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ORIGINAL RESEARCH

Development and Validation of Nomograms to Predict the Overall Survival and Progression-Free Survival in Patients with Advanced Unresectable Intrahepatic Cholangiocarcinoma

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Purpose: This study aimed to develop and validate clinical nomograms for predicting progression-free survival (PFS) and overall survival (OS) in unresectable ICC patients.

Patients and Methods: Patients with ICC between 1 January 2018 and 31 May 2023 were selected and randomized into a training set and an internal validation set as a 7:3 ratio. Data analysis and modeling were conducted through R software. The univariate and multivariate Cox regression models were used to analyze the prognosis factors affecting OS and PFS. Survival analysis was conducted using the Kaplan–Meier (KM) method, and comparisons were made using the Log rank test. Then, two nomogram models were constructed to predict OS and PFS, respectively. The nomogram was evaluated and calibrated using the Harrell's C-index, receiver operating characteristic curve (ROC), and calibration plots, and the decision curve analysis (DCA) was conducted to assess its clinical utility.

Results: A total of 110 patients were enrolled in this study, with 77 to the training set and 33 to the validation set. In the entire population, the OS rates at 6 and 12 months were 75.5% and 35.5%, respectively, while the PFS rates at 6 and 12 months were 47.3% and 20%, respectively. Cox regression analyses showed that ECOG, Tumor volume, HBsAg and AFP were the prognosis factors of OS, and the predictors in the model of PFS included Gender, Stage of tumor, CDC20 expression and AFP. The nomograms were constructed based on the predictors above. The C-index for predicting OS was 0.802 (0.755, 0.849) in the training set, 0.813 (0.764, 0.862) in the internal validation set; the C-index for predicting PFS was 0.658 (0.568, 0.748) in the training set, and 0.795 (0.705, 0.885) in the internal validation set. Finally, calibration curves and DCA indicated that two nomograms showed favorable performance.

Conclusion: Two practical and effective prognostic nomograms were developed to assist clinicians in evaluating OS and PFS in patients with unresectable ICC.

Keywords: intrahepatic cholangiocarcinoma, overall survival, progression-free survival, nomogram, prognostic model

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a highly lethal malignant tumor, accounting for 20% of primary liver cancers and 3% of gastrointestinal tumors.[1] Over the past few decades, the incidence of intrahepatic cholangiocarcinoma (ICC) has been steadily increasing at a rate of 4%.[2]

The mortality rate for patients with ICC is extremely high, with an overall 5-year survival rate of approximately 9%.[3] Complete surgical resection remains the only curative treatment for ICC, but about 80% patients present with unresectable disease at diagnosis.[4] Even after radical resection, most patients experience disease recurrence, with a 5-year overall survival (OS) rate of only 20%–35%.[5] For unresectable ICC, a multidisciplinary approach based on gemcitabine and cisplatin is recommended.[6,7] The choice of combined treatment regimens should be tailored to the patient's different prognosis, making

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effective prognostic prediction crucial for ICC patients. Unfortunately, there are currently no reliable tools available for clinical adoption to predict the prognosis of ICC patients.

The American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) system is the most commonly used method for assessing the prognosis of ICC patients.[8] However, the TNM system has significant limitations as it does not consider factors such as gender, age, oncogenes (eg, cell cycle division protein 20 (CDC20)), tumor marker levels, and patient physical fitness.[9,10] A predictive model that combines multiple individual survival-related parameters may have significant clinical value.

The nomogram, as a clinical predictive tool, can integrate different prognostic factors to generate clinical features.[11] Clinical prediction models based on nomograms are intuitive and have been widely employed for predicting outcomes in cancer patients and aiding in the decision-making process for individualized optimal treatment plans.[12–14] This study aims to explore prognostic factors and develop two new nomograms to predict OS and PFS in ICC patients using collected clinical data from ICC patients.

Materials and Methods

Patients and Potential Predictor Variable

Data on patients with unresectable ICC were collected from the two centers (Sichuan Cancer Hospital and Nanchong Central Hospital) between 1 January 2018 and 31 May 2023. The follow-up period extended until 31 May 2024. The collected information included age, gender, hospitalization number, TNM stage, efficacy, status, eastern cooperative oncology group (ECOG) score, tumor volume, the maximum diameter of tumor, number of tumors in liver, HBsAg, CDC20, etc. Survival data comprised OS, defined as the time from diagnosis to the last follow-up or death, and PFS, which measures the time from the start of treatment to disease progression.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients were diagnosed with ICC by histopathological examinations; (2) patients with newly diagnosed, unresectable advanced intrahepatic cholangiocarcinoma (ICC) or those who refuse surgical resection or have experienced postoperative recurrence. The exclusion criteria were as follows: (1) patients who relapsed after previous chemotherapy; (2) patients for whom tissue paraffin blocks are not available; (3) patients with incomplete data.

Immunohistochemistry Revision CDC20

Immunohistochemical (IHC) analysis of CDC20 expression was performed on tumor tissues from all enrolled cases. Tissue sections were incubated overnight at 4°C with rabbit anti-CDC20 antibody (diluted 1:200; HUABIO). A 1% bovine serum albumin (BSA) solution served as the negative control without primary antibody. Subsequently, sections were incubated with secondary anti-rabbit IgG antibodies conjugated with horseradish peroxidase (HRP) (HUABIO, Zhejiang, China) for 20 minutes at room temperature. All immunohistochemistry slides were independently evaluated by two researchers who were unaware of the clinical and pathological characteristics of the patients. Firstly, the percentage score for positive cells was graded as follows: 0, 0%; 1+, 1–10%; 2+, 11–50%; or 3+, 51–100%. Subsequently, staining intensity was graded as following: Grade 0, negative; 1+, weakly positive; 2+, moderately positive; or 3+, strongly positive. Based on these immunohistochemistry scores, CDC20 expression was categorized into two groups: low CDC20 expression (score ≤ 3) and high CDC20 expression (score ≥ 4).

Model Development

The study cohort listed the clinical characteristics of ICC. Before modeling, we deleted variables with missing values >50%, and the missing values of the remaining variables were replaced by random forests (Supplementary Table 1). Then, all patients were randomly divided into a training and a validation cohort in a 7:3 ratio. The training cohort was used for variable selection and model development, while the validation cohort was used for model performance validation. Univariate and multivariate Cox regression analyses were performed to identify variables with $p < 0.05$, which were considered independent risk factors affecting OS and PFS in ICC patients and were used to construct the nomogram. The hazard ratio (HR) values were derived using a backward stepwise regression method in the Cox model, which were then used as weights to calculate the risk score for prognostic prediction.

