Construction and External Validation of a Nomogram for Predicting Survival of Intrahepatic Cholangiocarcinoma Patients Without Lymph Node and Distant Metastasis

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Research

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Abstract

Background

The purpose of this study was to construct and external validate a nomogram for predicting overall survival(OS) in intrahepatic cholangiocarcinoma (ICC) patients classified as N0M0 according to the 7th edition of American Joint Committee on Cancer (AJCC) TNM staging system.

Methods:

812 ICC patients without distant and lymph node metastasis between 2011 to 2015 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, then randomly assigned to the training cohort(n=648) or internal validation cohort(n=164), external validation cohort consisted of 136 ICC patients with N0M0 stage treated in West China Hospital of Sichuan University from 2013 to 2015. The precision of the nomogram was validated internally using SEER validation cohort and externally using the patients' data of West China Hospital.

Results :

The nomogram was established to predict 1-year, 3-year and 5-year OS and the calibration curve showed nomogram prediction performance was in good agreement with the actual results. The C-index of the nomogram was 0.750(95% CI:0.731-0.769) in the training cohort, and the internal and external validated C-indexes were 0.803(95% CI:0.783-0.823) and 0.681(95% CI:0.524-0.838), respectively. In the training, internal and external validation cohort, the 1-year, 3-year and 5-year AUCs were (0.772,0.809,0.798), (0.896,0.868,0.896) and (0.673,0.786,0.886), respectively.

Conclusions

This nomogram has an excellent predictive effect on the 1-,3-, 5-year OS of ICC patients with stage N0M0 and guide the optimal treatment for these type of patients.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a highly malignant tumor originating from second-degree and above bile duct branches epithelial cells, accounting for 15%~20% of primary liver cancer and about 20% of cholangiocarcinoma[1, 2].The incidence of ICC is only lower than that of hepatocellular carcinoma in primary liver cancer[3]. Over the past few decades, the morbidity and mortality of ICC has been steadily increasing[4–6].Radical surgical resection is still the only potential curative treatment for early-stage ICC at present[5],and regional lymph node dissection should be performed routinely[1, 7]. However, not all ICC patients without metastasis have the opportunity to undergo radical resection. After preoperative evaluation, some patients can only receive radiofrequency ablation(RFA), transcatheter arterial chemoembolization (TACE), palliative resection, etc. Despite partial hepatectomy, the 5-year survival rate is only about 30%, and the postoperative recurrence rate is as high as 60%-70%[8]. Compared with other subtypes of cholangiocarcinoma, local and intrahepatic recurrence of intrahepatic cholangiocarcinoma is the main

problem after surgery. Therefore, local and systemic treatment after surgery are theoretically necessary. Systemic chemotherapy based on gemcitabine and cisplatin(GC strategy) is usually recommended for patients with advanced or metastasis ICC who have lost the chance of surgery ,yet the median survival is disappointing to less than a year[5].Therefore, early detection and early treatment are particularly important for ICC.

In 2016, the latest edition of American Joint Committee on Cancer(AJCC) staging system, the 8th edition, was released[9]. Compared with the previous staging system, the concept and content of T staging were updated and improved, including adding tumor size as one of the staging factors. In addition, the staging system also highlights the influence of vascular invasion and the relationship between tumor and surrounding tissue on ICC prognosis, but T staging is still controversial. It has been reported that T staging does not well distinguish all ICC patients with different outcomes. Kang et al.[10] found that overall survival was similar in T2 and T3 patients using the 8th edition TNM staging, and that the 8th edition staging system did not significantly improve prognostic performance compared with the 7th edition(C-index:0.628 vs 0.626). Svolverato et al.[11]found that according to the 8th edition of TNM, the risk of death in T3 patients was lower than that in T1b and T2 patients.

Therefore, for ICC patients with N0M0 stage whose prognosis is mainly predicted by T stage, developing a survival prediction tool has good clinical application value. To our best knowledge, there is currently no survival prediction facility for N0M0 staging ICC been reported, and it would be valuable to establish a model that can well predict the prognosis of early ICC. Since the ability of T stage of the 8th editon AJCC TNM staging system to distinguish prognosis is still controversial and the staging information of patients before 2015 is not available, data were extracted from the SEER database to screen N0M0 ICC patients using the 7th edition of the AJCC staging system.

Previous studies have shown that a nomogram is an optimal tool that can be used to quantify the prognosis of tumor development by a variety of predictive factors, which is simple and intuitive to apply, and can provide individualized monitoring and follow-up programs for patients, providing support for clinical decision-making[12, 13].For some cancers, the use of nomograms is even superior to the traditional staging system[14–16].

