

## Research Article

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## Log Odds of Positive Lymph Nodes Predict Surgical Prognosis in Intrahepatic Cholangiocarcinoma based on Seer Cohort and Nomogram Model

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### ABSTRACT

**Background:** Intrahepatic cholangiocarcinoma (ICC) has a high postoperative recurrence rate, but quantitative assessment of lymph node metastasis (LNM) by AJCC staging remains inadequate. The log odds of positive lymph nodes (LODDS) have prognostic value in digestive system tumors, but its application in ICC has yet to be studied.

**Method:** Based on the SEER database (2010-2017), 593 ICC patients after hepatectomy or choledochotomy surgery, Cox regression was applied to analyze the association between LODDS and the risk of all-cause mortality (ACM) and cancer-specific mortality (CSM), and risk thresholds were determined by restricted cubic spline (RCS), and a nomogram predictive model was constructed based on variables screened by Boruta's algorithm. Patients were stratified by optimal nomogram cutoff, and survival was compared via Kaplan-Meier curves.

**Results:** LODDS was positively linear correlated with ACM (HR=2.062, 95% CI: 1.683, 2.527, P<0.001) and CSM (HR=2.068, 95% CI: 1.632, 2.622, P<0.001), with the optimal cutoff value of -0.63. The risk of death was increased 1.7 times in the high LODDS group (>-0.477) compared with the baseline group. The nomogram integrating variables such as LODDS, T-staging, and tumor size had a C-index of 0.711, which had a good predictive performance. Survival differences were statistically significant for both LODDS-based stratification and nomogram-based risk groups.

**Conclusion:** LODDS is an independent prognostic factor for post-operative ICC survival, enabling optimized risk stratification and personalized follow-up strategies.

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### Introduction

Intrahepatic cholangiocarcinoma (ICC) has been an essential malignant hepatic tumor arising from the intrahepatic ducts, and is the 2nd most universal essential malignant hepatic tumor only to hepatocellular carcinoma (HCC). In the past few years, the rate of its incidence and mortality has been on the rise globally [1]. Due to significant differences in biological characteristics from HCC and extrahepatic cholangiocarcinoma, it grows rapidly and is more aggressive [2]. The only curative treatment is surgical resection; unfortunately, the median survival time of ICC patients after resection surgery is usually from 25 to 40 months. Moreover, the risk of recurrence after resection surgery is high; as many as 50% to 80% of patients would recur within 2 years, resulting in poor

prognosis [3]. These alarming data highlight the needs to improve the risk stratification evaluation of patients postoperatively and to emphasize the follow-up and therapy of patients in high-risk stratification to improve prognosis.

Lymph node metastasis (LNM) is the main determinative factor of recurrence and prognosis in the ICC [4]. The eighth version of the AJCC staging system suggests that not less than 6 lymph nodes should be dissected in patients with ICC so as to obtain accurate N staging [5]. However, the AJCC staging of ICC did not adequately consider the quantity of LNM, and only depicts the status of the lymph node as lymph node-negative (N0) and lymph node-positive (N1), which is unable to quantitatively stratify the postoperative risk. In contrast, the quantity of metastatic lymph nodes (MLNS) was further subdivided to N1 (1 to 3 lymph node metastases) and N2 ( $\geq 4$  lymph node metastases) in gallbladder cancer, hilar or distal cholangiocarcinoma [6, 7].

LNM evaluation not only reflects the tumor's aggressiveness, but also influences the therapeutic decision and postoperative prognosis. In the past few years, as a new lymph node evaluation indicator, log odds of positive lymph nodes (LODDS) gradually attracted attention. LODDS is considered as the log ratio of the quantity of positive lymph nodes to the quantity of lymph nodes sent for inspection. By including the ratio of the quantity of metastatic lymph nodes to non-metastatic lymph nodes, it was able to comprehensively consider dissection scope and metastatic burden of the lymph node, overcoming limitations of traditional lymph node indicators [8].

LODDS has been presented to have stronger prognostic predictive capability in an array of digestive tract tumors like gastric, colorectal, gallbladder and pancreatic cancers [9, 10], but studies on its application to ICC have been limited. As a broadly coverage, information-rich tumor registry database, SEER (Surveillance, Epidemiology, and End Results) database covers over 28% of the U.S. population, provides the possibility to perform large-scale, population-based researches [11]. Therefore, investigating the correlation between LODDS and postoperative prognosis of ICC patients on the basis of the SEER database not only helps to further validate the predictive value of LODDS, but also may provide new perspectives on postoperative risk stratification and individualized therapy of ICC patients.

## Methods

### Study Population

SEER\*Stat 8.4.4 version software was adopted to obtain data in the SEER database for patients with ICC who underwent surgery. The database chose for the study was "Incidence-SEER research data, 17 Registries Nov. 2023 Sub (2000-2021)" from the SEER\*Stat database released in April 2023. Patients who satisfied the following standards were incorporated: ICC patients were incorporated based on histology and site coding, and identified through International Classification of Diseases in Oncology, Third Version (ICD-O-3) coding C22.0 (liver) and morphological codes 8160 and 8161 or (ICD-O-3) code C22.1 (intrahepatic duct) and morphological codes 8032, 8033, 8070, 8071, 8140, 8141, 8160, 8161, 8260, 8480, 8481, 8490 and 8560 [12]. A total of 9173 patients with ICC were diagnosed from 2010 to 2017. Exclusion standards included: (1) patients who did not receive resection surgery or whose surgery status was unknown with RX Summ--Surg Prim Site coding 00,10,99; (2) missing information on the quantity of lymph nodes sent for inspection; (3) unknown marital status; (4) unknown racial information; (5) unknown Grade Recode; (6) missing information on 7th AJCC staging or unknown T--staging or missing; (7) radiotherapy information was recommended or unknown if administered; (8) missing tumor size information. Figure S1 summarizes the detailed procedure of case selection and incorporation and exclusion. The local ethics committee has exempted ethical review because the SEER database is available in public and the data has been desensitized.

