Development and validation of a nomogram model to predict the prognosis of intrahepatic cholangiocarcinoma

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Research Article

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Abstract

Background

The effective method for predicting prognosis of ICC is still lack. This study aims to establish and verify an effective prognostic nomogram for intrahepatic cholangiocarcinoma (ICC) after partial hepatectomy.

Methods

A nomogram model was developed in a cohort of 127 patients from January 2015 to December 2019. General clinical characteristics including preoperative physical examination data and postoperative pathological features were obtained. The independent risk factors identified by univariate and multivariate COX proportional hazards regression models were used to construct nomogram model. Predictive accuracy and discriminative ability were determined using a concordance index and a calibration curve. In addition, the clinical significance of postoperative pathological subtypes was analyzed by Kaplan-Meier.

Results

Univariate analysis and multivariate COX regression analysis revealed that CEA, maximum diameter, tumor number, and large duct type ICC. These variables were incorporated into the nomogram and the C-index for one year and three year overall survival prediction was 0.765 (95% CI: 0.672–0.814) and 0.695 (95% CI: 0.672–0.814), respectively. Postoperative pathological analysis showed that the large duct ICC had a distinct clinicopathological features and poor outcome.

Conclusion

The proposed nomogram enables a prognostic prediction for patients with ICC and postoperative subclassification of ICC is of great significant to the prognosis of ICC.

Background

Intrahepatic cholangiocarcinoma (ICC) originated from the secondary bile duct and its branch bile duct epithelium, accounts for 10%-15% of primary liver cancer and is now becoming a highly aggressive malignant tumor [1, 2]. The incidence of ICC keeps increasing in recent years, and most patients lose the best treatment opportunity due to the lack of early ICC diagnosis method [3]. Although ICC patients receive surgical resection and postoperative chemotherapy, postoperative recurrence and extrahepatic metastasis still occur, which seriously affects the prognosis of patients and imposes a heavy medical burden on families and the public medical system [4]. Therefore, early prediction of surgical prognosis of ICC patients is an urgent need for clinical decision and early postoperative intervention for ICC recurrence.

At present, numerous factors identified by clinicians can influence the prognosis of ICC patients after resection[5–7]. However, there is no international consensus on the prognostic factors that can significantly and independently affect the survival rate and recurrence rate in ICC patients. Currently the American Joint Committee on cancer (AJCC) TNM staging system introduced a new staging system for ICC, which subdivided ICCs based on a size cutoff of 5 cm, lymph node metastasis, vascular invasion and extrahepatic metastasis. However, this staging system ignores other significant clinical information such as pathological subtype and preoperative serological indicators, which makes it difficult for clinicians to accurately evaluate the prognosis of ICC [8]. Two pathological subtypes of ICC including large and small duct-type with unique clinicopathological and genetic characteristics were also proposed in the 2019 WHO Guidelines [9]. The large duct type ICC possesses features of tall columnar tumor cells with low nucleocytoplasmic ratio, abundant clear, eosinophilic or mucinous cytoplasm. Their nuclei are usually high grade and arranged in a large sized glandular or papillary structure with abundant extracellular mucus[10]. The small duct type ICC is composed of low columnar to cuboidal tumor cells with mild or moderate heteromorphic nucleus. The tumor cell structure is similar with epithelial cells of small bile ducts and forms trabecular, cribriform, micro-papillary or solid structures[10]. Compared with large duct-type ICC, mutations of Isocitrate dehydrogenase 1/2 (IDH1/2) and fibroblast growth factor receptor 2 (FGFR2) rearrangement are more common in small duct type ICC, while KRAS mutation rate was relatively lower[10, 11]. Therefore, the ICC classification standard plays a key role in evaluating the prognosis of patients. However, the effects of pathological subtypes on the postoperative outcome in Chinese ICC patient need to be confirmed by evidence-based medicine.

In this study, preoperative serological indicators and postoperative pathological indicators were included to construct a nomogram to predict the prognosis of postoperative ICC patients. To best of our knowledge, this is the first nomogram statistical method that was used to evaluate the prognosis of ICC patients by incorporating pathological classification of ICC.

