Construction and Validation of a Nomogram for The Prediction of Overall Survival in Intrahepatic Cholangiocarcinoma

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Abstract

Objective: This study aimed to establishand validates a nomogram to predict the overall survival (OS) of patients with intrahepatic cholangiocarcinoma (ICC).

Patients and methods: The ICC patients were collected from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2015. Then, the independent prognosis-related factors were obtained from the training set using the Cox regression model for the establishment of a nomogram.

Results: We identified 3675 eligible patients with a median survival time of 9 months (0–153 months). According to multivariate analysis, age, sex, marital status, grade, T stage, N stage, M stage, surgery, chemotherapy and radiotherapy were identified as the factors to independently predictthe prognosis for ICC (all $P<0.05$). Thereafter, the above factors were incorporated for the construction of a nomogram. In comparison with the AJCC 8th TNM classification system and the SEER summary stage system, our constructed nomogram showed higher ability in discrimination, as revealed by the C-index (all $P<0.001$).Besides, the internal as well as external calibration curve analysis demonstrated that the predicted results were highly consistent with the actual ones. On the other hand, our nomogram outperformed the AJCC 8th TNM classification system and the SEER summary stage system in predicting the 3- and 5-year OS, as suggested by time-independent area under the curve (tAUC) values.

Conclusion: Our constructed nomogram performs well, indicating its potential as an efficient approach to evaluate the prognosis of ICC patients.

Introduction

Intrahepatic cholangiocarcinoma (ICC) accounts for an uncommon liver cancer, whose morbidity is much lower than hepatocellular carcinoma (HCC), and it is originated from intrahepatic bile duct epithelium [1]. ICC is associated with the lowest incidence among all types of cholangiocarcinomas, in comparison with those originated from the upper 1/3 of biliary tract or the 2/3that involves the common hepatic duct bifurcation (Klatskin tumors)[2]. Despite of the rarity, ICC shows an increasing incidence within the past few decades[3]. Besides, its clinical characteristics and prognostic outcomes show significant differences from HCC [4,5]. Due to the rarity and heterogeneous nature of ICC, identifying reliable prognostic features have been a challenge.

At present, the 8th edition of the Tumor-Node-Metastasis (TNM) classification system developed by the American Joint Commission on Cancer (AJCC)[6] has been extensively applied in evaluating the prognosis for ICC. The TNM classification system is usually used to predict cancer outcomes through evaluatingthe tumor site and size (T), involvement of regional lymph node (N) together with distant metastasis (M). But additional vital factors, including age, race, gender, degree of tumor differentiation as well as treatment, may also affect individual patient survival [7]. Additionally, the TNM 8th classification system can not

sufficient predicts the prognosis for individual patients. As a result, it is urgently needed to establish an approach to classify ICC prognosis with technical feasibility and easy accessibility.

Nomogram is the facile approach used for statistical prediction, which is extensively utilized for prognosis prediction clinically [8–10]. To construct a nomogram, it is necessary to take the prognostic weights of all factors into account during the calculation of an outcome probability; in addition, it is also required to integrate several independent factors for drawing the optimal conclusion. In comparison with the AJCC TNM classification system, nomogram is able to precisely evaluate patient survival through combining the vital prognosis-related factors [11]. As far as we know, no nomogram has been constructed to predict the prognosis for ICC. In this regard, this work aimed to construct and validate a nomogram to predict the OS for ICC patients collected from the Surveillance, Epidemiology, and End Results (SEER) database.

Materials And Methods

Ethical statement

In the SEER program organized by the National Cancer Institute, the population-based data are used for developing the integrated sources, which cover approximately 30% US population from diverse geographic regions[12,13]. To extract data from the SEER database, we signed the Research Data Agreement using the reference number 19858-Nov2018. In line with the verified guidelines, data were obtained according to research methods. All the collected information was public and de-identified. Therefor, this study did not require approval by the institutional review board.

Study population

The eligible cases were screened using the SEER*State v8.3.6 approach (released on August 8th, 2019).In this work, we applied the International Classification of Diseases for Oncology third edition (ICD-O-3) in identifying ICC cases and selecting themusing the ICD-O-3 site codes C22.0 or C22.1 (liver and intrahepatic bile duct). Besides, ICC was identified using the 8160/3 ICD-O-3 histological codes [7].Patients conforming to the following criteria were excluded: (1) those with over one primary tumor; (2)those only with the clinical diagnosis, or those diagnosed based on autopsy or the death certificate; (3)those with insufficient clinicopathological data, such as TNM stage or surgical classification; (4) those with no data on prognosis; (5)those with no data on race or marital status. The remaining participants were included into the initial SEER cohort.