### Variable Collection

Clinical variables were obtained for each patient, involving year of diagnosis, age, gender, marital status, race, tumor size, tumor grading, surgical status at diagnosis, American Joint Committee on Cancer (AJCC) 7th version TNM staging, hepatic fibrosis score, number of survival months, reason of death, chemotherapy status, radiotherapy status, quantity of examined lymph nodes (ELN) and quantity of positive lymph nodes (PLN). The 7th version of the AJCC tumor staging system applicable to patients from 2010 to 2017 was converted into the 8th version on the basis of tumor features [13, 14]. Tumor dimension was divided to

two groups: up to 5 cm in diameter and more than 5 cm. Tumor grading was divided into 3 groups: high differentiation, moderate differentiation, poor differentiation and undifferentiated. Surgical procedures were divided into 3 groups: hepatic wedge resection and segmental resection, hepatic lobectomy, and hepatectomy or choledochotomy. Hepatic fibrosis score was divided as: Unknown, Ishak 0-4, and Ishak 5-6. The chemotherapy and radiotherapy were classified according to whether to receive the therapy. Overall survival (OS) was defined as the period from diagnosis until death or the last follow-up, whereas cancer-specific survival (CSS) excluded deaths from other causes.

The LODDS index was calculated by using the following formula:  $LODDS = \log [(PLN + 0.5)/(ELN - PLN + 0.5)]$  [15]. Based on the LODDS distribution among postoperative ICC patients, the cohort was stratified into low, medium, and high groups according to interquartile cutoff values of -0.845 and -0.477.

### Statistical Analysis

Continuous variables were depicted through mean (standard deviation (SD)) or median (interquartile range (IQR)), and between-group comparison was performed by the t-test or Mann-Whitney U-test according to the data's properties. Classified variables were expressed as frequencies and percentages (%), and between-group comparison was performed by the Fisher exact test or the Pearson chi-square test. Adopt Kaplan-Meier to compare the survival status of patients with diverse levels of LODDS.

Cox proportional hazard models were adopted to compute hazard ratios (HRs) and 95% confidence intervals (CIs) of the LODDS index and the incidence of cancer-specific mortality (CSM) and all-cause mortality (ACM) in different groups, adjusting many variables. Model 1 was unadjusted. Model 2 adjusted for age, gender, marital status, and race. Model 3 further included tumor grade, T and M staging, surgical procedures, presence of radiotherapy or chemotherapy, hepatic fibrosis score, and tumor size. The LODDS index was analyzed both as a continuous and classified variable, with the lowest tertile group serving as the reference in all models.

In addition, restricted cubic spline plots (RCS) was adopted to research the potential nonlinear correlation between the LODDS index and CSM and ACM. Cutoff points were calculated for risk division.

Subgroup analysis was performed to explore uniformity of the prognostic value of the LODDS index in diverse subgroups, as well as interactions between variables. These subgroups were divided based on sex (female and male), age (<65 and ≥ 65 years), marital status (married and unmarried), race (white persons and others), tumor grading (high differentiation, moderate differentiation, poor differentiation and undifferentiated), T staging (T0-T1, T2 and T3-T4), surgical procedures (hepatic wedge resection and segmental resection, hepatic lobectomy, hepatectomy or choledochotomy), radiotherapy and chemotherapy status (yes and no), and tumor size (≤50 mm and >50 mm). Each subgroup was analyzed by COX regression model, and the outcomes were presented in forestplot forms revealing HR values and 95% CIs. Adopt likelihood ratio tests to assess the correlation between the LODDS index and the variables applied for stratification.

### Predictive Model Construction and Validation

In order to verify crucial variables, we used the Boruta algorithm for feature variable selection, which compares the Z-score of each real variable to that of shadow features. Variables with significantly

higher Z-scores than the maximum shadow Z-score were deemed important and selected for model development [16].

Based on the screening results of Boruta’s algorithm, the “survival” (survival analysis), “foreign” (data processing related), and “rms” (regression modeling and statistical analysis) software packages in the R language were used to construct a nomogram for predicting OS of patients. Then, the “survminer” (survival data visualization and optimal cutpoint determination) package was applied to determine the optimal cutoff value for stratifying patients into high- and low-risk groups based on nomogram scores, followed by survival analysis using Kaplan-Meier curves.

The predictive ability of the nomogram was assessed through the consistency index (C-index), time-dependent receiver operating characterization curve (tdROC) as well as area under curve (AUC value). The calibration curve was adopted to evaluate the precision and discrimination ability of the nomogram, then decision curve analysis (DCA) was constructed to show the clinical advantage of the nomogram.

All statistical analyses were performed in R software (4.4.2 edition). Two-tailed p-values smaller than 0.05 were seen as statistically significant.

## Results

### Cohort Characteristics

593 patients were incorporated in the study totally (all with histology coding: 8160/3: Cholangiocarcinoma, and all with primary site coding C22.1 (intrahepatic ducts)), as shown in Figure S1. In the study population of ICC patients, 279 patients were male and 314 patients were female. ICC patients were divided to three separate groups rooted in LODDS triplicate (L1: LODDS < -0.845, L2: LODDS -0.845 to -0.477, and L3: LODDS > -0.477). Baseline characteristics were described according to LODDS triplicate (Table 1). The results showed that the incidence of CSM and ACM occurred in 33.9% and 44.0% of patients with low LODDS (L1), 38.5% and 55.4% of patients with moderate LODDS (L2), and 52.0% and 68.6% of patients with high LODDS (L3), respectively.

Patients with higher levels of LODDS were more likely to have more advanced AJCC staging ( $p < 0.001$ ), LNM N staging ( $p < 0.001$ ), higher T staging ( $p = 0.001$ ), shorter survival times ( $p < 0.001$ ), higher CSM, and lower overall survival ( $p < 0.001$ ).