Methods

Patients

A retrospective study was performed on a total of 106 patients diagnosed with ICC from January 2015 to December 2019 at the Mengchao Hepatobiliary Hospital of Fujian Medical University (Fuzhou, China). Inclusion criteria were as follows: (1) patients with radical resection of intrahepatic bile duct tumor in our hospital (R0), and complete resection of liver tumors, (2) patients with full records of clinicopathological data, (3) postoperatively histopathologically proven ICC, (3) no history of other anti-tumor therapies before surgery, (4) no history of other malignancies. Exclusion criteria included the following: (1) Patients died within 30 days after surgical operation. (2) Patients with mixed intrahepatocellular carcinoma diagnosed by pathology after operation. This study was approved by the Ethics Committee at Mengchao Hepatobiliary Hospital of Fujian Medical University (approval number: 2021-044-01), and all methods were performed in accordance with the relevant guidelines and regulations. The clinical information and

characteristics were recorded and analyzed after written consent was obtained from the patients and their families.

Diagnosis and Treatment

After a baseline history and detailed physical examination, blood was obtained from patients in order to detect the serological indicators, including hepatitis B surface antigen, hepatitis B virus DNA level, anti-hepatitis C virus (HCV) antibody, serum albumin, total bilirubin, ALT, CA125, CA 19-9, and carcinoembryonic antigen (CEA). All patients were assessed with the contrast-enhanced CT or magnetic resonance, and positron emission tomography was chosen to determine whether there existed intrahepatic or extrahepatic metastases. According to tumor features and anatomy of the liver, partial liver resection combined with regional lymph node dissection in the hepatoduodenal ligament and retropancreatic and/or para-aortic lymph nodes was performed.

Postoperative pathological diagnosis and classification of ICC pathological subtypes

A serial slide was cut from representative formalin-fixed paraffin-embedded (FFPE) samples, stained with hematoxylin and eosin (H&E) and then observed under microscope by two independent pathologist. Tumor pathological indicators were recorded, including tumor size, number, tumor envelope, gross classification (mass type, peritubular infiltration type, and intratubular growth type), tumor differentiation (poorly differentiated, moderately differentiated, and well-differentiated), extrahepatic metastasis, bile duct invasion, lymph node metastasis and liver cirrhosis. According to histologic appearance and immunohistochemical index, ICCs was sub-classified into large duct and small duct types [12, 13].

KRAS and IDH1/2 gene mutation detection

Since IDH1/2 and KRAS mutations were reported to be the most frequent genetic alterations according to several large-scale genomic analyses, tumor tissues were macro-dissected from FFPE tissue blocks. Then, the total DNA of ICC tissues was extracted by a commercial kit (DNB400-50RXN, Merck, Germany) according to manufacturer's instructions. This study focus on the mutation hot spot of exon 4 at codon 132 of IDH1, exon 4 at codon 172 of IDH2, and exon 2 of KRAS by polymerase chain reaction (PCR). The primer pairs were showed as follows: IDH1-R132: F: 5'-GATGAGAAGAGGGTTGAGGAGTT-3' and R: 5'-TACCTTGCTTAATGGGTGTAGATAC-3'. IDH2-R172: F: 5'-AGCTGAAGAAGATGTGGAAAAGTC-3' and R: 5'-TTTGGGGTGAAGACCATTTTG-3'. KRAS: F: 5'-ACGTCTGCAGTCAACTGGAATT-3' and R: 5'-TCTGTATCAAAGAATGGTCCTGC-3'. The PCR productions were analyzed by 3730xl DNA Analyzer (Applied Biosystems; USA).

Follow-Up

ICC patients were followed up every 3 months after surgery. At each post-surgery visit physical examinations were carried out. Blood was collected to detect serum level of CA19-9, CA125, CEA and contrast-enhanced CT or magnetic resonance imaging was also performed. When the patients were suspected of tumor recurrence or metastasis, the contrast-enhanced CT or magnetic resonance could be

performed earlier. In this study, the endpoint of follow-up was defined as tumor recurrence confirmed by two radiologic images or death caused by ICC. Overall survival (OS) was defined as the interval between the date of surgery and death or the last date of follow-up. Relapse-free survival (RFS) was defined as the time from the date of surgery to the time of recurrence or death.