Internal Validation of the Model

The nomogram was validated using the concordance index (C-index), time-dependent receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA). The C-index reflects the predictive accuracy of the nomogram, while ROC curves indicate its sensitivity and specificity. In general, a C-index of 0.50 to 0.70 indicates a low accuracy, 0.71 to 0.90 indicates a moderate accuracy, and greater than 0.90 indicates a high accuracy. Calibration curves at 6 months and 12 months were plotted to compare the predicted OS and PFS with the observed outcomes in the model, with the 45-degree line serving as the reference for the model's actual results.

Statistical Analysis

Categorical variables were reported as counts and percentages. Chi-square test or Fisher's exact test was used to identify statistical differences. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range. The Student's *t*-test or Mann–Whitney test was used to identify statistical differences in clinical case data among ICC patients. Two-tailed p-values <0.05 were considered statistically significant. Kaplan–Meier survival curves and the Log rank test were used to analyze prognostic differences between risk groups. Fisher's Exact Test was applied to variables with expected cell frequencies less than 5. All statistical analyses for this study were conducted using the R software version 4.4.0 (http://www.r-project.org/). The nomogram was constructed using the rms package in R software.

Results

Patient Characteristics

The patient data selection process is shown in Figure 1. A total of 110 ICC patients were enrolled and randomized into a training cohort (n = 77) and a validation cohort (n = 33). Entire population was followed for a median period of 11.6 months, while the interquartile ranges were 8.0–19.4. A total of 83 (75.5%) patients died during the course of follow-up. The median survival time was 9.6 months (range 1.16–64.8 months). The median PFS times for the entire population,

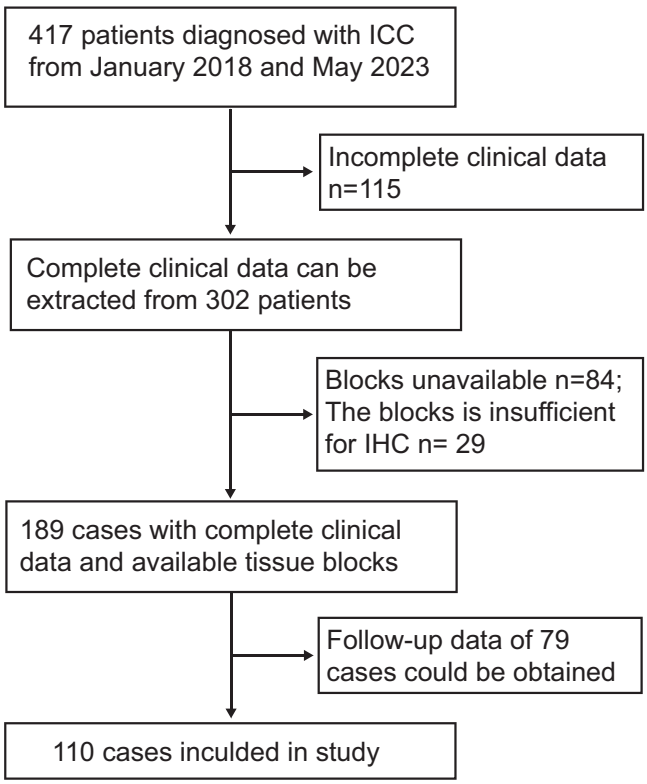

Figure 1 Consort diagram of patient data selection process.

training cohort, and validation cohort were 5 months, while the median OS times were 10, 9, 10 months, respectively. The characteristics of all patients included in this study are shown in Table 1. Figure 2 presents the Kaplan–Meier curve of the entire cohort, with a total follow-up period of 60 months.

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Group			Statistic	p-value
	Overall N = 110	Training Set N = 77	Test Set N = 33		
Gender				χ^2=1.41	0.234
Female	44 (40.0%)	28 (36.4%)	16 (48.5%)		
Male	66 (60.0%)	49 (63.6%)	17 (51.5%)		
Age	59 (51, 65)	58 (49, 63)	60 (54, 68)	Z=1045.00	0.141
ECOG				χ^2=0.17	0.676
0–1	50 (45.5%)	34 (44.2%)	16 (48.5%)		
2–5	60 (54.5%)	43 (55.8%)	17 (51.5%)		
Stage				χ^2=0.88	0.645
I-II	24 (21.8%)	15 (19.5%)	9 (27.3%)		
III	27 (24.5%)	19 (24.7%)	8 (24.2%)		
IV	59 (53.6%)	43 (55.8%)	16 (48.5%)		
Child-Pugh score				N/A	0.080
5	75 (68.2%)	48 (62.3%)	27 (81.8%)		
6	21 (19.1%)	16 (20.8%)	5 (15.2%)		
7	14 (12.7%)	13 (16.9%)	1 (3.0%)		
Tumor volume(mm^3)	146 (79, 283)	137 (68, 283)	155 (92, 323)	Z=1153.50	0.447
Maximum diameter(cm)	6.35 (4.80, 7.88)	6.30(4.80, 7.40)	6.70 (5.60, 8.00)	Z=1135.00	0.378
Number of tumors in liver				χ^2=0.00	>0.999
1	60 (54.5%)	42 (54.5%)	18 (54.5%)		
≥2	50 (45.5%)	35 (45.5%)	15 (45.5%)		
Lymph node				χ^2=0.21	0.647
No	53 (48.2%)	36 (46.8%)	17 (51.5%)		
Yes	57 (51.8%)	41 (53.2%)	16 (48.5%)		
Vascular tumor thrombosis				χ^2=0.38	0.539
No	81 (73.6%)	58 (75.3%)	23 (69.7%)		
Yes	29 (26.4%)	19 (24.7%)	10 (30.3%)		
Extrahepatic metastasis				χ^2=0.06	0.801
No	62 (56.4%)	44 (57.1%)	18 (54.5%)		
Yes	48 (43.6%)	33 (42.9%)	15 (45.5%)		
HBsAg				χ^2=0.02	0.896
Negative	71 (64.5%)	50 (64.9%)	21 (63.6%)		
Positive	39 (35.5%)	27 (35.1%)	12 (36.4%)		
Targeted therapy				χ^2=0.38	0.539
No	81 (73.6%)	58 (75.3%)	23 (69.7%)		
Yes	29 (26.4%)	19 (24.7%)	10 (30.3%)		
Chemotherapy				N/A	0.001
Without gemcitabine	38 (34.5%)	20 (26.0%)	18 (54.5%)		
With gemcitabine	58 (52.7%)	43 (55.8%)	15 (45.5%)		
Non-chemotherapy	14 (12.7%)	14 (18.2%)	0 (0.0%)		
ICIs				χ^2=0.92	0.337
No	59 (53.6%)	39 (50.6%)	20 (60.6%)		
Yes	51 (46.4%)	38 (49.4%)	13 (39.4%)		

(*Continued*)

Table 1 (Continued).