**Table 1: Baseline Characteristics of Patients with ICC Who Received Surgery**

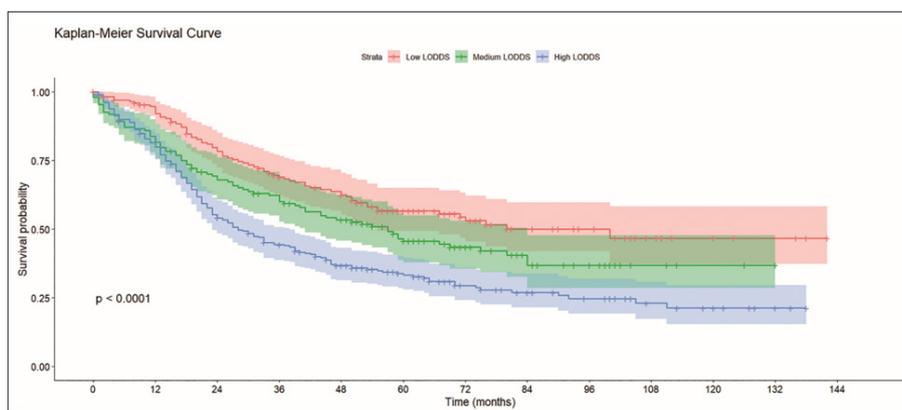
Variables	Overall	L1	L2	L3	P value
<b>N</b>	<b>593</b>	<b>168</b>	<b>148</b>	<b>277</b>	
Age	64.00 [56.00, 71.00]	65.00 [58.00, 72.50]	65.00 [54.00, 72.25]	63.00 [57.00, 71.00]	0.597
Sex					0.036
Male	279 (47.0)	65 (38.7)	73 (49.3)	141 (50.9)	
Female	314 (53.0)	103 (61.3)	75 (50.7)	136 (49.1)	
Marital status (%)					0.35
Married	381 (64.2)	103 (61.3)	102 (68.9)	176 (63.5)	
Unmarried	212 (35.8)	65 (38.7)	46 (31.1)	101 (36.5)	
Race (%)					0.282
White	472 (79.6)	134 (79.8)	124 (83.8)	214 (77.3)	
Others	121 (20.4)	34 (20.2)	24 (16.2)	63 (22.7)	
Diferentiation (Grade (%))					0.562
Well differentiated	68 (11.5)	20 (11.9)	21 (14.2)	27 (9.7)	
Moderately differentiated	329 (55.5)	96 (57.1)	82 (55.4)	151 (54.5)	
Poorly differentiated&Undifferentiated	196 (33.1)	52 (31.0)	45 (30.4)	99 (35.7)	
AJCC_stage (%)					<0.001
I	170 (28.7)	70 (41.7)	50 (33.8)	50 (18.1)	
II	131 (22.1)	53 (31.5)	38 (25.7)	40 (14.4)	
III	39 (6.6)	10 (6.0)	15 (10.1)	14 (5.1)	
IVA/IVB	253 (42.7)	35 (20.8)	45 (30.4)	173 (62.5)	
T_stage (%)					0.001
T0-T1	208 (35.1)	75 (44.6)	60 (40.5)	73 (26.4)	
T2	242 (40.8)	61 (36.3)	53 (35.8)	128 (46.2)	
T3-T4	143 (24.1)	32 (19.0)	35 (23.6)	76 (27.4)	
N_stage (%)					
M0	566 (95.4)	162 (96.4)	145 (98.0)	259 (93.5)	
M1	27 (4.6)	6 (3.6)	3 (2.0)	18 (6.5)	
Surgery (%)					0.973

Wedge or segmental resection	153 (25.8)	43 (25.6)	36 (24.3)	74 (26.7)	
Lobectomy	306 (51.6)	85 (50.6)	79 (53.4)	142 (51.3)	
Hepatectomy or bile duct resection	134 (22.6)	40 (23.8)	33 (22.3)	61 (22.0)	
Radiation (%)					0.144
None	515 (86.8)	152 (90.5)	130 (87.8)	233 (84.1)	
Yes	78 (13.2)	16 (9.5)	18 (12.2)	44 (15.9)	
Chemotherapy (%)					0.063
None	282 (47.6)	90 (53.6)	74 (50.0)	118 (42.6)	
Yes	311 (52.4)	78 (46.4)	74 (50.0)	159 (57.4)	
Fibrosis_score (%)					0.266
Unknown	459 (77.4)	131 (78.0)	110 (74.3)	218 (78.7)	
Ishak 0-4	108 (18.2)	34 (20.2)	29 (19.6)	45 (16.2)	
Ishak 5-6	26 (4.4)	3 (1.8)	9 (6.1)	14 (5.1)	
Tumor_size	54.00 [33.00, 80.00]	45.00 [29.75, 77.50]	55.50 [35.00, 77.00]	55.00 [35.00, 85.00]	0.106
Survival_months	39.00 [17.00, 65.00]	50.50 [24.00, 72.25]	44.50 [17.00, 70.25]	27.00 [14.00, 55.00]	<0.001
CSS (%)					<0.001
Alive	247 (41.7)	94 (56.0)	66 (44.6)	87 (31.4)	
Dead (attributable to ICC)	258 (43.5)	57 (33.9)	57 (38.5)	144 (52.0)	
Dead of other cause	88 (14.8)	17 (10.1)	25 (16.9)	46 (16.6)	
OS (%)					<0.001
Survival	247 (41.7)	94 (56.0)	66 (44.6)	87 (31.4)	
Death	346 (58.3)	74 (44.0)	82 (55.4)	190 (68.6)	

### K-M Curve and Cox Regression Analysis

LODDS was correlated with survival rate in ICC patients. Analysis of the K-M survival curves showed that the high LODDS (L3) group had lower overall survival rates (log-rank  $P < 0.001$ ) than the moderate and low level of LODDS groups, as shown in Figure 1. The influence of LODDS on outcome indicators was evaluated by using multifactor COX regression model, adjusting covariates. The results are shown in Table 2. (Model 1: Unadjusted. Model 2: Adjusted for age, gender, marital status and race. Model 3: Adjusted for age, gender, marital status, race, tumor grading, T and M staging, surgical procedures, presence of radiotherapy or chemotherapy, hepatic fibrosis score, and tumor size). In all models, L1 served as the reference group.

