

Development of a Nomogram Model Based on Contrast-Enhanced CT Histogram Analysis for Preoperative Prediction of Ki-67 Expression Status in Patients with Clear Cell Renal Cell Carcinoma

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Abstract

Objective: To develop a nomogram model integrating contrast-enhanced CT histogram analysis with clinico-radiological features for preoperative prediction of Ki-67 expression in clear cell renal cell carcinoma (ccRCC).

Methods: We retrospectively analyzed 213 surgically treated, pathologically confirmed ccRCC patients (Jan 2022–Dec 2024). Based on immunohistochemistry, patients were grouped into Ki-67 high-expression (n=159) and low-expression (n=54), then randomly assigned 7:3 to training (n=152) and validation (n=61) cohorts. Two radiologists independently assessed conventional CT features. Whole-tumor histogram parameters were extracted using Fire Voxel from axial contrast-enhanced CT images obtained in the corticomedullary phases (CMP) and nephrographic phases (NP). LASSO logistic regression selected variables, which were then entered into multivariable logistic regression to build a combined nomogram incorporating clinico-radiological and histogram features for preoperative Ki-67 prediction.

Results: LASSO and multivariable logistic regression identified four independent predictors: CMP-Skewness, monocyte count, neutrophil-to-lymphocyte ratio (NLR), and tumor size, forming the nomogram. The model showed excellent performance, with AUC of 0.862 (95%CI:0.784–0.940) in the training cohort. DeLong's test demonstrated significantly higher AUC versus monocyte count, NLR, tumor size, and CMP-Skewness alone ($P=0.003$, $P<0.001$, $P=0.014$, $P<0.001$), confirming superior discriminative ability of the combined model. In validation, AUC remained 0.864 (95%CI:0.741–0.987). Calibration and DCA curves indicated good agreement between predicted and actual Ki-67 status, and higher net benefit over "treat-all" or "treat-none" strategies, supporting clinical utility.

Conclusion: The nomogram integrating contrast-enhanced CT histogram analysis with clinico-radiological features offers good accuracy and practicality for predicting Ki-67 expression in ccRCC, providing an efficient preoperative decision-making tool for clinicians.

Keywords: Clear cell renal cell carcinoma; Ki-67; Histogram analysis; Nomogram model

Introduction

Renal cell carcinoma (RCC) originates from the renal tubular epithelium and is the most common primary renal malignancy. It has the highest mortality rate among urological tumors, and its incidence has been increasing annually. However, its etiology remains unclear to date [1]. RCC comprises multiple subtypes, among which clear cell renal cell carcinoma (ccRCC) is the most common, accounting for 70%–80% of all renal cancers, and is associated with the highest invasiveness and the poorest prognosis [2].

Ki-67 is a nuclear protein expressed during the active phases of the cell cycle but absent in quiescent cells, and it is involved in numerous key mitotic processes, including nucleolar segregation and rRNA transcription [3]. The Ki-67 nuclear protein is a critical biomarker closely associated with tumor heterogeneity and aggressiveness, and it can promote the proliferative activity and abundance of cells in malignant tumors. Ki-67 expression levels have been widely used to predict the malignant potential and prognosis of various solid tumors, demonstrating favorable

predictive performance. It has been recognized as an important risk factor for renal cell carcinoma; in clear cell renal cell carcinoma, high Ki-67 expression is associated with higher TNM stage and Fuhrman grade, as well as shorter overall survival (OS) and disease-free survival (DFS) [4]. However, conventional methods for Ki-67 detection rely on immunohistochemical staining analysis of tissue samples, which are associated with limitations such as high invasiveness and poor reproducibility. Therefore, it is particularly important to develop a non-invasive and reproducible approach for monitoring Ki-67 levels.

Histogram analysis, as an emerging image analysis technique, is an objective, quantitative, and reproducible method of image analysis. By measuring all voxels within a tumor, it can reflect tissue heterogeneity (expressed as differences in image gray-level distribution) and provide quantitative information reflecting the tumor microenvironment. It has demonstrated favorable value in the preoperative diagnosis and treatment evaluation of various tumors [5,6].

To date, no studies have been reported on the use of contrast-enhanced CT histogram parameters to predict Ki-67 expression status in ccRCC. Therefore, this study aimed to construct a nomogram model based on contrast-enhanced CT histogram analysis combined with clinical and imaging features to predict Ki-67 expression status in ccRCC, thereby providing a clinical reference for preoperative assessment and postoperative prognosis.

Materials and Methods

General Data

This study was approved by the Ethics Review Committee of our hospital. Informed consent was waived owing to the retrospective nature of the study, and all patient information was anonymized. The clinical, imaging, and pathological data of 386 patients with ccRCC who underwent surgical treatment at our hospital between January 2022 and December 2024 were retrospectively analyzed. Inclusion criteria: (1) postoperative pathological diagnosis of ccRCC; (2) complete clinical, imaging, and pathological data; and (3) CT examination performed within 1 week before surgery. Exclusion criteria: (1) an interval of more than 1 month between preoperative imaging examination and pathological examination; (2) preoperative radiotherapy, chemotherapy, targeted therapy, or other treatments; (3) concomitant other diseases; and (4) poor CT image quality or incomplete sequences. A total of 213 patients were ultimately enrolled in the study and randomly allocated to the training and validation cohorts at a ratio of 7:3 (Fig.1).

Examination Methods

Examinations were performed using a Siemens dual-source CT scanner. Patients were placed in the supine position, and the scanning range extended from the upper margin of the liver to the anterior superior iliac spine. Scanning parameters were as follows: tube voltage, 80-120 kV; automatically regulated tube current; collimation width, 0.625 mm; rotation time, 0.7 s/r; pitch ratio, 0.992:1; and slice thickness, 1.25 mm. Iohexol (300 mgI/mL; dose, 1 mL/kg) was administered via bolus injection through the antecubital vein at a flow rate of 3.5-4.0 mL/s. Triggered monitoring was performed at the abdominal aorta (threshold, 100 HU), and corticomedullary and nephrographic phase scans were acquired at 20 s and 60 s after triggering, respectively, to obtain axial, sagittal, and coronal contrast-enhanced images of each phase.

