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Research Article

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Development of a Predictive Nomogram for Very Early Recurrence After Radical Resection of Intrahepatic Cholangiocarcinoma

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Abstract

Backgroud: Intrahepatic cholangiocarcinoma (iCCA) is a common subtype of primary liver cancer. A subset of patients who undergo curative resection of iCCA experience very early recurrence (VER) after surgery, the AJCC staging system is inadequate for effectively predicting VER.The study aimed to develop and validate a clinical nomogram for predicting VER after surgery for iCCA.**Methods:** Clinicopathological datas of patients with postoperative recurrent iCCA were obtained from cBioPortal and TCGA. Patients were categorized into VER and non-VER groups. Logistic regression was used to identify independent risk factors for VER, and a nomogram was constructed and validated in an external cohort.**Results:** Among 215 patients with recurrent iCCA, 85 had VER and 130 had non-VER. After propensity score matching (PSM), 68 patients remained in each group. The VER group exhibited inferior 2- and 5-year survival before and after PSM (P<0.001). Multiple tumors, fatty liver, viral hepatitis, elevated log-transformed CA19-9, and lymph node metastasis were independent risk factors for VER,and based on these five factors, the constructed nomogram achieved an AUC of 0.760 (bias-corrected AUC=0.741), which was superior to CA19-9 alone (AUC = 0.661, P= 0.003). External validation in 46 patients with recurrent iCCA yielded an AUC of 0.745.**Conclusions:** The nomogram based on viral hepatitis, multiple tumors, fatty liver, lymph node metastasis, and log-transformed CA19-9 can effectively predict VER for iCCA after surgery.

Keywords: intrahepatic cholangiocarcinoma; very early recurrence; nomogram

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is a primary liver malignancy that arises from the epithelial cells lining the intrahepatic bile ducts. Among primary liver

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cancers, its incidence ranks second only to hepatocellular carcinoma[1]. However, only 20%–30% of patients are eligible for surgical resection at the time of diagnosis[2]. Among patients undergoing radical resection, the recurrence rate reaches approximately 70%, with a 5-year survival rate of only about 30%[3]. Very early recurrence (VER) is defined as recurrence within 6 months after initial resection, occurs in approximately 25%–32.35% of iCCA patients with a poor 1-year survival [4, 5]. Patients with VER are generally considered unsuitable for immediate repeat surgery and may instead be candidates for neoadjuvant systemic chemotherapy[6].Therefore, accurate preoperative identification of patients at high risk of VER is crucial for selecting the most appropriate treatment strategy.

Currently, the 8th edition of the American Joint Committee on Cancer (AJCC) staging system remains the most widely used framework for guiding treatment and predicting prognosis in iCCA. However, it can only be applied postoperatively and failed to effectively predict VER [4]. Consequently, there is an urgent need to develop a noninvasive, early, and comprehensive assessment approach to evaluate the likelihood of VER in iCCA patients .

Patients and Methods

Patient selection and data sources

We obtained the clinicopathological characteristics of patients with postoperative recurrence of intrahepatic cholangiocarcinoma (iCCA) through the cBioPortal (**http://www.cbioportal.org**) and TCGA (**http://portal.gdc.cancer.gov**) data portals. This dataset was used to establish a nomogram for predicting VER .

Inclusion criteria: (1) pathological intrahepatic cholangiocarcinoma (ICD-O-3 code, primary tumor site code C22.1, histology/behavior code: 8160/3); (2) tumor TNM (Tumor Nodes Metastasis, TNM) stage $T_XN_XM_0$, indicating no metastasis to other sites; (3) underwent surgical treatment, including segmental hepatectomy, or lobar and extended lobar hepatectomy; (4) R0 resection (no residual cancer cells at the microscopic margin) and postoperative recurrence; (5) complete clinicopathological and follow-up datas; (6) survival time greater than 1 month.

Exclusion criteria: (1) without surgery or surgical information was unknown, or

local tumor destruction (such as photodynamic therapy, laser, radiofrequency ablation, cryotherapy, embolization, ethanol injection, etc.); (2) preoperative radiotherapy or chemotherapy; (3) R1 resection, with cancer residue at the margin of the surgical specimen; (4) missing clinical data or prognostic information; (5) hepatocellular carcinoma or mixed hepatocellular carcinoma; (6) survival time less than 1 month; (7) concomitant other tumors or development of other systemic tumors after surgery; (8) cause of death not due to recurrence of intrahepatic cholangiocarcinoma; (9) tumor TNM stage $T_XN_XM_1$, indicating metastasis to other organs.

To validate the nomogram's predictive performance, we assembled an external validation cohort of patients with intrahepatic cholangiocarcinoma (iCCA) admitted to the Department of Hepatobiliary Surgery, Fujian Provincial Hospital Affiliated to Fuzhou University. We retrospectively reviewed patients who underwent curative-intent resection and experienced postoperative recurrence between January 2018 and December 2022. Inclusion required no preoperative antitumor therapy (e.g.chemoradiotherapy,radiofrequency ablation, cryotherapy, or embolization) and postoperative pathological confirmation of iCCA. Follow-up continued until May 2025, with 99 patients completing postoperative follow-up. Exclusion criteria were concomitant tumors at other sites, perioperative death, preoperative radiotherapy or chemotherapy, and incomplete clinical data. Ultimately, 46 patients constituted the external validation cohort. Follow-up occurred every 3 months within 2 years after surgery and every 6 months thereafter. The study was approved by the hospital ethics committee (approval number: K2024-12-080).