Statistical Analysis

Categorical variables were displayed as mean±SD, and categorical variables were expressed as frequency. All recorded variables associated with prognosis were firstly analyzed by univariate Cox regression analysis. Subsequently, the potential variables those are potentially associated with prognosis at a significant level by univariate Cox regression analysis were further enrolled in multivariate Cox regression analysis to verify the independent risk factors. Nomogram was plotted based on these independent differential factors by using the package of rms in R version 4.0.3 (http://www.r-project.org/). The performance of the nomogram was measured by concordance index (C-index) and assessed by 1 000 bootstrap samples to compare nomogram-predicted versus observed Kaplan-Meier estimates of survival probability. Then, Receiver operating characteristic (ROC) curve analysis was used for comparison between our nomogram and other models on the basis of C-index. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. P 0.05 was considered statistically significant.

Results

Characteristics of patients and postoperative recurrence and survival

The basic characteristic of the entire cohort was shown in Table 1. Approximately a half of the cases were male (n = 68 [53.54 %]), tumor size ≥ 5 cm (n = 71 [55.91 %]), and poorly or moderate differentiated (n = 105 [82.68%]). A part of patients was hepatitis B surface antigen (HBsAg)-negative (n = 42 [33.07 %]) and none patients was found to be seropositive for hepatitis C virus (HCV). Vascular invasion and lymph node metastasis were found in 67 (52.79 %) and 46 (36.22 %) patients, respectively.

Table 1. Demographics and Clinicopathological Characteristics of Patients With ICC

Factors	No. of Patients	%
Age, years mean±SD	61.19±11.02	
Sex		
male	68	53.54
female	59	46.46
HBV positive (yes vs. no)	42	33.07
CA199 (Median Range)	73.935,0.1-1000	
CA125(Median Range)	25.12,0.1-1000	
CEA(Median Range)	3.00,0.7-200	
Maximum diameter		
5 cm	56	44.09
≥ 5 cm	71	55.91
Tumor number		
Single	96	75.59
Multiple	31	24.41
Visual classification		
Periductal infiltration	35	27.56
Intraductal growth type	60	47.24
Mass-forming type	32	25.20
Tumor differentiation		
Poorly	38	29.92
Moderate	67	52.76
Well	21	16.54
Extrahepatic metastasis	28	22.05
Vascular invasion	67	52.76
Bile duct invasion	20	15.75
lymph node metastasis	46	36.22
Liver cirrhosis	22	17.32
Large duct type ICC	47	37.01

IDH1/2 mutation	26	20.47
Kras mutation	17	13.39

Univariate and multivariate Cox regression results

As shown in table 2, Univariate and multivariate COX analysis identified several independent risk factors for OS that showed as follows: CEA (Hazard Ratio [HR], 1.010; 95% Confidence Interval (CI), 1.003–1.017; P = 0.004), maximum diameter (HR, 1.303; 95% CI, 1.176–1.443; P = 0.000), tumor number (HR, 2.094; 95% CI: 1.153-3.801; P = 0.015), and large duct type ICC (HR, 2.831; 95% CI: 1.298-6.175; P = 0.009).

Table 2. Prognostic factors of ICC

Factors	Univariate COX regression			Multivariate COX regression		
	HR	95% CI	P	HR	95% CI	P
Age mean±SD	1.382	0.819-2.332	0.225			
gender (male vs. female)	1.438	0.845-2.446	0.180			
HBV positive (yes vs. no)	1.000	1.000-1.1001	0.912			
CA19-9 (mean±SD)	1.002	1.001-1.002	**0.000**	1.000	0.999-1.001	0.579
CA125 (mean±SD)	1.000	1.000-1.1001	0.180			
CEA (high vs. normal)	1.013	1.008-1.018	**0.000**	1.010	1.003-1.017	**0.004**
Bilirubin level (high vs. normal)	1.408	0.598-4.761	0.473			
Maximum diameter (≥ 5 cm vs. 5 cm)	1.25	1.163-1.344	**0.000**	1.303	1.176-1.443	**0.000**
Tumor number (multiple vs. single)	2.442	1.420-4.119	**0.001**	2.094	1.153-3.801	**0.015**
Visual classification (periductal infiltration/ intraductal growth type vs. mass-forming type)	1.755	1.012-3.045	**0.045**	1.492	0.761-2.923	0.244
Tumor differentiation (well/moderate vs. poorly)	0.372	0.148-0.933	**0.035**	0.837	0.317-2.206	0.718
Extrahepatic metastasis (yes vs. no)	2.359	1.347-4.134	**0.003**	0.670	0.346-1.297	0.235
Vascular invasion (yes vs. no)	1.274	0.756-2.147	0.363			
Bile duct invasion (yes vs. no)	0.697	0.316-1.536	0.371			
lymph node metastasis (yes vs. no)	1.412	0.839-2.377	0.194			
Liver cirrhosis (yes vs. no)	0.609	0.298-1.242	0.172			
Large duct type ICC (yes vs. no)	3.677	2.154-6.277	**0.000**	2.831	1.298-6.175	**0.009**

