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Original Article

A New Prognostic Model Covering All Stages of Intrahepatic Cholangiocarcinoma

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Abstract

Background and Aims: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy that causes a poor survival. We aimed to identify its prognostic factors and to develop a nomogram that will predict survival of ICC patients among all stages. ***Methods:*** A total of 442 patients with pathology-proven ICC registered at the Fifth Medical Center of PLA General Hospital between July 2007 and December 2019 were enrolled. Subjects were followed for survival status until June 30, 2020. A prognostic model visualized as a nomogram was constructed in the training cohort using multivariate cox model, and was then validated in the validation cohort. ***Results:*** The median age was 55 years. With a median follow-up of 50.4 months, 337 patients died. The median survival was 11.6 months, with 1-, 3- and 5-year survival rates of 48.3%, 22.7% and 16.2%, respectively. Factors associated with overall survival were multiple tumors, lymph node involvement, vascular invasion, distant metastasis, decreased albumin, elevated lactate dehydrogenase (LDH), decreased iron, elevated fibrinogen, elevated CA125 and elevated CA19-9. A nomogram predicting survival of ICC patients at the time of diagnosis achieved a Harrel's c-statistic of 0.758, significantly higher than the 0.582 of the TNM stage alone. Predicted median survivals of those within the low, mid and high-risk subgroups were 35.6, 12.1 and 6.2 months, respectively. ***Conclusions:*** A nomogram based on imaging data and serum biomarkers at diagnosis showed good ability to predict survival in patients with all stages of ICC. Further studies are needed to validate the prognostic capability of our new model.

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Keywords: Intrahepatic cholangiocarcinoma; Prognostic model; Nomogram; Risk stratification.

Abbreviations: AJCC, American Joint Committee on Cancer; ALB, albumin; AUC, area under the curve; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; FDR, false discovery rate; FIB, fibrinogen; HBc, anti-hepatitis B core protein; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICC, intrahepatic cholangiocarcinoma; OS, overall survival.

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Introduction

Intrahepatic cholangiocarcinoma (ICC), a subgroup of cholangiocarcinoma, the second most common malignancy arising from the liver, originates from the peripheral bile ducts within the liver parenchyma, proximal to the secondary biliary radicals.[1] The incidence of ICC has been increasing globally.[2] Surgical treatment is the only potentially curative therapy in ICC, although many patients are not eligible for resection because of locally advanced or metastatic disease;[1] even for the eligible ones, the prognosis is unsatisfactory, with a high recurrence rate.[3] The 5-year overall survival rate is reportedly less than 5%[4] and the 5-year survival after resection has been reported in the range of 22–44%.[5] As such, an upfront comprehensive assessment of the prognosis is essential for the clinical decision of multidisciplinary treatment.

Unlike hepatocellular carcinoma, there is no internationally recommended staging-guided roadmap for the treatment of ICC. The American Joint Committee on Cancer (AJCC) TNM staging system is widely used, but it performs relatively poorly in differentiating between patients with various prognoses, with substantial inter-patient differences in the survival even among those within the same TNM stages.[6,7] In addition to the AJCC system, several prognostic models or nomograms have been developed[7–17] and additional prognostic factors have been reported to predict

overall survival of ICC patients, such as levels of C-reactive protein,[13] hepatoma-derived growth factor,[18] DNA index,[19] and Homer1.[20]

Most of the published prognostic nomograms for ICC were established based on the patients undergoing surgical resection.[7–16] The resulting models rely on the parameters from surgical and pathological reports to predict the outcome post-hepatic resection, thus limiting the use of the models in the majority of patients who are non-surgical candidates.[7–16] Given the lack of an ideal treatment method for ICC, the outcome of the disease depends on multidisciplinary collaboration. Therefore, a prognostic model based on pre-treatment parameters can help doctors and patients make the optimal choice, which needs to meet the following points: covering the population at all stages, instead of just the patients after surgery; involving common and easily accessible parameters in clinical practice; and long follow-up time, to obtain more endpoint events and predict a longer survival outcome. To address these key points, we explored novel prognostic factors and developed a nomogram to predict survival probability of ICC patients using variables available at the time of diagnosis and determining its risk stratification to guide optimal patient management.