The results showed that when LODDS was used as continuous variable, in the Model 1 (HR = 2.444, 95% CI: 2.203, 2.952,  $P < 0.001$ ), Model 2 (HR = 2.443, 95% CI: 2.018, 2.958,  $P < 0.001$ ), and Model 3 (HR = 2.062, 95% CI: 1.683, 2.527,  $P < 0.001$ ), high LODDS patients had a obviously higher risk of ACM. When LODDS was used as classified variable, in the Model 1 (L2: HR = 1.398, 95% CI: 1.021, 1.914,  $P < 0.05$ ; L3: HR = 2.056, 95% CI: 1.570, 2.691,  $P < 0.001$ ), Model 2 (L2: HR = 1.390, 95% CI: 1.014, 1.905,  $P < 0.05$ ; L3: HR = 2.020, 95% CI: 1.514, 2.684,  $P < 0.001$ ), and Model 3 (L2: HR = 1.372, 95% CI: 0.997, 1.887,  $P = 0.052$ ; L3: HR = 1.737, 95% CI: 1.318, 2.287,  $P < 0.001$ ), patients in the L3 group had an obviously increased risk of ACM compared to those in the L1 group. For L2 group, no significant difference was observed in Model 3. The result of the trend test ( $P$  for trend  $< 0.001$ ) indicated that the risk of ACM in patients increased with each increasing grade of LODDS.



**Figure 1:** Kaplan-Meier Survival Curves for Patients with ICC based on LODDS Groups. (LODDS tertile L1: LODDS  $< -0.845$ , L2:  $-0.845$  to  $-0.477$ , L3: LODDS  $> -0.477$ ). ICC, Intrahepatic Cholangiocarcinoma; LODDS, The Log Odds of Positive Lymph Nodes. x-Axis: Survival Time (Months). y-Axis: Survival Probability.

**Table 2: Multivariable cox Regression Models Evaluating the Association between LODDS and OS and CSS**

Variables	Model 1		Model 2		Model 3	P value
OS						
LODDS continuous	2.444 (2.023,2.952)	< 0.001	2.443 (2.018, 2.958)	< 0.001	2.062 (1.683,2.527)	< 0.001
LODDS grouped	P for trend: < 0.001		P for trend: < 0.001		P for trend: < 0.001	
T1	—		—		—	
T2	1.398 (1.021,1.914)	0.037	1.390 (1.014,1.905)	0.04	1.372 (0.997,1.887)	0.052
T3	2.056 (1.570,2.691)	< 0.001	2.020 (1.541,2.648)	< 0.001	1.737 (1.318,2.287)	< 0.001
CSS						
LODDS continuous	2.480 (1.991,3.088)	< 0.001	2.457 (1.969,3.066)	< 0.001	2.068 (1.632,2.622)	< 0.001
LODDS grouped	P for trend: < 0.001		P for trend: < 0.001		P for trend: < 0.001	
T1	—		—		—	
T2	1.262 (0.874,1.821)	0.215	1.246 (0.863,1.800)	0.241	1.197 (0.825,1.737)	0.344
T3	2.036 (1.497,2.769)	< 0.001	1.993 (1.463,2.716)	< 0.001	1.669 (1.217,2.287)	0.001

**Model 1:** unadjusted

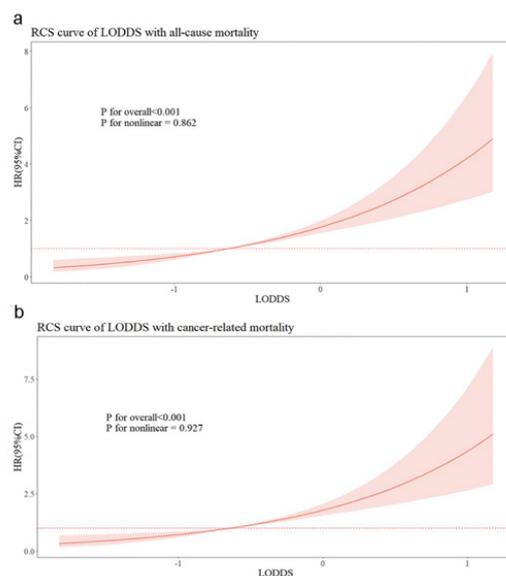
**Model 2:** adjusted for Age, Sex, Marital status, Race

**Model 3:** adjusted for Age, Sex, Marital status, Race, Grade, T\_stage, M\_stage, Surgery, Radiation, Chemotherapy, Fibrosis\_score, Tumor\_size\_grp

Additionally, we analyzed the influence of LODDS on CSM outcomes by using multifactor COX regression methods and obtained similar results (Table 2). When LODDS was used as continuous variable, CSM was obviously higher in patients with high LODDS. While LODDS was used as classified variable, CSM was obviously elevated in patients in the L3 group compared to the L1 group. For patients with L2, no significant difference was noted in Model 2 and Model 3. The result of the trend test (P for trend < 0.001) indicated that the risk of CSM in patients increased with each increasing grade of LODDS.

**Curve Fitting Analysis**

Smooth curves for the LODDS and the risk of ACM and CSM in ICC patients were constructed by using restricted cubic spline model (RCS) (Figure 2(a) and (b)). LODDS showed approximately linear relationships with the risk of ACM and CSM (OS: P for nonlinear=0.862; CSS: P for nonlinear=0.927). When LODDS>-0.63, HR value>1, the risk of ACM and CSM in ICC patients both linearly increased significantly with increasing LODDS levels.

