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ORIGINAL REPORT

# Prognostic Nomogram for Intrahepatic Cholangiocarcinoma After Partial Hepatectomy

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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## ABSTRACT

### Purpose
This study aimed to establish an effective prognostic nomogram for intrahepatic cholangiocarcinoma (ICC) after partial hepatectomy.

### Patients and Methods
The nomogram was based on a retrospectively study on 367 patients who underwent partial hepatectomy for ICC at the Eastern Hepatobiliary Surgery Hospital from 2002 to 2007. The predictive accuracy and discriminative ability of the nomogram were determined by concordance index (C-index) and calibration curve and compared with five currently used staging systems on ICC. The results were validated using bootstrap resampling and a prospective study on 82 patients operated on from 2007 to 2008 at the same institution.

### Results
On multivariate analysis of the primary cohort, independent factors for survival were serum carcinoembryonic antigen, CA 19-9, tumor diameter and number, vascular invasion, lymph node metastasis, direct invasion, and local extrahepatic metastasis, which were all selected into the nomogram. The calibration curve for probability of survival showed good agreement between prediction by nomogram and actual observation. The C-index of the nomogram for predicting survival was 0.74 (95% CI, 0.71 to 0.77), which was statistically higher than the C-index values of the following systems: American Joint Committee on Cancer (AJCC) seventh edition (0.65), AJCC sixth edition (0.65), Nathan (0.64), Liver Cancer Study Group of Japan (0.64), and Okabayashi (0.67; $P < .001$ for all). It was also higher (0.74) in predicting survival for the mass-forming type of ICC ($P < .001$). In the validation cohort, the nomogram discrimination was superior to the five other staging systems (C-index: 0.75 *v* 0.60 to 0.63; $P < .001$ for all).

### Conclusion
The proposed nomogram resulted in more-accurate prognostic prediction for patients with ICC after partial hepatectomy.

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## INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a neoplasm that originates from the endothelial cells of segmental or proximal branches of the bile duct.[1] It accounts for 5% to 30% of all primary liver malignancies[2,3] and has an incidence inferior only to hepatocellular carcinoma (HCC). Three gross pathologic types of ICC are defined by the Liver Cancer Study Group of Japan (LCSGJ); these are the mass-forming (MF) type, periductal infiltrating type, and intraductal growth type.[1] In recent years, the incidence and mortality of ICC are increasing worldwide.[4] Partial hepatectomy remains the mainstay of curative treatment for ICC.[5,6] Unfortunately, prognosis after partial hepatectomy is unsatisfactory, with a high incidence of locoregional recurrence and/or distant metastases.[7-9] ICC differs from HCC in carcinogenesis and biologic behaviors.[10] It also differs from hilar and distal bile duct cholangiocarcinoma in clinical features, imaging manifestations, and therapeutic strategies.[11] Therefore, ICC is a distinct hepatobiliary malignancy and requires a distinct prognostic predictive model.

The most commonly used staging system for ICC is the TNM classification system. Okabayashi et al[12] proposed a new staging system for the MF type of ICC based on the TNM staging system, but the tumor diameter is not used as a parameter because of its irrelevance to prognosis of resectable ICC. However, Yamasaki[13] reported that ICC with a diameter greater than 2 cm had a relatively poor prognosis. Thus, 2 cm was regarded as a cutoff value for the T classification, and this is adopted as an

 

important parameter by the LCSGJ system.[13] The widely used sixth edition of the American Joint Committee on Cancer (AJCC) TNM staging system concludes that patients with ICC with a tumor greater than 5 cm in diameter have a poorer prognosis. However, this system is based on the data from HCC, and its applicability to ICC is still uncertain.[14,15] Nathan et al[16] proposed an improved TNM staging system in which the tumor diameter was excluded in the T classification. This view is further adopted in the seventh edition of the AJCC TNM staging system (Appendix Table A1, online only).[17] The lack of consensus on which staging system to use has led to considerable confusion.

Currently, nomograms have been developed in the majority of cancer types.[18-20] The use of nomograms has compared favorably to the traditional staging systems for many cancers, and thus, it has been proposed as an alternative or even as a new standard.[21-23] To our knowledge, this study is the first attempt to establish a prognostic nomogram for resectable ICC based on the clinicopathologic data of 367 patients with ICC who underwent partial hepatectomy, to determine whether this model provides more-accurate prediction of patient survival when compared with the currently available staging systems.

## PATIENTS AND METHODS

### Patients and Study Design

A retrospective study was conducted on a primary cohort of patients who underwent partial hepatectomy for ICC between September 2002 and February 2007 at the Eastern Hepatobiliary Surgery Hospital (Shanghai, China). Inclusion criteria included the following: no history of previous anticancer therapy; no history of other malignancies; complete resection of macroscopic liver tumors; and histopathologically proven ICC. Exclusion criteria were as follows: hilar or extrahepatic cholangiocarcinoma, including intrahepatic metastasis of extrahepatic cholangiocarcinoma; tumors of uncertain origin or probable metastatic liver tumor; mixed type of primary liver cancer as confirmed histopathologically; and perioperative mortality.

From September 2007 to April 2008, an independent cohort of consecutive patients who underwent partial hepatectomy for ICC was prospectively studied, using the same inclusion and exclusion criteria. These patients formed the validation cohort of this study.

