Development and Validation of Nomograms for Predicting Prognosis in Intrahepatic Cholangiocarcinoma Patients with Lymph Node Metastasis

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Research

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Abstract

Background. Lymph node metastasis (LNM) is one of the common metastatic sites of in advanced-stage intrahepatic cholangiocarcinoma (ICC), and the prognosis of ICC patients with LNM is worse than patients without it. Our study aimed to identify the prognostic factors of ICC patients with LNM, and develop an effective nomogram to quantify the prognosis of ICC patients with LNM.

Methods. We retrospectively reviewed the data of ICC patients between 2010 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate logistic analysis were used to determine the independent predictors for LNM in patients with ICC. Univariate and multivariate Cox analyses were used to identify the independent prognostic factors for ICC patients with LNM. Finally, two nomograms for predicting overall survival (OS) and cause-specific survival (CSS) were established, and the nomogram of predicting OS was evaluated by calibration curves, receiver operating characteristic (ROC) curves, and decision curve analysis (DCA).

Results. A total of 1539 patients with ICC were enrolled into our analysis, including 381 cases (24.76%) with LNM at initial diagnosis and 1158 cases (75.24%) without it. The independent risk factors for LNM in newly diagnosed ICC patients are age, T stage, and tumor size. The independent prognostic factors for ICC patients with LNM are grade, chemotherapy, and surgery of primary site. For the prognostic nomogram for OS, the AUCs of 6-, 12-, and 24-months were 0.809, 0.780, and 0.755 in the training set and 0.806, 0.780, and 0.753 in the testing set, respectively. The calibration curves and decision curve analysis indicated the good performance of the nomogram.

Conclusions. The individualized nomogram could predict OS of ICC patients with LNM with good performance, which could be served as an effective tool for prognostic evaluation and individual treatment strategies optimization in ICC patients with LNM, and clinical utility may benefit for clinical decision-making.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is rare, but it is the second most common primary liver tumor after hepatocellular carcinoma. A research reported that ICC accounts for 10–20% of all primary liver tumors, and it also accounts for 8–10% of biliary tract cancers [1]. ICC has been regarded as aggressive, and complete resection offers the only potentially curative treatment, which can provides patients with ICC a median overall survival (OS) of 14.4 to 38.8 months[2–7]. However, surgical resection can improve the prognosis of ICC patients, but it is estimated that 70% of ICC patients initially present with advanced-stage disease and considered unresectable[8]. Patients with clinically lymph node (LN) metastasis are deem advanced-stage disease, and their prognosis is typically considered to be similar to unresectable ICC patients. During a standard portal lymphadenectomy, the pericholedochal, periportal, and common hepatic artery lymph nodes are all excised, and these are also the most common sites of lymph node metastasis. Several clinicopathological factors of tumor, including tumor number, lymph node metastasis

and distant organ metastasis, have been regarded as risk factors of overall survival. Among the parameters studied, it is report that lymph node metastasis (LNM) is one of the most relevant factors[5, 9–11].Lymph node (LN) metastasis is one of the major prognostic factors in ICC patients, with only less than 20% of ICC patients with LNM surviving 5 or more years after surgical resection[5]. Lymph node metastasis strongly impacts the prognosis of ICC patients after surgical resection, so adjuvant strategy is needed[12], including adjuvant chemotherapy and radiotherapy. Therefore, it is important to establish predictive models for predicting the prognosis of ICC patients with LNM. Nomogram is a simple and multivariable visualization tool in oncology research, which is used to predict and quantify the rate of the outcome of individual patient [13]. The nomogram is also used to aid clinical decision-making and promote the development of precision medicine. Therefore, based on the data from the Surveillance, Epidemiology, and End Results (SEER) database, we aimed to develop an individual nomogram for predicting the overall survival (OS) of ICC patients with LNM.

Methods

Study population

Our data in this population-based study were retrieved from the US National Cancer Institute (NCI) open public database, the Surveillance, Epidemiology, and End Results (SEER) database. To identify the patients diagnosed with intrahepatic cholangiocarcinoma (ICC) from 2010 to 2015, the detailed population selection procedure was summarized in Fig. 1. The inclusion criteria in the present study were following: (1) All patients were enrolled from 2010 to 2015; (2) All patients with a primary site of “intrahepatic bile duct”, with ICD-O-Histology/behavior codes of 8160/3 (cholangiocarcinoma) and with single primary intrahepatic cholangiocarcinoma. Cases diagnosed at autopsy or via death certificates, with unspecified follow-up, with live, brain, lung and bone metastasis, and unknown lymph node metastasis information were excluded. Because our study used previously collected data from SEER database, it was exempt from the ethical review of the ethics board of the Fifth Affiliated Hospital of Guangxi Medical University. SEER*Stat version 8.3.8 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc. Calverton, MD, USA) was used for case listing.

Statistical analysis

All statistical analysis in our present study was conducted with SPSS 25.0 and R software (version 4.0.4). The chi-square test was used to compare the variables between the training set and the testing set. In the present study, a p-value < 0.05(two sides) was considered as statistical significance. Univariate logistic analysis was applied to identify LNM-related factors. The variables with p value < 0.1 in the univariate logistic analysis were included in the multivariate binary logistic regression analysis to determine independent risk factors of LNM in initially diagnosed ICC patients. For prognostic factors, the univariate Cox regression analysis was applied to identify prognostic variables. Then, significant variables in the

univariate Cox regression analysis were incorporated into the multivariate Cox regression analysis, and the independent prognostic factors of ICC with LNM were identified.