Covariates and endpoint

The clinicopathological features shown below were examined, including age(65, ≥65 years); gender (male,female); marital status (married, unmarried); race (white, black, others); insurance status (uninsured/unknown, any medicaid/insured); T stage (T1-4); N stage (N0-1); M stage (M0-1);grade (I/II, III/IV, unknown); surgery(no surgery, local tumor removal/segmental resection, lobectomy/hepatectomy);

radiotherapy(yes, no/unknown) and chemotherapy (yes, no/unknown). The widowed or single (never married or having a domestic partner) or divorced or separated patients were classified as unmarried [14,15]. Age was grouped according to previous studies [16,17]. Besides, cancer stage was classified according to the AJCC 6th classification system adapting to SEER-derived patients diagnosed between 2004 and 2015. Further, the qualified patients were divided in line with the AJCC 8th classification system. In this study, the endpoint was set as overall survival (OS), which referred to the duration between diagnosis and death due to all causes.We preliminarily determined the deadline till November 2018 based on the SEER 2018 submission database. Finally, the deadline was set as November 31st, 2018.

Statistical analysis

Nomogram construction

Categorical variables were compared by Fisher's exact test or chi-square test and expressed in the manner of proportions and frequencies. We carried out univariate as well as multivariate regression analysis using the Cox proportional hazards model analysis to identify factors significantly related to prognosis, and they were presented as hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). Upon univariate analysis, factors of P<0.1were combined for multivariate backward stepwise analysis to identify independent risk factors.We established the nomogram model based on all independent prognosis factors obtained from the training set to predict the 3- and 5–year OS by the R package rms function (version 3.51).

Nomogram validation

The constructed nomogram was validated by measuring its discrimination and calibration abilities using the internal (training) and external(validation) set, respectively.In addition, we used the concordance index (C-index) to evaluate our model discrimination performance and assess the heterogeneities in the predicting ability between the predicted and observed results[18]. As a result, the greater C-index value indicated the better patient discrimination ability among different prognostic outcomes. Also, we employed the R package Rcorrp.cens function of Hmisc to compare the different results obtained by our constructed nomogram from those acquired by the existing TNM classification or the SEER summary stage system, and utilized the C-index to assess the results. The marginal estimate versus model was employed to establish a calibration plot representing the calibration between nomogram-predicted and observed survival. A calibration plot along the 45-degree line implicated a perfect model, with great consistency between the predicted and actual outcomes. On the other hand, the Receiver Operating Characteristic (ROC) curves were drawn for validating the nomogram score. In this study, R (version 3.51, www.r-project.org) and SPSS19.0 (SPSS Inc., Chicago, USA) were applied in statistical analysis. A difference of P<0.05 (two-tailed) was deemed to be statistically significant.

Results

Patient characteristics

Altogether 3675 qualified ICC cases diagnosed from 2004 to 2015 were recruited into the present work, including 2573 in training set while 1102 in validation set. Figure 1 shows the data collection flow chart. The age of included patients ranged from 14 to 104 (median, 65) years, with the male-to-female ratio of nearly 1:1. Most patients were insured (83.13%), white (76.71%) and married (59.40%). As for AJCC stage, many cases were at the early stages, including T0/T1(38.20%), N0(72.98%) and M0(65.28%). More than half of the included patients received chemotherapy in both sets, but only 16.65% received radiotherapy.The follow-up period ranged from 0 to 153 (median, 9.0) months. Meanwhile, the 3-year and 5-year OS rates of all cases were 14.89% and 9.83%. Table 1 lists all the demographic and clinicopathological features in both groups. There was no significant statistical difference between the two groups in all variables.

Nomogram construction

Table 2 presents the independent factors that are significantly related to OS identified from multivariate analysis. Ten factors were identified as the independent variables after other risk factors were adjusted, which were age (P<0.001), gender (P<0.001), marital status (P=0.016), T stage(P<0.001), N stage(P<0.001), M stage(P<0.001), grade (P<0.001),surgery (P<0.001), radiotherapy (P<0.001) and chemotherapy (P<0.001).Additionally, we established a nomogram to predict the 3- and 5-year OS using the above-mentioned independent factors (Figure 2).It was discovered that,surgery made the greatest contribution to prognosis, chemotherapy ranked the second place, while AJCC stage ranked the third place. Then, the score of every screened factor was added to determine the survival probability for individual patient.