Propensity score matching

To control potential confounding bias, this study used propensity score matching (PSM) to perform 1:1 matching between the two groups. The propensity score was defined as the conditional probability of very early recurrence given baseline covariates, calculated using a multivariate logistic regression model. The matching method used nearest-neighbor matching, with the caliper value set at 0.2 times the standard deviation of the propensity score (i.e., caliper=0.2×SD), a matching ratio of 1:1, and no replacement. After matching, the standardized mean difference (SMD)

was used to evaluate covariate balance between the two groups, with SMD<0.1 (or <10%) as the criterion for good balance. After matching, the matched sample was used as the primary analysis population for subsequent analyses.

Statistical analysis

In this study, R 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis. Continuous variables were described as mean ± SD (normal distribution) or median (interquartile range) (skewed distribution), and compared using the independent-samples t-test or Mann-Whitney U test, respectively. Categorical variables were expressed as n (%) and compared using the Pearson chi-square test, or Fisher's exact test when expected frequencies were not met. All P values were two-sided, with P<0.05 considered statistically significant.

For prognostic factor screening, a univariate Cox proportional hazards regression was first used to screen factors affecting 5-year survival (inclusion criterion P<0.05), followed by multivariate Cox regression (CA19-9 levels were logarithmically transformed to satisfy model assumptions). To identify risk factors for very early recurrence (VER), univariate logistic regression was first performed to screen candidate variables (inclusion criterion: P < 0.1), followed by multivariate logistic regression. Model predictive performance was assessed using receiver operating characteristic (ROC) curves. Collinearity was diagnosed via the variance inflation factor (VIF). Finally, the Kaplan-Meier method was used to plot survival curves, and the log-rank test to compare between-group survival differences (P<0.05).

results

Baseline Clinicopathological Characteristics of Patients

215 patients with recurrent intrahepatic cholangiocarcinoma (iCCA) after surgery were ultimately included from the cBioPortal and TCGA databases. As shown **in table1**,The mean age was 61.4 ± 12.1 years, and the cohort comprised 99 males (45.8%) and 117 females (54.2%). The median maximum tumor diameter was 6.1 (4.5–8.6) cm. A single tumor was present in 169 patients (78.2%) and multiple tumors in 47 patients (21.8%). Concomitant viral hepatitis, cirrhosis, and fatty liver were present in 33 (15.3%), 28 (13.0%), and 52 (24.1%) patients, respectively. The tumor

mutational burden was 3.39 ± 4.79 mutations/Mb. Microvascular invasion was observed in 110 patients (50.9%) and lymph node metastasis in 41 patients (19.0%); the median CA19-9 level was 68.0 (20.8–271.5) U/ml.

Patients were categorized into the VER group (85 patients, 39.8%) and the nVER group(130patients,60.2%) according to postoperative recurrence. Baseline characteristics were summarized in Table 1. Compared with the nVER group, VER patients were younger (59.3 ± 12.7 vs. 62.8 ± 11.7 years, P = 0.037) ,more frequently had multiple tumors [26(30.2%) vs. 21(16.2%), P = 0.022] and concomitant viral hepatitis [20(23.3%) vs. 13 (10.0%), P = 0.014], but had a significantly lower fatty liver [11 (12.8%) vs. 41 (31.5%), P = 0.003]. In addition, the CA19-9 level was significantly higher in the VER group than in the nVER group [134.0 (39.9–1682.0) vs. 44.0 (17.0–189.0)U/ml, P < 0.001].

Table1 Baseline characteristics of patients and comparison of clinicopathological features between the VER group and the nVER group

Variables	**Total group** (n=215)	**VER group** (n=85,39.5%)	**nVER group** (n=130,60.5%)	**P-value**
Age(year)	62.8 ± 11.7	59.1 ± 12.7	62.8 ± 11.7	0.030*
Gender				0.750
Female	116 (54.0%)	47 (55.3%)	69 (53.1%)	
Male	99 (46.0%)	38 (44.7%)	61 (46.9%)	
Tumor size (cm)	6.1 (4.5-8.6)	6.6 (4.5-9.0)	6.0 (4.3-8.4)	0.347
Tumor lesions				0.012*
one	168 (78.1%)	59 (69.4%)	109 (83.8%)	
multi	47 (21.9%)	26 (30.6%)	21 (16.2%)	
Viral hepatitis				0.007*
No	182 (84.7%)	65 (76.5%)	117 (90.0%)	
Yes	33 (15.3%)	20 (23.5%)	13 (10.0%)	
Liver cirrhosis				0.225
No	187 (87.0%)	71 (83.5%)	116 (89.2%)	

Variables	Total group (n=215)	VER group (n=85,39.5%)	nVER group (n=130,60.5%)	P-value
Yes	28 (13.0%)	14 (16.5%)	14 (10.8%)	
Hepatic steatosis				0.002*
No	52 (24.2%)	11 (12.9%)	41 (31.5%)	
Yes	163 (75.8%)	74 (87.1%)	89 (68.5%)	
Tumor differentiation				0.188
Well-moderately differentiated	159 (74.0%)	67 (78.8%)	92 (70.8%)	
Poorly differentiated	56 (26.0%)	18 (21.2%)	38 (29.2%)	
TMB (Mutation/Mb)	2.4(1.3-3.9)	1.7 (1.0-4.0)	2.6 (1.7-3.9)	0.140
Microvascular invasion				0.417
No	106 (49.3%)	39 (45.9%)	67 (51.5%)	
Yes	109 (50.7%)	46 (54.1%)	63 (48.5%)	
Lymph node metastasis				0.089
No	174 (80.9%)	64 (75.3%)	110 (84.6%)	
Yes	41 (19.1%)	21 (24.7%)	20 (15.4%)	
CA19-9 (U/ml)	67.0(20.0-291.5)	135(43.5-2152.0)	40(14-169.5)	P<0.001*