The predictive and prognostic nomograms were developed by the “rms” package in R software based on the independent prognostic factors. Meanwhile, the time-dependent receiver operating characteristic (ROC) curve for the prognostic nomogram was generated[14]. The area under the curve (AUC) was used to evaluate the discrimination of nomogram. Moreover, the calibration curves and decision curve analysis (DCA) curves were established for the nomogram[15]. Finally, according to the median of risk score, all patients were divided into the high-risk and low-risk groups, and the survival curve with a log-rank test was used to verify the prognostic value of the nomogram[16].

Results

Risk factors of LNM in ICC patients

In 1539 ICC patients, 381 cases (24.76%) with LNM at initial diagnosis and 1158 cases (75.24%) without it. To identify LNM-related variables in ICC patients, the multivariate logistic regression analysis showed that age ($p = 0.002$), T stage ($p < 0.001$), and tumor size ($p < 0.001$) were independent predictors for LNM in newly diagnosed ICC patients (Table 1).

Table 1
Uni- and multivariable logistic analysis of characteristics of patients with ICC presenting with LNM at the initial diagnosis (2010–2015)

Variable	Total	with LNM	without LNM	univariate		multivariable	
				OR(95%)	p	OR(95%)	p
patients	1539	381	1158				
Age (year)					<0.001		0.002
<65	704	204	500	Reference		Reference	
≥ 65	835	177	658	0.659(0.523–0.832)	<0.001	0.685(0.540–0.869)	0.002
Sex					0.208		
Female	781	204	577	Reference			
Male	758	177	581	0.862(0.683–1.087)	0.208		
Race					0.362		
White	1179	302	877	Reference			
Black	145	31	114	0.790(0.520–1.199)	0.268		
Other	215	48	167	0.835(0.590–1.180)	0.307		
Grade					0.063		0.156
Grade I-II	423	96	327	Reference		Reference	
Grade III-IV	327	97	230	1.437(1.034–1.996)	0.031	1.389(0.993–1.943)	0.055
Unknown	789	188	601	1.066(0.805–1.410)	0.657	1.196(0.892–1.604)	0.231
T stage					0.001		<0.001
T1-T2	1153	260	893	Reference		Reference	
T3-T4	303	101	202	1.717(1.303–2.263)	<0.001	1.756(1.326–2.326)	<0.001
TX	83	20	63	1.090(0.647–1.837)	0.745	1.510(0.865–2.635)	0.147

Abbreviations: CI, confidence interval; OR: odds ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

Variable	Total	with LNM	without LNM	univariate		multivariable	
Tumor size (cm)	468	84	384		<0.001		<0.001
<5	748	233	515	Reference		Reference	
≥ 5	323	64	259	2.068(1.560–2.743)	<0.001	1.981(1.487–2.639)	<0.001
Unknown				1.130(0.787–1.621)	0.509	1.020(0.696–1.495)	0.919
Surgery					0.016		
NO	1012	270	742	Reference			
YES	517	111	416	0.733(0.570–0.943)	0.016		
Radiation					0.084		
NO	1439	349	1090	Reference			
YES	100	32	68	1.470(0.949–2.276)	0.084		
Chemotherapy					<0.001		
NO	743	128	615	Reference			
YES	796	253	543	2.239(1.758–2.851)	<0.001		

Abbreviations: CI, confidence interval; OR: odds ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

Prognostic factors of patients with ICC presenting with LNM

381 ICC patients with LNM were used to study the prognostic factors. Among 381 patients, the 204 (53.5%) patients were male, 177(46.5%) patients female. And the race of 302 (79.3%) patients were White, 31 (8.1%) patients were Africa American, and 48 (12.6%) patients were other. Meanwhile, 269 patients were randomly divided into the training set, and the remaining 112 patients were incorporated into the testing set. The chi-square test showed that there were no significant differences between the training set and the testing set (Table 2).

Table 2
Clinical characteristics of patients in the training set and testing set

Variable	Total	Training set	Validation set	X2	p
patients	381	269	112		
Age (year)					
<65	204(53.5%)	148(55%)	56(50%)	0.801	0.371
≥ 65	177(46.5%)	121(45%)	56(50%)		
Sex					
Female	204(53.5%)	152(56.5%)	52(46.4%)	3.228	0.072
Male	177(46.5)	117(43.5%)	60(53.6%)		
Race					
White	302(79.3%)	208(77.3%)	94(83.9%)	3.059	0.217
Black	31(8.1%)	22(8.2%)	9(8.0%)		
Other	48(12.6%)	39(14.5%)	9(8.0%)		
Grade					
Grade I-II	96(25.2%)	71(26.4%)	25(22.3%)	0.891	0.64
Grade III-IV	97(25.5%)	69(25.7%)	28(25.0%)		
Unknown	188(49.3%)	129(48.0%)	59(52.7%)		
T stage					
T1-T2	260(68.2%)	186(69.1%)	74(66.1%)	0.367	0.832
T3-T4	101(26.5%)	69(25.7%)	32(28.6%)		
TX	20(5.2%)	14(5.2%)	6(5.4%)		
Tumor size (cm)					
<5	84(22.0%)	57(21.2%)	27(24.1%)	0.664	0.718
≥ 5	233(61.2%)	168(62.5%)	65(58.0%)		
Unknown	64(16.8%)	44(16.4%)	20(17.9%)		
Surgery					
NO	270(70.9%)	193(71.7%)	77(68.8%)	0.334	0.557
YES	111(29.1%)	76(28.3%)	35(31.3%)		