Assessment of Ki-67 Expression

Ki-67 data were obtained from the pathological reports issued by the Department of Pathology of our hospital. Based on previous studies [7] and the distribution of Ki-67 expression data in the patients enrolled in this study, a cutoff value of 5% was selected. Patients with Ki-67 expression greater than or equal to 5% were assigned to the high Ki-67 expression group (n=159), whereas those with Ki-67 expression below 5% were assigned to the low Ki-67 expression group (n=54).

Analysis of Conventional CT Features

Two radiologists (with 8 and 15 years of experience, respectively) independently evaluated the CT findings of all patients in a double-blinded manner, including lesion size, location, shape, margin, calcification, hemorrhage, necrotic cystic degeneration, unenhanced CT attenuation, corticomedullary phase CT attenuation, nephrographic phase CT attenuation, enhancement homogeneity, and perirenal collateral circulation. Any discrepancies were resolved through discussion until a consensus was reached.

Histogram Parameter Analysis

Histogram analysis was independently performed by the two aforementioned radiologists in a double-blinded manner using Fire Voxel software (<https://firevoxel.org>). The procedure was as follows. First, the corticomedullary and nephrographic phase CT images of each patient were separately imported into Fire Voxel. Second, a volume of interest (VOI) was delineated along the tumor contour to extract histogram parameters; the delineated region of interest encompassed the entire tumor to comprehensively assess tumor heterogeneity. Finally, histogram parameters were extracted and recorded, including maximum, minimum, mean, standard deviation, variance, coefficient of variation, skewness, kurtosis, entropy, volume, and percentiles (Perc.1, Perc.5, Perc.10, Perc.25, Perc.50, Perc.75, Perc.90, Perc.95, and Perc.99), where Perc. values represent the percentiles of pixel values within the tumor region of interest. Representative cases and their corresponding histograms for the high and low Ki-67 expression groups are shown in Supplementary Material 1-Fig.S1.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided tests were used, and $P < 0.05$ was considered to indicate statistical significance. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation (Mean $\pm$ SD), and comparisons between groups were performed using the independent-samples t-test; non-normally distributed continuous variables were expressed as median (interquartile range), i.e., M (P25, P75), and comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were expressed as counts (percentages), and comparisons between groups were performed using the Pearson χ^2 test or Fisher's exact test. Inter-observer and intra-observer agreement were assessed using the intraclass correlation coefficient (ICC) based on a two-way mixed-effects model, with ICC >0.75 indicating good agreement. The dataset was randomly divided into a training cohort (70%) and a validation cohort (30%) at a ratio of 7:3. In the training cohort, univariate analysis was first performed for all predictors (using the corresponding between-group comparison methods described above) to screen for variables with $P < 0.05$. Subsequently, based on the glmnet package in R, the variables screened above were included in LASSO regression, and the optimal penalty parameter λ was determined using the minimum criterion (lambda.min) via 5-fold cross-validation; the selected variables served as the candidate predictor set. Collinearity was examined using the variance inflation factor (VIF), with

VIF<10 indicating no significant multicollinearity, and the final optimal feature subset was retained. A logistic regression model was constructed based on the optimal feature subset, and a nomogram was plotted to visualize the model. The discrimination of the model in the training and validation sets was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC); in the training set, the optimal cutoff value was determined using the Youden index, and the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the two groups were calculated accordingly. Differences in AUC were compared using the DeLong test. The calibration of the model was evaluated using calibration curves combined with the Hosmer-Lemeshow (H-L) goodness-of-fit test; decision curve analysis (DCA) was used to assess the clinical net benefit and practical value of the model.

Results

Study Subjects and Dataset Partitioning

A total of 213 patients with ccRCC were enrolled in this study and randomly divided into a training cohort (n=152) and a validation cohort (n=61) at a ratio of 7:3. No statistically significant differences were observed between the training and validation cohorts in terms of candidate variables, including age, BMI, peripheral blood indices, inflammatory markers, quantitative CT parameters, and imaging features (all $P>0.05$), indicating that the baseline characteristics of the two cohorts were well balanced and that the cohorts were suitable for model construction and validation (Supplementary Material 2-Table S1).

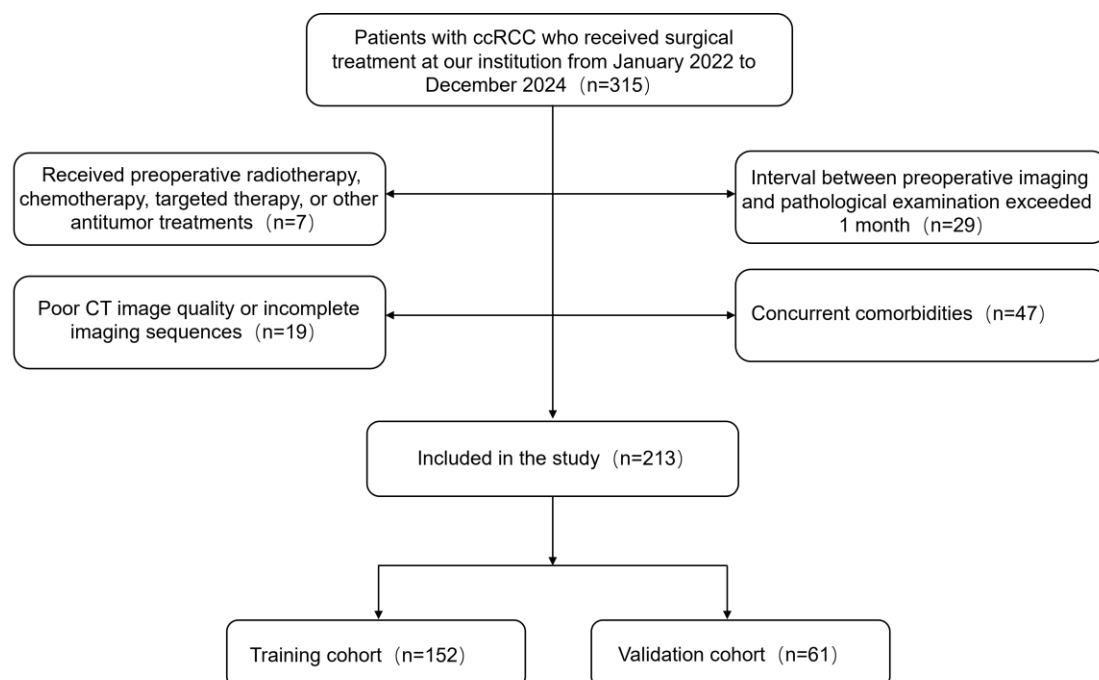


Fig.1 Flowchart of patient selection.