The aim of this study was to determine the factors affecting the prognosis of ICC patients with N0M0 stage, and to construct a prediction nomograph of prognosis, then the prognosis model was internally and externally validated based on data from SEER database and West China Hospital of Sichuan University,respectively.

Methods

Data Source And Selection

Clinical data of the the ICC patients(international tumor classification:ICD-O-2/ICD-O-3, histology type code : 8160, and the primary site code: C22.1)[17]that formed the training cohort were extracted from database from the SEER database (<http://seer.cancer.gov/>), to ensure adequate follow-up time, we collected patient

data between 2011 to 2015. Patients with distant metastases and lymph node metastases; patients without a pathological diagnosis of ICC; patients with incomplete or missing tumor information were excluded, and patients with incomplete survival time or other co-existing malignancies and serious underlying diseases were also excluded. A total of 812 patients met the inclusion criteria were eventually enrolled in the training cohort, the data collection process is shown in Fig. 1. The clinical data we extracted and analyzed in the analysis were as follows: age, gender; marital status, AJCC staging for tumor (T), lymph nodes (N), and presence of metastasis (M); tumor size, tumor number, tumor grade, chemotherapy, radiation, surgery, months of survival.

We applied the 7th edition of the AJCC staging system, which was available for patients between 2004 and 2015. To evaluate the general applicability of the nomogram based on the SEER database for predicting prognosis, we performed external validation using clinical data of 136 patients from West China Hospital of Sichuan University, this study was approved by the ethics committee of our hospital and informed consent of all validation cohort patients and their relatives. The SEER database is publicly available, the basic information of the patients included in the training cohort has been unlabeled, so informed consent was waived.

Statistical Analysis

Statistical analyses were achieved by R software (version 3.6.1, <http://www.r-project.org/>) and SPSS Statistics (version 23.0; IBM Corporation). Continuous variables were described as medians with interquartile ranges (IQRs), and frequencies and percentages were used for statistical description of count and grade data. Comparison of categorical variables were performed by the Pearson's chi-square test or the Fisher's exact test. Student's t-test or the Wilcoxon signed-rank test were used to compare continuous variables. We set OS as the main prognostic indicator of ICC patients. OS was defined as the time from diagnosis of ICC to death or final follow-up. Cox proportional hazards regression model was used for univariate analyses to evaluate predictors of long-term prognosis, variables with $p < 0.1$ were further analyzed by multivariate analyses. Hazard ratios (HRs) were showed with 95% CI. By using the independent risk factors, a nomogram was developed to predict the 1-, 3-, 5-year OS rates. Harrell's concordance index (C-index), calibration plot and area under the receiver operating characteristic (ROC) curve (AUC) were used to evaluate the discriminant ability of the nomogram. The values of C-index and AUC are between 0.5 and 1.0, and the higher the value, the stronger the distinguishing ability of the prediction model will be. The cutoff values of the total points in the nomogram were identified according the maximum of the Youden index, and patients in the training cohort and the validation cohorts were divided into high-risk and low-risk groups by cutoff values. Kaplan-Meier survival curves were analysing using the log-rank test.

Bilateral tests were used for all statistical tests, and a P-value < 0.05 was considered statistically significant.

Results

Patients Baseline Characteristics

A total of 812 eligible patients with a diagnosis of ICC in the SEER database from 2011 to 2015 were randomly enrolled in the training cohort(n = 648) and internal validation cohort(n = 164), in addition, 136 cases of ICC patients from the West China Hospital of Sichuan University from 2013 to 2015 were enrolled as an external validation cohort. The clinical characteristics of patients in these three cohorts were summarized in Table 1. In the training cohort, 333(51.4%) patients were aged over 65 years and 321(49.5%) were male, 208(32.1%) patients underwent resection; in the internal and external validation cohort, 86(52.4%) and 63(46.3%) patients were aged over 65 years, 83(50.6%) and 88(64.7%) were male, 61(37.2%) and 53(39.0%) patients underwent resection, respectively.

Table 1

Baseline clinical characteristics of training cohort, internal validation cohort and external validation cohort.