Abbreviations:. *P values were calculated by chi-square test

Variable	Total	Training set	Validation set	X2	p
Radiation					
NO	349(91.6%)	246(91.4%)	103(92.0%)	0.027	0.869
YES	32(8.4%)	23(8.6%)	9(8.0%)		
Chemotherapy					
NO	128(33.6%)	84(31.2%)	44(39.3%)	2.302	0.129
YES	253(66.4%)	185(68.8%)	68(60.7%)		
Abbreviations:. *P values were calculated by chi-square test					

As shown in Table 3 and Table 4, after the univariate Cox analysis, age, grade, surgery, chemotherapy, and radiation were significantly associated with OS and CSS, respectively. In the multivariate Cox analysis, grade(p<0.050), surgery (p<0.001), and chemotherapy(p<0.001) were identified as independent prognostic factors of OS and CSS, respectively.

Table 3
Uni- and multivariate cox analysis of overall survival for ICC with LNM

	Univariate Cox analysis			Multivariate Cox analysis		
Variable	HR	0.950	P-value	HR	0.950	P-value
Age (year)			0.001			0.241
<65		Reference			Reference	
≥ 65	1.531	1.179–1.989	0.001	1.179	0.896–1.551	0.241
Sex			0.080			
Female		Reference				
Male	1.264	0.973–1.642	0.080			
Race			0.667			
White		Reference				
Black	1.234	0.776–1.963	0.374			
Other	0.996	0.695–1.426	0.981			
Grade			<0.001			0.010
Grade I-II		Reference			Reference	
Grade III-IV	1.771	1.211–2.590	0.003	1.801	1.230–2.638	0.003
Unknown	1.954	1.406–2.715	<0.001	1.423	1.003–2.020	0.048
T stage			0.884			
T1-T2		Reference				
T3-T4	0.927	0.686–1.252	0.62			
TX	0.970	0.526–1.791	0.923			
Tumor size (cm)			0.569			
<5		Reference				
≥ 5	1.007	0.722–1.404	0.968			
Unknown	1.214	0.790–1.868	0.376			
Surgery			<0.001			<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

	Univariate Cox analysis			Multivariate Cox analysis		
NO		Reference				
YES	0.475	0.346–0.652	<0.001	0.473	0.334–0.668	<0.001
Chemotherapy			<0.001			<0.001
NO		Reference				
YES	0.357	0.270–0.473	<0.001	0.341	0.252–0.460	<0.001
Radiation			0.003			0.169
NO		Reference			Reference	
YES	0.449	0.266–0.760	0.003	0.686	0.401–1.174	0.069

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

Table 4
Uni- and multivariate cox analysis of cause-specific survival for ICC with LNM

	Univariate Cox analysis			Multivariate Cox analysis		
Variable	HR	0.950	P-value	HR	0.950	P-value
Age (year)			**0.002**			0.284
<65		Reference			Reference	
≥ 65	1.516	1.162–1.978	**0.002**	1.165	0.881–1.540	0.284
Sex			0.14			
Female		Reference				
Male	1.222	0.937–1.595	0.14			
Race			0.579			
White		Reference				
Black	1.279	0.803–2.036	0.3			
Other	1.002	0.695–1.443	0.993			
Grade			**<0.001**			**0.011**
Grade I-II		Reference			Reference	
Grade III-IV	1.778	1.212–2.609	0.003	1.799	1.224–2.644	0.003
Unknown	1.916	1.373–2.674	<0.001	1.39	0.975–1.983	0.069
T stage			0.949			
T1-T2		Reference				
T3-T4	0.964	0.712–1.304	0.81			
TX	0.921	0.485–1.750	0.803			
Tumor size (cm)			0.659			
<5		Reference				
≥ 5	1.001	0.715–1.401	0.997			
Unknown	1.182	0.762–1.834	0.455			
Surgery			**<0.001**			**<0.001**

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

	Univariate Cox analysis			Multivariate Cox analysis		
NO		Reference			Reference	
YES	0.481	0.349–0.663	<0.001	0.476	0.335–0.675	**<0.001**
Chemotherapy			**<0.001**			**<0.001**
NO		Reference			Reference	
YES	0.359	0.270–0.478	<0.001	0.342	0.252–0.464	**<0.001**
Radiation			**0.002**			0.127
NO		Reference			Reference	
YES	0.43	0.250–0.739	0.002	0.649	0.372–1.130	0.127

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC: intrahepatic cholangiocarcinom; LNM, lymph node metastasis.