Nomogram validation

Our constructed nomogram was validated internally and externally. According to internal validation based on training set, our constructed nomogram had the C-index of 0.737 (95% CI, 0.726–0.748) in predicting OS. Besides, external validation based on validation set suggested that, our nomogram had the C-index of 0.744(95% CI, 0.726–0.762) in predicting OS, which well consistent with the real OS. Besides, we compared our constructed nomogram with the TNM 8th classification system and the SEER stage system for their discrimination abilities based on both datasets. As a result, our constructed nomogram showed higher discrimination ability in predicting OS than the other two systems (all P<0.001) (Table 3). Furthermore, for our constructed nomogram of OS, its internal and external calibration plots displayed that the nomogram-predicted values were closely correlated with the actual results (Figure 3). The time-dependent area under the curve (tAUC) value regarding the 3–year OS was 0.847 (0.822–0.871), while that of 5– year OS was 0.869 (0.842–0.896) in training set. The tAUC value regarding the 3-year OS was 0.842 (95% CI: 0.803–0.882), while that of 5-year OS was 0.870 (95% CI: 0.823–0.918) in validation set, higher than those obtained by the other two systems(Figure 4).

Discussion

ICC is one of the bile duct adenocarcinoma subtypes that involve the small intrahepatic ducts [19]. ICC ranks the second place in terms of its morbidity among primary liver cancer, only second to HCC [20]. ICC is rare; as a result, its prognosis can not be accurately predicted using the conventional classification systems alone. Establishing the effective prognosis prediction system for estimating patient prognosis is important. Therefore, this study aimed to construct and validate a novel prognosis nomogram for ICC on the basis of SEER-derived samples. Altogether 3675 ICC cases were examined in this study. As a result, our constructed nomogram exhibited high discrimination ability, as validated internally and externally. In addition, as suggested by the calibration plots, the predicted OS was close to the actual result. Our nomogram outperformed the present AJCC TNM classification system, which might serve as the clinical approach to assist in popularizing patient counseling as well as individualized treatment.

In this work, altogether 10 clinicopathological factors were identified to independently predict prognosis, which were age, gender, marital status, T stage, N stage, M stage, grade, surgery, radiotherapy and chemotherapy.Among them, age is identified as the vital factor that affects OS in some articles [21,22]. It is also suggested previously that apart from histological grade and the AJCC classification system, gender [7] and marital status [15] are also identified as the prognosis-related factors for ICC. In addition, radical surgery is identified as the only efficient treatment, and aggressive surgery is recommended in many institutions [23].It is reported in numerous studies that, patients undergoing chemotherapy or radiotherapy show higher survival benefits [24-26], consistent with our results.

Nomogram accounts for a key part in the modern decision-making in the medical field [27]. It graphically presents a statistical prediction model for providing the specific outcome probability [28,29]. Therefore, the considered variables must be easily accessible and detectable. It is increasing reported that, nomogram outperforms the traditional AJCC TNM classification system in predicting the prognosis for several cancers, as a result, it is recognized to be the alternative tool or even the novel standard [30,31]. In comparison with the extensively applied TNM classification system, our nomogram was easily used and quantitatively predicted the prognosis. Moreover, nomogram can assist clinicians in managing the complicatedsituations where there is no fixed clinical guideline.

There are certain strengths in this work. We obtained sufficient clinicopathological data from the SEER-derived ICC cases, which ensured that we established an accurate prognosis nomogram. Our nomogram outperformed the TNM 8th classification system in terms of its discrimination ability of OS prediction. The presentation and validity of the nomogram were also confirmed by calibration. In addition, our work used 10 available clinical factors extensively used clinically, making it convenient for the use of our nomogram.

Nonetheless, several limitations must be noted as well. Firstly, selection bias was inevitable due to the retrospective nature. Secondly, some vital prognosis-related clinicopathological factors, including status of surgical margin, detailed data on radiotherapy and chemotherapy, were not available from the SEER database, and future research should focus on these aspects. Thirdly, our constructed nomogram, which

might serve as a user-friendly approach for the decision-making of doctors,did not incorporate each prognostic factor or always offer accurate prognosis prediction in clinical practice.

Conclusion

To sum up, this study first constructs and validates a nomogram for predicting the OS for ICC at 3 and 5 years by using a large population-based cohort. Our constructed nomogram performs well and may serve as the efficient approach to predict prognosis for ICC patients. Nonetheless, more external validation is also needed.

Declarations

Funding

This work received no funding.

Conflict of interest

All authors declare that they have no conflicts of interest associated with this study.