Abbreviations: VER: very early recurrence; nVER: non-very early recurrence; CA19-9: carbohydrate antigen 19-9; TMB: tumor mutational burden.Statistical analysis: Among continuous variables, age was normally distributed data and was expressed as mean ± standard deviation, with independent-samples t-test used for comparison between groups; tumor size, CA19-9, and TMB were skewed distribution data and were expressed as median (interquartile range, IQR), with the Mann-Whitney U test used for comparison between groups. Categorical variables were expressed as number of cases (percentage), and the Pearson chi-square test was used for comparison between groups; the Fisher exact test was used when the theoretical frequency did not meet the conditions.

3.2 Cumulative 2-year and 5-year survival time of the two groups

The median overall survival (OS) of the 215 patients was 33.0 months, with 2-year and 5-year OS rates of 62.5% and 26.7%, respectively. However, the VER group exhibited significantly worse 2-year (28.2% vs. 85.4%) and 5-year (1.2% vs. 33.1%) survival rates compared with the nVER group (both $P < 0.001$) (Figure 1A, 1B).

After propensity score matching (PSM) , a total of 136 patients were successfully matched (68 per group),and no significant differences were observed between the groups in age, sex, tumor size, number of tumors, fatty liver, viral hepatitis, cirrhosis, tumor differentiation, TMB, microvascular invasion, or lymph node metastasis (all $P > 0.05$). However, the CA19-9 level in the VER group remained significantly higher than that in the nVER group [109.5 (41.25–520.75) vs. 53.0 (17.0–211.0) U/ml, $P = 0.012$] (Table 3). The 2-year and 5-year survival rates of the VER group were 32.4% and 1.5%, respectively, both significantly lower than those of the nVER group (80.9% and 26.5%, respectively), $P < 0.001$.(Figures 2A and 2B).

3.3 Univariate and multivariate Cox analysis of risk factors affecting 5-year survival time

The Cox proportional hazards regression model was used to identify risk factors affecting 5-year survival in patients with recurrent intrahepatic cholangiocarcinoma after surgery (Table 2). Univariate analysis revealed that age (HR = 0.973, 95% CI: 0.960–0.987, P = 0.0001), multiple tumors (HR = 1.038, 95% CI: 1.334–2.815, P = 0.005), comorbid fatty liver (HR = 2.168, 95% CI: 1.433–3.281, P = 0.0003), elevated CA19-9 (HR = 1.185, 95% CI: 1.094–1.283, P = 0.0001), and VER (HR = 8.134, 95% CI: 5.568–11.881, $P < 0.001$) were significant factors. In multivariate analysis, VER (HR = 6.590, 95% CI: 4.457–9.743, $P < 0.001$), multiple tumors (HR = 1.686, 95% CI: 1.157–2.458, P = 0.007), fatty liver (HR = 1.755, 95% CI: 1.143–2.659, P = 0.010), and elevated CA19-9 (HR = 1.105, 95% CI: 1.019–1.199, P = 0.016) were independent risk factors, whereas age (HR = 0.985, 95% CI: 0.971–0.998, P = 0.026) was an independent protective factor.

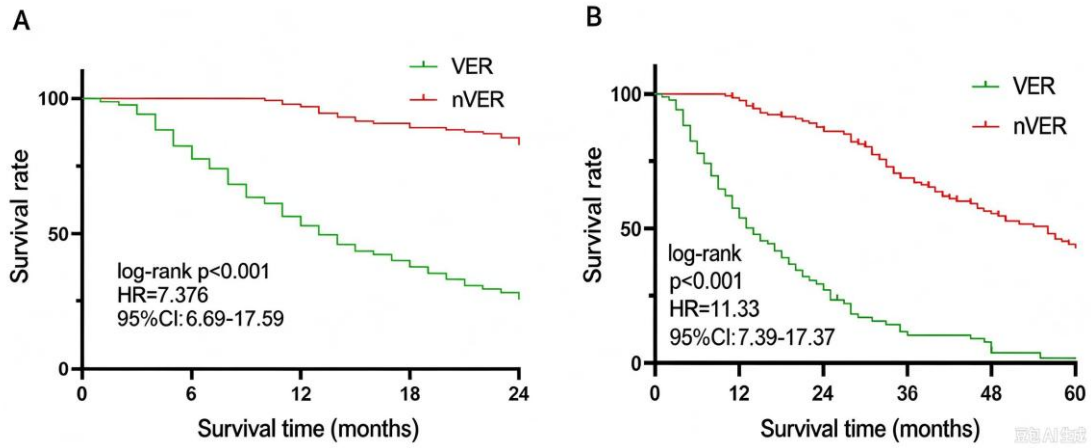

Figure 1 Comparison of overall survival curves between the VER group and the nVER group in patients before PSM (Kaplan-Meier method). (1A) 2-year survival curve; (1B) 5-year survival curve.