The study was censored on October 19, 2011. The study was approved by the institutional ethics committee. Informed consent was obtained before surgery.

### Diagnosis and Treatment

After a detailed history and a complete physical examination, blood was taken from the patients for hepatitis B surface antigen, hepatitis B virus DNA level, anti–hepatitis C virus (HCV) antibody, serum albumin, total bilirubin, ALT, $\gamma$-glutamyltransferase, $\alpha$-fetoprotein, CA 19-9, and carcinoembryonic antigen (CEA). Other routine investigations included chest x-ray, upper GI endoscopy, abdominal ultrasound, contrast-enhanced computed tomography (CT), and/or magnetic resonance imaging. In recent years, positron emission tomography was performed in patients with clinical or radiologic suspicion of intrahepatic or extrahepatic metastases. A preoperative diagnosis of ICC was based clinically, radiologically, and on raised serum markers.[24]

Partial hepatectomy was carried out according to tumor diameter, location, presence or absence of cirrhosis, and estimated volume of the future liver remnant. Liver resection was carried out based on Couinaud's segments, sectors, and hemilivers. Routine dissection of lymph nodes in the hepatoduodenal ligament and retropancreatic and/or para-aortic lymph nodes was performed for either preoperatively or intraoperatively diagnosed ICC. Direct invasions of adjacent structures and local extrahepatic metastases and newly found intrahepatic nodules identified intraoperatively were removed whenever possible. Hepaticojejunostomy was carried out in patients with tumor involvement of the primary and secondary bile ducts.

Histopathologic study of the resected specimens was carried out independently by three pathologists who came to a consensus by discussion if there was any controversy. The pathologic diagnosis of ICC was confirmed only if CK7 positive, CK19 positive, MUC1 positive, CK20 negative, HepPar1 negative, and glypican-3 negative phenotype was identified in an immunohistochemisty test.[25] Pathologic features, such as tumor diameter, number, capsule, site, surgical margin, vascular invasion, lymph node metastasis, hepatitis, and cirrhosis, were documented, and the degree of cell differentiation was determined.

### Follow-Up

Patients were observed once every 2 months in the first 2 years after surgery and then every 3 to 6 months thereafter. At each of the follow-up visits, a detailed history and a complete physical examination were carried out. Blood was taken for serum CA 19-9, CEA, $\alpha$-fetoprotein, and liver function tests, and an abdominal ultrasound was carried out. Contrast-enhanced CT or magnetic resonance imaging was performed once every 6 months or earlier when tumor recurrence or metastasis was suspected. Further investigation was carried out when clinically indicated. ICC recurrence/metastasis was defined as the appearance of a newly detected tumor confirmed on two radiologic images, with or without elevation of serum tumor markers. Overall survival (OS) and time to recurrence (TTR) were used as primary end points. OS was defined as the interval between partial hepatectomy and death or the last date of follow-up. TTR was calculated from surgery to the date when recurrence/metastasis was diagnosed.

### Categorization of Patients in Different Staging Systems

Patients were categorized according to five current staging systems (the sixth and seventh editions of the AJCC TNM classification and the Nathan, Okabayashi, and LCSGJ staging systems).[12-17]

### Statistical Analysis

Statistical analyses to identify risk factors were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL). Categorical variables were grouped based on clinical findings, and decisions on the groups were made before modeling. The results were compared using the $\chi^2$ test or Fisher's exact test. Continuous variables were compared using the *t* test or Mann-Whitney *U* test for variables with an abnormal distribution. Survival curves were depicted using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was used for multivariate analyses.

A nomogram was formulated based on the results of multivariate analysis and by using the package of *rms*[26] in R version 2.14.1 (http://www.r-project.org/). A final model selection was performed by a backward step-down selection process with the Akaike information criterion.[27] The performance of the nomogram was measured by concordance index (C-index) and assessed by comparing nomogram-predicted versus observed Kaplan-Meier estimates of survival probability. Bootstraps with 1,000 resample were used for these activities. Comparisons between the nomogram and other staging systems were performed with the rcorrp.cens package in *Hmisc*[28] in R and were evaluated by the C-index. The larger the C-index, the more accurate was the prognostic prediction.[29] During the external validation of the nomogram, the total points of each patient in the validation cohort were calculated according to the established nomogram, then Cox regression in this cohort was performed using the total points as a factor, and finally, the C-index and calibration curve were derived based on the regression analysis. $P < .05$ was considered statistically significant. The related computerized programs for nomograms with R are listed in the Appendix (online only).

## RESULTS

### Clinicopathologic Characteristics of Patients

In the primary cohort, of 421 patients with ICC who received partial hepatectomy during the study period, 367 met the inclusion