Consistency Analysis of Quantitative Parameter Measurements

ICC analysis demonstrated good to excellent measurement consistency for all quantitative parameters. The ICCs of conventional CT quantitative indices ranged from 0.861 to 0.996, among which the ICCs for maximum diameter, unenhanced lesion CT attenuation, corticomedullary phase lesion CT attenuation, and nephrographic phase lesion CT attenuation were 0.983, 0.861, 0.996, and 0.990, respectively. The ICCs of corticomedullary phase histogram parameters ranged from 0.825 to 0.997, and those of nephrographic phase histogram parameters ranged from 0.880 to 0.999. All parameters had ICCs greater than 0.75, indicating that the quantitative imaging features were highly reproducible and suitable for subsequent model construction.

Univariate Analysis of Different Ki-67 Expression Statuses

In the training cohort, there were 38 patients in the low Ki-67 expression group and 114 in the high Ki-67 expression group. Univariate analysis revealed that CMP-Skewness, CMP-Kurtosis, monocyte count, neutrophil-to-lymphocyte ratio (NLR), SIRI, tumor size, NP-95th Percentiles, and NP-99th Percentiles differed significantly between the different Ki-67 expression status groups (all $P < 0.05$, Table 1).

Table1 Univariate analysis of different Ki-67 expression statuses in the training and validation cohorts

Variable	Training cohort (n=152)			Validation cohort (n=61)		
	low-expression group (n=38)	High-expression group (n=114)	P	low-expression group (n=16)	High-expression group (n=45)	P
CMP-Min	952.39±56.43	953.30±50.95	0.927	998.00(966.75, 1016.75)	943.00(907.00, 988.50)	0.046 [*]
CMP-Max	1343.50(1259.00, 1395.50)	1320.00(1276.75, 1389.75)	0.714	1263.00(1219.75, 1316.50)	1325.00(1285.00, 1400.00)	0.008 [*]
CMP-Mean	1125.90(1093.31, 1158.10)	1128.25(1097.06, 1153.23)	0.959	1120.04±35.77	1127.26±37.01	0.502
CMP-SD	48.21(34.75, 65.30)	45.14(35.00, 56.55)	0.554	36.09(30.05, 42.59)	45.92(35.40, 58.27)	0.044 [*]
CMP-Variance	2324.48(1209.09, 4264.76)	2056.98(1244.46, 3229.78)	0.637	1302.08(903.00, 1815.10)	2108.88(1253.43, 3395.97)	0.044 [*]
CMP-CV	0.04(0.03, 0.06)	0.04(0.03, 0.05)	0.419	0.03(0.03, 0.04)	0.04(0.03, 0.05)	0.061
CMP-Skewness	0.52(0.32, 0.86)	0.40(0.14, 0.64)	0.012 [*]	0.41(0.24, 0.72)	0.34(0.12, 0.63)	0.577
CMP-Kurtosis	0.88(0.52, 1.46)	0.49(0.21, 0.96)	0.005 [*]	0.86(0.29, 1.24)	0.49(0.28, 0.97)	0.298
CMP-Entropy	3.87(3.59, 4.09)	3.88(3.65, 4.03)	0.861	3.92(3.62, 4.11)	3.90(3.68, 4.04)	0.768
CMP-1st Percentiles	1032.00(1008.00, 1051.75)	1033.50(1020.75, 1044.00)	0.637	1038.00(1025.25, 1045.00)	1028.00(1021.50, 1043.00)	0.346
CMP-5th Percentiles	1051.00(1032.00, 1074.50)	1053.50(1039.00, 1067.00)	0.553	1056.50(1041.75, 1067.25)	1049.00(1038.00, 1065.00)	0.465
CMP-10th Percentiles	1062.50(1039.75, 1091.75)	1067.00(1047.00, 1082.25)	0.611	1066.00(1056.25, 1078.50)	1061.00(1048.00, 1082.00)	0.572
CMP-25th Percentiles	1084.50(1056.50, 1128.50)	1093.50(1064.75, 1114.25)	0.787	1090.50(1072.25, 1107.50)	1086.00(1065.50, 1115.00)	0.768
CMP-50th Percentiles	1124.00(1078.25, 1161.00)	1128.50(1091.75, 1158.00)	0.800	1119.62±38.37	1125.18±39.37	0.628