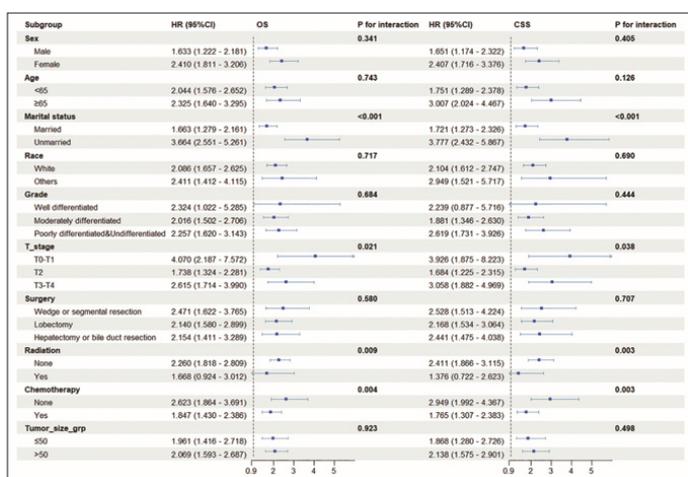


**Figure 2: RCS Curve of LODDS with Mortality. (a) RCS Curve of LODDS with all-Cause Mortality. (b) RCS Curve of LODDS with Cancer-Related Mortality. RCS, Restricted Cubic Spline; LODDS, The Log Odds of Positive Lymph Nodes**

### Subgroup Analysis

In addition, we performed the risk stratification analysis of the LODDS index for the primary endpoints in multiple subgroups based on characteristics such as gender, age, marital status, race, tumor grading, T staging, surgical procedures, presence of radiotherapy or chemotherapy and tumor size. Subgroup analysis confirmed LODDS's significant prognostic value across most clinical subgroups (Figure 3), showing consistent positive correlations with ACM/CSM risk ( $P < 0.05$ ) without significant interactions.

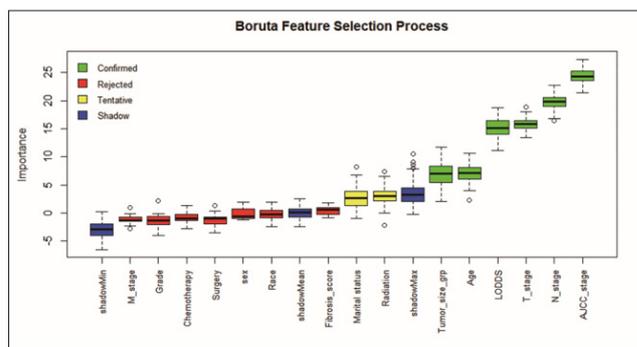
In contrast, significant interactions existed between marital status and the impact of LODDS on the risk of ACM/CSM ( $P$  for interaction  $< 0.001$ ). Unmarried patients had a significantly higher mortality risk than married patients (OS: HR = 3.664 vs 1.663; CSS: HR = 3.777 vs 1.721). T staging also showed significant interactions with LODDS (OS interaction  $P = 0.021$ ; CSS interaction  $P = 0.038$ ): T0-T1 stage patients exhibited the highest HRs (OS: HR = 4.070, 95% CI: 2.187–7.572; CSS: HR = 3.926, 95% CI: 1.875–8.223). T3-T4 stage patients had a significantly increased risk compared to T2 stage (OS: HR = 2.615 vs 1.738; CSS: HR = 3.058 vs 1.684). Both radiotherapy (OS:  $P=0.009$ , CSS:  $P=0.003$ ) and chemotherapy (OS:  $P=0.004$ , CSS:  $P=0.003$ ) showed significant interactions.



**Figure 3:** Forest Plots of HR for the OS and CSS in Different Subgroups. HR, Hazard Ratios; OS, Overall Survival; CSS, Cancer Specific Survival

### Boruta Algorithm Boruta

The Boruta algorithm was used in our study cohort for feature screening of overall survival prediction (Figure 4). In the Boruta algorithm, green features were identified as important, red as unimportant, and excluded. Z-score importance was calculated over 100 random forest iterations, with boxplots showing the distribution. Green indicates "Confirmed", red "Rejected", yellow "Tentative", and blue "Shadow". Six variables, namely tumor size, age, LODDS, T-stage, N-stage, and AJCC stage were confirmed to be significantly correlated with survival. Marital status and radiotherapy were tentative, while others (e.g., M-stage, grade, chemotherapy, surgery, gender, race, fibrosis score) were excluded.

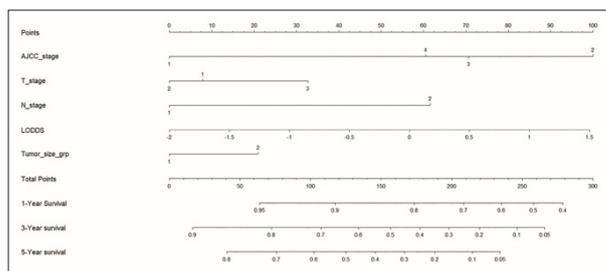


**Figure 4:** Feature Selection Based on Boruta Algorithm. The Horizontal Axis Shows the Name of Clinical Variables, and the vertical axis represents the Z-Score for Each Variable. The Box Plot Illustrates the Z-score Distribution of Each Variable During Model Computation. Green Boxes Represent Important Variables Identified by the Model (N=6), While Red Boxes Indicate Unimportant Variables (N=7). Blue Box Represents the Significance of the Minimum, Average, and Maximum Shadow Features, Respectively, Namely the Magnitude of the Z-Score

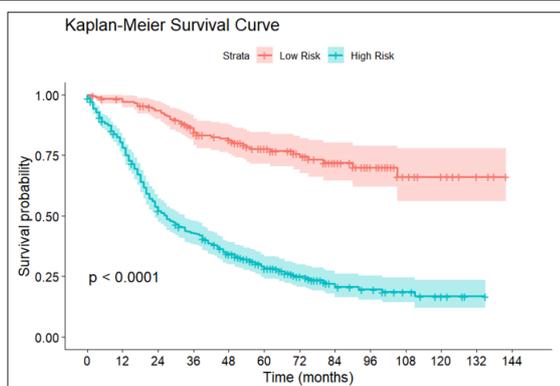
### Construction and Validation of the Nomogram

Based on the Boruta algorithm for screening clinical variables, we constructed the nomogram model to predict overall survival rate in ICC (Figure 5). Each predictor corresponded to the corresponding score on the scale, and the scores of all indicators were summed up to obtain the total score, which corresponded to the predictive possibility of the patient's overall survival rate at 1 year, 3 years and 5 years. The total score was higher, the predictive value of the patient's survival rate at 1 year, 3 years and 5 years was smaller. The Kaplan-Meier survival curve shows a significant difference in overall survival between high- and low-risk groups, which were stratified using the nomogram score cutoff value of 108.34 ( $p < 0.0001$ ); patients in the low-risk group had better survival outcomes (Figure 6).