IDH1/2 mutation (yes vs. no)	0.592	0.286-1.208	0.182
Kras mutation (yes vs. no)	0.801	0.382-1.806	0.609

Development and validation of nomogram

The prognostic nomogram that integrated all significant independent factors for OS during univariate and multivariate Cox regression was shown in Figure 1. In this model, every patient's score was calculated and the ones with a higher total score had worse prognosis for overall survival. The C-index for one-year and three-year overall survival prediction was 0.765 (95% CI: 0.672 - 0.814) and 0.695 (95% CI: 0.672 - 0.814), respectively.

Clinicopathological and prognostic characteristics in subtypes of ICC

The typical morphologic spectrum of large and small subtypes of ICC was shown in figure 2A. The tumor cells in large duct type ICC arranged in a large sized glandular or papillary structure with abundant extracellular mucus. The large duct type ICC stained positive for S100P and negative for N-cadherin and CD56. The tumor cell structure in small duct type is similar with epithelial cells of small bile ducts and forms trabecular, cribriform, micro-papillary or solid structures as arrows indication. The tumor is lack of columnar tumor cells that can produce mucin. The small duct type ICC always stained positive for N-cadherin and CD56, while negative for S100P.

In addition, patients with large duct type ICCs had a significantly worse recurrence-free and overall prognostic outcome than those with small duct type ICC ($p<0.001$; Figure. 2B).

Discussion

Despite of the lower incidence in liver cancers, intrahepatic cholangiocarcinoma (ICC) has poorer prognosis. Therefore, early prediction of post-operative prognosis is significant in prediction of postoperative recurrence and early intervention in key populations. Currently, several studies have been carried out to predict the prognosis of ICC patients by constructing nomogram statistical model. It was found that indicators including lymph node metastasis, tumor size, tumor stage and serum CA19-9 had a large impact on the clinical outcome of ICC patients. Although the significant role of pathological subtypes in ICC, none of these studies has included the pathological subtypes of ICC into the nomogram model. Hence, we included the preoperative serological indicators, postoperative pathological characteristics and pathological staging factors into univariate and multivariate regression analysis in the current study. Additionally, CEA, large duct type ICCs, multiple tumors, and tumors with diameter larger than 5 cm were all incorporated into the nomogram model to predict the 1-year and 3-year survival of ICC

patients after radical resection. Our results suggested that the nomogram model holds a good predictive performance in predicating ICC prognosis.

Due to its insidious onset and poor prognosis, ICC is prone to recurrence after surgery. The 5-year survival rate and 5-year recurrence rate of patients undergoing ICC surgery in our hospital were 40.30% and 57.01%, respectively, which were slightly higher than research results in other centers [7]. The reason may attribute to the small sample size, and the lost follow-up. Nomogram can incorporate a variety of potential influencing factors to construct a prognostic prediction model, which can assist doctors in evaluating prognosis of patients. Several clinical studies based on the statistical model have shown that nomogram displays higher application value than traditional AJCC staging. For example, compared with traditional AJCC staging and scoring system developed by the Liver Cancer Study Group of Japan, a single-center clinical study on 367 patients found that the nomogram built by incorporating CA 19 − 9, diameter and number of tumors, vascular invasion, lymph node metastasis and local extrahepatic metastasis was more powerful (concordance index [C-index]: 0.74 vs. 0.65 vs. 0.64) [7]. In addition, another study focused on factors affecting postoperative recurrence in ICC patients showed that the nomogram model built by tumor diameter, hepatitis B virus infection and lymph node metastasis could predict the prognosis of patients [14]. Nevertheless, apart from lymph node metastasis, tumor diameter and other well-known indicators, pathological subtypes of ICC were not included in these studies. In this study, ICC subtypes and other common prognostic factors were included in multivariate analysis, and we found that CEA, large duct type ICC, multiple tumors, and tumors with diameter larger than 5 cm were independent risk factors affecting the prognosis of patients. Furthermore, the nomogram model incorporating the pathological subtypes had higher C-index (C-index: 0.765; 95% CI: 0.672–0.814) in prognosis prediction, indicating that the classification of the postoperative ICC subtypes could improve the predictive efficiency of nomogram model for evaluating ICC prognosis.