Characteristic	Group			Statistic	p-value
	Overall N = 110	Training Set N = 77	Test Set N = 33		
Effect				χ^2=0.44	0.505
PD	58 (52.7%)	39 (50.6%)	19 (57.6%)		
SD+PR+CR	52 (47.3%)	38 (49.4%)	14 (42.4%)		
CDC20				χ^2=0.15	0.701
Low expression	43 (39.1%)	31 (40.3%)	12 (36.4%)		
High expression	67 (60.9%)	46 (59.7%)	21 (63.6%)		
TBIL	15 (11, 20)	16 (12, 24)	13 (10, 19)	Z=1524.50	0.098
ALB	39.1 (37.2, 42.8)	39.3 (37.0, 42.7)	38.9 (37.4, 43.3)	Z=1226.00	0.774
ALT	38 (22, 60)	37 (22, 63)	38 (22, 59)	Z=1273.00	0.990
AST	38 (26, 62)	37 (27, 65)	39 (25, 60)	Z=1324.00	0.729
AFP	8 (4, 20)	7 (3, 21)	9 (5, 20)	Z=1169.00	0.510
CA199	93 (30, 524)	74 (30, 497)	118 (37, 875)	Z=1192.00	0.610
Status				χ^2=6.08	0.014
Survival	27 (24.5%)	24 (31.2%)	3 (9.1%)		
Death	83 (75.5%)	53 (68.8%)	30 (90.9%)		
PFS(months)	5 (3, 10)	5 (2, 10)	5 (3, 9)	Z=1295.50	0.873
OS(months)	10 (6, 17)	9 (5, 18)	10 (7, 17)	Z=1209.00	0.691

Notes: Z value from the *U*-test, χ^2 value from the Chi-square test; N/A, Fisher's Exact Test was performed where applicable.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBsAg, Hepatitis B Surface Antigen; ICIs, Immune checkpoint inhibitors; CDC20, cell division cycle 20; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CA199, Carbohydrate Antigen 19–9; ICIs, Immune checkpoint inhibitors; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; PFS, progress-free survival; OS, overall survival.

Prognostic Factors of PFS and OS

To explore the factors influencing PFS and OS in patients with intrahepatic cholangiocarcinoma, Cox regression analysis was conducted. The proportional hazards (PH) assumption test was conducted, and the results indicated that the proportional hazards assumption was valid, allowing for the multivariate Cox analysis (Supplementary Figure 1). In the univariate Cox analysis, seven variables were confirmed as OS-related factors, and ten variables were identified as PFS-related factors. Furthermore, multivariate a multivariate Cox analysis identified ECOG the ECOG score (hazard ratio [HR]: 0.36, 95% confidence interval [CI]: 0.17–0.73, p=0.005), HBsAg (HR: 0.16, 95% CI: 0.07–0.36, p<0.001), tumor volume (HR: 1.01, 95% CI: 1.01–1.01, p=0.009), AFP (HR: 1.01, 95% CI: 1.01–1.03, p<0.001) as independent

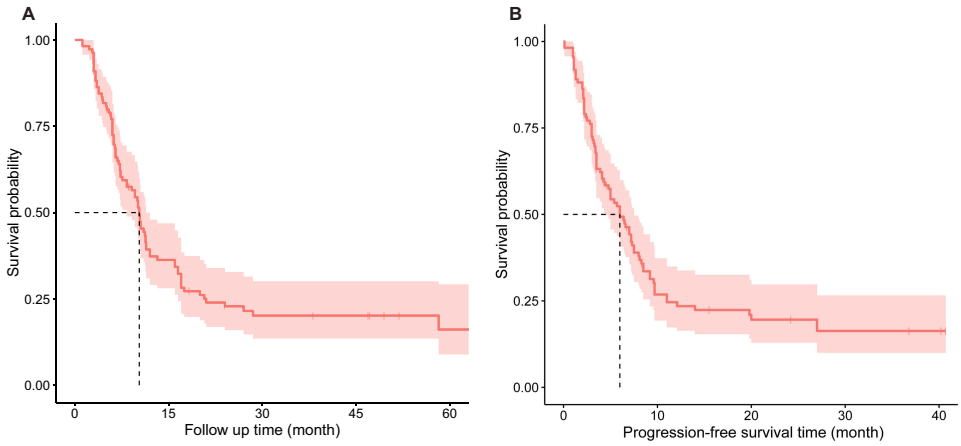

Figure 2 Kaplan-Meier survival curves for overall survival. (**A**) and progression-free survival, (**B**) in the total cohort.

risk factors for OS (Table 2), and Gender (HR: 0.53, 95% CI: 0.31–0.93, p=0.026), CDC20 (HR: 27.97, 95% CI: 10.56–74.07, p<0.001), stage (HR: 3.04, 95% CI: 1.51–6.13, p=0.002), AFP (HR: 1.01, 95% CI: 1.01–1.03, p=0.021) for PFS (Table 3). The results were illustrated as forest plots in Supplementary Figures 2 and 3. Based on the results of multivariate Cox regression analysis, the survival curves of independent prognostic factors on in PFS and OS were shown in Figure 3.

Table 2 Results of Univariate and Multivariate Cox Regression Analyses to Identify Variables That Can Predict Overall Survival of Patients with Unresectable Intrahepatic Cholangiocarcinoma