Table 2 Univariate and multivariate Cox regression analysis of factors affecting 5-year overall survival in patients with intrahepatic cholangiocarcinoma.

Variables	**Univariate analysis HR (95% CI)**	P Value	**Mutivariate analysis HR (95% CI)**	P Value
Age(year)	0.973（0.960-0.987）	0.0001*	0.985（0.971-0.998）	0.026*
Gender		0.163		
Female	Ref.			
Male	0.794（0.574-1.098）			
Tumor size (cm)	1.038 (0.992-1.086)	0.110		
Tumor lesions		0.607		
one	Ref.			
multi	0.906(0.621-1.321)			
Lymph node metastasis		0.081		
No	Ref.			
Yes	1.446 (0.955-2.19)			
Microvascular invasion		0.291		

No	Ref.			
Yes	1.191 (0.861-1.648)			
Hepatic steatosis		0.0003*		0.010*
No	Ref.		Ref.	
Yes	2.168 (1.433-3.281)		1.755(1.143-2.695)	
Liver cirrhosis		0.679		
No	Ref.			
Yes	1.106 (0.686-1.784)			
Tumor lesions		0.0005*		0.007*
one	Ref.		Ref.	
multi	1.038 (1.334-2.815)		1.686 (1.157-2.458)	
Viral hepatitis		0.127		
No	Ref.			
Yes	1.408 (0.919-1.002)			
TMB	0.959 (0.94-1.01)	0.061		
CA19-9（log）	1.185(1.094-1.283)	0.0001*	1.105 (1.019-1.199)	0.016*
VER		<0.001*		<0.001*
No	Ref.		Ref.	
Yes	8.134(5.568-11.881）		6.590(4.457-9.743)	

HR: hazard ratio; CI: confidence interval; CA19-9: carbohydrate antigen 19-9; TMB: tumor mutational burden; variables with P<0.05 in univariate analysis were included in the multivariate Cox proportional hazards regression model. HR>1 indicates a risk factor, and HR<1 indicates a protective factor. CA19-9 levels were logarithmically transformed before analysis. * indicates a statistically significant difference (P<0.05)

Table 3 Baseline characteristics of the nVER and VER groups after PSM

Variables	**Total group** (n=136)	**VER group** (n=68)	**nVER group** (n=68)	P-value
Age(year)	59.3±13.3	58.5±13.7	60.1±13.0	0.489
Gender				1.000
Female	63(46.3%)	32(47.1%)	31(45.6%)	

Variables	Total group (n=136)	VER group (n=68)	nVER group (n=68)	P-value
Male	73(53.7%)	36（52.9%）	37(54.4%)	
Tumor size (cm)	6(4.35,8.5)	6(4.5,9)	6(4,7.85)	0.483
Tumor lesions				0.695
one	101(74.3%)	52(76.5%)	49（72.1%）	
multi	35(25.7%)	16(23.5%)	19(27.9%)	
Viral hepatitis				0.525
No	108(79.2%)	52（76.5%）	56（82.4%）	
Yes	28(20.6%)	16（23.5%）	12（17.6%）	
Liver cirrhosis				0.621
No	117(86.0%)	57(83.8%)	60(88.2%)	
Yes	19(14.0%)	11（16.2%）	8(11.8%)	
Hepatic steatosis				1.000
No	20(14.7%)	10（14.7）	10（14.7）	
Yes	116(85.3%)	58（85.3%）	58（85.3%）	
Tumor differentiation				1.000
Well-moderately differentiated	105(77.2%)	53（77.9%）	52（76.5%）	
Poorly differentiated	31(22.8%)	15(22.1%)	16(23.5%)	
TMB (Mutation/Mb)	1.96(1.02,3.91)	1.71(1,4..1)	1.96(1.53,3.9)	0.609
Microvascular invasion				1.000
No	66(48.5%)	33(48.5%)	33(48.5%)	
Yes	70(51.5%)	35(51.5%)	35(51.5%)	
Lymph node metastasis				1.000
No	102(75.0%)	51(75.0%)	51(75.0%)	
Yes	34(25.0%)	17(25.0%)	17(25.0%)	
CA19-9（U/ml）	80(24.5,271.5)	109.5(41.25,520.75)	53(17,211)	0.012*

Abbreviations: VER: very early recurrence; nVER: non-very early recurrence; CA19-9: carbohydrate antigen 19-9; TMB: tumor mutational burden.

Statistical analysis: Continuous variables: age is expressed as mean ± standard deviation, and the t-test was used for difference analysis; tumor size, CA19-9, and TMB are expressed as median (IQR), and the Mann-Whitney U test was used for difference analysis; Categorical variables: the Pearson chi-square test or Fisher's exact test was used.