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Author contributions

Chun-jiao Wu designed this study. Yong-jing Yang, Ling Cao, Ling Yan, Jing Zhu and Qiang Li wrote the main manuscript text. Chun-jiao Wu revised the manuscript finally. All authors reviewed the manuscript.

Ethical Approval

The data analysis was considered by the Office for Human Research Protection to be non-human subjects who were researched by the United States Department of Health and Human Services, as they were publicly available and de-identified. Thus, it did not require approval by the institutional review board.

Data Availability Statement

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

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Tables

Table 1. Patient demographics and pathological characteristics.

Variables	All patients (n=3675)	Training Set (n=2573)	Validation Set (n=1102)	*P*-value
Age				0.142
<65	1762 (47.95%)	1254 (48.74%)	508 (46.10%)	
≥65	1913 (52.05%)	1319 (51.26%)	594 (53.90%)	
Sex				0.980
female	1822 (49.58%)	1276 (49.59%)	546 (49.55%)	
male	1853 (50.42%)	1297 (50.41%)	556 (50.45%)	
Race				0.992
black	317 (8.63%)	221 (8.59%)	96 (8.71%)	
white	2819 (76.71%)	1974 (76.72%)	845 (76.68%)	
other	539 (14.67%)	378 (14.69%)	161 (14.61%)	
Marital status				0.528
unmarried	1492 (40.60%)	1036 (40.26%)	456 (41.38%)	
married	2183 (59.40%)	1537 (59.74%)	646 (58.62%)	
Insured stutus				0.496
uninsured/unknown	620 (16.87%)	427 (16.60%)	193 (17.51%)	
any medicaid/insured	3055 (83.13%)	2146 (83.40%)	909 (82.49%)	
Grade				0.912
grade I/II	1045 (28.44%)	731 (28.41%)	314 (28.49%)	
grade III/IV	793 (21.58%)	560 (21.76%)	233 (21.14%)	
unknown	1837 (49.99%)	1282 (49.83%)	555 (50.36%)	

T stage				0.287
T0/T1	1404 (38.20%)	964 (37.47%)	440 (39.93%)	
T2	581 (15.81%)	402 (15.62%)	179 (16.24%)	
T3	1085 (29.52%)	767 (29.81%)	318 (28.86%)	
T4	605 (16.46%)	440 (17.10%)	165 (14.97%)	
N stage				0.429
N0	2682 (72.98%)	1868 (72.60%)	814 (73.87%)	
N1	993 (27.02%)	705 (27.40%)	288 (26.13%)	
M stage				0.670
M0	2399 (65.28%)	1674 (65.06%)	725 (65.79%)	
M1	1276 (34.72%)	899 (34.94%)	377 (34.21%)	
Surgery				0.188
no surgery	2709 (73.71%)	1905 (74.04%)	804 (72.96%)	
Local tumor excision /Segmental resection	467 (12.71%)	335 (13.02%)	132 (11.98%)	
Lobectomy/Hepatectomy	499 (13.58%)	333 (12.94%)	166 (15.06%)	
Chemotheray				0.688
no/unknown	1716 (46.69%)	1207 (46.91%)	509 (46.19%)	
yes	1959 (53.31%)	1366 (53.09%)	593 (53.81%)	
Radiotherapy				0.810
no/unknown	3063 (83.35%)	2147 (83.44%)	916 (83.12%)	
yes	612 (16.65%)	426 (16.56%)	186 (16.88%)	

Table 2. Univariate and multivariate analyses of overall survival in the training set.

Variables	Univariate analysis		Multivariate analysis	
	HR(95%CI)	*P*-value	HR(95%CI)	*P*-value
Age		<0.001		<0.001
<65	Reference			
≥65	1.303(1.198-1.417)		1.16(1.064-1.265)	
Sex		<0.001		<0.001
female	Reference			
male	1.191(1.095-1.295)		1.183(1.085-1.289)	
Race		0.234	NI	
black	Reference			
white	0.906(0.78-1.053)	0.198		
other	0.856(0.716-1.024)	0.089		
Marital status		0.003		0.016
unmarried	Reference			
married	0.879(0.807-0.957)		0.898(0.822-0.98)	
Insured stutus		0.154	NI	
uninsured/unknown	Reference			
any medicaid/insured	0.923(0.828-1.03)			
Grade		<0.001		<0.001
grade I/II	Reference			
grade III/IV	1.489(1.316-1.685)	<0.001	1.374(1.214-1.556)	<0.001
unknown	1.885(1.702-2.088)	<0.001	1.195(1.073-1.331)	0.001
T stage		<0.001		<0.001
T0/T1	Reference			
T2	1.012(0.889-	0.859	1.184(1.038-	0.012