Variables	OS Univariate					OS Multivariate				
	β	*S.E*	*Z*	*P*	HR(95% CI)	*β*	*S.E*	*Z*	*P*	HR(95% CI)
Gender										
Female					1.00(Reference)					1.00(Reference)
Male	−0.68	0.22	−3.06	0.002	1.51(1.33 ~ 1.78)	−0.36	0.25	−1.47	0.141	1.70(1.43 ~ 2.13)
Age	0.02	0.01	1.73	0.084	1.02(1.00 ~ 1.05)					
ECOG										
0–1					1.00(Reference)					1.00(Reference)
≥2	0.72	0.23	3.19	0.001	2.06(1.32 ~ 3.21)	−1.03	0.36	−2.83	0.005	0.36(0.17 ~ 0.73)
Stage										
I-II					1.00(Reference)					1.00(Reference)
III-IV	0.98	0.34	2.88	0.004	2.67(1.37 ~ 5.20)	0.09	0.36	0.26	0.796	1.10(0.54 ~ 2.23)
Child-Pugh score										
5					1.00(Reference)					
6	0.10	0.28	0.34	0.733	1.10(0.63 ~ 1.92)					
7	−0.33	0.38	−0.88	0.380	0.72(0.34 ~ 1.51)					
Tumor volume	0.01	0.00	3.60	<0.001	1.01(1.01 ~ 1.01)	0.01	0.00	2.62	0.009	1.01(1.01 ~ 1.01)
Maximum Diameter	0.01	0.01	1.05	0.294	1.01(0.99 ~ 1.03)					
Number of tumors in liver										
1					1.00(Reference)					
≥2	0.21	0.22	0.96	0.336	1.24(0.80 ~ 1.90)					
Lymph Node										
No					1.00(Reference)					
Yes	0.24	0.22	1.10	0.273	1.28(0.83 ~ 1.97)					
Vascular tumor thrombosis										
No					1.00(Reference)					
Yes	−0.20	0.27	−0.76	0.448	0.82(0.48 ~ 1.38)					
Extrahepatic metastasis										
No					1.00(Reference)					
Yes	0.14	0.22	0.63	0.528	1.15(0.75 ~ 1.77)					
Targeted therapy										
No					1.00(Reference)					
Yes	−0.08	0.25	−0.33	0.740	0.92(0.56 ~ 1.50)					
Chemotherapy										
Without Gemcitabine					1.00(Reference)					
With Gemcitabine	−0.22	0.23	−0.94	0.350	0.81(0.51 ~ 1.27)					
Non-chemotherapy	−0.82	0.49	−1.70	0.089	0.44(0.17 ~ 1.14)					
ICIs										
No					1.00(Reference)					
Yes	−0.17	0.22	−0.74	0.457	0.85(0.55 ~ 1.31)					
HBsAg										
Negative					1.00(Reference)					1.00(Reference)
Positive	−1.22	0.25	−4.86	<0.001	0.30(0.18 ~ 0.48)	−1.85	0.43	−4.33	<0.001	0.16(0.07 ~ 0.36)

(*Continued*)

Table 2 (Continued).

Variables	OS Univariate					OS Multivariate				
	β	*S.E*	*Z*	*P*	HR(95% CI)	*β*	*S.E*	*Z*	*P*	HR(95% CI)
CDC20										
Low					1.00(Reference)					
High	21.39	3241.79	0.01	0.995	2.02×10^{9}(0.00 ~ Inf)					
TBIL	−0.00	0.01	−0.68	0.499	1.00(0.99 ~ 1.01)					
ALB	0.01	0.01	0.69	0.488	1.01(0.99 ~ 1.03)					
ALT	0.00	0.00	0.31	0.757	1.00(1.00 ~ 1.00)					
AST	0.00	0.00	1.44	0.149	1.00(1.00 ~ 1.01)					
AFP	0.02	0.00	4.88	<0.001	1.02(1.01 ~ 1.03)	0.02	0.00	3.92	<0.001	1.02(1.01 ~ 1.03)
CA199	0.01	0.00	3.39	<0.001	1.01(1.01 ~ 1.01)	0.00	0.00	1.67	0.094	1.00(1.00 ~ 1.00)

Abbreviations: OS, overall survival; ECOG, Eastern Cooperative Oncology Group; HBsAg, Hepatitis B Surface Antigen; ICIs, Immune checkpoint inhibitors; CDC20, cell division cycle 20; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CA199, Carbohydrate Antigen 19–9; HR, Hazard Ratio; CI: Confidence Interval; *β*, Beta coefficient; SE, Standard Error; Z, Z value; Inf, Infinity.

Table 3 Results of Univariate and Multivariate Cox Regression Analyses to Identify Variables That Can Predict Progression-Free Survival of Patients with Unresectable Intrahepatic Cholangiocarcinoma

Variables	PFS Univariate					PFS Multivariate				
	β	*S.E*	*Z*	*P*	HR(95% CI)	*β*	*S.E*	*Z*	*P*	HR(95% CI)
Gender										
Female					1.00(Reference)					1.00(Reference)
Male	−0.77	0.22	−3.48	<0.001	1.46(1.30 ~ 1.71)	−0.63	0.28	−2.23	0.026	1.53(1.31 ~ 1.93)
Age	0.01	0.00	3.02	0.240	1.02(0.99 ~ 1.04)					
ECOG										
0–1					1.00(Reference)					1.00(Reference)
≥2	0.57	0.23	2.52	0.012	1.77(1.13 ~ 2.75)	0.02	0.42	0.05	0.963	1.02(0.45 ~ 2.30)
Stage										
I-II					1.00(Reference)					1.00(Reference)
III-IV	0.95	0.34	2.79	0.005	2.59(1.33 ~ 5.05)	1.11	0.36	3.12	0.002	3.04(1.51 ~ 6.13)
Child-Pugh score										
5					1.00(Reference)					
6	0.09	0.28	0.31	0.760	1.09(0.63 ~ 1.90)					
7	−0.23	0.38	−0.60	0.550	0.80(0.38 ~ 1.67)					
Tumor volume	0.01	0.00	3.02	0.003	1.01(1.01 ~ 1.01)	−0.00	0.00	−0.77	0.439	1.00(1.00 ~ 1.00)
Maximum Diameter	0.00	0.01	0.45	0.650	1.00(0.99 ~ 1.02)					
Number of tumors in liver										
1					1.00(Reference)					
≥2	0.04	0.22	0.19	0.846	1.04(0.68 ~ 1.61)					
Lymph Node										
No					1.00(Reference)					
Yes	0.34	0.23	1.49	0.135	1.40(0.90 ~ 2.18)					
Vascular tumor thrombosis										
No					1.00(Reference)					
Yes	−0.24	0.27	−0.88	0.379	0.79(0.47 ~ 1.34)					
Extrahepatic metastasis										
No					1.00(Reference)					
Yes	0.07	0.22	0.30	0.767	1.07(0.69 ~ 1.65)					

(*Continued*)

Table 3 (Continued).

