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A personalized prognostic model for long-term survival in patients with intrahepatic cholangiocarcinoma: a retrospective cohort study

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Purpose: This study aimed to determine the optimal cutoff points for age and tumor size of patients with intrahepatic cholangiocarcinoma (ICC) and to establish and verify a predictive nomogram of overall survival at 1, 3, and 5 years.
Methods: From the SEER (Surveillance, Epidemiology, and End Results) database, 1,325 ICC patients were selected and randomly divided into training and testing cohorts at a 7:3 ratio. Using the X-tile software, age and tumor size were classified into 3 subgroups: ≤61, 62–74, and ≥75 years and ≤35, 36–55, and ≥56 mm. Subsequently, univariate and multivariate Cox regression analyses were performed using the R software in the training cohort to determine independent risk factors, compile the prediction nomogram, and verify it with the testing cohort findings.
Results: The C-indexes of the new prediction nomograms in the training and testing cohorts were 0.738 (95% confidence interval [CI], 0.718–0.758) and 0.750 (95% CI, 0.72–0.78), respectively. Furthermore, the areas under the 1-, 3-, and 5-year receiver operating characteristic (ROC) curves based on the nomogram were 0.792, 0.853, and 0.838, respectively, higher than the ROC based on the 7th and 8th editions of the American Joint Cancer Commission (AJCC) staging system.
Conclusion: This study established and verified a prognostic nomogram that improved the accuracy of the 1-, 3-, and 5-year survival predictions for ICC patients, compared with that based on the 7th and 8th editions of the AJCC staging system, and can help clinicians make personalized survival predictions.
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Key Words: Cholangiocarcinoma, Nomograms, Survival, Neoplasms

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary liver cancer, and its incidence and mortality rate are increasing worldwide [1]. Compared with other malignant tumors, ICC has a poor prognosis and is difficult to diagnose early; the 1- and 5-year overall survival (OS) rates are approximately 30% and 18%, respectively [2]. Surgery is still the main treatment for ICC, but only 20%–30% of the patients are eligible for resection [3], and even after radical surgical resection, the OS rate of ICC patients is still poor; the 5-year survival rate after surgery is only 25%–40% [4-6]. Surgical resection is accompanied by postoperative complications, including pneumonia, heart failure, surgical site infections, and renal failure that have a negative impact on survival [7-9], especially in older adults. Moreover, most patients with ICC are often diagnosed when they reach advanced disease stages [10].

Therefore, accurate staging is of great importance for

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patients when choosing appropriate treatment plans and predicting treatment outcomes. At present, the influence of age and tumor size on the long-term survival of ICC patients remains controversial. Age is an important factor for the prognosis of ICC; however, there is no unified understanding of the definition of its cutoff points. The MEGNA (referring to multifocality, extrahepatic extension, grade, nodal status, and age) prognostic scoring system shows that age >60 years is independently associated with poor OS [11], while Liu et al. [12] used 70 years as the cutoff point. Whether tumor size is a prognostic factor of ICC is still controversial. Nathan et al. [13] analyzed the SEER database and concluded that tumor size alone cannot predict the survival rate of postoperative ICC patients, but both the first ICC grading system of the Liver Cancer Study Group of Japan, based on TNM and the TNM8 staging system incorporated tumor size into the scoring system [14,15]. However, in terms of the cutoff points for tumor size, the staging systems have not led to consistent findings. Li et al. [16] proposed a classification of 7 cm as the cutoff point for tumor size. The critical value of the T1 tumor category, subdivided into T1a and T1b, is 7 cm instead of 5 cm.

Consequently, we tried to explore the optimal cutoff points for age and tumor size in ICC and their prognostic value based on data from the United States National Cancer Institute's SEER program. Prediction of prognosis is a key factor in personalized clinical treatment. The risk factors involved in tumor development can be combined to form a graph for clinical decision-making [17]. Such graphs have been used to treat many cancers [18,19]. This study aimed to evaluate the optimal cutoff points for age and tumor size in ICC and to construct a nomogram that combined important factors obtained from the SEER database to predict the probability of OS in ICC patients.