	1.152)		1.351)	
T3	1.398(1.261-1.549)	<0.001	1.345(1.209-1.497)	<0.001
T4	1.444(1.278-1.631)	<0.001	1.343(1.183-1.524)	<0.001
N stage		<0.001		0.013
N0	Reference			
N1	1.267(1.154-1.391)		1.133(1.027-1.25)	
M stage		<0.001		<0.001
M0	Reference			
M1	1.986(1.818-2.169)		1.613(1.464-1.777)	
Surgery		<0.001		<0.001
no surgery	Reference			
Local tumor excision /Segmental resection	0.314(0.272-0.362)	<0.001	0.322(0.276-0.376)	<0.001
Lobectomy/Hepatectomy	0.286(0.247-0.332)	<0.001	0.284(0.241-0.334)	<0.001
Chemotheray		<0.001		<0.001
no/unknown	Reference			
yes	0.684(0.629-0.744)		0.461(0.419-0.506)	
Radiotherapy		<0.001		<0.001
no/unknown	Reference			
yes	0.711(0.634-0.796)		0.786(0.7-0.882)	

Table 3. C-indexes for the nomogram and other stage systems in patients with intrahepatic cholangiocarcinoma.

Classification	Training set		Validation set	
	C-index(95%CI)	*P*-Valuew	C-index(95%CI)	*P*-Valuew
Nomogram	0.737(0.726,0.748)		0.744(0.726,0.762)	
AJCC 8th stage	0.600(0.587,0.613)	<0.001	0.598(0.578,0.618)	<0.001
SEER summary stage	0.603(0.590,0.616)	<0.001	0.600(0.580,0.620)	<0.001

wAll are compared with the Nomogram; HR: hazard ratio; CI: confidence interval.