Variables	PFS Univariate					PFS Multivariate				
	β	*S.E*	*Z*	*P*	HR(95% CI)	*β*	*S.E*	*Z*	*P*	HR(95% CI)
Targeted therapy										
No					1.00(Reference)					
Yes	−0.17	0.25	−0.70	0.486	0.84(0.51 ~ 1.37)					
Chemotherapy										
Without Gemcitabine					1.00(Reference)					1.00(Reference)
With Gemcitabine	−0.43	0.23	−1.83	0.067	0.65(0.41 ~ 1.03)	−0.41	0.30	−1.36	0.173	0.66(0.36 ~ 1.20)
Non-chemotherapy	−1.00	0.49	−2.06	0.039	0.37(0.14 ~ 0.95)	−1.13	0.60	−1.88	0.060	0.32(0.10 ~ 1.05)
ICIs										
No					1.00(Reference)					
Yes	−0.21	0.22	−0.94	0.347	0.81(0.52 ~ 1.26)					
HBsAg										
Negative					1.00(Reference)					1.00(Reference)
Positive	−1.02	0.25	−4.07	<0.001	0.36(0.22 ~ 0.59)	0.25	0.51	0.49	0.621	1.29(0.47 ~ 3.49)
CDC20										
Low					1.00(Reference)					1.00(Reference)
High	3.02	0.44	6.91	<0.001	20.50(8.71 ~ 48.28)	3.33	0.50	6.70	<0.001	27.97(10.56 ~ 74.07)
TBIL	−0.00	0.01	−0.09	0.931	1.00(0.99 ~ 1.01)					
ALB	0.01	0.01	0.70	0.482	1.01(0.99 ~ 1.03)					
ALT	0.00	0.00	0.80	0.426	1.00(1.00 ~ 1.00)					
AST	0.01	0.00	1.99	0.047	1.01(1.01 ~ 1.01)	0.00	0.00	1.72	0.086	1.00(1.00 ~ 1.01)
AFP	0.02	0.00	4.18	<0.001	1.02(1.01 ~ 1.03)	0.01	0.01	2.30	0.021	1.01(1.01 ~ 1.03)
CA199	0.01	0.00	3.86	<0.001	1.01(1.01 ~ 1.01)	0.00	0.00	1.90	0.058	1.00(1.00 ~ 1.00)

Abbreviations: PFS, progress-free survival; ECOG, Eastern Cooperative Oncology Group; HBsAg, Hepatitis B Surface Antigen; ICIs, Immune checkpoint inhibitors; CDC20, cell division cycle 20; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CA199, Carbohydrate Antigen 19–9; HR, Hazard Ratio; CI: Confidence Interval; *β*, Beta coefficient; SE, Standard Error; Z, Z value; Inf, Infinity.

Nomogram for Predicting OS and PFS

According to the results of the multivariate Cox regression analysis, these four independent prognostic factors (ECOG score, HBsAg, tumor volume, AFP) affecting OS were integrated to construct a nomogram for predicting mortality risk at 6 and 12 months (Figure 4). Further, to predict the mortality risk at 6 and 12 months for ICC patients with different PFS, the four statistically significant factors (gender, CDC20, stage, AFP) affecting PFS were selected to construct a nomogram (Figure 5). Each variable in the figure is represented by a line segment marked with scales, where the values on the scales reflect the contribution of that factor to the outcome event. By summing the scores corresponding to each variable across different values, a total score is obtained, which can be projected downwards to obtain the survival probability of ICC patients at 6 and 12 months. The scores assigned to each parameter for the nomogram are shown in Supplementary Table 2.

Verification of the Nomogram

The Harrell's C-index and area under the curve (AUC) values were calculated to evaluate the predictive capacity of the nomogram for prognosis. The C-index for predicting the OS was 0.802 (95% CI: 0.755–0.849) in the training cohort and 0.658 (95% CI: 0.568–0.748) in the validation cohort. Meanwhile, the C-index for predicting PFS was 0.813 (95% CI: 0.764–0.862) in the training cohort and 0.795 (95% CI: 0.705–0.885) in the validation cohort. These results were presented in Table 4, which provided detailed values for each cohort and additional statistical metrics, such as AUC, that further support the model's prognostic performance.

The ROC curve was used to assess the predictive ability of the nomogram. The AUC values for predicting 6- and 12-month OS were 0.822 and 0.848, respectively, in the training cohort, and 0.853 and 0.971 in the validation cohort as shown in Figure 6 and Table 5. The AUC values for predicting 6 and 12 months PFS were 0.962 and 0.94, respectively,

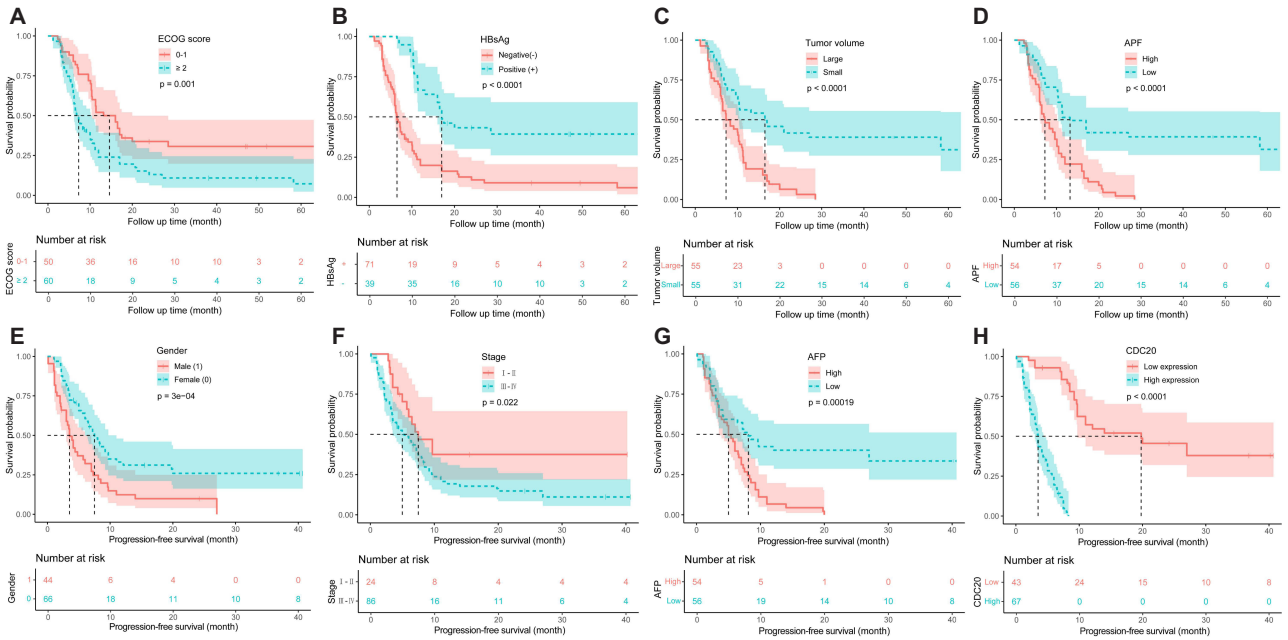

Figure 3 The Kaplan–Meier curves of clinicopathological factors affecting OS and PFS based on multivariate analyses. (**A-D**) the survival curves of OS-related prognostic factors, (**E-H**) the survival curves of PFS-related prognostic factors.