**Table 1.** Demographics and Clinicopathologic Characteristics of Patients With Intrahepatic Cholangiocarcinoma

| Demographic or Characteristic | Primary Cohort (n = 367) | | Validation Cohort (n = 82) | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Sex | | | | |
| Male | 246 | 67.0 | 52 | 63.4 |
| Female | 121 | 33.0 | 30 | 36.6 |
| Age, years | | | | |
| Median | 53 | | 56 | |
| Range | 27-78 | | 37-79 | |
| History of hepatitis | | | | |
| Yes | 148 | 40.3 | 31 | 37.8 |
| No | 219 | 59.7 | 51 | 63.2 |
| History of biliary disease* | | | | |
| Yes | 60 | 16.3 | 10 | 12.2 |
| No | 307 | 83.7 | 72 | 87.8 |
| AFP, μg/L | | | | |
| Median | 4.2 | | 4.2 | |
| Range | 0.6-1,210 | | 0.6-1,210 | |
| CEA, μg/L | | | | |
| Median | 2.5 | | 2.8 | |
| Range | 0.1-809.6 | | 0.3-809.6 | |
| CA 19-9, U/mL | | | | |
| Median | 41.2 | | 36.1 | |
| Range | 0.4-1,000 | | 0.6-1,000 | |
| TBIL, μmol/L | | | | |
| Median | 13.2 | | 13.6 | |
| Range | 4.7-333.9 | | 4.2-304.2 | |
| ALB, g/L | | | | |
| Median | 42.2 | | 43.7 | |
| Range | 29.8-64.8 | | 23.4-61.9 | |
| ALT, U/L | | | | |
| Median | 28.6 | | 24.6 | |
| Range | 3.5-2,649 | | 3.0-2,048 | |
| GGT, U/L | | | | |
| Median | 75.5 | | 86 | |
| Range | 0.9-1,502 | | 10-1,000.5 | |
| HBsAg | | | | |
| Positive | 187 | 51.0 | 43 | 52.4 |
| Negative | 180 | 49.0 | 39 | 47.6 |
| HBeAg | | | | |
| Positive | 36 | 9.8 | 9 | 10.9 |
| Negative | 331 | 90.2 | 73 | 89.1 |
| Anti-HCV | | | | |
| Positive | 8 | 2.2 | 0 | 0 |
| Negative | 331 | 97.8 | 82 | 100 |
| Blood transfusion | | | | |
| Yes | 61 | 16.6 | 15 | 18.3 |
| No | 306 | 83.4 | 67 | 81.7 |
| Tumor size, cm | | | | |
| Median | 5.5 | | 5.0 | |
| Range | 0.4-22.0 | | 1.2-15.0 | |
| Tumor number | | | | |
| ≥ 3 | 42 | 11.4 | 1 | 1.2 |
| < 3 | 325 | 88.6 | 81 | 98.8 |
| Surgical margin, cm | | | | |
| Median | 0.5 | | 0.4 | |
| Range | 0.1-3.1 | | 0.1-3.5 | |
| Cirrhosis | | | | |
| Yes | 78 | 21.3 | 18 | 21.9 |
| No | 289 | 78.7 | 64 | 78.1 |

(continued on following page)

  

**Table 1.** Demographics and Clinicopathologic Characteristics of Patients With Intrahepatic Cholangiocarcinoma (continued)

| Demographic or Characteristic | Primary Cohort (n = 367) | | Validation Cohort (n = 82) | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Capsule | | | | |
| Incomplete | 311 | 84.7 | 70 | 85.3 |
| Complete | 56 | 15.3 | 12 | 14.7 |
| Microvascular invasion | | | | |
| Yes | 37 | 10.1 | 8 | 9.7 |
| No | 330 | 89.9 | 74 | 90.3 |
| Vascular invasion | | | | |
| Yes | 54 | 14.7 | 12 | 14.6 |
| No | 313 | 85.3 | 70 | 85.4 |
| Lymph node metastasis | | | | |
| Yes | 82 | 22.3 | 18 | 21.9 |
| No | 285 | 77.7 | 64 | 78.1 |
| Direct invasion and local extrahepatic metastasis† | | | | |
| Yes | 35 | 9.5 | 7 | 8.5 |
| No | 332 | 90.5 | 75 | 91.5 |

Abbreviations: AFP, α-fetoprotein; ALB, albumin; CEA, carcinoembryonic antigen; GGT, γ-glutamyltransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TBIL, total bilirubin

*Included, in the primary and validation cohorts, cholelithiasis (51 and seven patients, respectively), primary sclerosing cholangitis (five and two patients, respectively), and parasite infection (four patients and one patient, respectively).

†Included, in the primary and validation cohorts, invasion of transverse colon (10 and three patients, respectively) and stomach (eight and two patients, respectively) and solitary metastatic nodule in diaphragm (six patients and one patient, respectively) and adrenal gland (five patients and one patient, respectively) and, in the primary cohort, solitary nodule in omentum (five patients) and cystic duct (one patient).

criteria be entered onto this study. For the validation cohort, we studied 82 consecutive patients. The clinicopathologic characteristics of patients in the primary and validation cohorts are listed in Table 1. The gross pathologic types of ICC were MF type (n = 345; 94.0%), periductal infiltrating type (n = 20; 5.5%), and intraductal growth type (n = 2; 0.5%).[1]

### Tumor Recurrence and OS in the Primary Cohort

The median follow-up time was 39.3 months (range, 7.5 to 107.2 months), the median TTR was 13.8 months (range, 1.3 to 63.6 months), and the postoperative 1-, 3-, and 5-year recurrence rates were 48.9%, 62.5%, and 67.3%, respectively. The median OS was 21.0 months (range, 1.6 to 105.7 months), and the 1-, 3-, and 5-year OS rates were 61.9%, 40.8%, and 35.2%, respectively.