The diameter of tumors has always been a prognostic factor concerned by clinical workers, but the definite impact of various tumor sizes on prognosis still remains inconclusive [15, 16]. Specifically, the tumor size was subdivided further in AJCC TNM staging of intrahepatic cholangiocarcinoma (8th edition), where the T1 stage was divided into T1a stage and T1b stage with the single tumor diameter of 5 cm as the boundary [9]. However, according to the LCSGJ staging raised by the Liver Cancer Study Group of Japan, the ICC patients with the tumor size larger than 2 cm had poorer prognosis [17]. This study showed that tumor diameter ≥ 5 cm was an independent risk factor affecting the prognosis of patients. This may be attributed to the fact that larger tumor not only means higher tumor staging, but also result in longer surgery time, and both of them are disadvantageous for prognosis. Similarly, multiple tumors are extensive and invade both left and right lobes, which can be difficult for radical resection. Since the residual cancer tissues are more likely to remain at the resection margins, it would be radiographically negative micrometastases in the remnant liver. All of these could increase the probability of postoperative recurrence and metastasis and thus results in poor prognosis.

As a result of significant tissue heterogeneity, ICC presents different growth patterns [13]. In order to further carry out precise molecular typing of ICC and take targeted treatment measures, WHO

Classification of Tumors of the Digestive System (5th Edition) divides ICC into two special histological subtypes: large duct type and small duct type, tumor tissues of which are different in histological characteristics and gene mutation characteristics [9]. Liau J and Aishima S confirmed that patients with large duct type ICC had the poorest prognosis in different ICC patient cohorts, and it was closely related to the pathological features of malignant tumors including lymph node metastasis and vascular infiltrating [12, 18]. This study also showed that the large duct type ICC was an independent risk factor affecting prognosis of ICC patients, and the large duct patitents had significantly poorer prognosis than those with the small duct type. Compared with the large duct type ICC, the small duct type ICC had a higher mutation frequency in IDH1/2 and FGFR2 [10]. Thus, targeted drugs for IDH1/2 mutation and FGFR2 would improve the therapeutic outcome in ICC patients [19, 20]. These findings collectively suggest that for patients with advanced ICC who have lost the opportunity for treatment, targeted genetic testing can be performed to provide patients with potential targeted therapy strategies after diagnosis of small duct type ICC by needle biopsy. However, this study also has limitations. Firstly, the population included was small and the study was single-center, thus, statistical results may be biased; secondly, the loss to follow-up would also result in differences between the statistical results and previous studies.

Conclusions

In conclusion, we provide a new nomogram model that can improve the predictive efficiency of prognosis for ICC patients, and postoperative subclassification of ICC is of great significant to the prognosis of ICC.

Abbreviations

ICC
Intrahepatic cholangiocarcinoma
HBV
Hepatitis B virus
NCAM
neural cell adhesion molecule. CA19-9:Carbohydrate antigen 19 – 9
CA125
Carbohydrate antigen 125
CEA Carcinoembryonic antigen
HR
Hazard ratio
CI
Confidence interval

Declarations

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Not applicable.

Author Contributions

LC and BW conceived and designed the experiments. YC and LH analyzed the data. YC, LC, and ZW wrote the paper. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

The datasets generated or analyzed during the current study are not publicly available due to the privacy of patients enrolled but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee at Mengchao Hepatobiliary Hospital of Fujian Medical University (approval number: 2021-044-01). The written informed consent obtained from human participants in the manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest to report regarding the present study.