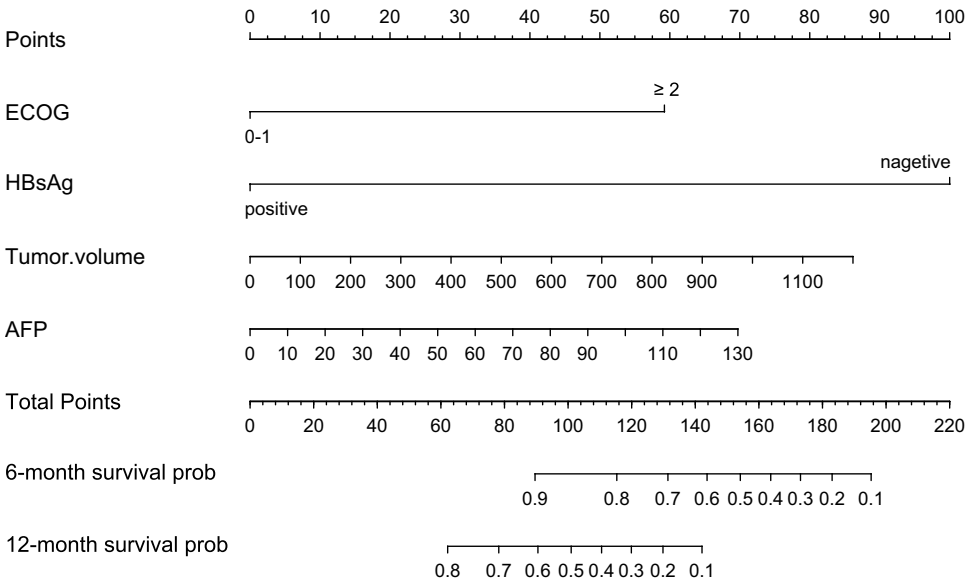

Figure 4 Nomogram for predicting overall survival (OS) in intrahepatic cholangiocarcinoma.

in the training cohort, 0.89 and 0.988 in the validation cohort as shown in Figure 6 and Table 5. In both the training and validation cohorts, the nomogram demonstrated strong predictive capability.

Calibration curves were used to evaluate the calibration performance of the model. All results indicated good clinical applicability of the nomogram for predicting OS and PFS. Furthermore, the calibration curves for both OS and PFS closely follow the ideal 45° dashed line, indicating strong consistency between predicted and observed values (Figure 7). The DCA was shown in Figure 8. When the threshold probability for OS was over 0.06, the net benefit was significantly higher than "no intervention" and "full intervention" groups. Similarly, for PFS, when the threshold probability was between 0.04 and 0.9, the net benefit was significantly higher than "no or full intervention" groups.

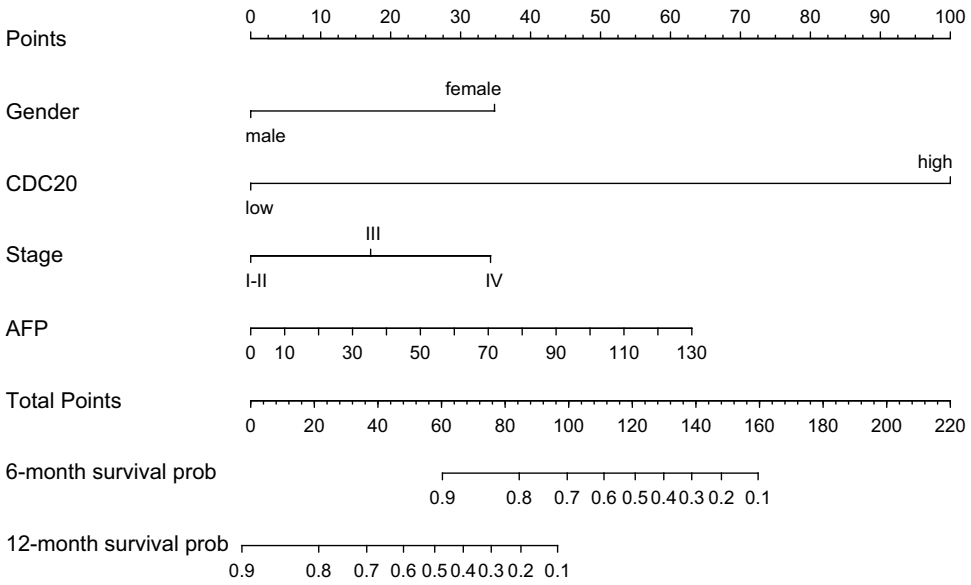

Figure 5 Nomogram for predicting survival for ICC patients with different PFS.

Discussion

Unresectable ICC is characterized by poor treatment efficacy and high mortality. Previous studies have primarily focused on predicting the recurrence of ICC post-surgery, with few evaluations of the prognosis for unresectable ICC. This study analyzed the clinical characteristics and survival outcomes of unresectable ICC based on clinical data and constructed a nomogram to predict patient prognosis. The results confirmed that ECOG score, tumor volume, HBsAg status, and AFP were independent factors affecting OS in patients with unresectable ICC, while gender, tumor stage, CDC20 expression, and AFP are independent factors influencing PFS.

This present study indicated that ECOG score ≥2 was associated with a poor OS (p=0.005). Other studies also showed significantly longer survival in ECOG 0 or 1 groups.[15,16] ECOG is a scoring system used to evaluate the daily living abilities of cancer patients. Higher scores indicate poorer status, which significantly limits the combination and dosage of medications.[17,18] Additionally, the tumor size was positively correlated with OS in patients with unresectable ICC (p=0.009), which was similar to previous studies.[19,20] Several large cohort studies have demonstrated that tumor size is a prognostic factor for overall survival (OS) in ICC.[21] Hyder et al confirmed this through a multicenter study,[22] and Wang et al reached the same conclusion in a study involving 367 ICC patients.[23] Consequently, tumor size has been incorporated into the latest AJCC staging system. However, the optimal cutoff value for predicting prognosis remains controversial. In addition, HBsAg negative and AFP high were associated with poorer OS in unresectable ICC ($p < 0.05$). Although hepatitis B virus has been confirmed to be involved in the pathogenesis of ICC,[24] ICC patients with HBV infection often showed favorable clinicopathological features and better survival rates.[25–27] The reason was that HBV infection activated the immune response in ICC patients, thereby enhancing the immune system's ability to clear the tumor.[25] AFP, as a sensitive biomarker for liver cancer, has also been previously confirmed to be associated with poorer OS.[28] In addition, gender, stage,

Table 4 C-Index Value of the Nomogram

Nomogram	Training Set		Validation Set	
	C-Index	95% CI	C-Index	95% CI
Nomogram on OS	0.802	(0.755, 0.849)	0.813	(0.764, 0.862)
Nomogram on PFS	0.658	(0.568, 0.748)	0.795	(0.705, 0.885)

Abbreviations: PFS, progress-free survival; OS, overall survival; CI, confidence interval.