Prognostic nomogram for ICC patients with LNM

Two prognostic nomograms for predicting OS and CSS were established based on three independent prognostic factors(Fig. 2a and b). For the prognostic nomogram for OS, the AUCs of 6-, 12-, and 24-months were 0.809, 0.780, and 0.755 in the training set, respectively(Fig. 3a,b and c). In the testing set, the AUCs of 6-, 12-, and 24-months were 0.806, 0.780, and 0.753, respectively (Fig. 3d, e and f). In addition, in the training set, the Kaplan-Meier survival curve showed that ICC patients with LNM in the high-risk group have a worse prognosis than patients in the low-risk group (Fig. 4a). Similarly, in the testing set, the OS of ICC patients with LNM in the high-risk group was also worse than patients in the low-risk group (Fig. 4b).The calibration curves for the probability of 6-, 12-, and 24-months OS also indicated a good consistency between nomogram predicted OS and the actual outcome in the training set (Fig. 5a, b and c) and in testing set (Fig. 5d, e and f), respectively. In addition, the DCA curves showed that the nomogram had a good predictive efficiency for OS of ICC patients with LNM in the training set(Fig. 6a, b and c) and in testing set (Fig. 6d, e and f), respectively.

Discussion

Intrahepatic cholangiocarcinoma frequently metastasizes to regional lymph node, which be associated with tumor recurrence after curative-intent resection. The association between lymph node metastasis and prognosis of ICC patients has not been fully investigated and validated. In the current study, lymph node metastasis was present in roughly 40% of ICC patients who underwent surgical resection. Even several studies have reported an higher incidence rate of lymph node metastasis in patients with ICC, as high as 45–62%[17, 18].

Therefore, we attempted to identify valuable predictor for lymph node metastasis in patients with ICC, as this information might be helpful in clinical practice. Several studies reported that tumor number and tumor diameter are significant predictive factors for LN metastasis in ICC patients[19, 20].Our study found that age, T stage, and tumor size were the best-fit predictor for LN metastasis in ICC patients. In addition, poorly differentiated ICC was also associated with a higher rate of lymph node metastasis [20].

Lymph node metastasis was reported to be one of the most significant prognostic factors for survival from ICC patients[9, 21]. However, despite the prognostic relevance of the LN status, several investigators reported that lymph node dissection (LND) does not seem to improve the OS of patients with ICC[22, 23].Actually, a retrospective large cohort study suggested that adjuvant chemotherapy could improve survival of ICC patients with lymph node metastasis, or advanced-stage[24–28]. Despite making a progress in understanding the pathophysiology of ICC and the emergence of novel treatment options[29], liver resection remains the only potential cure for ICC patients, whose survival has not improved significantly in recent decades [5, 30, 31].

Our research showed that ICC patients with LNM with high grade, absence of chemotherapy, and absence of surgery had unfavorable prognosis. Based on three independent prognostic factors of ICC patients with LNM, an individual nomogram for predicting OS was established and evaluated. The results indicated that the nomogram can serve as an effective tool to identify high-risk patients. It is well accepted that tumor grade could explain some of the heterogeneity associated with the expected course and clinical outcome in patients with various tumors[32, 33]. Tumor grade is a measure of the degree of differentiation of the tumor and is related to the prognosis of patients with tumor. In the present study, tumor grade was also observed as an independent prognostic predictor for OS in ICC patients with LNM. As far as we know, it is the first study to build a nomogram for predicting OS in ICC patients with LNM. Our nomogram, incorporating easily accessible factors in clinical practice, enabled easy calculation of individualized OS probabilities for ICC patients with LNM. Moreover, the nomograms showed relatively high accuracy with OS, and calibration curves display well-fitted in both the training set and testing set. In addition, high predictive accuracy does not mean that the predictive model has high clinical practicability [13, 15]. Decision curve analysis is one of the recommended methods in previous research on prognostic predictive models. It can quantify the net benefits of predictive models according to the threshold probability, so as to evaluate the clinical practical value of a predictive model[34–36]. Therefore, we introduced the decision curve analysis to examine the effectiveness of our nomogram in clinical practice.

The decision curve analyses not only confirmed the clinical validity of our nomogram for OS, but also demonstrated that our nomogram had better clinical application value in ICC patients with LNM.

However, our research also has some limitations. First, limited patients (N = 381) of ICC with LNM may result the possible error in our study. Second, the information collected in the SEER database was about the ICC disease at the first diagnosis, which meant that the lymph node metastasis occur in the latter stage cannot be recorded. Third, this was a retrospective study in which patients' selection bias existed inevitably, and the information about detailed treatment and progress after treatment was not available in the SEER database. However, notwithstanding these limitations, our study is the first to use a nomogram combined with clinically feasible variables including tumor grade, chemotherapy, and surgery of primary site to predict the OS of ICC patients with LNM, which has clinical significance for predicting prognosis of ICC patients with LNM.

Conclusions

Our study showed that age, T stage, and tumor size were the risk factors of LNM from ICC patients. As for ICC patients with LNM, high grade, chemotherapy, and surgery of primary site were independent prognostic factors for OS and CSS. Two nomograms we created may be individual, convenient, and more intuitive visual tools for prognostic prediction for ICC patients with LNM.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Xianmao Shi, Yi Xiao, and Zhi Zhang designed the study. Xianmao Shi and Xin Qin collected and analyzed the data and drafted the manuscript. Xing Sun, Ze Su and Zhaoshan Fang revised the manuscript and contributed to data interpretation.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the SEER database at https://seer.cancer.gov/seerstat/.