Variable	Training cohort (n=152)		<i>P</i>	Validation cohort (n=61)		<i>P</i>
	low-expression group (n=38)	High-expression group (n=114)		low-expression group (n=16)	High-expression group (n=45)	
CMP-75th Percentiles	1161.61±52.92	1161.09±48.48	0.956	1147.12±46.01	1161.09±47.17	0.310
CMP - 90th Percentiles	1195.00(1161.50, 1235.00)	1191.00(1149.75, 1222.25)	0.611	1171.75±49.26	1190.13±53.99	0.237
CMP-95th Percentiles	1208.50(1179.75, 1253.25)	1205.00(1164.75, 1239.00)	0.593	1185.56±51.44	1206.36±56.47	0.201
CMP-99th Percentiles	1240.00(1214.25, 1279.50)	1236.00(1199.75, 1270.00)	0.518	1202.00(1159.50, 1238.75)	1236.00(1192.00, 1273.00)	0.087
CMP-Volume	21.69(10.15, 59.98)	39.16(15.72, 139.98)	0.056	12.23(6.05, 29.00)	43.52(11.97, 87.44)	0.008*
Age, y	57.89±11.65	59.46±9.78	0.418	58.00(49.50, 65.50)	59.00(53.00, 65.50)	0.634
BMI, kg/m ²	25.38±3.71	24.70±3.52	0.306	24.84±2.93	24.71±3.02	0.883
Lymphocyte count, ×10 ⁹ /L	1.72(1.37, 2.06)	1.60(1.14, 1.94)	0.104	1.81(1.36, 2.15)	1.45(1.12, 2.13)	0.417
Neutrophil count, ×10 ⁹ /L	3.50(2.77, 4.43)	3.92(3.18, 5.24)	0.072	3.27(2.20, 4.73)	3.50(2.80, 4.48)	0.389
Monocyte count, ×10 ⁹ /L	0.43(0.32, 0.55)	0.56(0.47, 0.64)	<0.001*	0.47(0.30, 0.59)	0.53(0.44, 0.64)	0.093
NLR	2.03(1.42, 2.88)	2.30(1.94, 3.62)	0.006*	1.73(1.40, 2.52)	2.58(1.69, 3.54)	0.063
SII	424.24(262.60, 575.92)	498.94(358.38, 776.01)	0.053	397.05(192.70, 555.49)	479.23(339.68, 740.70)	0.085
SIRI	0.84(0.52, 1.30)	1.43(0.96, 1.96)	<0.001*	0.83(0.47, 1.26)	1.35(0.91, 1.86)	0.015*
Size	3.75(2.48, 5.32)	6.25(4.60, 8.55)	<0.001*	2.80(1.85, 3.80)	6.40(5.15, 7.70)	<0.001*
Unenhanced CT attenuation (HU)	35.29±7.83	36.75±9.28	0.383	33.81±6.70	38.16±6.70	0.030*
CMP(HU)	161.50(129.75, 211.25)	149.50(117.75, 184.00)	0.210	135.31±48.57	167.67±47.81	0.024*
Corticomedullary phase enhancement	123.50(94.00, 169.25)	110.50(85.50, 152.00)	0.209	101.50±49.08	129.51±49.12	0.055
NP(HU)	128.03±36.39	118.33±29.63	0.102	112.00(95.25, 129.50)	128.00(96.00, 152.50)	0.241
Nephrographic phase enhancement	95.00(68.50, 111.25)	80.50(58.00, 98.00)	0.076	75.50(63.25, 94.25)	89.00(58.00, 115.50)	0.560
NP-Min	949.00(922.50, 1002.25)	957.00(911.75, 990.25)	0.593	974.88±51.30	960.51±47.15	0.310
NP-Max	1251.00(1225.00, 1289.50)	1236.00(1209.00, 1273.75)	0.195	1219.50(1194.25, 1270.25)	1255.00(1220.00, 1308.50)	0.024*
NP-Mean	1115.42(1099.96, 1143.49)	1120.94(1095.61, 1133.50)	0.586	1118.01±24.23	1118.40±27.97	0.961
NP-SD	36.33(25.22, 47.85)	31.88(26.84, 39.30)	0.291	33.06±10.50	33.89±9.09	0.764

Variable	Training cohort (n=152)		<i>P</i>	Validation cohort (n=61)		<i>P</i>
	low-expression group (n=38)	High-expression group (n=114)		low-expression group (n=16)	High-expression group (n=45)	
NP-Variance	1320.30(635.83, 2288.99)	1016.27(720.36, 1543.69)	0.289	883.55(582.42, 1885.81)	1130.48(710.70, 1691.66)	0.670
NP-CV	0.03(0.02, 0.04)	0.03(0.02, 0.03)	0.282	0.03(0.02, 0.04)	0.03(0.02, 0.04)	0.747
NP-Skewness	0.30(0.15, 0.70)	0.42(0.22, 0.66)	0.473	0.47(0.17, 0.62)	0.35(0.20, 0.52)	0.496
NP-Kurtosis	0.53(0.24, 1.04)	0.47(0.22, 1.25)	0.657	0.36(0.11, 1.19)	0.45(0.26, 1.06)	0.481
NP-Entropy	3.87(3.69, 4.04)	3.82(3.64, 3.96)	0.311	3.91(3.80, 4.02)	3.77(3.59, 3.96)	0.082
NP-1st Percentiles	1036.00(1013.75, 1061.25)	1036.00(1020.75, 1049.50)	0.888	1036.62±26.37	1036.22±21.67	0.952
NP-5th Percentiles	1054.50(1037.00, 1080.50)	1056.50(1040.00, 1074.00)	0.930	1059.88±22.29	1059.69±21.91	0.977
NP-10th Percentiles	1066.50(1046.00, 1098.50)	1068.50(1050.75, 1090.00)	0.958	1073.25±21.09	1072.62±23.68	0.926
NP-25th Percentiles	1092.50(1066.25, 1126.00)	1094.50(1070.75, 1112.00)	0.838	1097.38±25.07	1096.27±26.84	0.886
NP-50th Percentiles	1115.00(1094.00, 1146.25)	1124.00(1095.75, 1137.00)	0.914	1120.50±27.65	1121.09±29.46	0.945
NP-75th Percentiles	1142.00(1130.75, 1165.50)	1142.00(1117.00, 1158.00)	0.442	1140.81±28.21	1142.13±32.27	0.885
NP-90th Percentiles	1167.00(1149.25, 1188.25)	1156.00(1133.75, 1176.25)	0.096	1158.00±28.65	1159.53±34.51	0.874
NP-95th Percentiles	1178.50(1160.50, 1199.25)	1165.00(1145.00, 1188.25)	0.049*	1167.81±29.59	1169.47±35.90	0.869
NP-99th Percentiles	1201.50(1182.75, 1225.50)	1181.00(1164.75, 1202.25)	0.011*	1179.50(1159.00, 1219.25)	1188.00(1165.00, 1212.00)	0.640
NP-Volume	22.59(9.00, 58.78)	45.14(16.53, 143.04)	0.055	12.93(6.13, 30.47)	40.63(18.51, 88.55)	0.004*
Sex , n(%)			0.698			0.487
Female	13 (34.2%)	43 (37.7%)		8 (50.0%)	18 (40.0%)	
Male	25 (65.8%)	71 (62.3%)		8 (50.0%)	27 (60.0%)	
Hypertension, n(%)			0.287			0.629
no	21 (55.3%)	74 (64.9%)		10 (62.5%)	25 (55.6%)	
yes	17 (44.7%)	40 (35.1%)		6 (37.5%)	20 (44.4%)	
Diabetes mellitus, n(%)			0.268			0.606
no	35 (92.1%)	97 (85.1%)		15 (93.8%)	38 (84.4%)	
yes	3 (7.9%)	17 (14.9%)		1 (6.2%)	7 (15.6%)	
Symptoms, n(%)			0.687			0.206