### Independent Prognostic Factors in the Primary Cohort

The results of the univariate analysis are listed in Appendix Table A2 (online only). Multivariate analyses demonstrated that serum CEA, CA 19-9, tumor diameter and number, lymph node metastasis, vascular invasion, and direct invasion and local extrahepatic metastasis were independent risk factors for tumor recurrence and OS (Table 2).

### Prognostic Nomogram for OS

The prognostic nomogram that integrated all significant independent factors for OS in the primary cohort is shown in Figure 1. The C-index for OS prediction was 0.74 (95% CI, 0.71 to 0.77). The calibration plot for the probability of survival at 3 or 5 year after surgery showed an optimal agreement between the prediction by nomogram and actual observation (Figs 2A and 2B).

**Table 2.** Multivariate Analysis of the Primary Cohort

| Variable | Recurrence | | | Overall Survival | | |
|---|---|---|---|---|---|---|
| | *P* | HR | 95% CI | *P* | HR | 95% CI |
| CA 19-9 | .048 | 1.000 | 1.000 to 1.001 | .004 | 1.001 | 1.000 to 1.001 |
| CEA | .011 | 1.010 | 1.002 to 1.018 | .001 | 1.011 | 1.005 to 1.018 |
| Vascular invasion (yes *v* no) | .015 | 1.546 | 1.088 to 2.196 | .005 | 1.605 | 1.154 to 2.231 |
| Direct invasion and local extrahepatic metastasis (yes *v* no) | .026 | 1.572 | 1.055 to 2.342 | .025 | 1.592 | 1.061 to 2.390 |
| Lymph node metastasis (yes *v* no) | .001 | 1.702 | 1.241 to 2.335 | < .001 | 2.057 | 1.531 to 2.764 |
| Tumor diameter | .003 | 1.057 | 1.018 to 1.096 | < .001 | 1.078 | 1.041 to 1.116 |
| Tumor number | | | | | | |
| 1 nodule | | | | | | |
| 2-3 nodules | .040 | 1.586 | 1.021 to 2.464 | .045 | 1.582 | 1.011 to 2.474 |
| > 3 nodules, or periductal invasion | < .001 | 4.402 | 2.874 to 6.742 | < .001 | 6.096 | 4.059 to 9.155 |

Abbreviations: CEA, carcinoembryonic antigen; HR, hazard ratio.

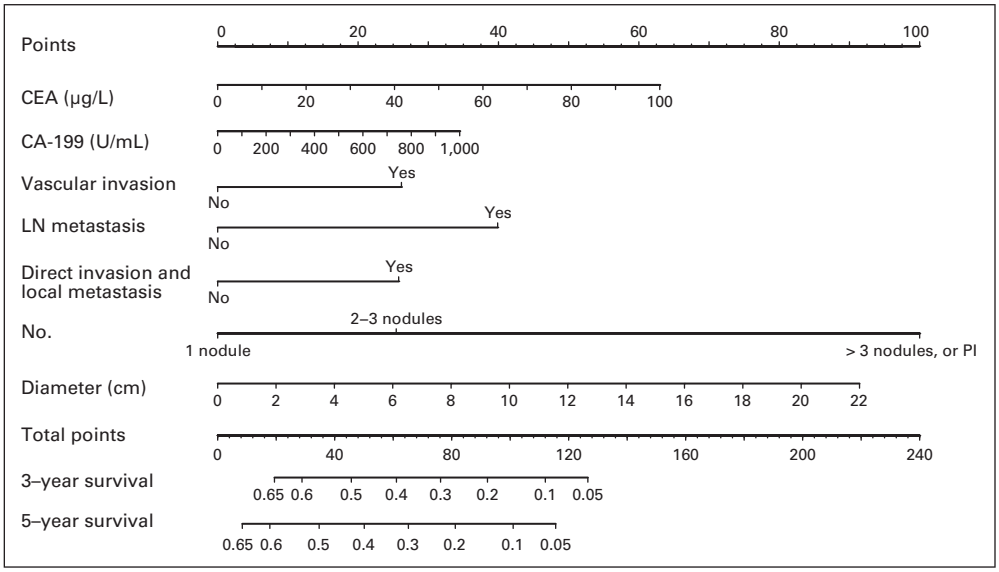


**Fig 1.** Intrahepatic cholangiocarcinoma survival nomogram. (To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the likelihood of 3- or 5-year survival). CA-199, preoperative level of serum CA 19-9; CEA, preoperative level of serum carcinoembryonic antigen; Direct invasion and local metastasis, direct invasion of adjacent structures and local extrahepatic metastasis; LN metastasis, regional lymph node metastasis; PI, periductal infiltrating type.

### *Comparison of Predictive Accuracy Between the Nomogram and a Single Independent Factor*

As shown in Table 2, the hazard ratios of tumor diameter and tumor number for survival were higher than the hazard ratios for the other factors. The predictive power for prognosis of ICC between the nomogram and tumor diameter and number was compared. The C-indices for OS prediction were 0.63 and 0.57 by tumor diameter and number, respectively, which were significantly lower than the C-index by the nomogram (0.74; $P < .001$).

### *Comparison of Predictive Accuracy for OS Between Nomogram and Conventional Staging Systems*

As shown in Figure 3, the AJCC seventh, Nathan, and LCSGJ systems showed good prognostic stratification for patients between stage I and stage II or later in both cohorts. However, in both cohorts, the LCSGJ system was unsatisfactory in stratifying patients between stages III and IV, and the AJCC seventh edition was unsatisfactory in stratifying patients between stages II and IV. The Nathan system was unsatisfactory in stratifying patients between stages II and III in the primary cohort. Meanwhile, the AJCC sixth edition and Okabayashi systems could stratify patients among stages I to III to a certain extent, whereas they were not as good as the other three systems in distinguishing patients between stages I and II, especially the AJCC sixth edition in the validation cohort.