Methods

Study cohort

During the study period (July 2007 and July 2019), a total of 1,240 in-hospital patients with suspected diagnosis of ICC were registered at the Fifth Medical Center of Chinese PLA General Hospital Beijing, China. We excluded patients who had imaging compatible with ICC but without pathological diagnosis (n=410), pathological diagnosis of ICC performed at an outside hospital (n=90), patients with peri-hilar (n=112) or distal (n=45) cholangiocarcinoma, patients with diagnosis of mixed or combined hepatocellular carcinoma-cholangiocarcinoma (n=68), and patients with gallbladder carcinoma (n=1). In addition, we also excluded patients who had died within 1 month after resection (n=5) and patients who were seen only at baseline without long-term follow up (n=67). Thus, a total of 442 patients with pathology-proven ICC constituted our study cohort, and the treatment modalities were decided by multidisciplinary consultation. The study was approved by the Ethics Review Committee at the Fifth Medical Center.

Data collection

All patients were evaluated with a baseline demographic history, physical examination, concurrent comorbidities, serum laboratory tests, and cross-sectional imaging either by contrast computed tomography or magnetic resonance imaging of the abdomen and pelvis. Tumor characteristics were abstracted from the imaging, including tumor size, tumor number, evidence of vascular invasion, and lymph node involvement. Information regarding treatment-related variables, such as type of therapy, and surgical and pathological features (for patients who underwent surgical resection; including nodal status, margin, and vascular invasion) were recorded. Tumor boundary type (distinct vs. obscure) was determined using the Fudan score.[10] Treatment modalities were classified into four groups based on the primary therapy, namely surgery, surgery+regional therapy, regional therapy, systemic therapy and palliative care. All patients were followed up at the Fifth Medical Center for survival outcomes, with the last date of follow-up being June 30, 2020.

Statistical analysis

Baseline characteristics were described. Continuous variables were summarized using median and interquartile range, while categorical variables were summarized using n and percentage. Median overall survival (OS) was estimated using the Kaplan-Meier method, and differences were tested using the log-rank test. Median follow-up time for OS was estimated using the reverse Kaplan-Meier method. Predictors with greater than 20% missing values were dropped from analysis.

The patients were randomly assigned to a training cohort (n=342) and a validation cohort (n=100) using a random seed of 20210130. The modeling was constructed in the training cohort and different models were then compared in the validation cohort. The model with highest performance in the validation cohort was then chosen to build the prognostic score. The final model was then estimated for the whole dataset.

The prognostic model was constructed using a two-stage method in the training cohort. In the first stage, the predictors were tested in a univariate cox regression model. The univariate p values were adjusted by the Benjamini-Hochberg method to maintain the false discovery rate (FDR) under a prespecified threshold (i.e. 0.10 and 0.01). In the second stage, predictors that had passed the FDR threshold were included in a multivariate cox regression model using stepwise variable selection based on Akaike information criterion or Bayesian information criterion. A naïve model included TNM staging as the only classifier and was used as benchmark. Taken together, there were five candidate models in the training step.

With the models obtained in the training step, the validation cohort was used to compare the candidate models to select the one with the best performance. The Harrel's c statistics as well as the area under the curve (AUC) by different landmark timepoints (6, 12, 18, 24, 30, 36 months) were calculated as the benchmark. The model with the highest Harrel's c was then chosen and re-trained in the pooled dataset to obtain the final model.

The model was calibrated using a bootstrap resampling method to construct the 95% confidence interval (CI) of the predicted survival rate at 12 months and was then plotted against the observed 12-month survival rate.

The prognostic score was constructed from the final model in the pooled dataset. The patients were classified into low, mid or high-risk subgroups based on their prognostic score. Ultimately, a nomogram visualizing the prognostic score was provided. All the above analyses were performed by R, version 4.0.0.

Results

Baseline demographic and clinical characteristics of the study cohort

Detailed demographic, clinical and tumor characteristics are shown in Table 1. The median age of patients in our study cohort was 55 years-old and 69.5% were men. Due to the nature of the random split method, there was no notable difference nor any variation between the training and validation cohorts. The leading causes of underlying liver diseases were hepatitis B virus (HBV) infection alone (38.2%), HBV infection and alcohol abuse (12.4%), and alcohol abuse alone (9.5%). The clinical features of HBV-infected patients are shown in Supplementary Figure 1 based on the status of hepatitis B e antigen (HBeAg), HBV DNA, transaminase, etc. Most of the patients showed negativity for HBeAg (n=177,