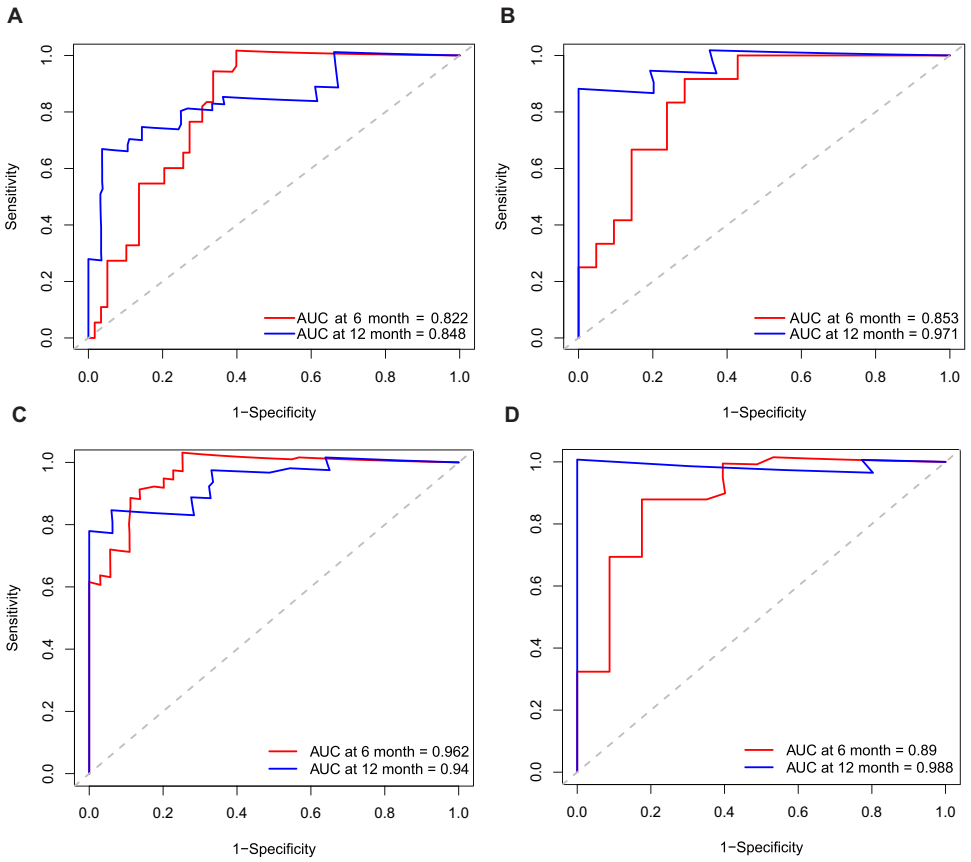

Figure 6 The ROC curves of nomogram predicting OS and PFS in intrahepatic cholangiocarcinoma. ROC curves of the 6 months and 12 months OS in the training set (**A**) and in the validation set (**B**), and the curves of 6 and 12 months PFS in the training set (**C**) and in the validation set (**D**).

and CA199 levels were also associated with OS in univariate analysis, but these associations were no statistically significant, necessitating further in-depth clinical analysis.

This study revealed that four factors are independent-imaging predictors of PFS. Our study found that male ICC patients have better PFS compared to female patients. Other studies have also confirmed that male ICC patients have higher recurrence rates after surgery and radioembolization than female patients ($p = 0.026$).[29,30] The present study was the first to mention the correlation between gender and the efficacy of non-surgical treatments in ICC patients.[31] In addition, our study results showed that patients with stage III–IV ICC have significantly worse PFS compared to those with stage I–II, which was consistent with the widely accepted view that later stages are associated with poorer prognosis.[31] CDC20 has become a research focus in recent years and has been shown to be significantly associated with the development, prognosis, and treatment resistance of many cancers.[32] Our study confirmed that high expression of CDC20 is associated with poor PFS, possibly due to CDC20 inducing drug resistance in ICC cells to chemotherapy and immunotherapy.[33] The specific mechanisms by which CDC20 regulates ICC are currently under investigation and will be published soon.

Table 5 Area Under the ROC Curve (AUC) of the Nomogram

ROC Curve	Training Set (95% CI)		Validation Set (95% CI)	
	6 Months	12 months	6 Months	12 Months
OS	0.822	0848	0.853	0.971
PFS	0.962	0.94	0.89	0.988

Abbreviations: PFS, progress-free survival; OS, overall survival; CI, confidence interval.