Characteristic		N (total)	Patients		p value	p value	
			Training cohort n(%)	Internal Validation cohort n(%)		External Validation cohort n(%)	
Total		948	648	164		136	
Age (years)	≤ 65	466	315(48.6%)	78(47.6%)	0.752	73(53.7%)	0.457
	> 65	482	333(51.4%)	86(52.4%)		63(46.3%)	
Gender	Male	492	321(49.5%)	83(50.6%)	0.273	88(64.7%)	0.001*
	Female	456	327(50.5%)	81(49.4%)		48(35.3%)	
Maritalstatus	Married	572	379(58.5%)	106(64.6%)	0.634	87(64.0%)	0.478
	Divorce	121	88(13.6%)	18(11.0%)		15(11.0%)	
	Other	255	181(27.9%)	40(24.4%)		34(25.0%)	
AJCC T stage	1–2	564	384(59.3%)	95(57.9%)	0.504	85(62.5%)	0.483
	3–4	384	264(40.7%)	69(42.1%)		51(37.5%)	
Tumor size (cm)	< 5	327	213(32.9%)	59(36.0%)	0.99	55(40.4%)	0.054
	5–10	324	227(35.0%)	46(28.0%)		51(37.5%)	
	> 10	297	208(32.1%)	59(36.0%)		30(22.1%)	
Tumor grade	I	63	38(5.9%)	11(6.7%)	0.506	14(10.3%)	0.181
	II	235	152(23.4%)	49(29.9%)		34(25.0%)	
	III-IV	194	128(19.8%)	37(22.5%)		29(21.3%)	
	Unknown	456	330(50.9%)	67(40.9%)		59(43.4%)	
Tumor number	1	896	608(93.8%)	160(97.6%)	0.99	128(94.1%)	0.896
	> 1	52	40(6.2%)	4(2.4%)		8(5.9%)	
Surgery	Resection	322	208(32.1%)	61(37.2%)	0.653	53(39.0%)	0.128
	Partial destruction	40	25(3.9%)	7(4.3%)		8(5.9%)	
	None	586	415(64.0%)	96(58.5%)		75(55.1%)	

Characteristic		N (total)	Patients			p value	p value
			Training cohort n(%)	Internal Validation cohort n(%)	External Validation cohort n(%)		
Chemotherapy	yes	437	294(45.4%)	76(46.3%)	0.390	67(49.3%)	0.408
	no/unknown	511	354(54.6%)	88(53.7%)		69(50.7%)	
Radiation	yes	147	111(17.1%)	19(11.6%)	0.414	17(12.5%)	0.184
	no/unknown	801	537(82.9%)	145(88.4%)		119(87.5%)	

Independent Risk Factors Of The Training Cohort

Univariate analysis showed that age, AJCC T stage, tumor size, tumor grade, tumor number, surgery, marital status, were independent factors affecting OS ($p < 0.05$), gender and radiation had no statistical significance on OS ($p > 0.05$). Then, multivariable cox regression analysis was carried out and the final results showed 5 factors with statistical significance: T stage (T3-T4: HR = 1.569, 95%CI: 1.302–1.892, $p < 0.001$), tumor size (5-10cm: HR = 1.18, 95%CI: 0.938–1.485, $p = 0.065$; >10cm: HR = 1.229, 95%CI: 0.972–1.554, $p = 0.043$), tumor grade (grade II: HR = 1.052, 95%CI: 0.662–1.672, $p = 0.830$; grade III-IV: HR = 1.595, 95%CI: 1.005–2.531; $p = 0.048$, grade unknown: HR = 1.520, 95%CI: 0.980–2.356; $p = 0.062$), surgery (partial destruction: HR = 0.254, 95%CI: 0.148–0.434, $p < 0.001$, resection: HR = 0.224, 95%CI: 0.172–0.293, $p < 0.001$), chemotherapy (HR = 0.629, 95%CI: 0.516–0.767, $p < 0.001$), the results of univariate and multivariate regression analysis are shown in Table 2.

Table 2: Results of univariate and multivariate Cox regression analysis of OS on training cohort.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p value	HR (95%CI)	p value
Age (years)				
≤65	Reference		Reference	
>65	1.401(1.175-1.670)	<0.001**	1.121(0.930-1.354)	0.231
Gender				
Male	Reference			
Female	0.931(0.782-1.109)	0.422		
Maritalstatus				
Other	Reference		Reference	
Married	0.792(0.650-0.965)	0.020*	0.978(0.793-1.207)	0.839
Divorce	0.860(0.644-1.149)	0.309	0.899(0.667-1.213)	0.487
T stage				
T1-T2	Reference		Reference	
T3-T4	1.705(1.428-2.035)	<0.001**	1.569(1.302-1.892)	<0.001**
Tumor size (cm)				
<5	Reference		Reference	
5-10	1.363(1.094-1.697)	0.006*	1.18(0.938-1.485)	0.065
>10	1.992(1.598-2.483)	<0.001**	1.229(0.972-1.554)	0.043
Tumor grade				
I	Reference		Reference	
II	0.955(0.605-1.508)	0.844	1.052(0.662-1.672)	0.830
III-IV	1.624(1.031-2.558)	0.036*	1.595(1.005-2.531)	0.048*
Unknown	2.547(1.663-3.899)	<0.001**	1.520(0.980-2.356)	0.062
Tumor number				
1	Reference		Reference	
>1	1.797(1.202-2.687)	0.004*	1.384(0.918-2.086)	0.120
Surgery				
None	Reference		Reference	
Partial destruction	0.272(0.162-0.456)	<0.001**	0.254(0.148-0.434)	<0.001**