The rectification curve (Figure S2) showed a high level of consistence between predictive and observation possibilities, denoting obvious reliability of the prognostic nomogram. The decisive curve DCA (Figure S3) indicated that the model's net profit was higher than the net benefit of both the full intervention curve and the non-intervention curve across a wide range of thresholds (0.2-0.8), suggesting that the model possessed a high predictive value. The predictive model performance was assessed through the AUC value and C-index. The ROC curve (Figure S4) revealed that the AUC values of the nomogram for the 1, 3 and 5-year groups were 0.760, 0.774 and 0.784, respectively, and C-index was 0.711. The combination of these indicators confirmed that LODDS has higher prediction value for patients' long-term prognosis, highlighting that it is reliable in clinical practice and can be used as a valuable predictive tool.



**Figure 5:** Nomogram Predictive Model for OS of Postoperative Patients with ICC. OS, Overall Survival; ICC, Intrahepatic Cholangiocarcinoma



**Figure 6:** Kaplan-Meier Survival Curves for Patients with ICC based on Nomogram Score Cutoff Value. ICC, Intrahepatic Cholangiocarcinoma

### Discussion

The research indicated a significant linear increasing relationship of LODDS with the risk of ACM and CSM in ICC patients. By using the curve-fitting technique, the reference point for the LODDS was determined as  $-0.63$ , which can be used for risk stratification.

LNM is a strong predictor of poor prognosis in resected cholangiocarcinoma. A multicenter study found that fewer than half of ICC patients undergoing liver resection received lymph node dissection, with 43% of those showing LNM positive in the presence of distant metastasis [17]. Therefore, forecasting the survival of ICC patients on the basis of the patients' LNM status for risk stratification has become an important clinical practice. Among the clinical prediction models, nomograms offer a practical tool for integrating multiple prognostic factors [18]. In studies of nomograms for ICC, it has been shown that tumor markers, lymph node invasion and distant metastasis, microvascular invasion, and perineural invasion are correlated with prognosis [19]. For predicting postoperative prognosis in ICC, previous studies have shown that both LODDS and the lymph node ratio ( $LNR = \text{metastatic lymph nodes}/\text{total dissected lymph nodes}$ ) outperform the current AJCC staging system in patients undergoing curative resection. LODDS demonstrated a slight advantage over LNR, particularly in cases with very low or high LNR values. Since LNR can be influenced by the total number of positive lymph nodes, LODDS is considered a more reliable staging method, especially in patients with few positive nodes [20]. Chen Herong et al demonstrated that LNR classification is an independent predictor of CSS in ICC patients, and the corresponding nomogram serves as a valid prognostic tool [21]. Restaging the quantity of metastatic lymph nodes was also performed in previous research, and subdividing N-staging based on the number has yielded meaningful results in prognostic risk stratification [22]. However, only about half of ICC patients on surgery resection and lymph node dissection received standard lymph node dissection, making it hard to maximize the accuracy of staging [23].

Therefore, in this study, the LODDS was incorporated into the predictive model of postoperative ICC. The LODDS indicator is easily accessible to most patients with ICC who have undergone surgery. Quantitatively, the lymph node evaluation indicator was transformed into continuous variable, which transformed the traditional AJCC N-staging dichotomy into continuous risk stratification, making the postoperative risk evaluation more accurate. Then, LODDS was integrated into the

nomogram optimized by machine learning algorithm, which was methodologically superior to the traditional nomogram model. The model achieved superior predictive performance ( $C\text{-index} = 0.711$ ), with a higher predictive performance than that of using LODDS alone for evaluating the prognosis in previous research ( $C\text{-index} = 0.626$ ) [20]. Distant metastasis is considered a risk factor for a poor prognosis in malignant tumors, accounting for approximately 90% of cancer-related deaths [24]. Distant metastasis (M1) typically contraindicates surgery in ICC, resulting in a small cohort of 16 M1 cases. This sample size was statistically inadequate for M-stage validation; consequently, M-stage metrics were excluded from the final model. In addition, significant interaction effect of LODDS with marital status was found in subgroup analysis (interaction  $P\text{-value} < 0.001$ ), introducing new social support and psychological dimensions for ICC prognostic evaluation. The significantly higher risk of death in unmarried patients ( $HR = 3.664$  vs  $1.663$ ) indicates that psychological factors of social support may modulate the biological impact of malignant tumors which may be explained by emotional burden and social support [25].

Further, T-staging also showed a significant interaction effect with LODDS. Interestingly, HR values were higher in both early (T0-T1) stage and advanced (T3-T4) stages than in T2 stage, and were highest in patients with early (T0-T1) stage. In early-stage ICC, a high LODDS (indicating a risk of LNM) exerts a “multiplier effect” on low baseline mortality, increasing the HR and reflecting greater tumor invasiveness. For advanced stages, competing factors (such as vascular invasion and hepatic decompensation) diminish the incremental value of nodal status, reducing the impact on the HR. Compared to the T2 stage, the HR increases in advanced stages, likely because a higher LODDS indicates more extensive regional metastasis or a greater lymphatic burden. Therefore, adjuvant therapy decisions in early T-staging patients critically depend on LODDS stratification. If postoperative LODDS is high in early T-staging patients with ICC, stronger adjuvant therapy may be added clinically. Furthermore, the prognostic power of LODDS diminishes due to the treatment-induced suppression of biology driven by LNM (local control, eradication of micrometastasis, immunomodulation), which occurs as a result of radiotherapy and chemotherapy [26]. In summary, LODDS guides postoperative stratification and personalized follow-up [27].

The main findings of this study provide an important clinical implications for the postoperative management of ICC patients. First, the LODDS, as continuous lymph node evaluation indicator, breaks through the dichotomous limitation of N-staging in traditional AJCC staging and is able to quantify the biological burden of LNM more accurately. For cases with inadequate lymph node dissection (e.g.,  $< 6$  lymph nodes sent for inspection), LODDS can reduce the risk of stage migration by incorporating negative lymph node information and provide a more reliable basis for prognostic evaluation. Second, the nomogram constructed based on LODDS, which is superior to the traditional N-staging and the prognosis prediction by using LNR and LODDS alone [20]. It can assist clinicians to quickly verify high-risk patients and develop individualized follow-up protocols, such as shortening the imaging review interval for high-risk patients. It provides references for adjuvant therapy strategies, such as strengthening postoperative adjuvant therapy for patients with high LODDS.