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Figures

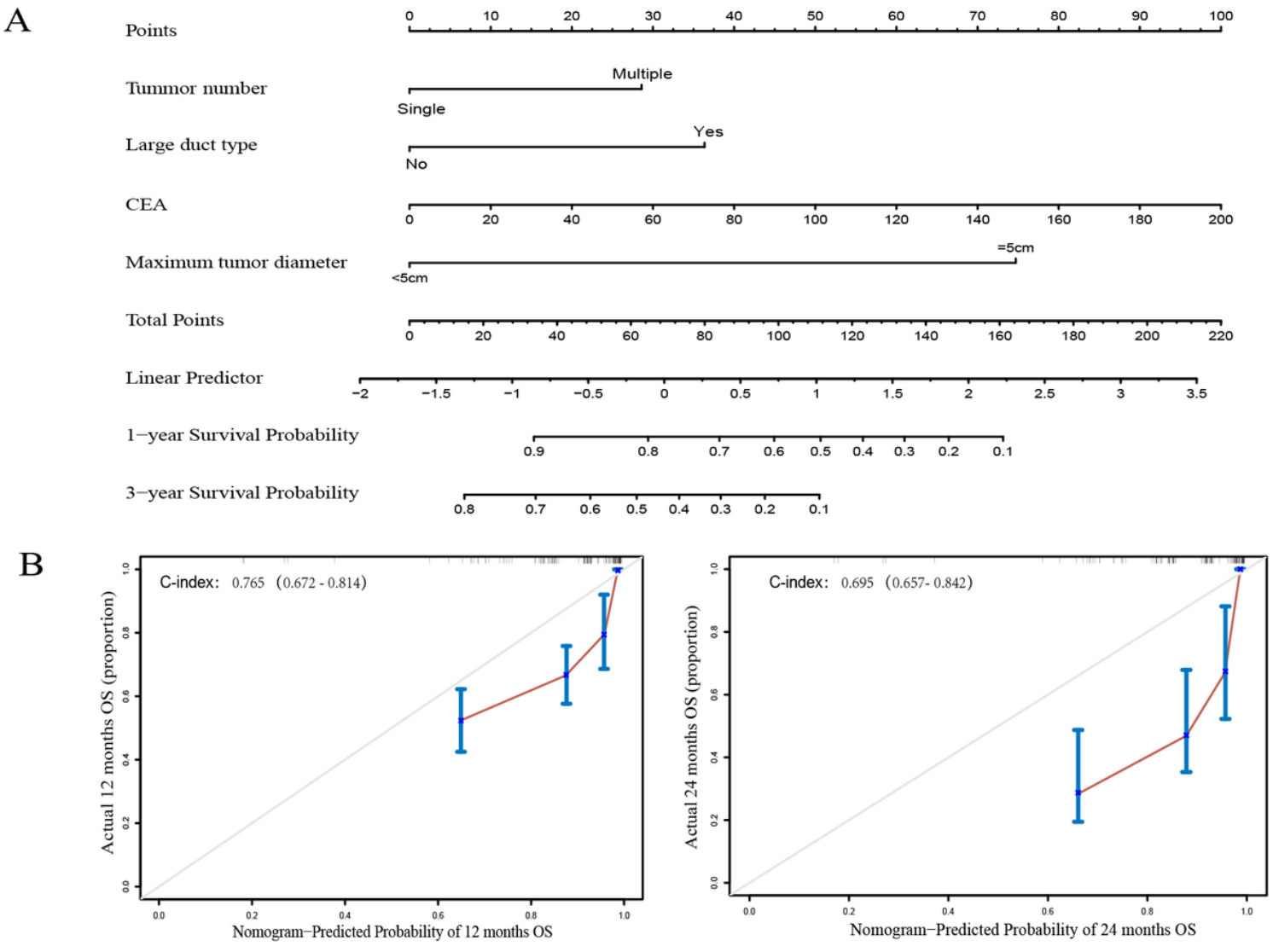

Figure 1

Construction and evaluation of nomogram structure. A. ICC survival nomogram based on tumor mumber, large duct type, CEA and maximum tumor diameter. B. The calibration curve for predicting patient survival within 1 year or 3 years.