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Figures

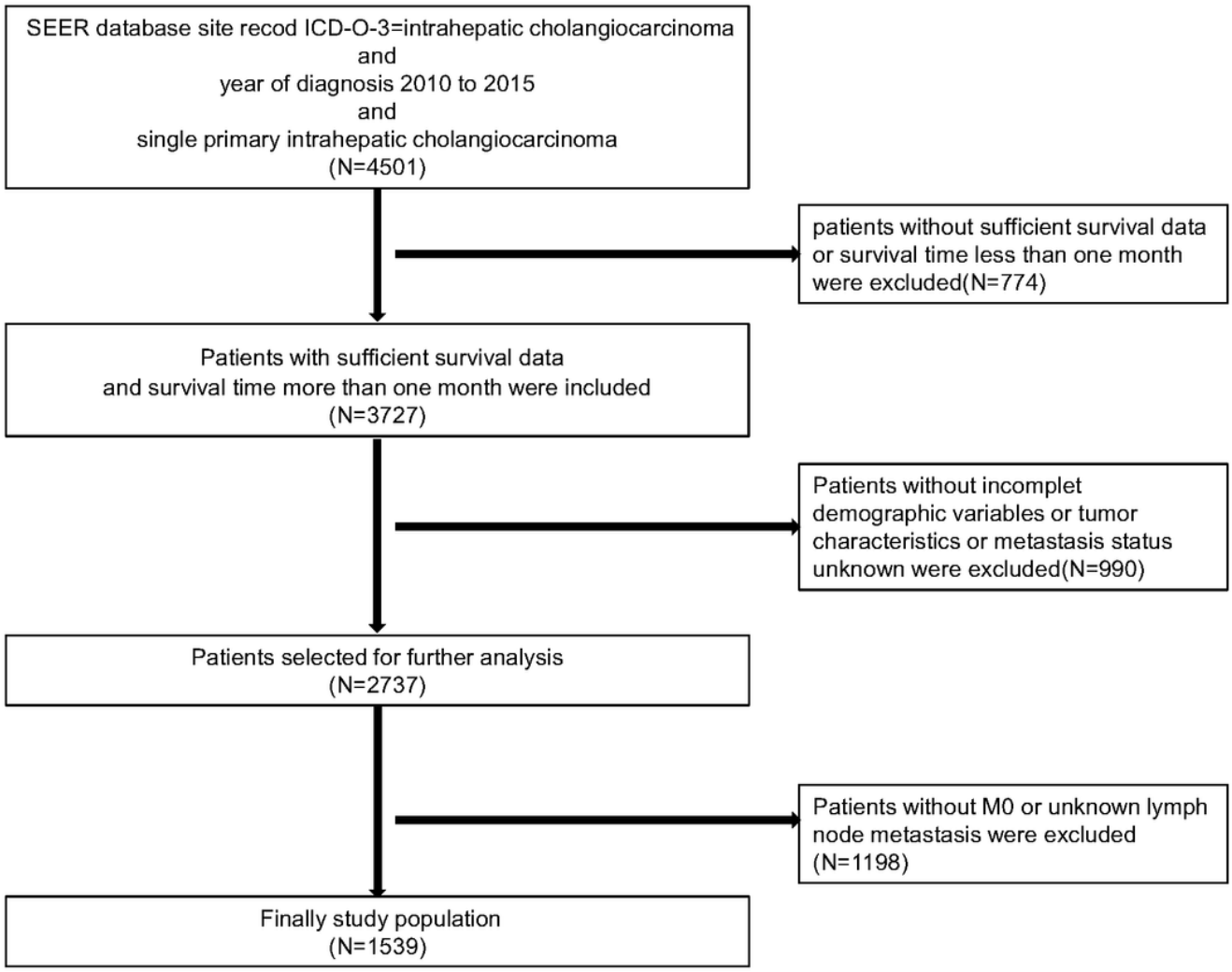

Figure 1

Flowchart of the enrolled patients in the study according to inclusion and exclusion criterion.