Our nomogram displayed better accuracy in predicting both short- and long-term survival in the primary cohort. The C-index of the nomogram was 0.74, which was significantly higher ($P < .001$) than the AJCC seventh editing staging system (0.65), the AJCC sixth edition staging system (0.65), the Nathan staging system (0.64), the Okabayashi staging system (0.67), and the LCSGJ staging system (0.64). There was no significant difference regarding C-indices among these staging systems (AJCC seventh edition *v* AJCC sixth edition, $P = .79$; AJCC sixth editing *v* Nathan, $P = .76$; Nathan *v* Okabayashi, $P = .80$; Okabayashi *v* LCSGJ, $P = .57$). The results suggest that the nomogram was a useful predictor for survival of patients with ICC in the primary cohort.

### *Comparison of Predictive Accuracy for OS in MF ICC Between Nomogram and Conventional Staging Systems*

In the primary cohort, the majority of patients (94%) had MF ICC. This is consistent the experience reported by others.[12,13] Because there are more therapeutic options for the MF ICC in clinical practice, the prognostic discrimination of any ICC staging system should also particularly look at MF ICC. The C-index of the nomogram was 0.74 (95% CI, 0.71 to 0.77), which was higher than the other staging systems for predicting OS of the MF ICC ($P < .001$). The C-indices of the other staging systems were 0.65 (AJCC seventh edition), 0.65 (AJCC sixth edition), 0.65 (Nathan), 0.67 (Okabayashi), and 0.64 (LCSGJ). There were no significant differences in the C-indices among these staging systems (AJCC seventh edition *v* AJCC sixth edition, $P = .75$; AJCC sixth edition *v* Nathan, $P = .74$; Nathan *v* Okabayashi, $P = .79$; Okabayashi *v* LCSGJ, $P = .65$). These results again suggest that the nomogram was useful for predicting survival of patients with MF ICC.

### *Validation of Predictive Accuracy of the Nomogram for OS*

In the validation cohort, the median follow-up time was 43.3 months (range, 16.3 to 51.1 months). The median TTR was 15.1 months (range, 0.36 to 50.4 months), and the postoperative 1- and 3-year recurrence rates were 32.9% and 46.6%, respectively. The median OS time was 30.6 months (range, 1.2 to 50.4 months), and the 1- and 3-year OS rates were 69.5% and 47.6%, respectively.

The C-index of the nomogram for predicting OS was 0.75 (95% CI, 0.68 to 0.83), and a calibration curve showed good agreement between prediction and observation in the probability of 3-year survival (Fig 2C). There were no significant differences in the C-indices among the different staging systems (AJCC seventh edition: 0.60; AJCC sixth edition: 0.61; Nathan: 0.60; Okabayashi: 0.60; LCSGJ: 0.63; $P \geq .17$ for all), and all C-indices were significantly lower than that of the nomogram ($P < .001$).

  