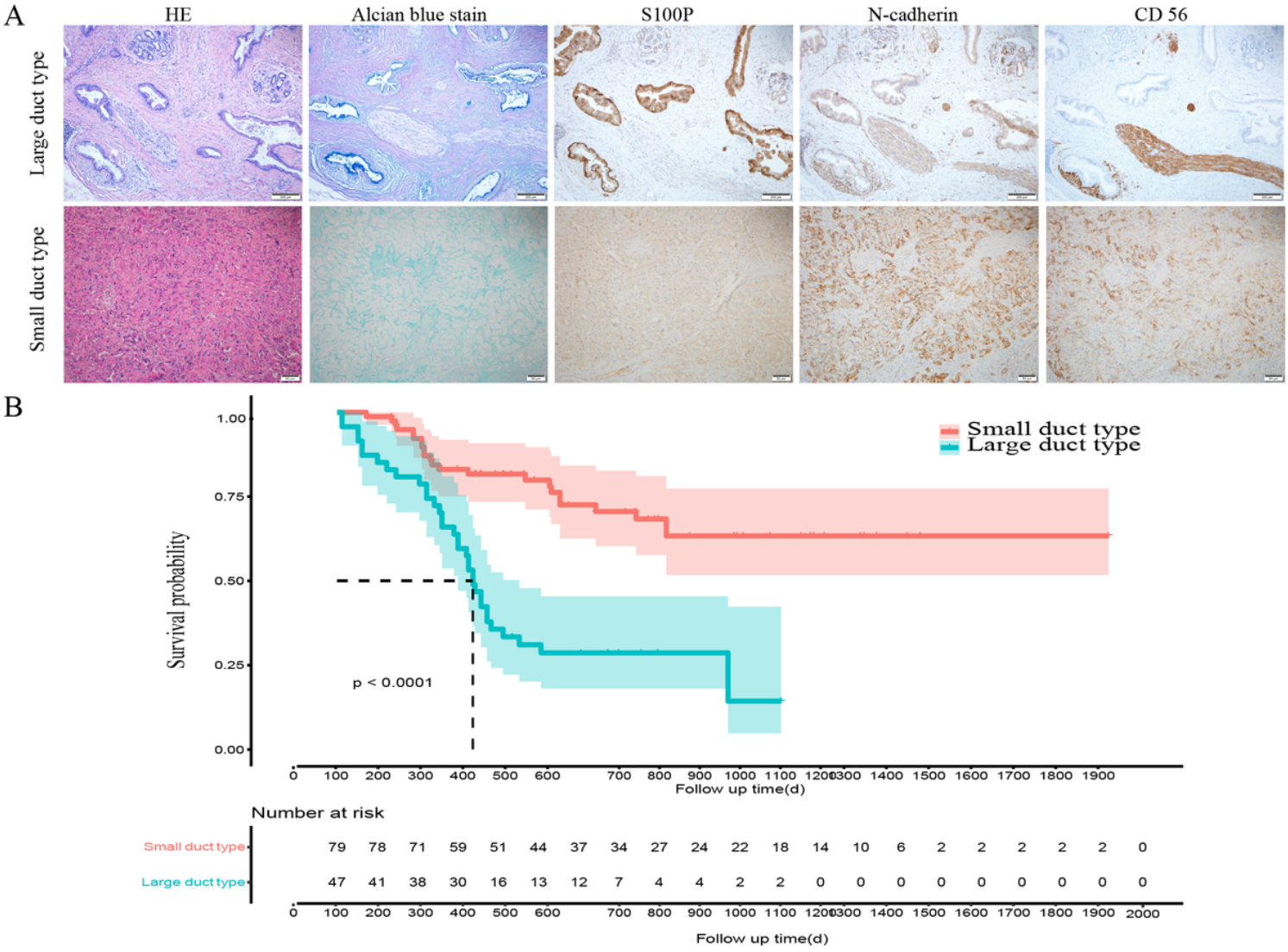

Figure 2

Clinicopathological and prognostic characteristics in subtypes of ICC. A. The expression pattern of mucin production, S100P, N-cadherin and NCAM between the large and small duct type ICC. B. Survival analysis of OS for large and small duct type ICCs.