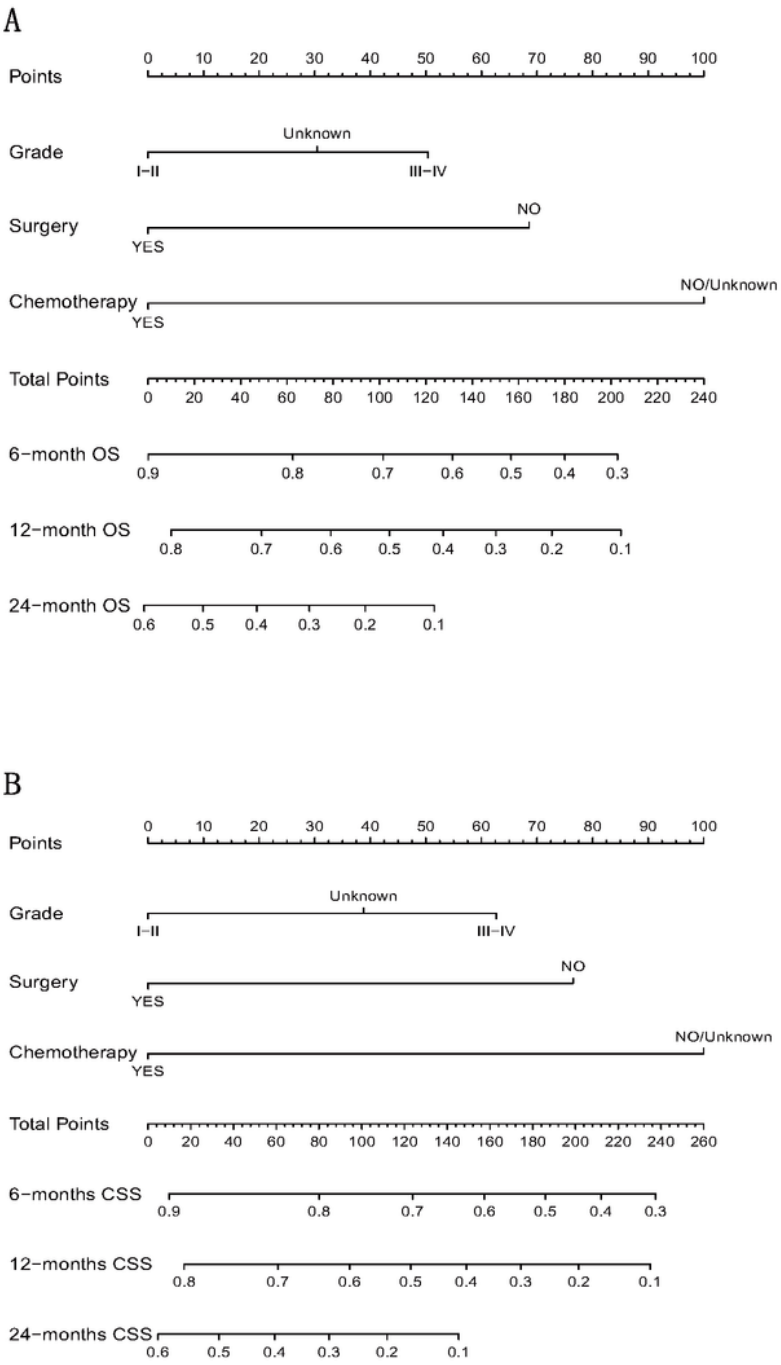

Figure 2

A prognostic nomogram for ICC patients with LNM, predicting overall survival(a) and predicting cause-specific survival(b).