Table 1. Demographics and baseline characteristics

Variables	Training cohort (*n*=342)	Validation cohort (*n*=100)	Total (*n*=442)
Age in years	55 (48–61)	54.4 (47–60)	55 (48–61)
Sex-male, *n* (%)	240 (70.2%)	67 (67%)	307 (69.5%)
Etiologies of liver diseases, *n* (%)			
HBV	129 (37.7%)	40 (40%)	169 (38.2%)
HBV + alcohol	42 (12.3%)	13 (13%)	55 (12.4%)
Alcohol	33 (9.6%)	9 (9%)	42 (9.5%)
Nonalcoholic fatty liver disease	20 (5.8%)	8 (8%)	28 (6.3%)
HCV	9 (2.6%)	1 (1%)	10 (2.3%)
HCV + alcohol	1 (0.3%)	1 (1%)	2 (0.5%)
Liver fluke	1 (0.3%)	0 (0%)	1 (0.2%)
Previous HBV infection (HBsAg-, anti-HBc+)	66 (19.3%)	19 (19%)	85 (19.2%)
Biliary disease	18 (5.2%)	10 (10%)	28 (6.3%)
ANA+	3 (0.9%)	0 (0%)	3 (0.7%)
AMA+	0 (0.0%)	1 (1%)	1 (0.2%)
Unknown (without any tendency)	38 (11.1%)	14 (14%)	52 (11.8%)
Cirrhosis, *n* (%)	177 (51.8%)	50 (50%)	227 (51.4%)
MELD score	7 (6–8)	6 (6–8)	6 (6–8)
Child-Pugh score	6 (5–7)	5 (5–7)	6 (5–7)
BMI in kg/m^2	24.0 (21.8–26.0)	25.1 (22.1–26.8)	24.1 (21.9–26.2)
Comorbidities, *n* (%)			
Diabetes	48 (14%)	14 (14%)	62 (14%)
CAD	9 (2.6%)	2 (2%)	11 (2.5%)
Hypertension	63 (18.4%)	24 (24%)	87 (19.7%)
Laboratory data			
ALB in g/L	39 (36–42)	39 (37–41)	39 (36–42)
Bilirubin in mg/dL	0.8 (0.6–5.9)	0.9 (0.6–7.5)	0.8 (0.6–6.5)
GGT in U/mL	75 (35–165)	67 (35.5–178.5)	74 (37–164)
Alkaline phosphatase in U/mL	115 (50.8–180)	109.5 (80.5–161.2)	115 (89–174)
Creatinine in mg/dL	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
LDH in U/L	193 (162–228)	197.5 (167.8–280.2)	194.5 (163.0–174.0)
Iron in μmol/L	14.3 (9.2–18.6)	14.1 (9.8–20.9)	14.3 (9.3, 19.2)
Cholesterol in mmol/L	4 (3.4–4.8)	4 (3.5–4.8)	4.0 (3.4–4.8)
CA125 in U/mL	25.4 (12.8,72.4)	21.9 (12.8–68.3)	24.5 (12.8–72.2)
CA19-9 in U/mL	39.4 (15.5–24.7)	37.2 (12–408.8)	38.2 (14.7–260.8)
CA724 in U/mL	2.0 (1.2–4.4)	2.2 (1.1–5.3)	2.0 (1.2–4.7)
CEA in U/mL	2.3 (1.5–6.2)	3.4 (1.5–6.3)	2.4 (1.5–6.3)
AFP in ng/mL	4.3 (2.5–10.6)	4.3 (2.5–13)	4.3 (2.5–11.0)
Tumor characteristics, *n* (%)			
Number of lesions			
Solitary	209 (61.1%)	62 (62%)	271 (61.3%)
Multiple, ≥2	131 (38.3%)	38 (38%)	169 (38.2%)
Max-diameter in cm	6.0 (4.5–8.5)	5.4 (3.1–8.6)	6.0 (4.0–8.5)

(continued)