However, we are also aware of certain limitations of the study. First, the SEER database was short of several key clinical data, for example, specific radiotherapy and chemotherapy protocols, surgical margin status, microvascular invasion status and molecular markers (e.g., IDH1/2 mutation, FGFR2 fusion, etc.),

which may miss important prognostic factors [28]. Second, the study was retrospective, and selection bias could not be evaded on account of the need for calculation of LODDS indicators, and the incorporated cases were all those who underwent surgery. In addition, although the nomogram was internally validated by the SEER database, the universality of the model needs to be further validated by multicenter prospective studies. These aspects will be key areas of focus that need to be improved for future studies.

### Conclusion

In the study, on the basis of large sample data from the SEER database, we established a linear positive correlation between LODDS and ACM/CSM mortality risk in ICC, with significantly increased death risk at LODDS > -0.63. The Boruta-derived nomogram integrating LODDS and other variables demonstrated robust predictability. Despite the limitations of the retrospective study, this study is the first to incorporate the LODDS in the construction of a clinical predictive model for ICC patients after surgery, providing a quantitative basis for adjuvant therapy and follow-up optimization. In the future, it will remain necessary to validate the universality of the model through multicenter prospective studies and explore the correlation of the LODDS with emerging targeted therapy and immunotherapy to promote individualized treatment systems.

### Statements & Declarations

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### Competing Interests

The authors have no conflict of interest to declare.

### Author Contributions

**Guoxia Jia:** Conceptualization, Methodology, Software.

**Shaochong Deng:** Data curation.

**Fan Luo:** Visualization, Investigation.

**Jianfu Zhao and Huizhong Wang:** Supervision.

**Jiabin Yin:** Software, Validation.

**Shan Li:** Writing- Reviewing and Editing, Writing- Original draft preparation. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### Data Availability Statement

The datasets generated and analysed during the current study are available in the SEER database repository, [<https://seer.cancer.gov>].

### Ethics Approval

Not applicable

### Consent to Participate

Not applicable

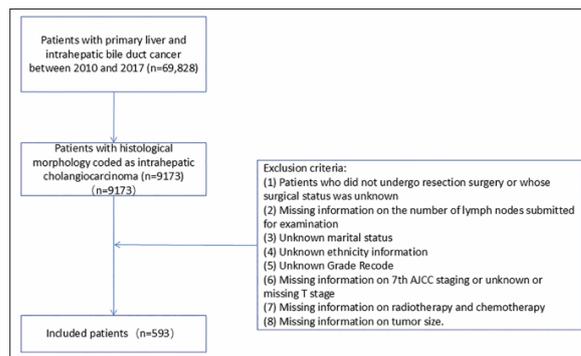
### Consent to Publication

Not applicable

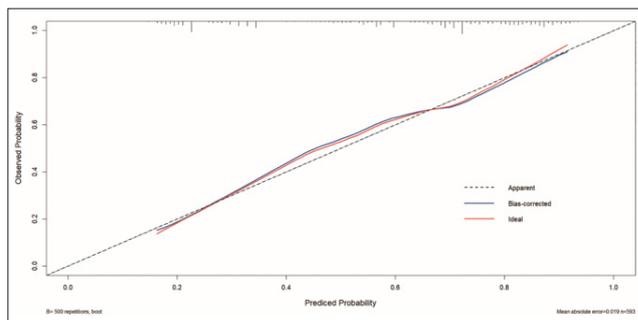
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Not applicable

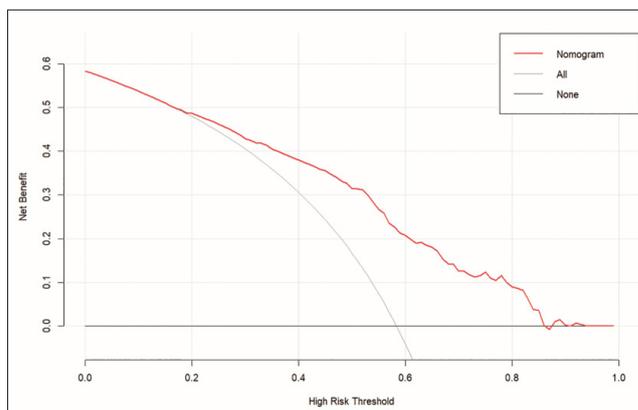
### Supplementary Documents



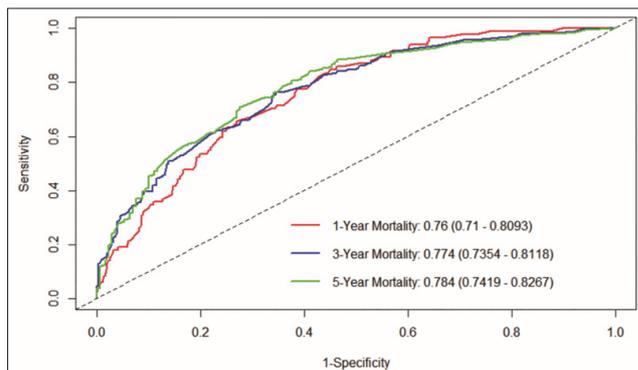
**Figure S1:** The Selection Process of Patients with ICC from the SEER Database. ICC, Intrahepatic Cholangiocarcinoma; SEER, Surveillance, Epidemiology, and End Results.