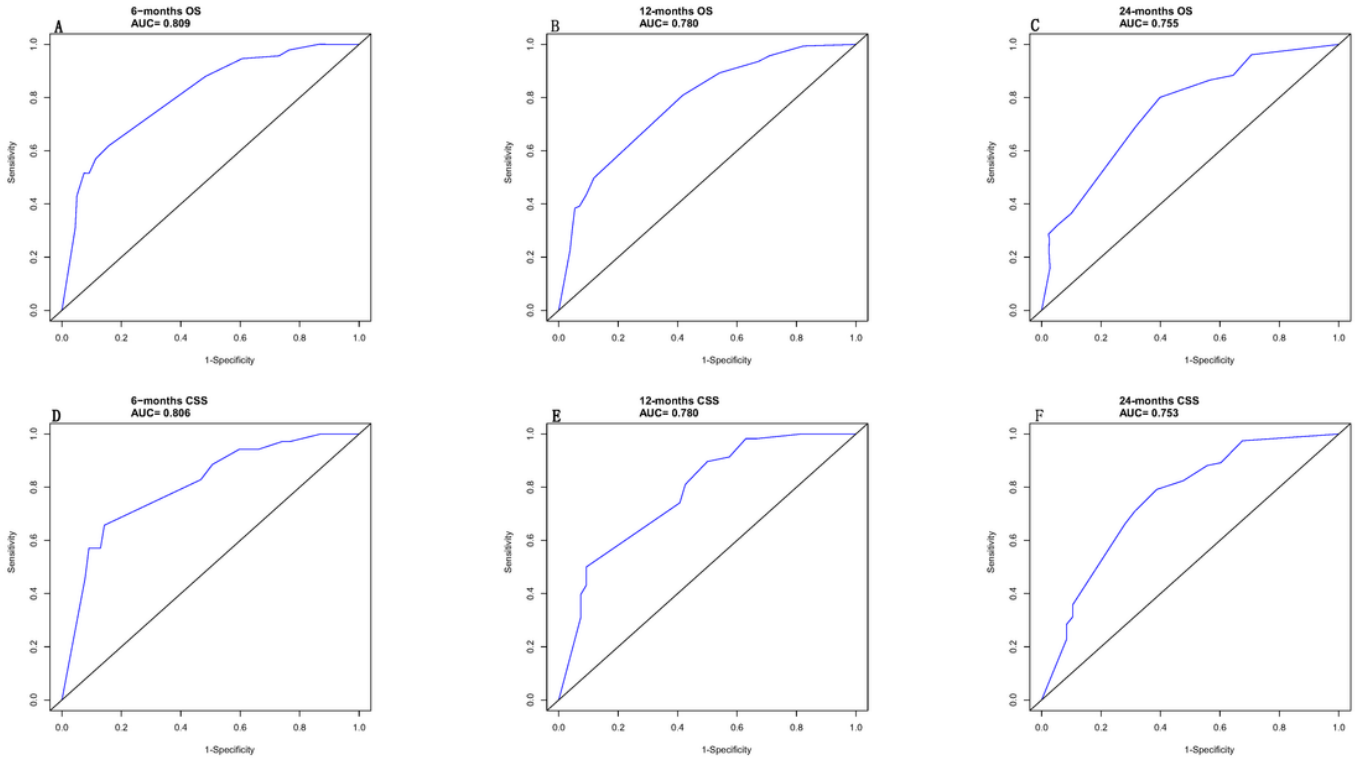

Figure 3

Receiver operating characteristic curves of 6-, 12-, and 24-months in the training set(a, b, and c); Receiver operating characteristic curves of 6-, 12-, and 24-months in the testing set(c, d, and e);

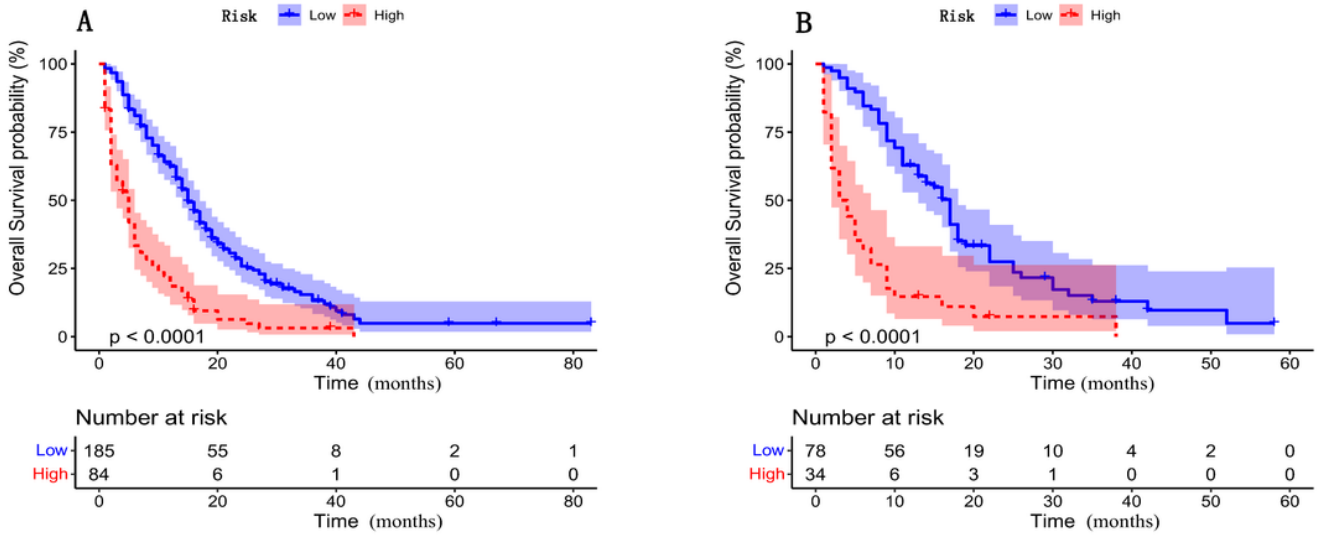

Figure 4

The Kaplan-Meier survival curve of the training set between high and low risk group(a); The Kaplan-Meier survival curve of the testing set between high and low risk group(b).