Table 1. *(continued)*

Variables	Training cohort (*n*=342)	Validation cohort (*n*=100)	Total (*n*=442)
Max-diameter in cm			
<5 cm	98 (28.7%)	42 (42%)	140 (31.7%)
5–10 cm	190 (55.6%)	41 (41%)	231 (52.3%)
>10 cm	50 (14.6%)	17 (17%)	67 (15.2%)
Vascular invasion	139 (40.6%)	50 (50%)	189 (42.8%)
Lymph node involvement	166 (48.5%)	38 (38%)	204 (46.2%)
Distal metastasis	39 (11.4%)	16 (16%)	55 (12.4%)
Tumor differentiation			
Poor	88 (25.7%)	25 (25%)	113 (25.6%)
Moderate	196 (57.3%)	65 (65%)	261 (59.0%)
High	7 (2%)	1 (1%)	8 (1.8%)
AJCC 8th TNM stage			
IA	40 (11.7%)	10 (10%)	50 (11.3%)
IB	59 (17.3%)	11 (11%)	70 (15.8%)
II	158 (46.2%)	54 (54%)	212 (48.0%)
IIIA	5 (1.5%)	2 (2%)	7 (1.6%)
IIIB	38 (11.1%)	7 (7%)	45 (10.2%)
IV	18 (5.3%)	9 (9%)	27 (6.1%)
IVB	21 (6.1%)	7 (7%)	28 (6.3%)
Principal treatment modality, *n* (%)			
No treatment	29 (8.5%)	13 (13%)	41 (9.3%)
Surgery	80 (23.4%)	20 (20%)	100 (22.6%)
Surgery + regional therapy	85 (24.9%)	24 (24%)	109 (24.7%)
Regional therapy	124 (36.3%)	38 (38%)	163 (36.9%)
Systemic therapy	24 (7.0%)	5 (5%)	29 (6.5%)

Continuous variables are presented as median (interquartile range). AFP, α-fetoprotein; BMI, body mass index; CA724, carbohydrate antigen 724; CAD, coronary artery disease; GGT, gamma-glutamyl transferase; HCV, hepatitis C virus.

79%). Only a small portion of patients (*n*=44, 19.6%) were treated by the nucleoside/nucleotide analogues and diagnosed as ICC during the routine follow-up, and most were admitted to the hospital because of the liver nodules instead of the HBV infection.

It is noteworthy that 19.2% of patients were judged as previous HBV infection-positive anti-hepatitis B core protein (HBc) and -negative hepatitis B surface antigen (HBsAg) in serum, which may have contributed to the occurrence of ICC. Unlike the etiology of ICC in the West, no primary sclerosing cholangitis or primary biliary cholangitis were clearly diagnosed in our cohort. Twenty-eight of the patients had a history of biliary diseases, such as cholelithiasis and gallbladder polyps, and a history of cholecystectomy. Underlying cirrhosis was found in 51.4% of our study cohort, as assessed by the pathological report. The median serum levels of total bilirubin, albumin (ALB), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), CA125, and LDH were 0.8 mg/dL, 39 g/L, 2.4 U/mL, 38.2 U/mL, 24.5 U/mL, and 194.5 U/L, respectively.

Regarding tumor characteristics, 61.3% of patients had a solitary tumor with a median diameter of 6.6 cm. Vascular invasion and lymph node involvement were found in 42.8% and 46.2% of patients, respectively. Twelve percent of patients had evidence of distant metastasis. The majority of patients had earlier stage (75% in stage I to II) tumors, based on the AJCC staging classification (8th edition). Most patients received regional therapy or surgery. The type of regional therapy and the proportions of patients who underwent such are listed in Supplementary Table 1. For the patients who received surgery and regional therapy, transcatheter arterial chemoembolization was the most frequently used regional therapy, accounting for 77.1%. For the patients who received regional therapy only, argon-helium cryoablation combined with intratumoral ethanol injection was the most frequently used modality, accounting for 45.4%, followed by microwave hyperthermia (28.3%) and transcatheter arterial chemoembolization (25.2%).

Model training and validation

Within the median follow-up of 50.4 months, 337 (76%) patients died. The median survival was estimated as 11.6 months (95% CI: 9.9–13.3 months). The 1-, 3- and 5-year survival rates were 48.3%, 22.7% and 16.2%, respectively.