Figures

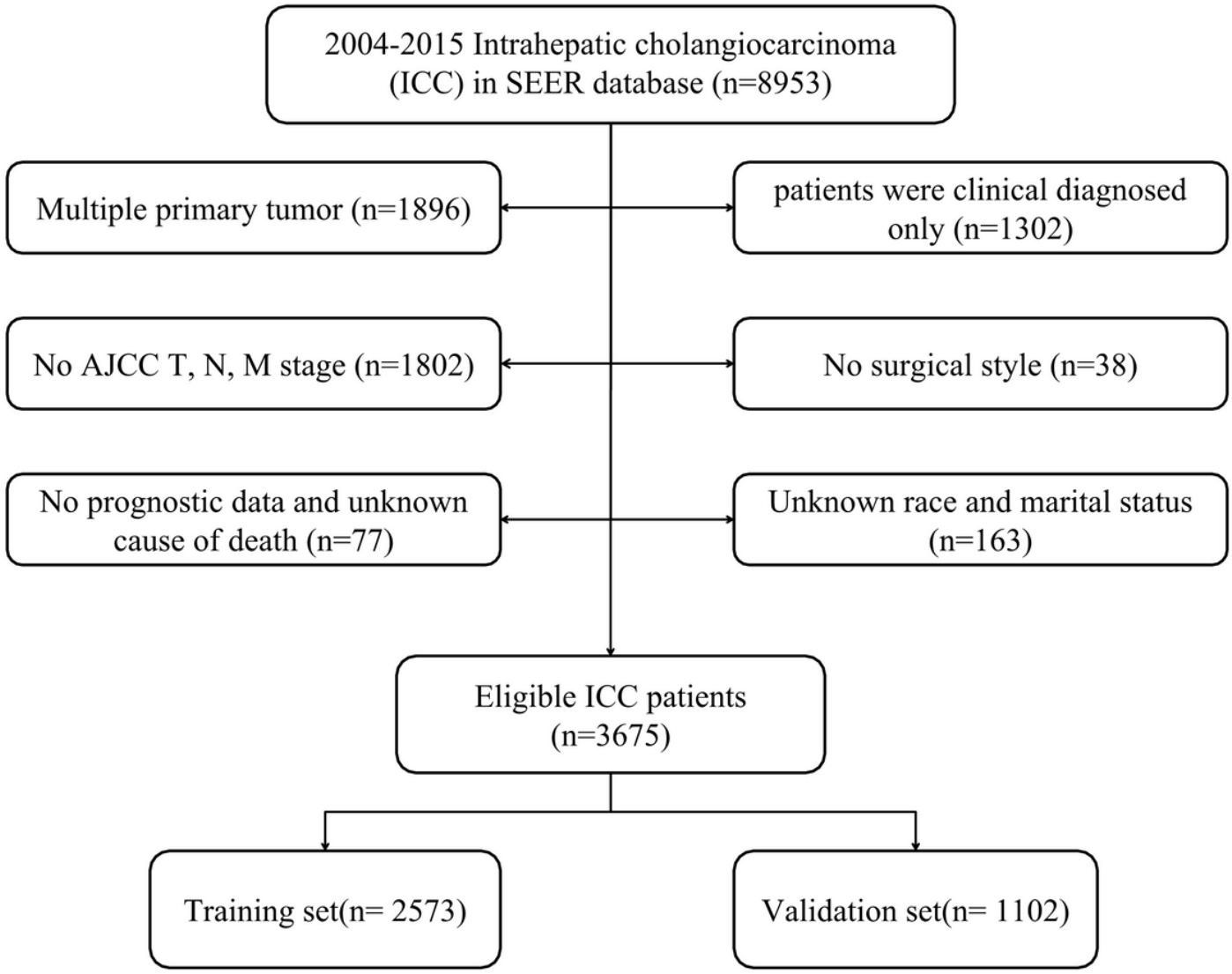

Figure 1

Flow chart for screening eligible patients.

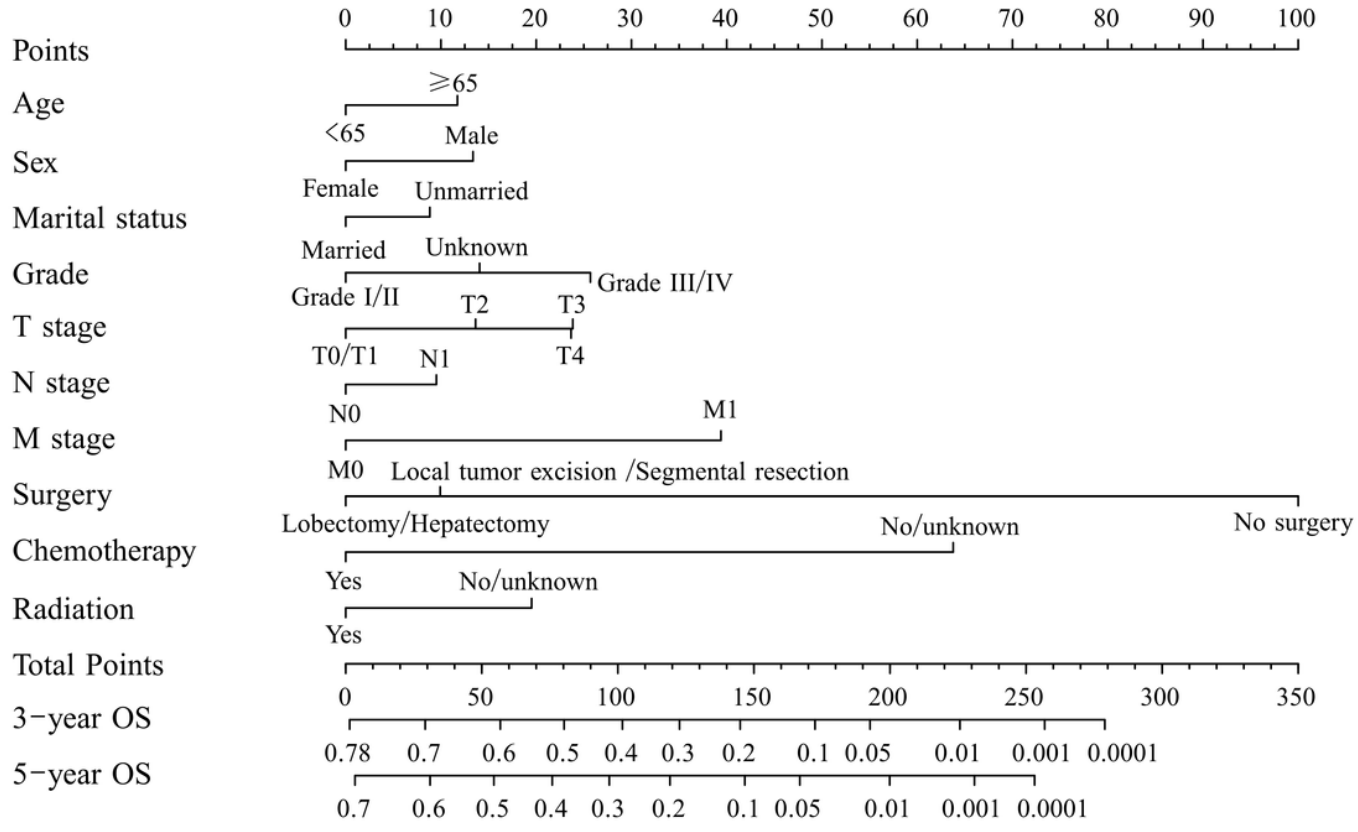

Figure 2

Nomograms for predicting 3- and 5-year overall survival (OS) of patients with intrahepatic cholangiocarcinoma (ICC).