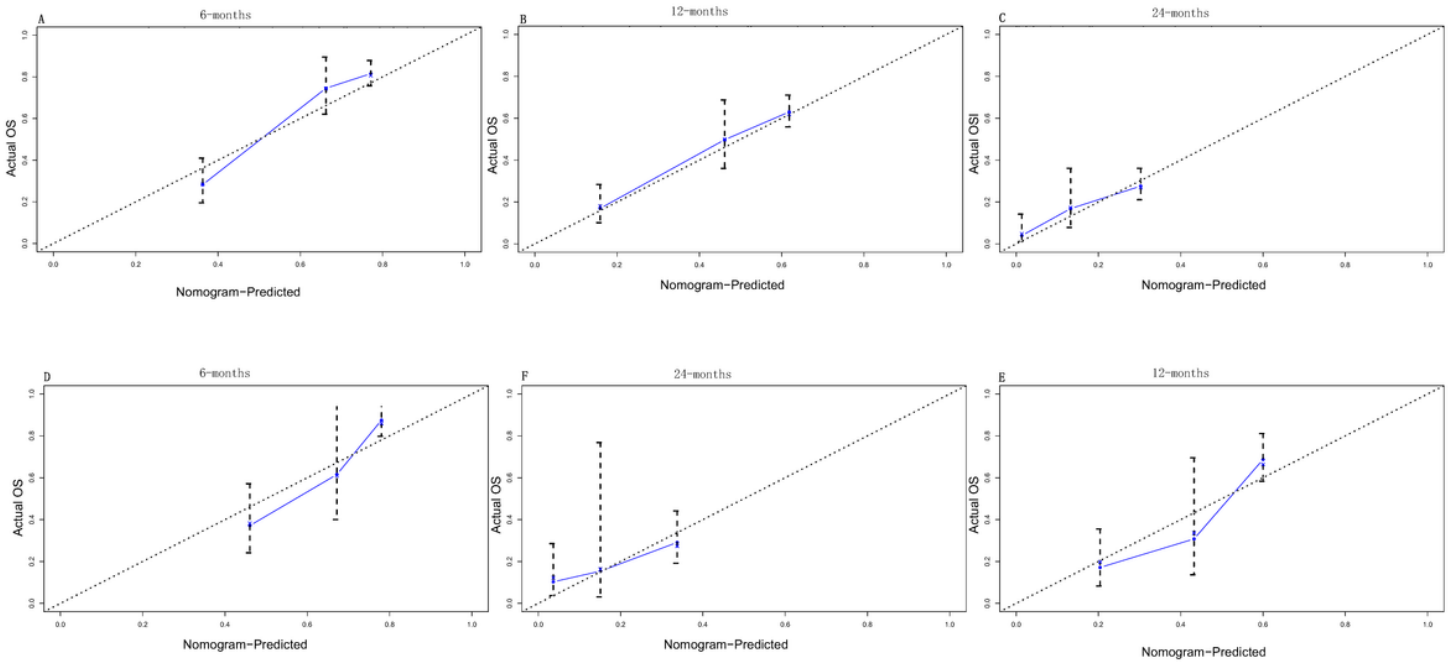

Figure 5

The calibration curves of the nomogram in the training set(a, b, and c); The calibration curves of the nomogram in the testing set(d, e, and f).

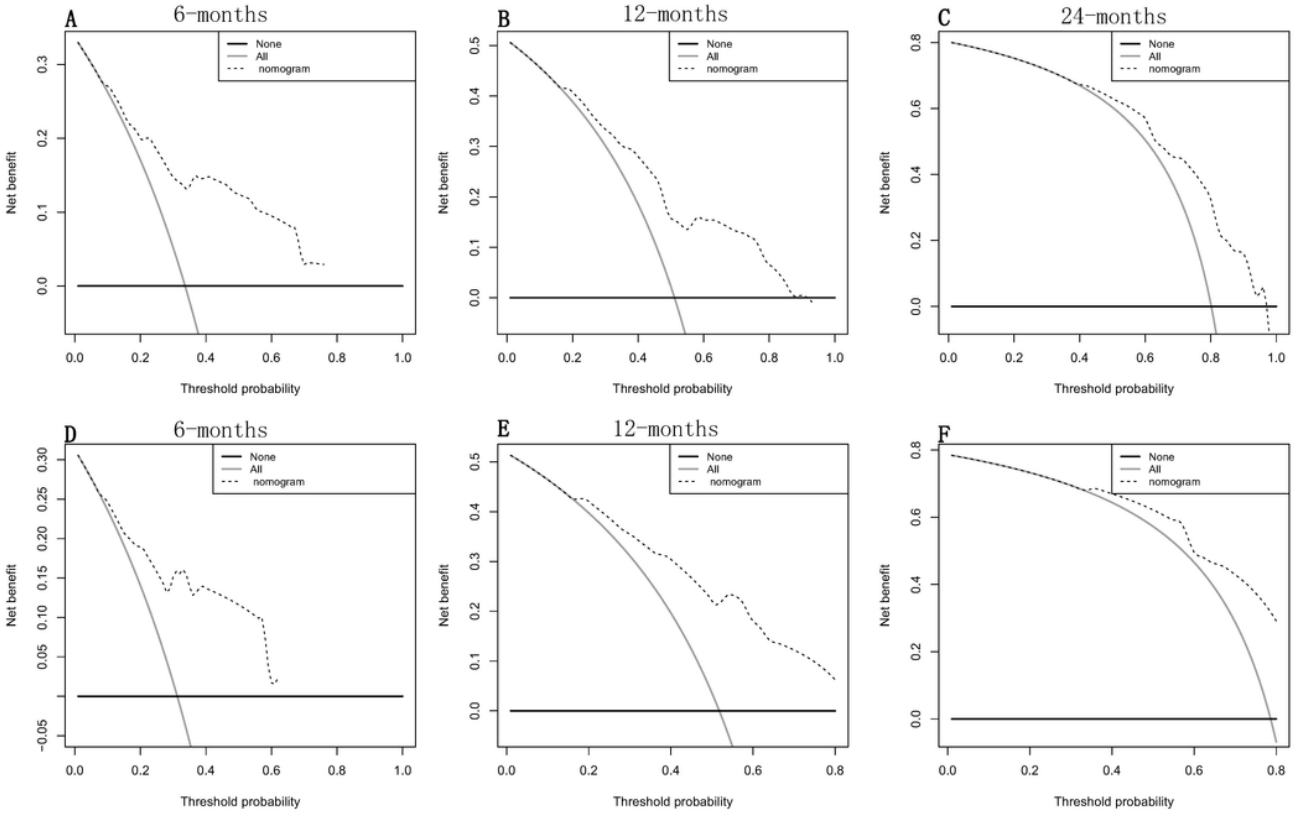

Figure 6

The decision curve analysis of the nomogram in the training set(a, b, and c); The calibration curves of the nomogram in the testing set(d, e, and f).