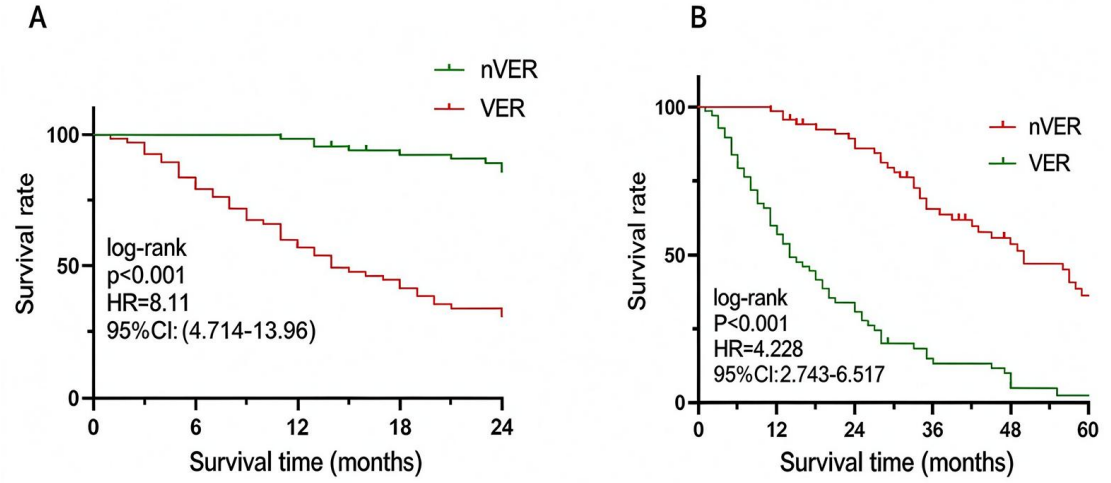

Figure 2 Comparison of overall survival curves between the VER group and the nVER group in patients with recurrent intrahepatic cholangiocarcinoma after surgery following PSM (Kaplan-Meier method). (A) 2-year survival curve; (B) 5-year survival curve;

3.3 Univariate and multivariate logistic regression analysis of risk factors affecting VER

Logistic regression was used to analyze risk factors for VER. Univariate analysis showed that age (OR = 0.975, 95% CI: 0.953–0.998, P = 0.032), fatty liver (OR = 3.099, 95% CI: 1.488–6.453, P = 0.003), multiple tumors (OR = 2.287, 95% CI: 1.186–4.410, P = 0.014), viral hepatitis (OR = 2.769, 95% CI: 1.293–5.929, P = 0.0087), and elevated logCA19-9 (OR = 1.344, 95% CI: 1.169–1.547, P < 0.001) were significantly associated with VER. Variables with P < 0.1 were entered into multivariate logistic regression with stepwise backward selection. Multiple tumors (OR = 2.829, 95% CI: 1.318–6.074, P = 0.008), fatty liver (OR = 3.141, 95% CI: 1.364–7.235, P = 0.007), viral hepatitis (OR = 3.367, 95% CI: 1.44–7.871, P = 0.0051), and elevated logCA19-9 (OR = 1.333, 95% CI: 1.149–1.547, P < 0.001) were independent risk factors for VER, whereas age lost significance (OR = 0.987, 95% CI: 0.963–1.013, P = 0.327) and had no independent predictive value. Notably, although lymph node metastasis was only marginally significant in univariate analysis (OR = 1.805, 95% CI: 0.909–3.582, P = 0.091), it emerged as an independent risk factor in multivariate analysis (OR = 2.293, 95% CI: 1.035–5.077, P = 0.041) (Table 4,

Figure 3).

Table 4 Univariate and multivariate logistic regression analysis of the occurrence of VER in the full cohort before matching.

Variables	Univariate analysis HR (95% CI)	P Value	Mutivariate analysis HR (95% CI)	P Value
Age(year)	0.975(0.953-0.998)	0.032*	0.987(0.963-1.013)	0.327
Gender		0.7498		
Female	Ref.			
Male	0.915(0.528-1.584)			
Tumor size (cm)	1.038(0.958-1.125)	0.3574		
Tumor differentiation		0.1899		
Well-moderately differentiated	Ref.			
Poorly differentiated	0.650(0.342-1.237)			
Lymph node metastasis		0.0914		0.0408*
No	Ref.		Ref.	
Yes	1.805(0.909-3.582)		2.293 (1.035-5.077)	
Microvascular invasion		0.4176		
No	Ref.			
Yes	1.254(0.725-2.17)			
Hepatic steatosis		0.0025*		0.0072*
No	Ref.		Ref.	
Yes	3.099(1.488-6.453)		3.141 (1.364-7.235)	
Liver cirrhosis		0.2276		
No	Ref.			
Yes	1.634(0.736-3.627)			
Tumor lesions		0.0135 *		0.0076*
one	Ref.		Ref.	

multi	2.287 (1.186-4.41)		2.829 (1.318-6.074)	
Viral hepatitis		0.0087*		0.0051*
No	Ref.		Ref.	
Yes	2.769 (1.293-5.929)		3.367 (1.44-7.871)	
TMB	0.945 (0.873-1.023)	0.1648		
CA19-9（log）	1.344 (1.169-1.547)	P<0.001*	1.333 (1.149-1.547)	0.002*

OR: odds ratio; CI: confidence interval; Ref: reference group. Variables with P<0.1 in univariate analysis were included in the multivariate logistic regression model, and stepwise backward regression was used for variable selection. OR>1 indicates a risk factor, and OR<1 indicates a protective factor. CA19-9 levels were logarithmically transformed before analysis (log-CA19-9). * indicates a statistically significant difference (P<0.05).

