacy and clinical utility in real-world settings and to promote the development of standardized operating procedures to ensure reproducibility and generalizability.³²

Summary and Clinical Implications

In summary, this study developed and validated a clinical-radiomics fusion model based on ubiquitous triphasic CECT. The model enables non-invasive, preoperative prediction of Ki-67 expression in HCC with robust performance, rooted in a biologically plausible framework that integrates features reflecting aberrant angiogenesis, proliferative microenvironment, and macroscopic invasiveness. By leveraging routinely acquired CT scans, this tool provides a feasible means for preoperative assessment of tumor proliferation potential and holds significant promise for aiding individualized treatment planning in HCC patients, meriting further prospective validation.

However, the generalizability of our findings is currently limited to patients with solitary lesions and HBV-predominant HCC from Chinese centers. Validation in broader populations with diverse etiologies is required before clinical implementation. Notably, the fusion model relies exclusively on preoperative data, whereas traditional clinical models often incorporate postoperative pathological features such as satellite nodules, giving our approach a distinct advantage for preoperative treatment planning and patient stratification.

Limitations and Future Directions

This study has limitations. Its retrospective design is subject to selection bias. Several additional limitations regarding generalizability should be acknowledged. First, our cohort consisted exclusively of patients with solitary lesions; the model's performance in multifocal HCC remains unknown. Second, the study population was predominantly HBV-related, reflecting the epidemiology of HCC in China. Validation in populations with different etiologies (*eg.*, HCV,

NASH, alcoholic liver disease) is warranted. Third, although dual-center validation was performed, both centers are located in China; international multi-center studies are needed to confirm the model's robustness across diverse populations. Finally, the external validation cohort had a relatively modest sample size, and larger studies may be required to definitively confirm the incremental value of the fusion model over single-phase approaches.

Although external validation was performed, the sample size, particularly of the validation set, could be expanded. Differences in CT scanners and protocols between centers, despite standardised preprocessing, may still affect feature stability. Future studies should validate the model's robustness through large-scale, prospective, multi-center research. Additionally, future work should aim to construct an "imaging-clinical-molecular" triad model incorporating serum biomarkers (*eg.*, lactate, tryptophan metabolites) or tissue-based molecular markers (*eg.*, ABCF1/ASH2L lactylation status, FTH1 expression) into the radiomics framework. Such integrated models could enhance both predictive accuracy and biological interpretability. Federated learning approaches may help address multi-center molecular data heterogeneity while preserving patient privacy, and exploring associations between model predictions and responses to targeted therapies (*eg.*, HIF1 inhibitors, anti-angiogenic agents, or ferroptosis inducers) could further strengthen the clinical translational value of radiomics-based biomarkers in HCC.^{33,34}

Abbreviations

AFP, alpha-fetoprotein; AUC, area under the curve; CECT, contrast-enhanced computed tomography; CI, confidence interval; DCA, decision curve analysis; GLCM, gray-level co-occurrence matrix; GLDM, gray-level dependence matrix; GLRLM, gray-level run length matrix; GLSZM, gray-level size zone matrix; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICC, intraclass correlation coefficient; IDI, integrated discrimination improvement; LASSO, least absolute shrinkage and selection operator; mRMR, minimum redundancy maximum relevance; MRI, magnetic resonance imaging; MVI, microvascular invasion; NGTDM, neighboring gray tone difference matrix; NRI, net reclassification index; OR, odds ratio; ROC, receiver operating characteristic; ROI, region of interest; SD, standard deviation; SN, satellite nodule; SOP, standard operating procedure; VOI, volume of interest.

Statistics and Biometry

One of the authors (Xianpan Pan, an employee of Shanghai United Imaging Intelligence Co., Ltd.) has significant statistical expertise.

AI Disclosure

DeepSeek-R1 was used to refine the language expression of this manuscript, focusing on grammatical accuracy and fluency.

Acknowledgments

This study received technical and nursing support from Fei He, Qin Shi, and Li Zhou. Special thanks to Qingping Zhao and Lifeng Huang for providing and confirming pathological material analysis.

Ethical Approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Nanning Second People's Hospital (Approval No.: Y2025341; Date: December 12, 2025). The requirement for informed consent was waived by the ethics committee owing to the retrospective nature of the study. Patient data confidentiality was strictly maintained throughout the study; all data were fully anonymized prior to analysis.

Informed Consent

Written informed consent was waived by the Institutional Review Board due to the retrospective nature of this study, which utilized anonymized data.

Funding

This study was supported by two Self-raised Projects of the Health Commission of Guangxi Zhuang Autonomous Region (Grant Nos. Z-A20241055 and Z20200953).

Disclosure

Haibo Huang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Jie Yang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Yingdan Zhang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Xianpan Pan reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Yingying Huang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Xiaocheng Wang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Wei Lu reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study; Zehe Huang reports grants from Health Commission of Guangxi Zhuang Autonomous Region, non-financial support from Shanghai United Imaging Intelligence Co., Ltd., during the conduct of the study. The authors report no other conflicts of interest in this work. Xianpan Pan and Lei Chen are employees of Shanghai United Imaging Intelligence Co., Ltd., which provided the uAI Research Portal platform used for radiomics analysis in this study. They did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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