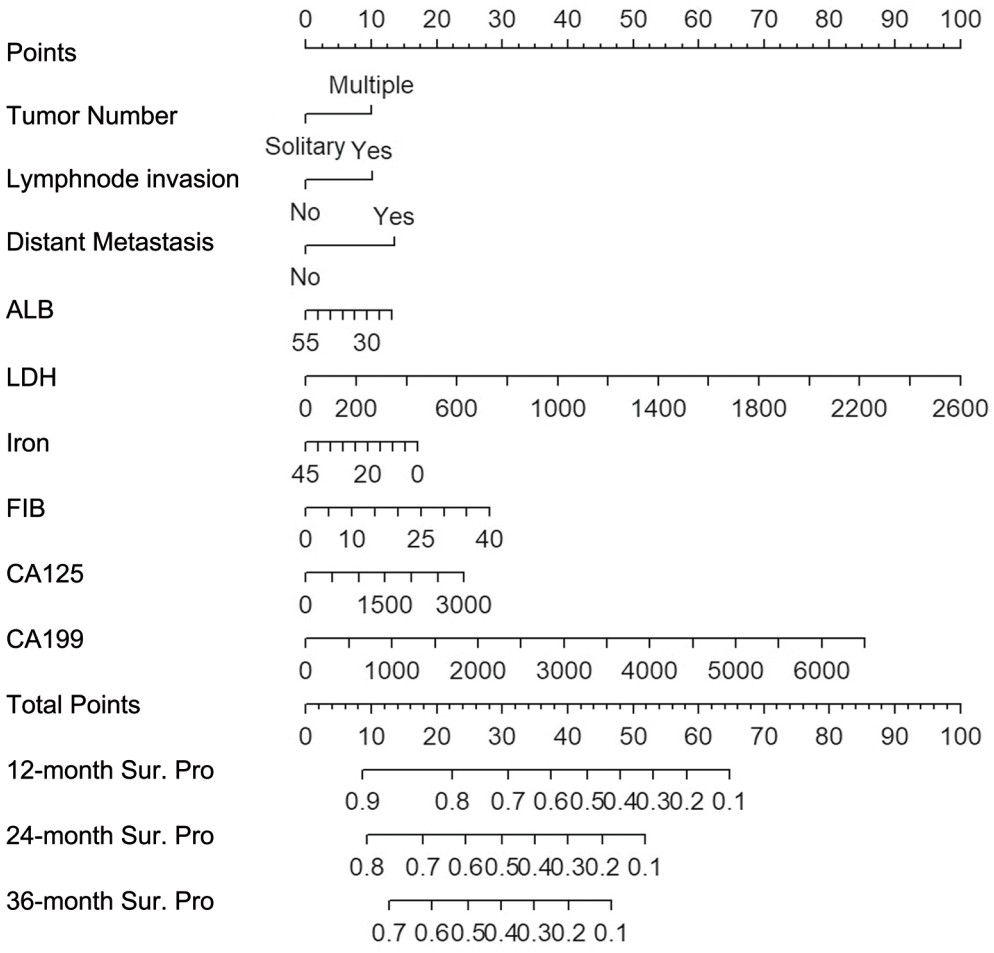

Fig. 1. Nomogram for prediction of survival probability at 12, 24 and 36 months. To use the nomogram, find the position of each parameter on the corresponding axis, draw a line to the point axis at the top for the number of points, add the total points from all of the variables, and draw a line from the total point axis to determine the OS probability at different time points at the bottom of the nomogram.

Under the different FDR thresholds of 0.1 and 0.01, a total of 38 and 21 predictors were selected in the univariate stage. The number of selected variables in multivariate cox regression, as well as the model performance are listed in Supplementary Table 2. Among the four candidate models, model 2 with an FDR threshold of 0.01 and the Akaike information criterion showed the highest performance. The Harrel's c statistic of that model was 0.758 and time-dependent AUC of 0.783, 0.732, 0.740, 0.758, 0.758 and 0.744 for 6, 12, 18, 24, 30 and 36-month OS rate (Supplementary Fig. 2B).

By applying model 2 to the pooled dataset, the variables selected by the final model were multiple tumors, lymph node involvement, distant metastasis, ALB, LDH, iron, fibrinogen (FIB), CA125 and CA19-9. Note that the estimate of final model is slightly different from model 2 in Table 2. This is because the final model, with the same parameter setting as model 2, was re-trained in the pooled dataset. The final model estimates as well as the risk score per unit change are listed in Table 3.

The nomogram visualizing the above using the final model is presented in Figure 1. The predicted 12-, 24- and 36-month survival rates could be easily read from the graph. The calibration plot for the probability of survival at 12 months after diagnosis showed a good agreement between the predicted OS and the actual OS (Fig. 2).

Risk stratification of the ICC patients by the new model

The patients in the pooled cohorts were divided into three risk groups according to the predicted prognostic score cut-off by 31 and 47. The OS curve separated noticeably between the three risk groups (Fig. 3). The median OS for the low, mid and high-risk groups were 35.6 months (95% CI: 24.7-not estimable), 12.1 months (95% CI: 9.8–14.6) and 6.2 months (95% CI: 5.3–8.2).