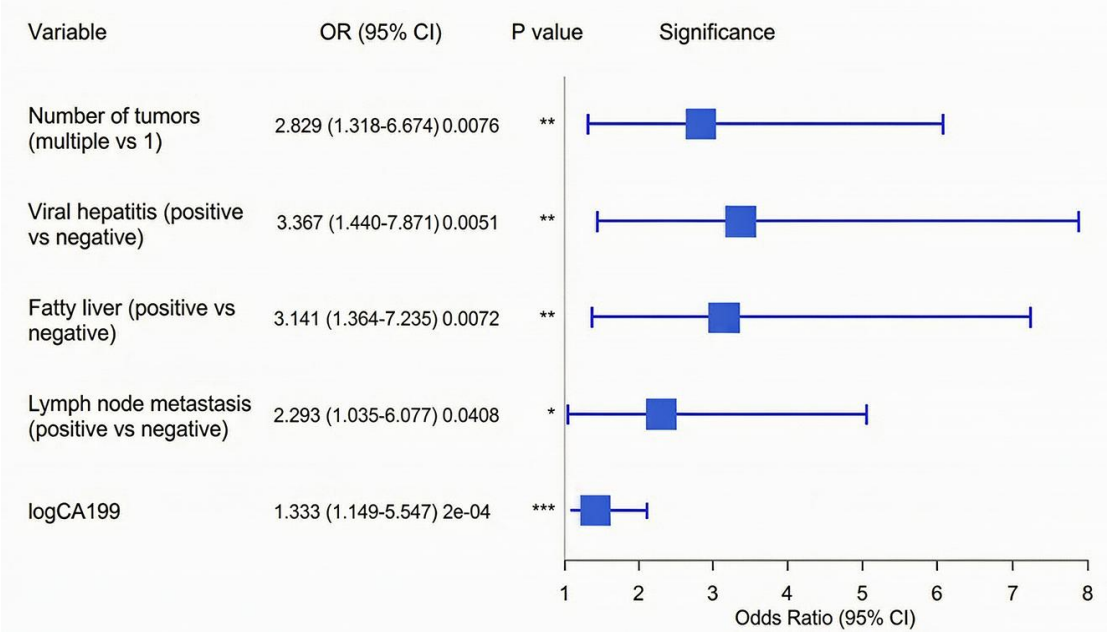

Figure 3 Odds ratios (OR) and 95% confidence intervals (CI) of each independent risk factor in the logistic regression model.Squares represent the point estimates of OR, horizontal line segments represent the 95% CI, and the vertical dashed line is the reference line at OR=1. If the 95% CI line segment of a variable lies entirely to the right of the reference line, the variable is an independent risk factor (P<0.05). CA19-9 levels were logarithmically transformed before analysis (logCA19-9).

3.5 Establishment of a nomogram for predicting VER and model evaluation

Based on the multivariate results, we constructed a nomogram for predicting VER using five variables: viral hepatitis, number of tumors, fatty liver, lymph node metastasis, and logarithmic (log) CA19-9. The nomogram assigns a score to each clinical characteristic, and the total score corresponds to the predicted probability of VER (Figure 4). Its predictive performance was evaluated using ROC curves, yielding

an AUC of 0.760 (corrected AUC = 0.741), indicating reasonable predictive efficacy (Figure 5). For comparison, the AUC of CA19-9 alone was 0.661, significantly lower than that of the nomogram (P = 0.003), confirming the model's superior predictive ability.

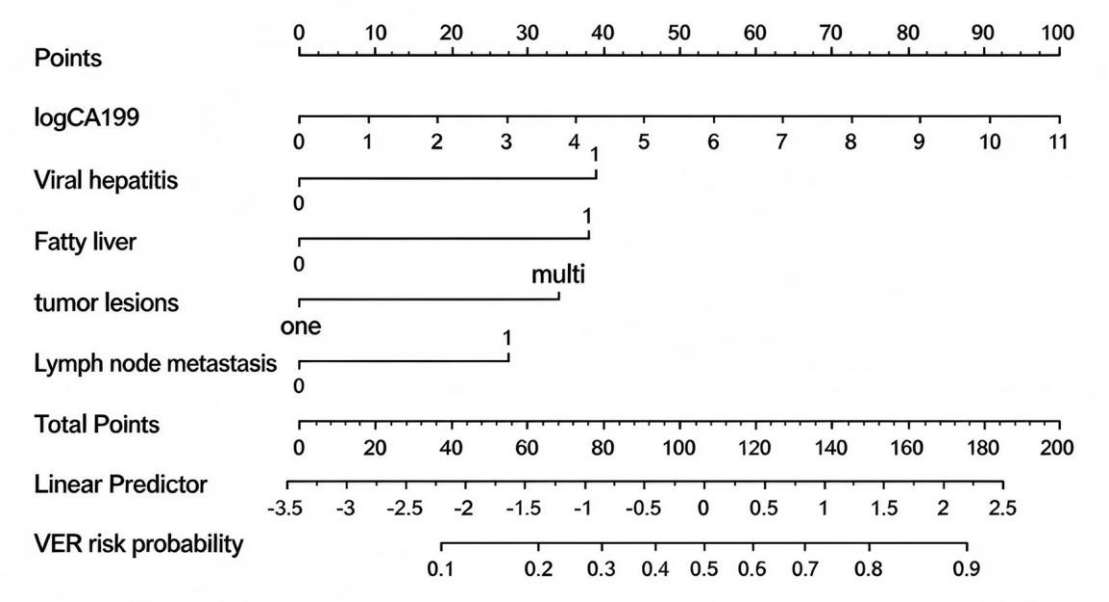

Figure 4 Nomogram for predicting VER.

Assignment of categorical variables (viral hepatitis: 0=no, 1=yes; fatty liver: 0=no, 1=yes; lymph node metastasis: 0=no, 1=yes).