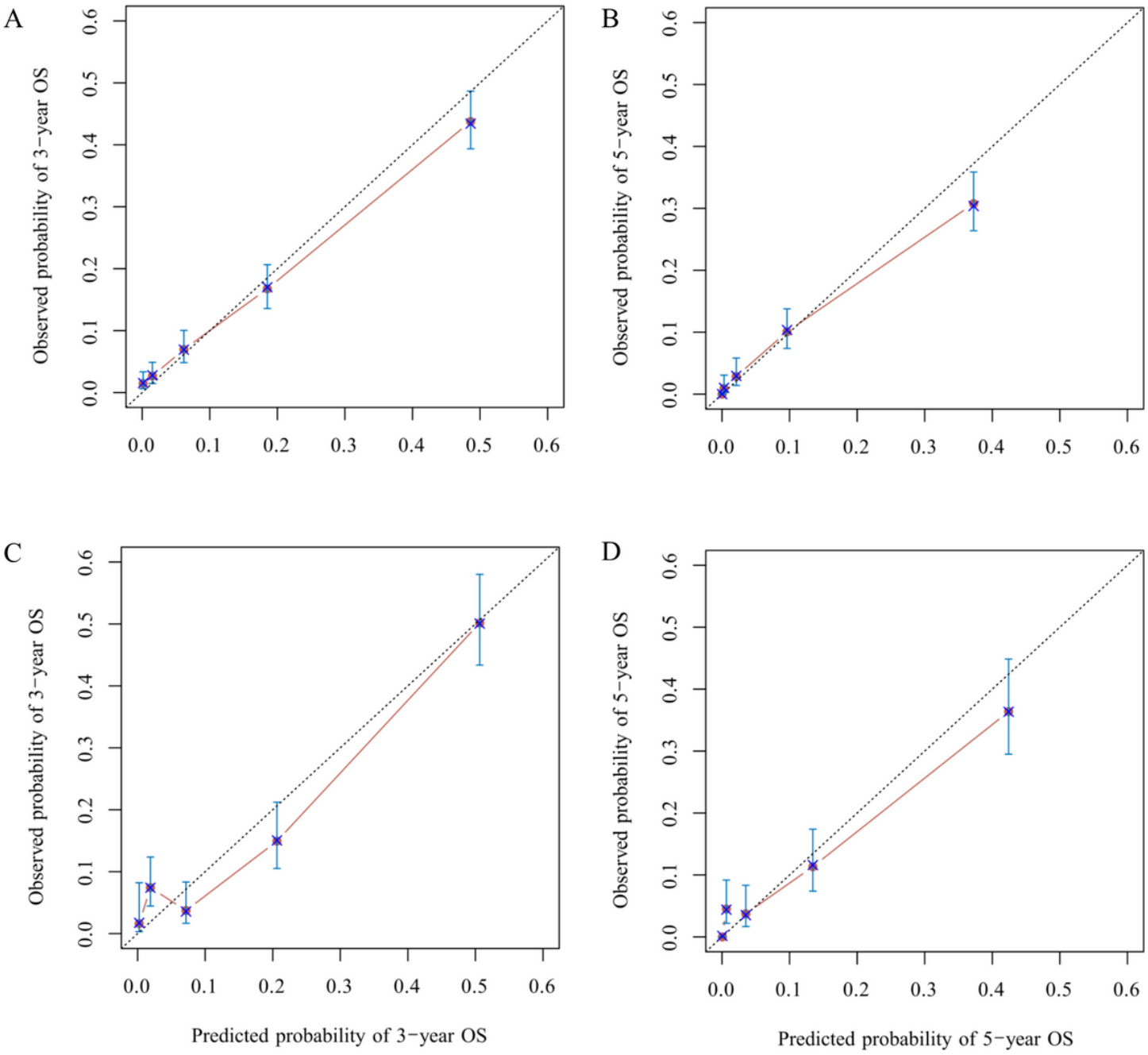

Figure 3

Calibration plots of the nomogram for 3-and 5-year overall survival (OS) (A, B) prediction in the training set, and 3-and 5-year OS (C, D) prediction in the validation set. The X-axis represents the nomogram-predicted probability of survival; the Y-axis represents the actual OS probability. Plots along the 45-degree line indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. Vertical bars indicate 95% confidence intervals.