From Table 4, we can see the distribution of treatment methods across different risk stratifications. Patients with lower risk had been treated with surgery more frequently than patients with higher risk, which is consistent with the real situation that reflects the eligibility of surgery resection as a major prognostic factor for survival. Therefore, the new nomogram was able to stratify patients and give guidance for determining clinical strategy.

Discussion

ICC, a major subclass of cholangiocarcinoma and the second most common primary hepatic malignancy, is a major public health problem, with significant morbidity and mor-

Table 2. Cox proportional hazards regression model for the independent predictors of survival in the training cohort (*n*=342)

Variables	Univariate analyses			Multivariate analyses	
	Hazard ratio (95% CI)	*p*	FDR	Hazard ratio (95% CI)	*p*
Multiple tumors	2.01 (1.63, 2.68)	<0.0001	<0.0001	1.38 (0.98, 1.93)	0.0624
Tumor diameter, per 5 cm	1.99 (1.67, 2.34)	<0.0001	<0.0001	–	–
Lymph node involvement	2.20 (1.72, 2.82)	<0.0001	<0.0001	1.82 (1.33, 2.50)	0.0002
Pathology lymph node invasion	1.89 (1.34, 2.59)	0.0001	0.0003	–	
Distant metastasis	2.24 (1.57, 3.20)	0.0012	0.0038	1.79 (1.10, 2.91)	0.0190
White blood cell count	1.09 (1.04, 1.14)	0.0005	0.0015	–	
Neutrophil-lymptocyte ratio	1.04 (1.02,1.06)	0.0005	0.0015	–	
Red blood cell count	0.69 (0.56, 0.85)	0.0004	0.0013	–	
Hemoglobin, per 10 g/L	0.88 (0.83, 0.94)	0.0001	0.0003	–	
ALB, per 10 g/L	0.55 (0.44, 0.70)	<0.0001	<0.0001	0.70 (0.48, 1.03)	0.0714
GLO, per 10 U/mL	1.46 (1.17, 1.81)	0.0007	0.0019	–	
Creatinine	0.20 (0.09, 0.47)	0.0002	0.0007	–	
LDH, per 100 U/mL	1.16 (1.12, 1.22)	<0.0001	<0.0001	1.45 (1.16, 1.80)	0.0009
Creatine kinase, per 50 U/m	0.70 (0.58, 0.84)	<0.0001	0.0001	–	
Iron, per 10 umol/L	0.58 (0.48, 0.71)	<0.0001	<0.0001	0.76 (0.58, 1.00)	0.0496
Apoprotein A1	0.35 (0.21, 0.60)	0.0001	0.0003	–	
FIB	1.09 (1.05, 1.12)	<0.0001	<0.0001	1.05 (1.00, 1.11)	0.0509
CA125, per 100 U/mL	1.08 (1.05, 1.12)	<0.0001	<0.0001	1.04 (0.99, 1.09)	0.1114
CA19-9, per 100 U/mL	1.04 (1.04, 1.07)	0.0001	0.0003	1.07 (1.02, 1.11)	0.0029
CEA, per 100 U/mL	1.36 (1.18, 1.56)	<0.0001	0.0001	–	–
TNM-8: Stage IB-IIIA vs. Stage IA	2.01 (1.32, 3.08)	0.0012	0.0032	–	–
TNM-8: Stage IIIB-IV vs. Stage IA	3.86 (2.42, 6.17)	<0.0001	<0.0001		

Categorical variables modeled: 1. Multiple tumor 2. Lymphnode involvement 3. Pathological lymphnode invasion 4. Distant metastasis 5. TNM stage.

tality. The OS of ICC patients is poor, as the majority of patients present at an advanced stage that prohibits curative surgical resection.[21] Several prognostication systems have been developed to predict the OS of ICC patients after hepatic resection, but few were constructed based on a population including the patients who were not appropriate candidates.[7–17]