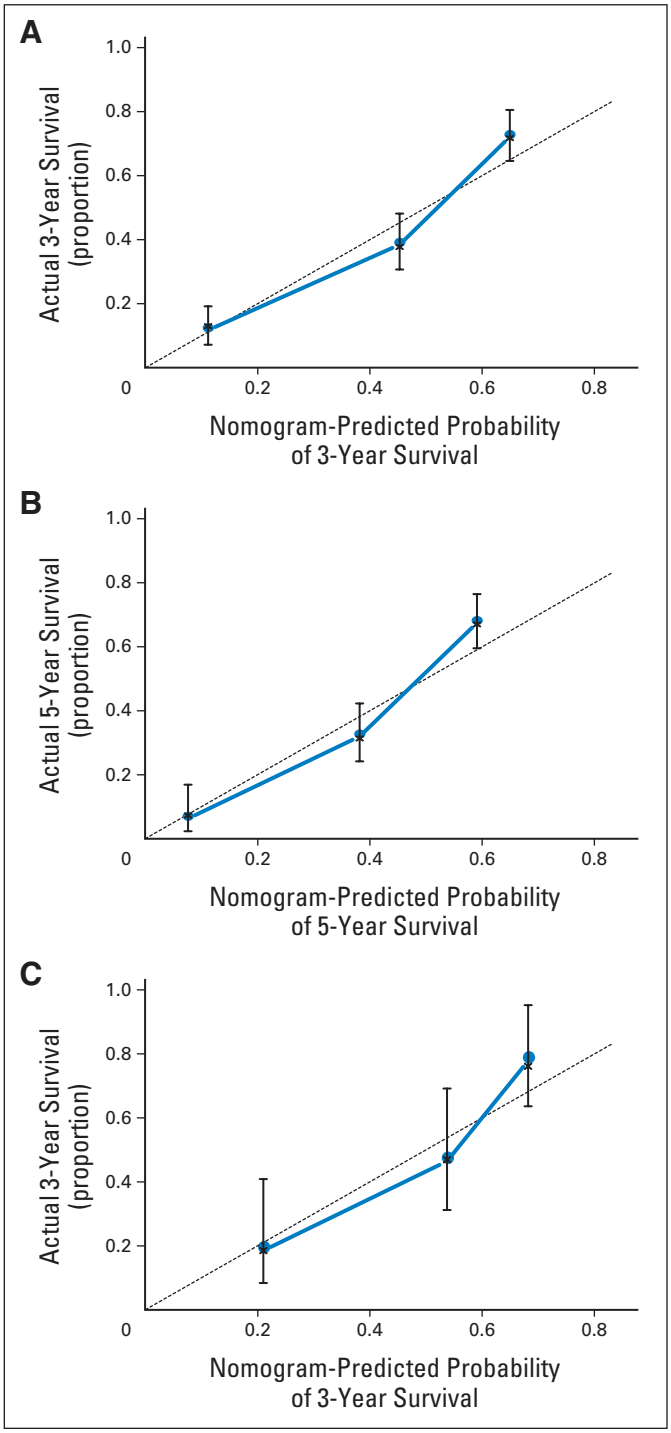


**Fig 2.** The calibration curve for predicting patient survival at (A) 3 years and (B) 5 years in the primary cohort and at (C) 3 years in the validation cohort. Nomogram-predicted probability of overall survival is plotted on the *x*-axis; actual overall survival is plotted on the *y*-axis.

## DISCUSSION

Five staging systems have been commonly used for ICC. Current controversies on the different staging systems focus on the following three aspects: whether tumor diameter is an independent risk factor for prognosis of ICC; whether additional risk factors, other than the TNM factors, are important parameters; and whether a distinct staging system should be used for the most common type of ICC, the MF type. Moreover, all of these systems are not specifically developed for postoperative prognostic prediction. The predictive accuracy of these systems for patients with ICC who undergo partial hepatectomy might be affected by these questions. Thus, we observed that the C-indices of these systems varied from 0.64 to 0.67 in survival prediction in the primary cohort.

Nomograms have been developed and shown to be more accurate than the conventional staging systems for predicting prognosis in some cancers.[21,30] Thus, a prognostic nomogram for patients with ICC after partial hepatectomy was constructed because liver resection is the only established curative modality for ICC.[5,6] The nomogram performed well in predicting survival, and its prediction was supported by the C-index (0.74 and 0.75 for the primary and validation cohorts, respectively) and the calibration curve. When compared with the other five staging systems, the nomogram showed better predictive accuracy for survival.

MF ICC accounts for approximately 78.6% to 90.0% of ICCs.[12,13] The percentage of MF ICC was 94.0% in the primary cohort of this study. Therefore, it is important to analyze the performance of the nomogram in the prognostic prediction for this type of ICC separately. The C-index of the nomogram in predicting survival of patients with this type of ICC was 0.74, which was also significantly higher than the other staging systems.

Controversies exist about the relationship between tumor diameter and number and survival of patients with ICC after partial hepatectomy. The LCSGJ staging system indicates that a tumor diameter greater than 2 cm and multiple tumors are risk factors influencing survival. The sixth edition of the AJCC TNM staging system indicates that patients with solitary/multiple tumors with a diameter $\leq$ 5 cm have better survival. On the contrary, the Okabayashi and Nathan systems proposed that tumor diameter was not an independent risk factor for survival, and this view has been accepted and incorporated into the seventh edition of the AJCC TNM staging system. In this study, tumor diameter and tumor number reflected the invasiveness of ICC, and they were significantly associated with prognosis on multivariate analysis (Table 2). Furthermore, number of tumor nodules more than three was a strong risk factor. The prognosis of the patients with large or multiple nodules was significantly poorer (Fig 1). For tumor diameter or number, although the weight accounted for a high proportion in the nomogram, their C-indices for prediction of prognosis were less than 0.70, and their predictive accuracies were significantly less than the proposed model in this study ($P < .001$).

The nomogram also includes comprehensive laboratory indices such as serum tumor markers, which have not been included as variables in the other five staging systems. Serum CA 19-9 and CEA levels have been suggested to be independent risk factors for prognosis of cholangiocarcinoma including ICC.[31,32] Although tumor markers have not been included in ICC staging systems, their role in increasing predictive performance has been observed in HCC staging systems.[33,34] Furthermore, a nomogram always contains more prognostic variables than the traditional staging systems.[30]

There are several limitations of this study. First, the nomogram was established based on data obtained from a single institution in China. Second, most patients (n = 187 [51%] and n = 43