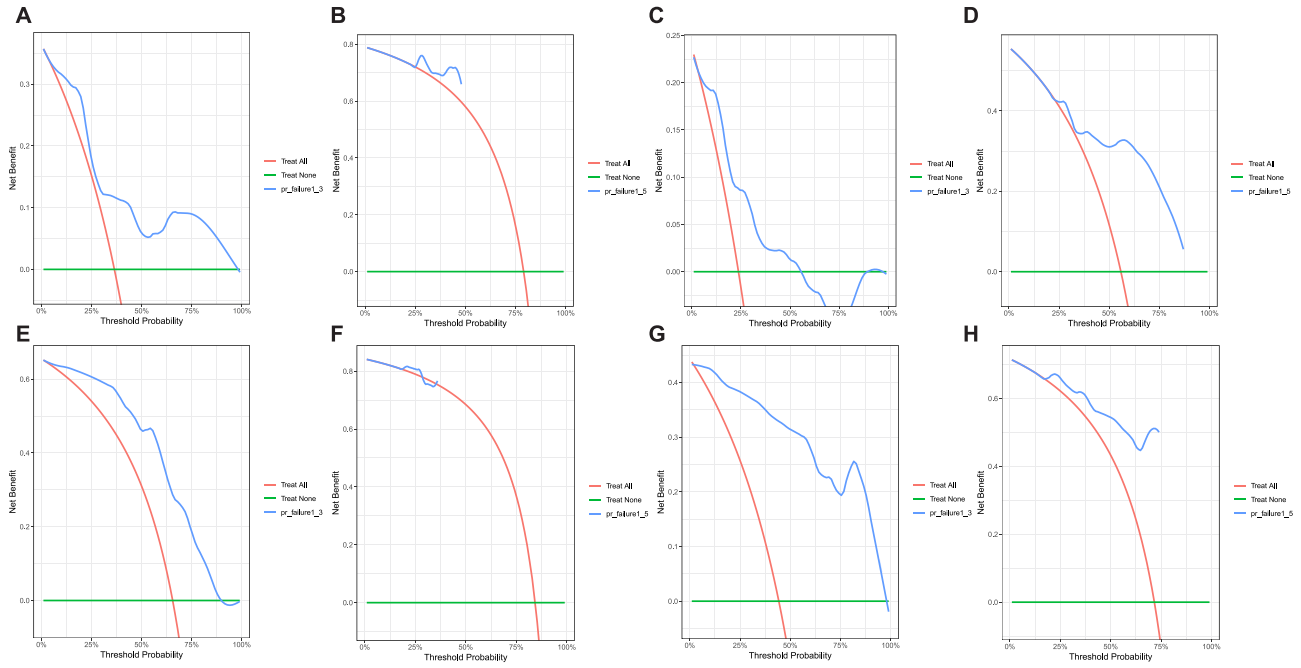

Figure 7 The DCA curves of nomogram predicting OS and PFS in intrahepatic cholangiocarcinoma. DCA curves of the 6 (**A**) and 12 months (**B**) OS in the training set and the 6 (**C**) and 12 months (**D**) OS in the validation set, and the curves of 6 (**E**) and 12 months (**F**) PFS in the training set and the 6 (**G**) and 12 months (**H**) PFS in the validation set.

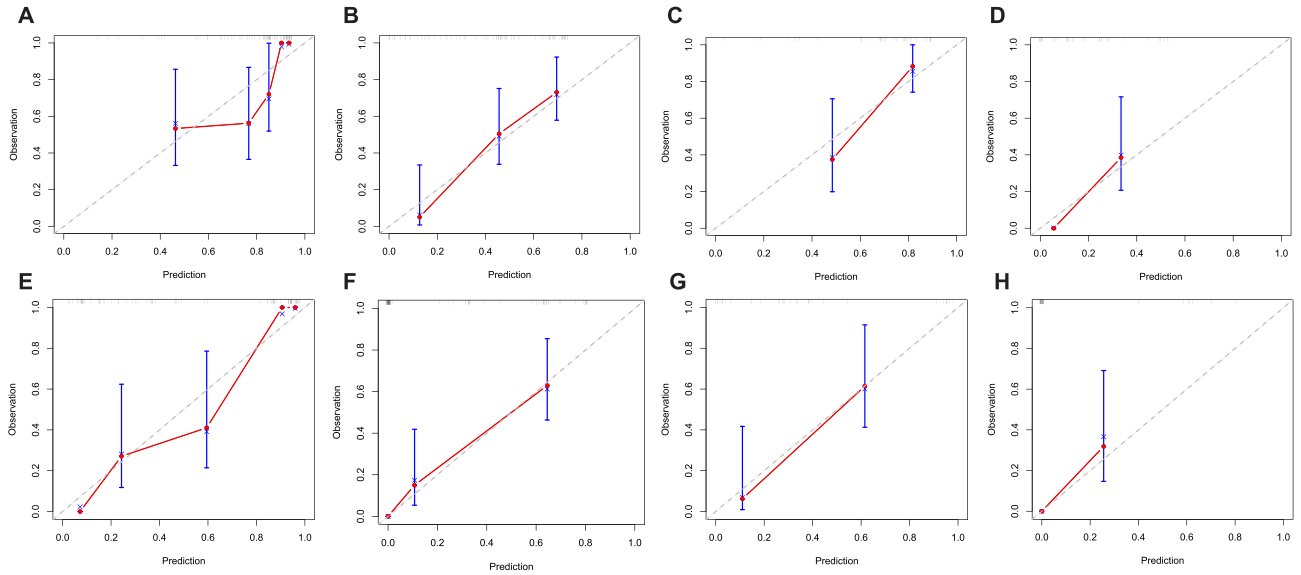

Figure 8 The calibration curves of nomogram predicting OS and PFS in intrahepatic cholangiocarcinoma. (**A** and **B**) Calibration curves of the 6- and 12-month OS in the training set, (**C** and **D**) Calibration curves of the 6- and 12-month OS in the validation set, (**E** and **F**) Calibration curves of the 6- and 12-month PFS in the training set, (**G** and **H**) Calibration curves of the 6- and 12-month OS in the validation set.

Clinicians typically use the AJCC staging system to assess patient prognosis; however, this system does not fully account for factors such as age, gender, tumor biomarkers, and adjuvant treatments. In contrast, the nomogram is a quantitative model that integrates multiple factors, including demographic and clinical characteristics, offering higher predictive accuracy and discriminative ability for survival prediction. Compared to the traditional AJCC staging system, the nomogram provides better predictive capability and clinical benefits.[34,35] In this study, we categorized ICC patients into low-risk and high-risk groups based on the total score from the nomogram. Kaplan-Meier and Cox proportional hazards model results indicate significant

differences in OS and PFS between these two groups. Given the poorer prognosis of the high-risk group, greater attention should be given to these patients.

The nomogram has potential value in clinical practice. For example, it can better predict patient prognosis, aid in the decision-making of advanced treatment options (such as radiotherapy, chemotherapy, or immunotherapy), and assist in developing and adjusting follow-up intervals for personalized disease monitoring. However, this study has some limitations. For instance, due to the rarity and low incidence of ICC, the sample size in this study was relatively small. Additionally, the retrospective data could lead to selection bias. Moreover, factors like nutritional status and psychological conditions, which could influence the prognosis of ICC patients, were not included due to challenges in data collection. Therefore, further multi-center, large-scale prospective studies are needed to explore clinical research on ICC.

Conclusion

ECOG, tumor volume, HBsAg and AFP were the independent prognosis factors affecting OS, and the gender, stage, CDC20 and the AFP were independent factors affecting PFS. The nomograms based on the above independent prognostic factors were used to predict OS and PFS in patients with unresectable ICC and have demonstrated consistent reliability and clinical utility in clinical assessments. It can serve as a useful tool for patient consultation and physician evaluation.

Data Sharing Statement

This research data can be obtained from the corresponding author or the first author.

Ethics Approval and Informed Consent

This study has been approved by the Academic Ethics Committee of Nanchong Central Hospital (No. 2022-079). Written informed consent was obtained from patients or their family members. Our study complies with the Declaration of Helsinki.

Consent for Publication

Written informed consent has been obtained from the patient(s) to publish this paper.

Acknowledgment

Thanks to all the authors for their serious responsibility and dedication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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