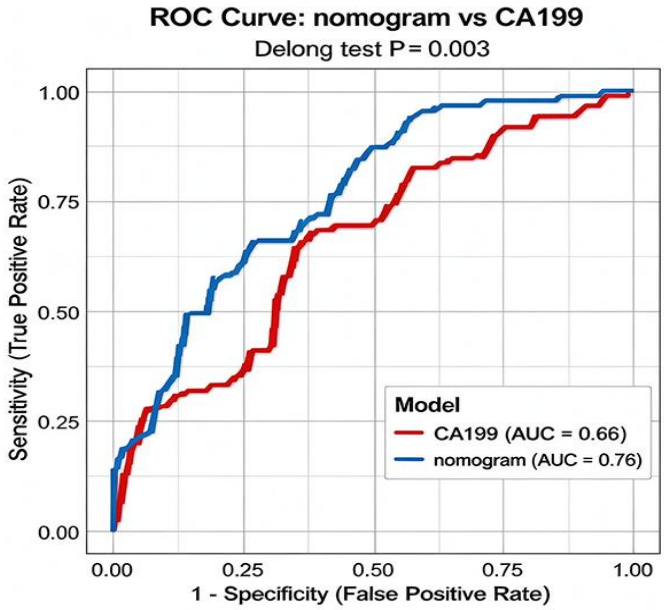

Figure 5 Calibration curve of the nomogram.

3.6 Predictive performance of the nomogram in the external validation set

Among 99 patients who were followed up after radical surgery for intrahepatic cholangiocarcinoma at the Department of Hepatobiliary Surgery, Fujian Provincial

Hospital, 46 (46.5%) developed postoperative recurrence.This included 23 VER cases and 23 nVER cases, baseline characteristics were detailed in Table 5. The two groups showed no significant differences in age, sex, tumor size, viral hepatitis, tumor differentiation, lymph node metastasis, or CA19-9 level (all P > 0.05). However, the proportions of multiple tumors (52.2% vs. 17.6%, P = 0.030) and fatty liver (73.9% vs. 26.1%, P = 0.003) were significantly higher in the VER group.When the nomogram model was applied to the external validation set, it achieved an AUC of 0.745, comparable to that of the training set (0.760) (Figure 7), indicating good discrimination, predictive performance, and clinical applicability.

Table 5 Clinical baseline characteristics of the external validation set.

Variables	**Total group (n=46)**	**nVER group (n=23，50%)**	**VER group (n=23，50%)**	**P-value**
Age(year)	62.33 ± 9.30	64.48 ± 9.61	60.17 ± 8.66	0.118
Gender				0.551
Male	28(60.9%)	15(65.2%)	13(56.5%)	
Female	18(39.1%)	8(34.8%)	10(43.5%)	
Tumor size (cm)	4.85(4.00, 6.50)	4.50(3.70, 5.85)	5.00(4.25, 7.50)	0.210
Tumor lesions				0.030*
one	30(65.2%)	19(82.4%)	11(47.8%)	
multi	16(34.8%)	4(17.6%)	12(52.2%)	
Viral hepatitis				0.721
No	36(78.3%)	17(73.9%)	19(82.6%)	
Yes	10(22.7%)	6(26.1%)	4(17.4%)	
Hepatic steatosis				0.003*
No	23(50.0%)	17(73.9%)	6(26.1%)	
Yes	23(50.0%)	6(26.1%)	17(73.9%)	
Tumor differentiation				
Well-moderately differentiated	29(63.0%)	14(60.9%)	15(65.2%)	

Variables	Total group (n=46)	nVER group (n=23，50%)	VER group (n=23，50%)	P-value
Poorly differentiated	17 (37. 0%)	9 (39. 1%)	8 (34. 8%)	
Lymph node metastasis				0. 131
No	28 (60. 9%)	17 (73. 9%)	11 (47. 8%)	
Yes	18 (39. 1%)	6 (26. 1%)	12 (52. 2%)	
CA19-9 (U/ml)	280. 4 (84. 3, 23 56. 0)	330. 0 (73. 4, 1648. 5)	196. 0 (86. 8, 903. 5)	0. 700

Abbreviations: VER: very early recurrence; nVER: non-very early recurrence; CA19-9: carbohydrate antigen 19-9; TMB: tumor mutational burden.

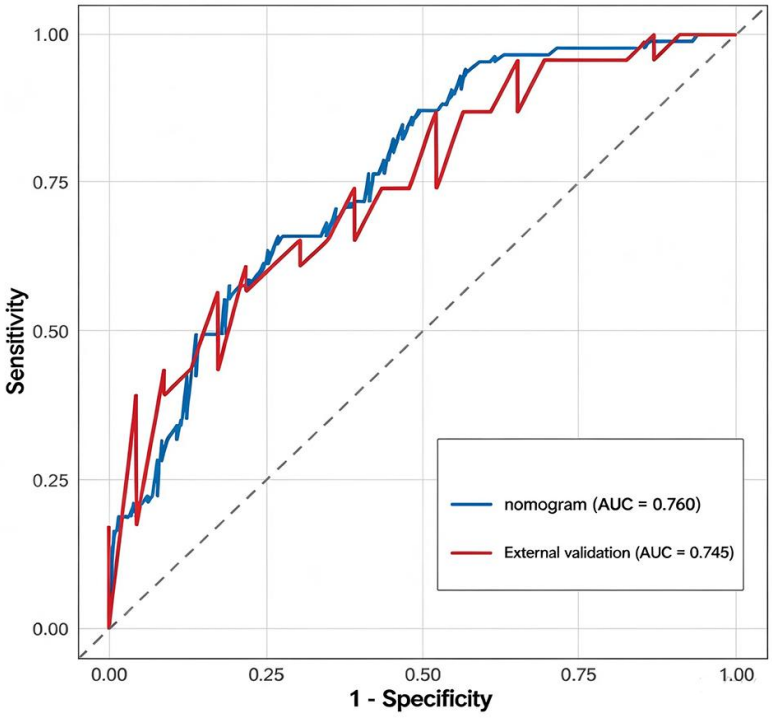

Figure 7 ROC curves of the nomogram in internal and external validation.