**Figure S2:** Calibration Curves of the Nomogram



**Figure S3:** Decision Curves of the Nomogram



**Figure S4:** ROC Curves of Nomogram for 1-Year Mortality, 3-Year Mortality, and 5-Year Mortality. ROC, Receiver Operating Characteristic

## References

- Huang T-F, Luo C, Guo L-B, Liu H-Z, Li J-T, et al. (2025) Preoperative prediction of textbook outcome in intrahepatic cholangiocarcinoma by interpretable machine learning: A multicenter cohort study. *World Journal of Gastroenterology* 31: 11.
- Vogel A, Bridgewater J, Edeline J, Kelley RK, Klumpen HJ, et al. (2023) Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 34: 127-140.
- Kawashima J, Akabane M, Khalil M, Woldesenbet S, Endo Y, et al. (2025) Tumour burden predicts outcomes after curative resection of multifocal intrahepatic cholangiocarcinoma. *British Journal of Surgery* 112 <https://academic.oup.com/bjs/article-abstract/112/4/znaf050/8100338?redirectedFrom=fulltext>.
- Li Z, Ma L, Chen M, Chen X, Sha M, et al. (2025) Single-cell analyses reveal metastasis mechanism and microenvironment remodeling of lymph node in intrahepatic cholangiocarcinoma. *JHEP Rep* 7: 1-16.
- Chun YS, Pawlik TM, Vauthey J-N (2017) 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. *Annals of Surgical Oncology* 25: 845-847.
- Liao S, Liao R, Wu H, Wang S, Zhou Y (2023) Proposal for a new N-stage classification system for intrahepatic cholangiocarcinoma. *Frontiers in Oncology* 13: 1-9.
- Kattan MW, Hess KR, Amin MB, Lu Y, Moons KG, et al. (2016) American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin* 66: 370-374.
- Chen C, Xia H-B, Yuan W-W, Zhou M-C, Zhang X, et al. (2025) Developing a novel model for predicting overall survival in late-onset colon adenocarcinoma patients based on LODDS: a study based on the SEER database and external validation. *Discover Oncology* 16: 99.
- Catalano G, Alaimo L, Chatzipanagiotou OP, Ruzzenente A, Aucejo F, et al. (2024) Advantage of Log Odds of Metastatic Lymph Nodes After Curative-Intent Resection of Gallbladder Cancer. *Annals of Surgical Oncology* 32: 1742-1751.
- Wang L, Ge J, Fang Y, Han H, Qin Y (2025) Construction and validation of a novel nomogram based on the log odds of positive lymph nodes to predict cancer-specific survival in elderly patients with gastric adenocarcinoma after radical surgery. *BMC Gastroenterology* 25: 1-12.
- Che WQ, Li YJ, Tsang CK, Wang YJ, Chen Z, et al. (2023) How to use the Surveillance, Epidemiology, and End Results (SEER) data: research design and methodology. *Mil Med Res* 10: 1-11.
- Lu S-N, Petrick JL, Yang B, Altekruse SF, Van Dyke AL, et al. (2017) Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: A population-based study in SEER-Medicare. *Plos One* 12: 1-14.
- Liu Y-G, Jiang S-T, Zhang J-W, Zhang L, Zhao H-T, et al. (2024) Development and validation of web-based nomograms for predicting survival status in patients with intrahepatic cholangiocarcinoma depending on the surgical status: a SEER database analysis. *Scientific Reports* 14: 1568.
- Lee AJ, Chun YS (2018) Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. *Chin Clin Oncol* 7: 52.
- Yu X, Bai C, Yu Y, Guo X, Wang K, et al. (2024) Construction of a novel nomogram for predicting overall survival in patients with Siewert type II AEG based on LODDS: a study based on the seer database and external validation. *Front Oncol* 14: 1396339.
- Shen Y, Lin K, Yang L, Zheng P, Zhang W, et al. (2025) Association between the lactate dehydrogenase-to-albumin ratio and 28-day mortality in septic patients with malignancies: analysis of the MIMIC-IV database. *BMC Cancer* 25: 637.
- Mazzaferro V, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G (2020) Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol* 72: 364-377.
- Hyder O, Marques H, Pulitano C, Marsh JW, Alexandrescu S, et al. (2014) A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 149: 432-438.
- Zhou SN, Jv DW, Meng XF, Zhang JJ, Liu C, et al. (2023) Feasibility of machine learning-based modeling and prediction using multiple centers data to assess intrahepatic cholangiocarcinoma outcomes. *Ann Med* 55 :215-223.
- Kim Y, Spolverato G, Amini N, Margonis GA, Gupta R, et al. (2015) Surgical Management of Intrahepatic Cholangiocarcinoma: Defining an Optimal Prognostic Lymph Node Stratification Schema. *Ann Surg Oncol* 22: 2772-2778.
- Chen X, Rong D, Zhang L, Ni C, Han G, et al. (2021) Evaluation of nodal status in intrahepatic cholangiocarcinoma: a population-based study. *Ann Transl Med* 9: 1359.
- Zhang XF, Xue F, Dong DH, Weiss M, Popescu I, et al. (2021) Number and Station of Lymph Node Metastasis After Curative-intent Resection of Intrahepatic Cholangiocarcinoma Impact Prognosis. *Ann Surg* 274: e1187-e1195.
- Sahara K, Tsilimigras DI, Merath K, Bagante F, Guglielmi A, et al. (2019) Therapeutic Index Associated with Lymphadenectomy Among Patients with Intrahepatic Cholangiocarcinoma: Which Patients Benefit the Most from Nodal Evaluation? *Ann Surg Oncol* 26: 2959-2968.
- Liu Z, Chen J, Ren Y, Liu S, Ba Y, et al. (2024) Multi-Stage mechanisms of tumor metastasis and therapeutic strategies. *Signal Transduct Target Ther* 9: 270.
- Aizer AA, Chen MH, McCarthy EP, Mendu ML, Koo S, et al. (2013) Marital status and survival in patients with cancer. *J Clin Oncol* 31: 3869-3876.
- Yu WD, Sun G, Li J, Xu J, Wang X (2019) Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. *Cancer Lett* 452 :66-70.
- Wang S, Wei J, Guo Y, Xu Q, Lv X, et al. (2022) Construction and validation of nomograms based on the log odds of positive lymph nodes to predict the prognosis of lung neuroendocrine tumors. *Front Immunol* 13: 987881.
- Kelley RK, Bridgewater J, Gores GJ, Zhu AX (2020) Systemic therapies for intrahepatic cholangiocarcinoma. *J Hepatol* 72: 353-363.

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