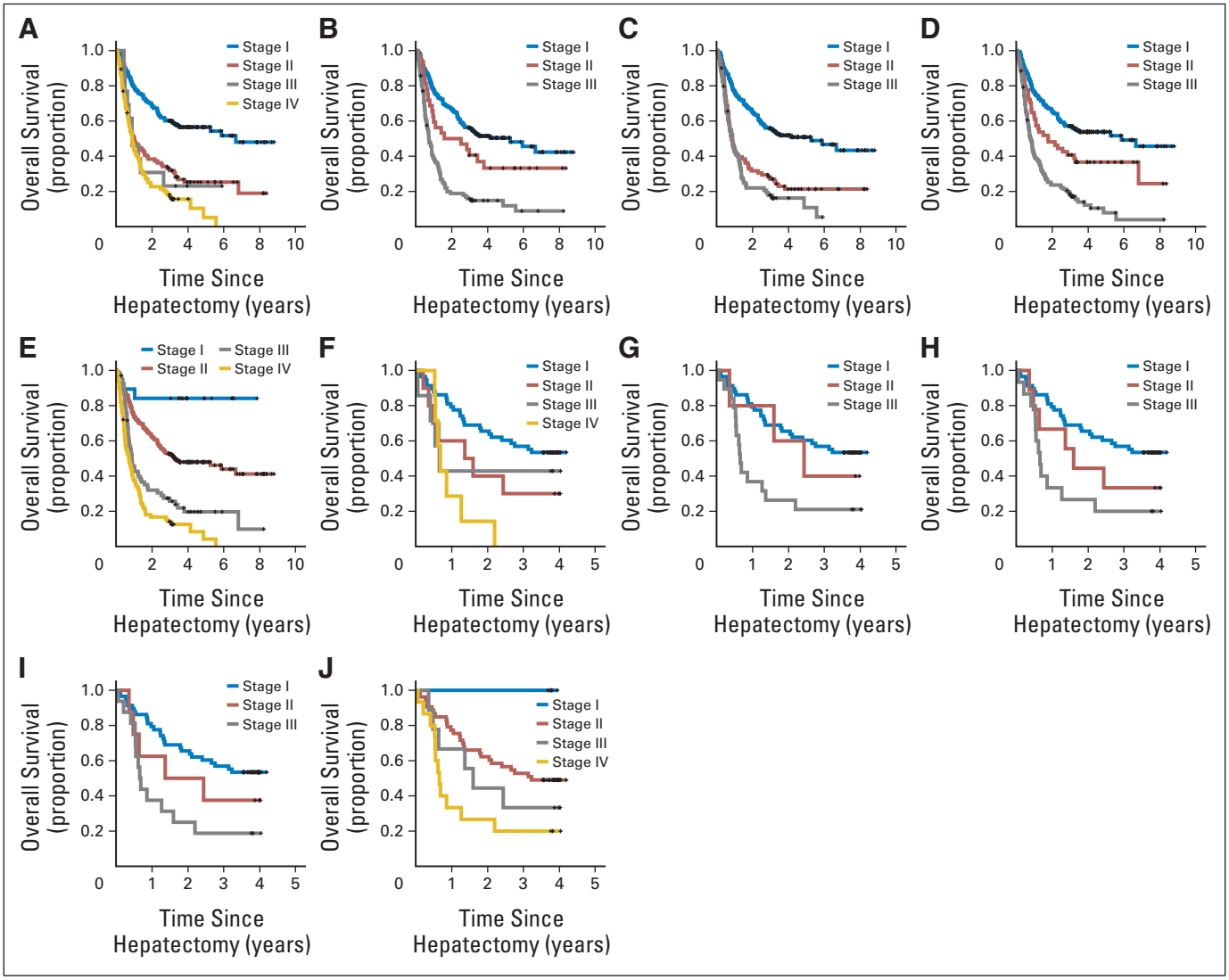


**Fig 3.** Kaplan-Meier survival curves of the primary cohort ([A] American Joint Committee on Cancer [AJCC] seventh edition; [B] AJCC sixth edition; [C] Nathan; [D] Okabayashi; [E] Liver Cancer Study Group of Japan [LCSGJ]) and the validation cohort ([F] AJCC seventh edition; [G] AJCC sixth edition; [H] Nathan; [I] Okabayashi; [J] LCSGJ) categorized by different staging systems.

[52.4%] in the primary and validation cohorts, respectively) had a background of hepatitis B virus infection, whereas eight patients in the primary cohort and seven patients in both cohorts had anti-HCV positivity and primary sclerosing cholangitis, respectively. Because HCV infection and primary sclerosing cholangitis are important factors in carcinogenesis of ICC, especially in Western countries, whether this staging system is applicable to patients with a Western background is still unclear.[25,35] Third, in this study, the assessment of lymph node status as no metastasis was based on the absence of adenopathy on imaging and surgical exploration in 74 and 15 patients in the primary and validation cohorts, respectively. Although enhanced CT or positron emission tomography can give a high negative predictive value (nearly 99%) in patients without lymphadenopathy and our criteria have been adopted by other studies,[36,37] this is still a limitation that might affect the results to a certain extent. Finally, whether this nomogram can be applied to patients who receive treatment other than partial hepatectomy remains to be determined.[38]

In conclusion, the nomogram as proposed in this study objectively and accurately predicted the prognosis of patients with ICC after partial hepatectomy. Additional studies are required to determine whether it can be applied to other patient groups.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Yizhou Wang, Jun Li, Kui Wang, Dong Wu, Lehua Shi, Wanyee Lau, Mengchao Wu, Feng Shen
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## REFERENCES