Resection	0.210(0.168-0.263)	<0.001**	0.224(0.172-0.293)	<0.001**
Chemotherapy				
no/unknown	Reference		Reference	
yes	0.888(0.745-1.059)	0.094	0.629(0.516-0.767)	<0.001**
Radiation				
yes	Reference			
no/unknown	0.827(0.654-1.044)	0.11		

Constructing Prognostic Nomograms For Os

Based on the significant independent risk factors of multivariate analysis, a nomogram was constructed to predict the 1-,3-,5-year OS of N0M0 stage ICC patients(Fig. 2). The nomogram shows that the most affected factor for the OS is the surgery, followed by chemotherapy, AJCC T stage, tumor grade and tumor size. The total points is calculated by adding up the points corresponding to each factor, then locating it on the bottom scale to help clinicians predict 1-,3-,5-year OS for each independent N0M0 stage ICC patient. A higher total points reflects a poorer prognosis.

Discrimination And Calibration Of The Nomogram

In the training cohort ,internal and external validation cohort, the calibration plots of the OS predicting nomogram all show good agreement between the predictions and the actual observations of the 1-, 3-, and 5-year OS.(Fig. 3A-I)

The C-index values for OS prediction were 0.750(95% CI:0.731–0.769) in the training cohort, 0.803(95% CI:0.783–0.823) in the internal validation cohort, and 0.681(95% CI:0.524–0.838) in the external validation cohort, which revealed a good prognostic accuracy of the nomogram. We plotted the ROC curves for all cohorts, the AUC values of 1-, 3- and 5-year OS in the training cohort were 0.772,0.809,0.798, respectively; 0.896,0.868,0.896 in the internal validation cohort, respectively, and 0.673,0.786,0.886 in the external validation cohort, respectively, which reveals a nice discriminated ability of the normogram(Fig. 4A-I).

Stratification Of Risk Groups

From the maximum values of the Youden indexes of the ROC curves, we obtained the cutoff values of 110 based on the nomogram. ICC patients in the training cohort, the internal and external validation cohort were then divided into high-risk(total points ≥ 110) and low-risk(total points < 110) groups respectively. The Kaplan-Meier survival curves of the three cohorts were drawn, and the curves all showed that patients in the low-risk group obtained significantly better OS than patients in the high-risk group. (Fig. 5A-C).

Discussion

Intrahepatic cholangiocarcinoma is a type of primary liver cancer originating from intrahepatic bile duct epithelial cells with poor prognosis and lack of effective treatment. The incidence of intrahepatic cholangiocarcinoma has been increasing worldwide in the last 30 years[18]. For some patients of early stage ICC, surgical treatment has been recognized as the most effective treatment to improve the OS[5, 19]. Due to the insidious and invasive characteristics of ICC, it is often not diagnosed in time. Many ICC patients already metastasis at the time of initial diagnosis, losing the chance of surgery always means a bad prognosis.

Nomogram is a intuitive, and effective graphical math model developed based on independent prognostic factors of cancer, it is used for survival prediction of various cancers[20–22]. A good nomogram can predict prognosis even better than traditional TNM staging systems[15, 16].

In our study, based on the SEER database, we constructed and internally validated a nomogram to predict the OS at 1-, 3- and 5- years of ICC patients with stage N0M0. External validation was performed using a validation cohort composed of included ICC patients from West China Hospital(C-index:0.681,95% CI:0.524–0.838). To our knowledge, this is the first prognostic tool specifically for N0M0-stage ICC patients, five indicators(surgery,chemotherapy, AJCC T stage, tumor grade, tumor size) are included in this nomogram. Consistent with other studies on ICC for different purposes[23, 24], we find that surgery is the most important factor affecting OS among the 5 indicators in the nomogram, meanwhile, it reveals that chemotherapy can also improve the prognosis of ICC patients,which is consistent with previous studies that reported that surgery combined with adjuvant chemotherapy has better efficacy than surgery alone[25–27].