Variable	Training cohort (n=152)		<i>P</i>	Validation cohort (n=61)		<i>P</i>
	low-expression group (n=38)	High-expression group (n=114)		low-expression group (n=16)	High-expression group (n=45)	
no	27 (71.1%)	77 (67.5%)		10 (62.5%)	37 (82.2%)	
yes	11 (28.9%)	37 (32.5%)		6 (37.5%)	8 (17.8%)	
Shape, n(%)			0.284			0.029*
no	27 (71.1%)	70 (61.4%)		15 (93.8%)	27 (60.0%)	
yes	11 (28.9%)	44 (38.6%)		1 (6.2%)	18 (40.0%)	
Margin, n(%)			0.574			0.793
no	17 (44.7%)	57 (50.0%)		7 (43.8%)	18 (40.0%)	
yes	21 (55.3%)	57 (50.0%)		9 (56.2%)	27 (60.0%)	
necrosis, n(%)			0.287			0.075
no	17 (44.7%)	40 (35.1%)		9 (56.2%)	14 (31.1%)	
yes	21 (55.3%)	74 (64.9%)		7 (43.8%)	31 (68.9%)	
Calcification, n(%)			0.695			0.377
no	33 (86.8%)	96 (84.2%)		15 (93.8%)	36 (80.0%)	
yes	5 (13.2%)	18 (15.8%)		1 (6.2%)	9 (20.0%)	
Enhancement homogeneity, n(%)			0.349			0.796
no	13 (34.2%)	30 (26.3%)		4 (25.0%)	8 (17.8%)	
yes	25 (65.8%)	84 (73.7%)		12 (75.0%)	37 (82.2%)	
Perirenal collateral circulation, n(%)			0.149			0.022*
no	27 (71.1%)	66 (57.9%)		14 (87.5%)	25 (55.6%)	
yes	11 (28.9%)	48 (42.1%)		2 (12.5%)	20 (44.4%)	

SD, standard deviation; CV, coefficient of variation; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Predictor Selection and Nomogram Model Construction

Based on the candidate variables screened by univariate analysis in the training cohort, LASSO logistic regression was further applied for variable dimensionality reduction. Five-fold cross-validation yielded a lambda.min of 0.027638; at this λ value, LASSO retained 5 variables with non-zero coefficients, including CMP-Skewness, monocyte count, NLR, tumor size, and NP-99th Percentiles (Fig.2).

To further optimize the prediction model, stepwise regression based on the AIC criterion was used for secondary screening of the 5 features selected by LASSO. The AIC values for the various variable combinations are detailed in Table 2. The results showed that the four-variable model comprising CMP-Skewness, monocyte count, NLR, and tumor size had the lowest AIC value (AIC=135.075) and was therefore included in the final multivariable logistic regression model, and a nomogram prediction model was constructed (Fig.3). After adding NP-99th Percentiles to this model, the AIC value increased to 136.856, indicating that NP-99th Percentiles did not provide additional effective predictive information; therefore, this variable was not included in the final model. In addition, among the univariate analyses, tumor size had the lowest AIC value (145.253), indicating that it was the most important univariate predictor.

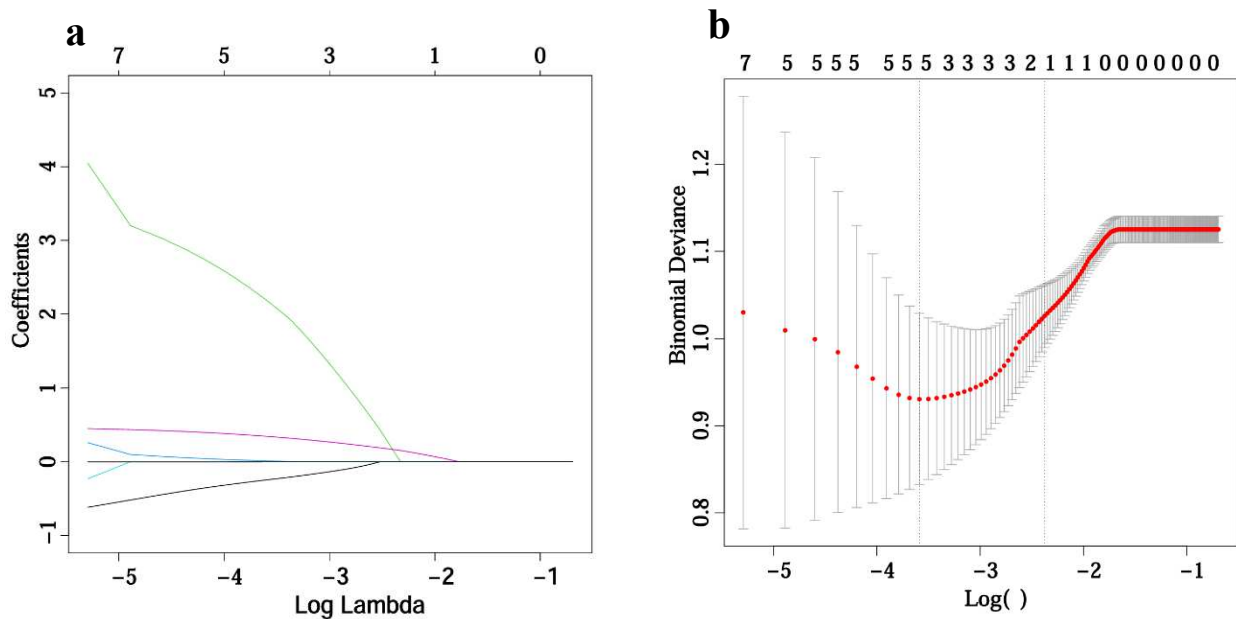


Fig.2 Radiomic feature selection via LASSO regression. (a) Plot of λ values and coefficient paths. (b) Coefficient distribution at selected $\log(\lambda)$.