Nomograms are statistical tools that account for the abil-

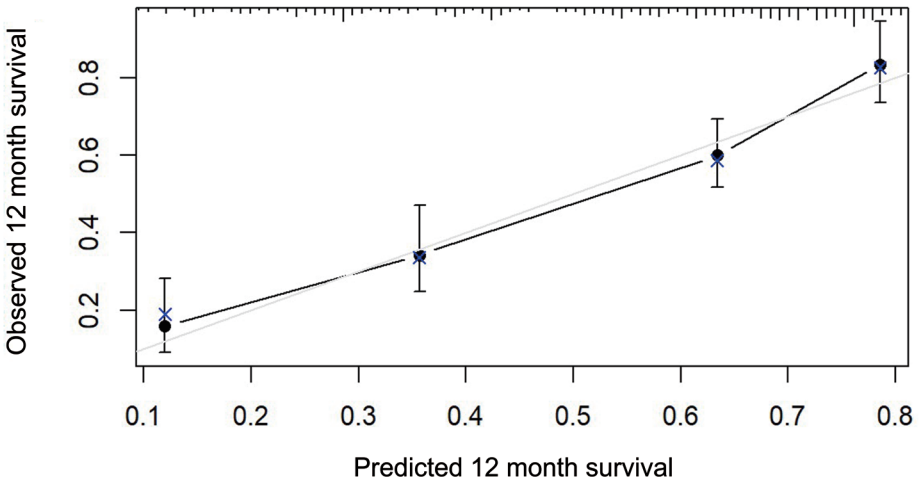

Fig. 2. Calibration plot for the new nomogram associated with the prediction of 12-month survival.

Table 3. Final model for the selected predictors of survival in the pooled cohorts (*n*=442)

Variables	Cox regression model		Prognostic score		
	Hazard ratio (95% CI)	*p*	Baseline value	Prognostic score per unit change	Median prognostic score
Multiple tumors	1.65 (1.24, 2.22)	0.0006	No	10	3.8
Lymph node involvement	1.82 (1.38, 2.39)	<0.0001	No	10	4.6
Distant metastasis	2.00 (1.37, 2.93)	<0.0001	No	14	1.7
ALB, per 10 g/L	0.77 (0.55, 1.07)	0.1244	55	4	6.4
LDH, per 100 U/mL	1.25 (1.10, 1.42)	0.0005	0	4	7.6
Iron, per 10 μmol/L	0.80 (0.64, 1.01)	0.0604	45	4	12
FIB, per U	1.05 (1.00, 1.11)	0.0670	0	0.8	2.8
CA125, per 100 U/mL	1.04 (1.00, 1.08)	0.0692	0	0.8	0.16
CA19-9, per 100 U/mL	1.09 (1.05, 1.13)	<0.0001	0	1.4	0.56

Note: for ALB and iron, the prognostic score will be added per unit decrease based on the baseline value.

ity of multiple variables to influence the probability of long-term survival for a particular patient. To our knowledge, a nomogram model to predict the OS of ICC patients in various stages from the time of the diagnosis which has utility to guide clinical decisions has not been reported. We have developed and validated a new nomogram in a large cohort of ICC patients with a fairy long follow-up that more accurately predicts the survival probability at the time of diagnosis.

Our model consists of nine variables based on the tumor features and clinical biomarkers. By integrating these variables into nomogram scores, we are able to stratify patients into different groups based on the prognosis and OS (Fig. 3). Several commonly used clinical blood parameters were independently associated with survival in our ICC patients,