The staging system of ICC is constantly being updated and properly modified but the effect of tumor size on the prognosis of ICC patients has been controversial, prior to the 7th edition of the AJCC staging system, tumor diameter was not considered as a staging factor[28]. Although there are some differences in selected cut-off values, tumor size has been reported to be correlated with the prognosis of ICC patients[29–31]. What's more, tumor size has been included in the 8th edition AJCC staging system and based on a large body of evidence-based medical evidence,the tumor diameter of 5cm was selected as the cut-off for the T1 stage refinement(T1a,T1b)[9], later, some scholars also verified it[32]. Due to the lack of 8th edition AJCC staging system information for ICC patients in the earlier SEER database, and the lack of specific information of the tumor, we could not directly convert from 7th or 6th stage to 8th stage. We used T staging of the 7th AJCC staging system as a variable and included tumor size as a separate predictor and we used 5cm and 10cm as the cutoff values for classifying tumor size. We found that both tumor size and the AJCC T stage were impact factors of prognosis, patients with larger tumors have a worse prognosis,

which is consistent with published studies and justifies the inclusion of tumor size as a staging indicator in the 8th edition of the staging system.

This nomogram had some certain advantages, for instance, the training cohort and the internal validation cohort are mainly composed of patients from the United States, while the external validation cohort mainly contains yellow race from China, indicating this nomogram is suitable for predict the prognosis of ICC patients at N0M0 stage from different regions and ethnic groups. Then, there was no age limit for patients in our inclusion criteria, all the range of ages meet the criteria were included, not as some other studies just include the young or the old, so the nomogram is suitable for all the ICC patients at N0M0 stage. This nomogram does not include age as one of the indicators, because multivariate analysis did not find a significant effect of age on OS in the training group, which may be due to the relatively small effect of age on prognosis due to the significantly shortened survival time of ICC patients, similarly, Horgan et al.[33] found that for patients with biliary tract cancers, there was no significant difference in survival rates between younger and older patients after surgical treatment.

To verify the predictive stability of this nomogram, we performed external validation, as evaluated by the AUCs and c-index values, the nomogram all showed good predictive performance. The validation plots of the 1-, 3-, and 5-year OS predicting nomogram all demonstrated the relatively good accurate between the predictions and the actual observations. This means that this nomogram will be helpful for clinicians' formulation of personalized treatment stratage for specific ICC patients with a N0M0 stage.

Although the establishment of the model was based on a large sample size, and the external validation cohort was selected from relatively representative hospitals in China, our study still had some limitations. First, the data analysed in this study were collected retrospectively, and there may be potential bias due to unknown confounding factors. Second, all the variables used in the modeling were selected from the SEER database, but some data that might be related to prognosis were not provided in this database, such as the specific radiotherapy dose and chemotherapy stratage, the specific site of lymph node dissection, tumor marker such as carbohydrate antigen 199(CA19-9), and resection margins. Finally, we excluded some patients with incomplete clinical data, which may also lead to selection bias.

Conclusion

We developed a nomogram to predict 1-, 3-, and 5-year OS in N0M0 stage ICC patients.Using the SEER and the external validation datasets of West China Hospital reveals good resolution and calibration ability. Therefore, this nomogram may help predict individual survival in ICC patients without lymph nodes or distant metastasis and guide clinicians in the development of treatment strategies.

Declarations

Acknowledgments

Not Applicable.

Authors' contributions

Conception and design: CJ, FT, YYT. Drafted the initial manuscript: CJ. Data collection:CJ,FT,YMC. Analysis and interpretation of the data:FT,ZQZ. Analyses, reviewed and revised the manuscript:ZYC. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The Ethics Committee of West China Hospital of Sichuan University approved the study and informed consent was obtained from all patients in the validation cohort and their relatives.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The flow diagram of the screening process for the target ICC patient population from the Surveillance, Epidemiology, and End Results (SEER) database.

Figure 2

The nomogram for predicting 1-, 3- and 5-year overall survival rates of N0M0 stage ICC patients. T:AJCC T stage

Figure 3

Calibration plots predicting the 1-, 3- and 5-year OS of patients in the training cohort (A,B,C), internal validation cohort(D,E,F) and external validation cohort(G,H,I).

Figure 4

ROC curves and AUCs of 1-; 3- and 5-year OS in training cohort (A,B,C), internal validation cohort(D,E,F) and external validation cohort(G,H,I). AUC: area under the curve; ROC: receiver operating characteristic; TP: true positive rates; FP: false positive rate.

Figure 5

Kaplan-Meier curves of high-risk and low-risk patients in the training cohort(A),internal validation cohort(B) and external validation cohort(C).