Table2 Akaike information criterion (AIC) results

AIC	form
172.0089789	NP-99th Percentiles
169.5838585	CMP-Skewness
169.1621305	CMP-Skewness + NP-99th Percentiles

168.5326606	NLR + NP-99th Percentiles
168.1581779	NLR
165.2316234	CMP-Skewness + NLR + NP-99th Percentiles
164.3205164	CMP-Skewness + NLR
160.663592	Monocyte count + NP-99th Percentiles
160.4958486	Monocyte count + NLR + NP-99th Percentiles
159.9502438	Monocyte count
159.2214663	Monocyte count + NLR
156.5804158	CMP-Skewness + Monocyte count + NP-(99th Percentiles
156.0947411	CMP-Skewness + Monocyte count + NLR + NP-99th Percentiles
155.5017432	CMP-Skewness + Monocyte count
154.4614005	CMP-Skewness + Monocyte count + NLR
145.7651262	Size + NP-99th Percentiles
145.2534108	Size
143.9139639	NLR + Size + NP-99th Percentiles
142.8607128	NLR + Size
142.6693349	CMP-Skewness + Size + NP-99th Percentiles
141.6139104	CMP-Skewness + Size
140.8455409	CMP-Skewness + NLR + Size + NP-99th Percentiles
140.0053106	Monocyte count + Size + NP-99th Percentiles
139.4716019	Monocyte count + NLR + Size + NP-99th Percentiles
139.338806	CMP-Skewness + NLR + Size
138.9432183	Monocyte count + Size
137.9823309	Monocyte count + NLR + Size
137.3656606	CMP-Skewness + Monocyte count + Size + NP-99th Percentiles
136.8558523	CMP-Skewness + Monocyte count + NLR + Size + NP-99th Percentiles
135.8990975	CMP-Skewness + Monocyte count + Size
135.075309	CMP-Skewness + Monocyte count + NLR + Size

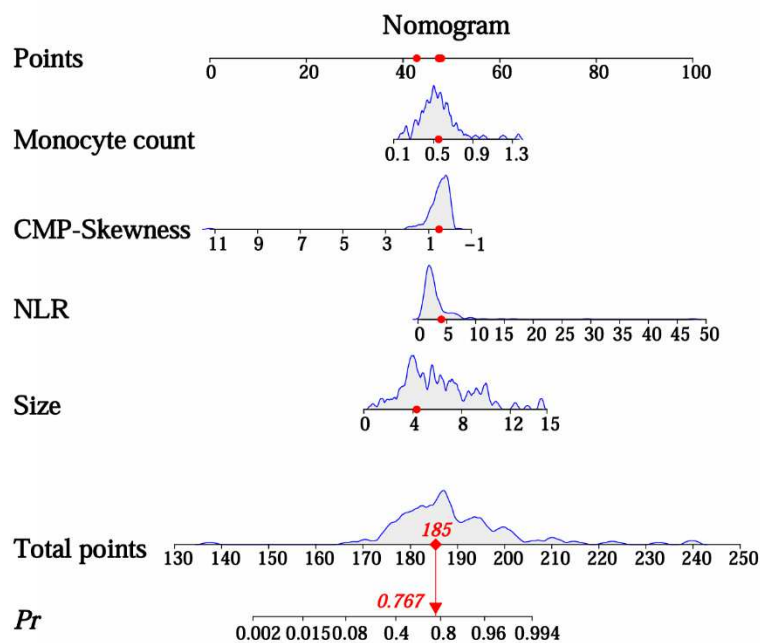


Fig.3 Dynamic nomogram for preoperative prediction of Ki-67 expression status in ccRCC.

Model Discrimination and Validation

In the training cohort, the nomogram model achieved an AUC of 0.862 (95% CI: 0.784–0.940) for predicting Ki-67 expression status, with a sensitivity, specificity, accuracy, PPV, and NPV of 0.842, 0.789, 0.829, 0.923, and 0.625, respectively (Table 3, Fig.4a). The DeLong test showed that the AUC of the nomogram model was significantly higher than those of monocyte count, NLR, tumor size, and CMP-Skewness, with all differences being statistically significant ($P=0.003$, $P<0.001$, $P=0.014$, and $P<0.001$, respectively), indicating that the combined model had superior discriminatory ability compared with any single predictor. In the validation cohort, the nomogram model maintained comparable discriminatory ability, with an AUC of 0.864 (95% CI: 0.741–0.987), a sensitivity of 0.844, a specificity of 0.875, an accuracy of 0.852, a PPV of 0.950, and an NPV of 0.667 (Fig.4b).

Table 3 Diagnostic performance in training cohort

Indicator	Nomogram	Monocyte count	NLR	Size	CMP-Skewness
AUC	0.862 (0.784–0.940)	0.713 (0.614–0.812)	0.649 (0.544–0.754)	0.792 (0.700–0.884)	0.636 (0.538–0.733)
Sensitivity	0.842 (0.775–0.909)	0.763 (0.685–0.841)	0.868 (0.806–0.930)	0.860 (0.796–0.923)	0.421 (0.330–0.512)
Specificity	0.789 (0.660–0.919)	0.605 (0.450–0.761)	0.447 (0.289–0.605)	0.658 (0.507–0.809)	0.842 (0.726–0.958)
Accuracy	0.829 (0.827–0.831)	0.724 (0.721–0.726)	0.763 (0.761–0.765)	0.809 (0.807–0.811)	0.526 (0.523–0.530)
PPV	0.923	0.853	0.825	0.883	0.889
NPV	0.625	0.460	0.531	0.610	0.327

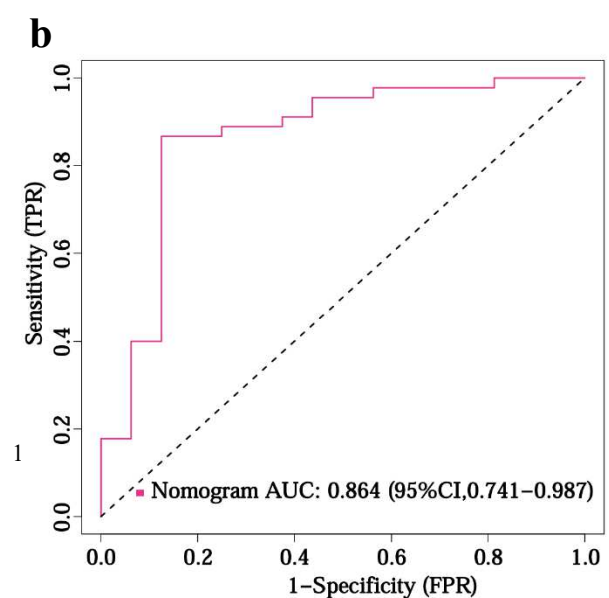
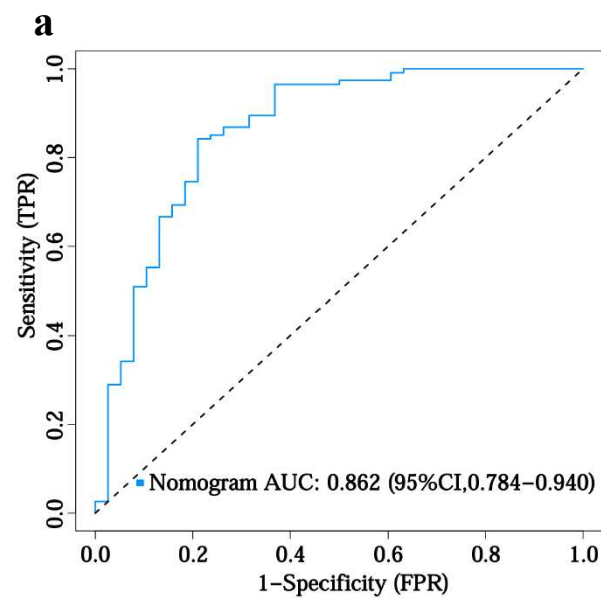