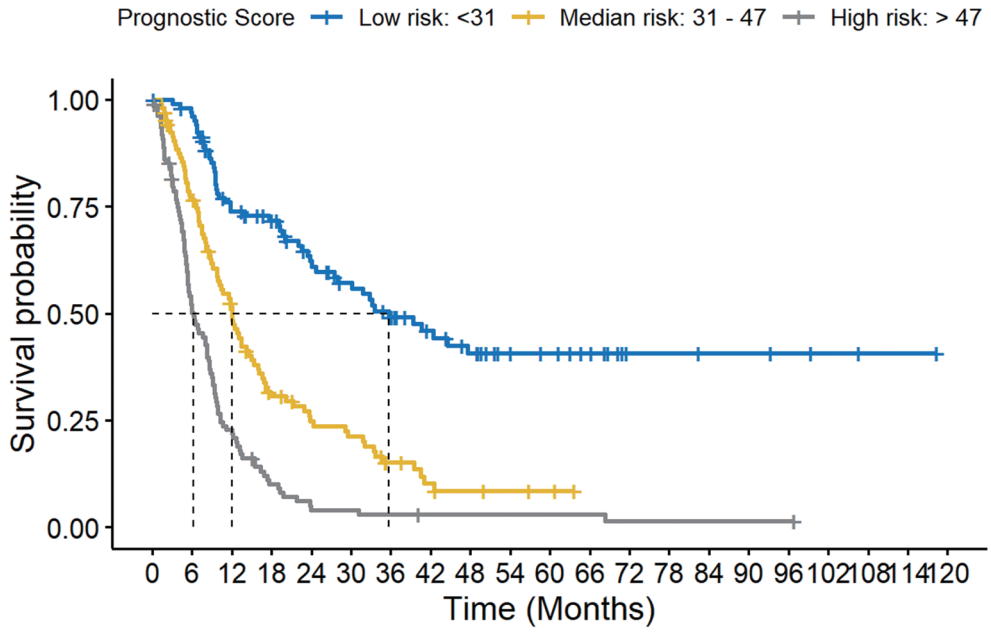

Fig. 3. Kaplan-Meier curves demonstrating the differences in OS among low, mid and high-risk patients stratified by the prognostic score for ICC.

Table 4. Distribution of risk stratification across different treatment modality

Treatment modality	Low risk, *n* (%)	Mid risk, *n* (%)	High risk, *n* (%)
Palliative care	1 (1.0)	7 (6.8)	24 (22.4)
Surgery	45 (43.7)	20 (19.4)	15 (14.0)
Surgery + Regional therapy	36 (35.0)	33 (32.0)	12 (11.2)
Regional therapy	15 (14.6)	38 (36.9)	48 (44.9)
Systemic therapy	6 (5.9)	5 (4.9)	8 (6.5)

such as ALB, FIB, carbohydrate antigen 125 (CA125), LDH and iron. ALB has been used frequently as a prognostic indicator of ICC, for its relation with liver reserve function and nutritional status.[22,23] FIB was also reported as a prognostic factor of CCA.[24] Elevated FIB indicates a hypercoagulable state which may be related to tissue hypoxia caused by a growing tumor and procoagulant factors. Previous studies have shown the utility of both CA125 and LDH as prognostic biomarkers for various cancers, such as hepatocellular carcinoma,[25–28] lung, ovarian, and cervical cancer.[19–21] CA125 and LDH-A expression in ICC tissue samples are considered evidence-proven prognostic factors of poor survival,[29,30] and we found a significant relationship between the serum levels of CA125 per 100 U/m: (hazard ratio=1.04, 95% CI: 1.00–1.08) and LDH per 100U/L (hazard ratio=1.25, 95% CI: 1.10–1.42) on the OS of patients with ICC. The level of serum iron was also introduced into the nomogram to jointly predict the prognosis of ICC, which is a novel biomarker, although iron homeostasis has been reported disordered in cholangiocarcinoma. [31,32]

The strengths of our study are the well-characterized cohorts of patients with pathology-proven ICC, the follow-up data on the survival outcome, sample size, and the broader applicability. However, we acknowledge several limitations. Our nomogram was derived from a homogenous cohort who were seen at a single institution. Despite the fact that our model was internally validated, future studies are needed to determine the prognostic accuracy in another group of patients. In view of the distinguishment of etiology among different countries, the nomogram tends to be suitable for the ICC population mainly caused by HBV infection and admitted in the hospital for pathological analyses and further treatment. Additionally, almost half of the patients had liver cirrhosis. Although the degree of cirrhosis has weight in clinical decision-making, statistical analysis shows that, compared with factors associated with the tumor, cirrhosis has no significant effect on the prognosis. It can be seen from the model for end-stage liver disease score or Child-Pugh score in Table 1 that most of the patients involved in this study had good liver function reserve, and this selective bias may be caused by the diagnosis of ICC relying on pathological evidence so that patients with end-stage cirrhosis could not be involved due to the lack of pathology. Thus, the prognostic model will be updated with the improvement of diagnosis and treatment methods.

In conclusion, we proposed a new prognostic model suitable for the comprehensive ICC population at all stages, which can stratify the risk of patients before treatment to help doctors and patients make reasonable clinical decisions or seek new therapies. Further external studies are needed to validate the prognostic ability of this new model.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (NZ, YYL), drafting of the manuscript (NZ, SNZ, DWJ), critical revision (LRR, SL), analysis and interpretation of data (SNZ, DWJ, XX), recruitment and follow-up (SSL, XXL, LXY), and collection of the data (SNZ, SSL).

Data sharing statement

The data are available upon reasonable request.

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