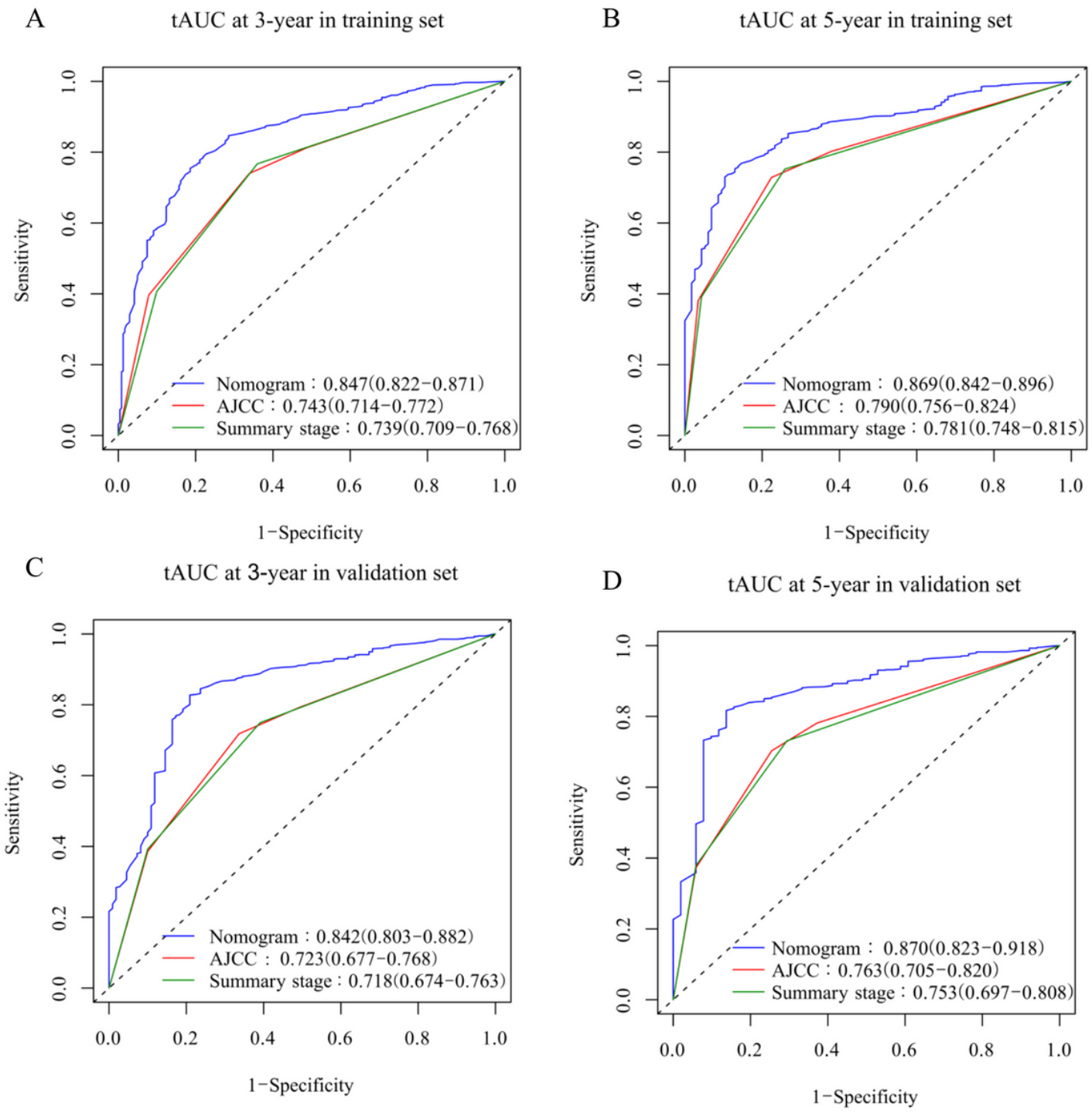

Figure 4

Discriminatory accuracy for predicting OS assessed by receiver operator characteristics (ROC) analysis calculating time independent area under the curves (tAUCs). 3–year (A) and 5 –year (B) in the training cohort; 3–year (C) and 5 –year (D) in the validation cohorts.