Fig.4 ROC curves and AUCs of the nomogram for predicting Ki-67 expression in ccRCC patients in the training (a) and validation (b) cohorts.

Model Calibration and Clinical Net Benefit

Calibration analysis showed that the Hosmer-Lemeshow test was not statistically significant in the training cohort ($\chi^2=6.686$, $P=0.571$), with a Brier score of 0.116; in the validation cohort, the Hosmer-Lemeshow test likewise indicated no significant lack of fit ($\chi^2=7.533$, $P=0.480$), with a Brier score of 0.118, indicating good calibration consistency between the predicted probabilities and the actual Ki-67 expression status (Fig.5a,b). Decision curve analysis (DCA) showed that, within the range of clinically relevant threshold probabilities, the model yielded a higher net benefit than the "treat-all" and "treat-none" strategies, suggesting its potential clinical utility (Fig.5c,d).

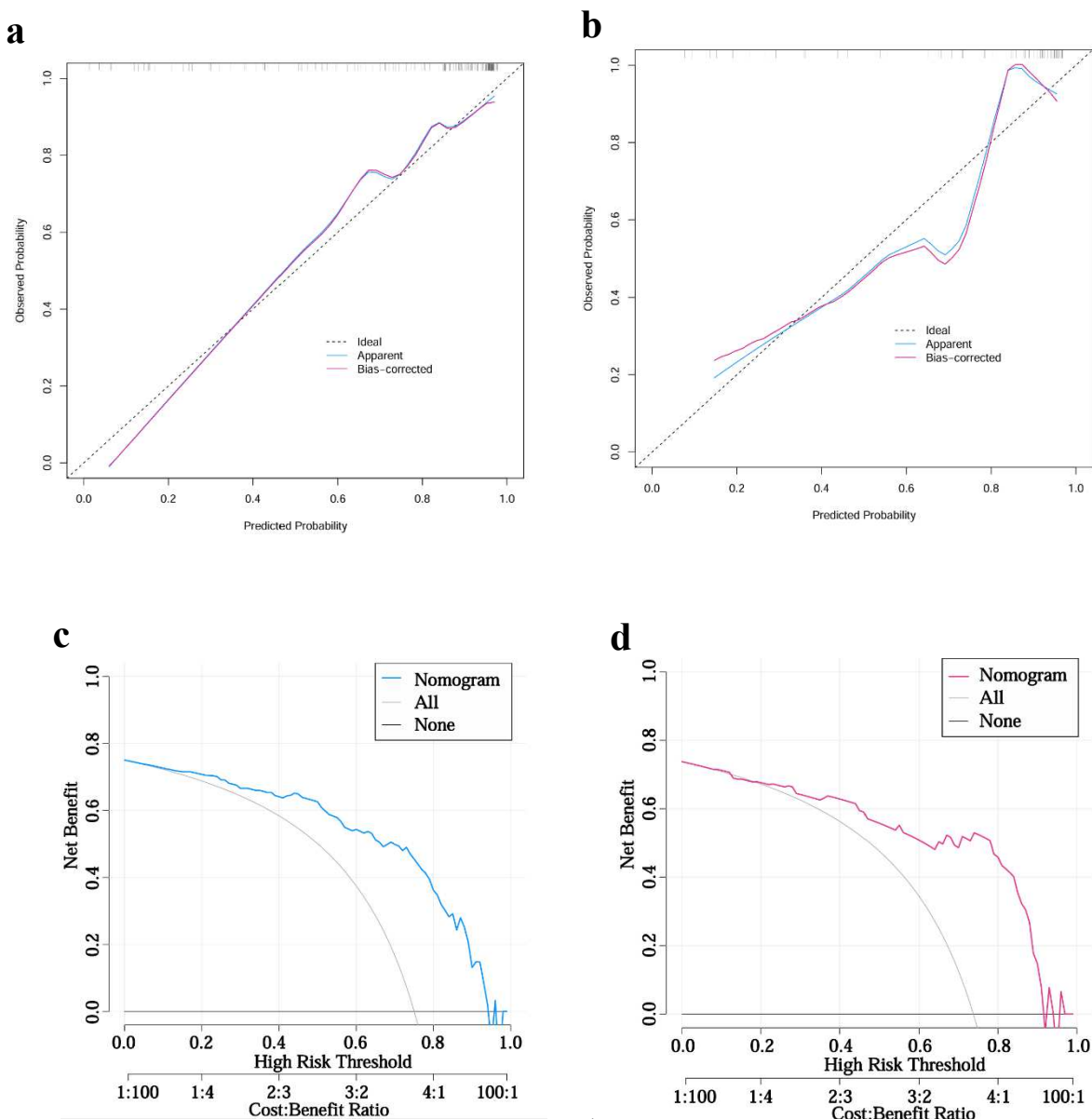


Fig.5 Calibration curves of the nomogram for predicting Ki-67 expression status in ccRCC patients in the training (a) and validation (b) cohorts. Decision curve analysis (DCA) of the nomogram for predicting Ki-67 expression status in ccRCC patients in the training (c) and validation (d) cohorts.