IV. Discussion

Intrahepatic cholangiocarcinoma (iCCA) is a common hepatobiliary malignancy with the second highest incidence among liver cancers. Patients with VER have an even worse prognosis . In this study, the VER group showed a significantly worse 2-year and 5-year survival than the nVER group (all $P < 0.001$). Multiple tumors with

iCCA has a shorter overall survival [3], and nonalcoholic fatty liver disease (NAFLD) had a lower 5-year overall survival rate and higher early recurrence rates than HBV-related disease[7],NAFLD have likewise been recognized as risk factors for overall survival, and patients with nonalcoholic fatty liver disease were more prone to early recurrence than those with hepatitis-related iCCA[8]. Both multiple tumors and fatty liver were identified as independent risk factors for 5-year survival in intrahepatic cholangiocarcinoma in this study.

Additionally, age was an independent protective factor for 5-year survival in this study, indicating that older patients had shorter survival, further studies had confirmed age as an independent prognostic factor for overall survival in iCCA patients,and a key variable for predicting survival[9].In this study,logistic regression analysis showed that age was a risk factor for VER, but not an independent risk factor in multivariate analysis, However,age was an independent risk factors for VER in intrahepatic cholangiocarcinomain ohter report[10].

It was reported that preoperative CA19-9 > 54 U/ml predicts iCCA recurrence. And Elevated CA19-9 was associated with poorer overall survival and recurrence-free survival[11].Among patients with very early iCCA, higher CA19-9 levels was correlated with a greater likelihood of lymph node metastasis, microvascular invasion, and macrovascular invasion, identifying a subgroup with worse prognosis and greater tumor invasiveness[12].

Although HBV and HCV infection were established pathogenic factors for intrahepatic cholangiocarcinoma[13], this study did not identify cirrhosis as a risk factor for VER. A meta-analysis [14] similarly found no significant association of cirrhosis, sex, or HBV infection status with early recurrence or 24-month disease-free survival, although cirrhosis was independently associated with increased risk of late intrahepatic recurrence[10]. Although lymph node metastasis independently could predict early recurrence in intrahepatic cholangiocarcinoma[14],it also was an independent risk factor for VER in this study.

Although this study did not identify tumor size as a risk factor for VER, some scholars considered tumor diameter > 5 cm as an independent risk factor for VER[15].

Radiomics showed that radiomic features related to tumor size, three-dimensional morphology, texture, and voxel intensity extracted from contrast-enhanced CT were closely associated with VER. These features provided more comprehensive three-dimensional morphological information than simple size and better reflect tumor heterogeneity through texture and voxel intensity.

This study also has several limitations: (1) key prognostic variables after iCCA liver resection—such as surgical margin, vascular invasion, degree of biliary obstruction, and liver function grading—had substantial missing data and were excluded; (2) owing to the update timeliness of the TCGA and cBioPortal databases, the cohort may be subject to selection bias; (3) all datas came from the TCGA public database, with patients predominantly of European and American Caucasian descent and very few East Asian samples, so future multicenter prospective randomized controlled trials are still needed for validation; (4) the database lacked records on neoadjuvant chemoradiotherapy, immunotherapy, targeted drug use, drug dosage, efficacy evaluation, or post-recurrence treatment, and recorded only rough survival endpoints. This precluded stratified analysis of drug interference on the prognostic value of molecular markers; only survival analysis under a no-intervention state was possible, and the findings cannot guide clinical drug stratification.

Conclusion

VER of intrahepatic cholangiocarcinoma (iCCA) had a significantly shorter cumulative 5-year survival;and viral hepatitis, lymph node metastasis, fatty liver, multiple tumors, and elevated CA19-9 were independent risk factors for VER. A nomogram constructed based on these five independent risk factors exhibited good predictive performance.

Abbreviation

iCCA	intrahepatic cholangiocarcinoma
AJCC	American Joint Committee on Cancer
TMB	Tumor Mutational Burden
OS	Overall Survival
DFS	Disease Free Survival
RFS	Recurrence-Free Survival
CSS	Cancer-Specific Survival

VER	Very early recurrence
nVER	non Very early recurrence
PSM	Propensity score matching
SMD	standardized mean difference
CA19-9	Carbohydrate Antigen 19-9
HR	Hazard Ratio
CI	Confidence Interval
OR	Odds Ratio
NAFLD	Nonalcoholic Fatty Liver Disease

Author contributions

Guohua Yang analyzed and interpreted the patient datas, designed and writing – original draft, and writing – review and editing;JianminWang and JingfengLiu:conceptualization, supervision, investigation, project administration, and writing – review and editing.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the FuJian provincal Hospital. This study was conducted in accordance with the Declaration of Helsinki, Written informed consent was obtained from each patient before receiving the start of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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