1. Liver Cancer Study Group of Japan: Intrahepatic cholangiocarcinoma, macroscopic typing, in Okamoto E (ed): Classification of Primary Liver Cancer. Tokyo, Japan, Kanehara, 1997, pp 6-7
2. The Liver Cancer Study Group of Japan: Primary liver cancer in Japan: Clinicopathologic features and results of surgical treatment. Ann Surg 211:277-287, 1990
3. Kaczynski J, Hansson G, Wallerstedt S: Incidence, etiologic aspect and clinicopathologic features in intrahepatic cholangiocellular carcinoma: Astudy of 51 cases from a low-endemicity area. Acta Oncol 37:77-83, 1998
4. Shaib Y, El-Serag HB: The epidemiology of cholangiocarcinoma. Semin Liver Dis 24:115-125, 2004
5. Tan JC, Coburn NG, Baxter NN, et al: Surgical management of intrahepatic cholangiocarcinoma: A population based study. Ann Surg Oncol 15:600-608, 2008
6. Farges O, Fuks D, Boleslawski E, et al: Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: A multicenter study by the AFC-IHCC-2009 study group. Ann Surg 254:824-829, 2011
7. Farges O, Fuks D: Clinical presentation and management of intrahepatic cholangiocarcinoma. Gastroenterol Clin Biol 34:191-199, 2010
8. Ohtsuka M, Ito H, Kimura F, et al: Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. Br J Surg 89:1525-1531, 2002
9. Nathan H, Pawlik TM, Wolfgang CL, et al: Trends in survival after surgery for cholangiocarcinoma: A 30-year population-based SEER database analysis. J Gastrointest Surg 11:1488-1496, 2007
10. Paik KY, Jung JC, Heo JS, et al: What prognostic factors are important for resected intrahepatic cholangiocarcinoma? J Gastroenterol Hepatol 23:766-770, 2008
11. Petrowsky H, Hong JC: Current surgical management of hilar and intrahepatic cholangiocarcinoma: The role of resection and orthotopic liver transplantation. Transplant Proc 41:4023-4035, 2009
12. Okabayashi T, Yamamoto J, Kosuge T, et al: A new staging system for mass-forming intrahepatic cholangiocarcinoma: Analysis of preoperative and postoperative variables. Cancer 92:2374-2383, 2001
13. Yamasaki S: Intrahepatic cholangiocarcinoma: Macroscopic type and stage classification. J Hepatobiliary Pancreat Surg 10:288-291, 2003
14. Vauthey JN, Lauwers GY, Esnaola NF, et al: Simplified staging for hepatocellular carcinoma. J Clin Oncol 20:1527-1536, 2002
15. Greene FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Manual (ed 6). New York, NY, Springer-Verlag, 2002
16. Nathan H, Aloia TA, Vauthey JN, et al: A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol 16:14-22, 2009
17. Edge SB: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer-Verlag, 2009
18. International Bladder Cancer Nomogram Consortium,Bochner BH, Kattan MW, Vora KC: Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. J Clin Oncol 24:3967-3972, 2006
19. Karakiewicz PI, Briganti A, Chun FK, et al: Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol 25:1316-1322, 2007
20. Wierda WG, O'Brien S, Wang X, et al: Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. Blood 109:4679-4685, 2007
21. Sternberg CN: Are nomograms better than currently available stage groupings for bladder cancer? J Clin Oncol 24:3819-3820, 2006
22. Mariani L, Miceli R, Kattan MW, et al: Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. Cancer 103:402-408, 2005
23. Wang L, Hricak H, Kattan MW, et al: Prediction of organ-confined prostate cancer: Incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. Radiology 238:597-603, 2006
24. Endo I, Gonen M, Yopp AC, et al: Intrahepatic cholangiocarcinoma: Rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 248:84-96, 2008
25. Sempoux C, Jibara G, Ward SC, et al: Intrahepatic cholangiocarcinoma: New insights in pathology. Semin Liver Dis 31:49-60, 2011
26. Frank E, Harrell Jr: Rms: Regression Modeling Strategies. R Package version 3.4-0. http://CRAN.R-project.org/package=rms
27. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996
28. Frank E, Harrell Jr: Hmisc: Harrell Miscellaneous. R Package version 3.9-2. http://CRAN.R-project.org/package=Hmisc
29. Huitzil-Melendez FD, Capanu M, O'Reilly EM, et al: Advanced hepatocellular carcinoma: Which staging systems best predict prognosis? J Clin Oncol 28:2889-2895, 2010
30. Touijer K, Scardino PT: Nomograms for staging, prognosis, and predicting treatment outcomes. Cancer 115:3107-3111, 2009 (suppl 13)
31. Hatzaras I, Schmidt C, Muscarella P, et al: Elevated CA 19-9 portends poor prognosis in patients undergoing resection of biliary malignancies. HPB (Oxford) 12:134-138, 2010
32. Cho SY, Park SJ, Kim SH, et al: Survival analysis of intrahepatic cholangiocarcinoma after resection. Ann Surg Oncol 17:1823-1830, 2010
33. Llovet JM, Brú C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
34. Chevret S, Trinchet JC, Mathieu D: A new prognostic classification for predicting survival in patients with hepatocellular carcinoma: Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 31:133-141, 1999
35. El-Serag HB, Engels EA, Landgren O, et al: Risk of hepatobiliary and pancreatic cancers after hepatitis C virus infection: A population-based study of U.S. veterans. Hepatology 49:116-123, 2009
36. Choi SB, Kim KS, Choi JY, et al: The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: Association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 16:3048-3056, 2009
37. Grobmyer SR, Wang L, Gonen M, et al: Perihepatic lymph node assessment in patients undergoing partial hepatectomy for malignancy. Ann Surg 244:260-264, 2006
38. Schwartz JJ, Hutson WR, Gayowski TJ, et al: Liver transplantation for cholangiocarcinoma. Transplantation 88:295-298, 2009