Discussion

In this study, we successfully constructed and validated a nomogram model based on contrast-enhanced CT histogram parameters (CMP-Skewness) combined with clinical and imaging features (monocyte count, NLR, and tumor size). To our knowledge, this is the first study to integrate CT quantitative histogram features with imaging features and inflammatory markers in a deeply fused manner for the preoperative non-invasive prediction of Ki-67 expression status in patients with ccRCC. The model demonstrated good discrimination in both the training and validation cohorts, with AUCs of 0.862 and 0.864, respectively, and the calibration curves indicated good agreement between predicted probabilities and actual observed probabilities. This discriminatory performance was significantly superior to that reported in previous studies relying solely on imaging characteristics or inflammatory markers [8]. The nomogram model showed good accuracy and clinical utility in predicting Ki-67 protein expression levels in patients with ccRCC, providing clinicians with a convenient and efficient tool for preoperative decision-making.

Histogram analysis based on CT images can provide more objective, comprehensive, and reliable analysis for evaluating the potential heterogeneity throughout the entire tumor. Histogram skewness measures the degree of asymmetry in the gray-level distribution and is more sensitive to local gray-level abrupt changes than standard deviation or mean. In ccRCC, Ki-67 serves as a biomarker of tumor proliferative activity; its high expression indicates active tumor cell proliferation and increased heterogeneity, and is often accompanied by extreme inhomogeneity in microvessel density (MVD) [9], resulting in a more uneven distribution of enhancement intensity within the solid tumor components and a corresponding shift in skewness values. Therefore, the direction of CMP-Skewness shift quantitatively reflects the degree of polarization in tumor tissue blood perfusion. Previous studies on gliomas and hepatocellular carcinoma have also confirmed that histogram skewness is significantly correlated with the Ki-67 index [10,11], the mechanism of which lies in the fact that increased tumor heterogeneity can lead to elevated malignant potential and neovascularization [12]. Although the above evidence is largely based on MRI, the core conclusion it substantiates—that histogram skewness can reflect tumor heterogeneity and proliferative activity—shares the same underlying principle as the contrast-enhanced CT histogram analysis in this study, and together they provide a radiological theoretical basis for the biological plausibility of CMP-Skewness in

predicting Ki-67 expression in ccRCC.

Various inflammatory cells and inflammatory cytokines in the tumor microenvironment can serve as important prognostic indicators for patients with cancer, and certain combinations of indicators, such as the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and platelet-to-lymphocyte ratio (PLR), are considered particularly valuable [13]. As a simple and readily available hematological inflammatory marker, NLR is regarded as a potential prognostic factor for human cancers and has been widely applied in prognostic studies of various malignancies [14]. Studies have shown that elevated NLR is associated with poorer prognosis in multiple cancers, including urothelial carcinoma [15], lung cancer [16], colorectal cancer [17], and breast cancer [18]. NLR plays an important role in the prognosis of RCC, possibly because NLR reflects the systemic inflammatory response and also indicates a decline in antitumor immune function, thereby contributing significantly to tumor progression and metastasis [19]. Monocytes likewise play a key role in the immune system and are closely associated with the tumor microenvironment, serving as important regulators of cancer initiation and progression [20]. Studies have found that elevated monocyte count is significantly associated with reduced overall survival (OS) and progression-free survival (PFS) in patients with RCC [21]. Therefore, we propose that ccRCC with high Ki-67 expression is often accompanied by stronger activation of the inflammatory microenvironment, which provides a mechanistic bridge for peripheral blood inflammatory indicators in predicting proliferative activity.

Tumor size is a core determinant of TNM staging and surgical decision-making in ccRCC, and its positive association with Ki-67 expression levels has been validated in multiple studies. Larger tumors generally imply a longer growth period, thereby accumulating more proliferation-related gene mutations, which may lead to elevated Ki-67 levels [22]. Some scholars retrospectively analyzed the clinical data of 185 patients with ccRCC and found that tumor size was an independent predictor of Ki-67 expression levels [23]. In the univariate analysis of this study, tumor size had the lowest AIC value (145.253), indicating that it was the most important univariate predictor, which is consistent with the findings of previous studies.

Previous studies on the prediction of Ki-67 expression status in ccRCC based on ADC gray-level histogram analysis showed that parameters such as standard deviation and variance differed significantly between the high and low Ki-67 expression groups; however, the AUCs of these models were all lower than that of the present study, and no comprehensive prediction model was constructed, thus limiting their clinical translational value [24]. In contrast, the nomogram model introduced in this study combined imaging parameters with clinical indicators, achieving an AUC of over 0.86, which is superior to most unimodal models. Zhang T et al. used contrast-enhanced CT radiomics to extract thousands of radiomic features to predict Ki-67 expression status; although a relatively

high AUC was obtained, the model complexity was excessively high [25]. In comparison, the present study selected only a single histogram parameter with clear physiological significance (CMP-Skewness) and still achieved performance comparable to that of complex radiomics models, while significantly improving the convenience of clinical application.

The nomogram model developed in this study, as a visualized risk assessment tool, enables preoperative non-invasive assessment of Ki-67 expression status and allows individualized prediction based on patients' preoperative indicators. Its value lies in assisting the clinical decision-making process: for patients assessed as high risk, the model results can provide clinicians with clearer directional guidance, such as adopting more aggressive surgical strategies (e.g., radical nephrectomy rather than partial nephrectomy) or formulating more intensive postoperative follow-up plans. In particular, when assisting physicians in evaluating tumor proliferative activity, this tool can provide valuable quantitative reference information, thereby supporting more precise physician-patient communication and shared decision-making.

This study has several limitations. First, as a retrospective study, the enrolled population was concentrated in a single tertiary medical center, and cases with poor CT image quality (e.g., severe respiratory motion artifacts) were excluded, which may have introduced selection bias. Future studies with larger sample sizes, prospective designs, and multicenter validation are needed to further improve the generalizability of the model and the reliability of the conclusions. Second, the measurement of CMP-Skewness depends on the consistency of CT scanning parameters, and different scanners, slice thicknesses, and contrast agent injection protocols may affect the stability of the features. Third, this study was a cross-sectional prediction study and did not include follow-up data on disease-free survival (DFS) or overall survival (OS); therefore, the value of this model for predicting long-term prognosis remains to be evaluated.

In summary, the nomogram model constructed in this study can preoperatively and non-invasively assess Ki-67 expression status in ccRCC, and its risk stratification function can provide intuitive decision-making reference for clinical practice, showing promising application prospects.

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