METHODS

Ethical statement

This is a retrospective study, and the data were collected from the United States public SEER database. Therefore, this study did not require informed patient consent or ethics committee approval.

Data sources and samples

Patients' data were obtained from the SEER database of the American Cancer Institute (http://seer.cancer.gov/) and filtered

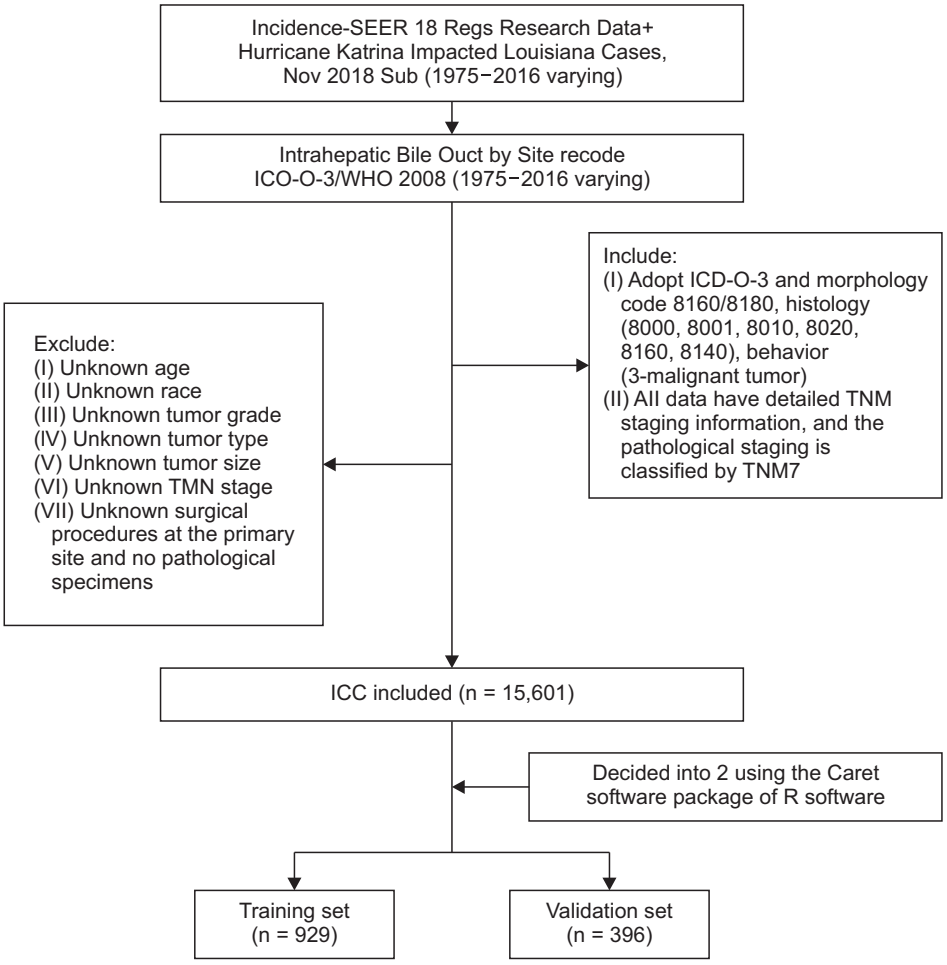

Fig. 1. Flowchart displaying the extraction and grouping process of resected intrahepatic cholangiocarcinoma (ICC) cases in the SEER (the Surveillance, Epidemiology, and End Results) database. ICD-O-3, International Classification of Diseases for Oncology, the 3rd edition; WHO, World Health Organization; TNM7, the 7th edition of the American Joint Cancer Commission TNM classification (2010).

using the SEER Stat Software (ver. 8.3.8; National Cancer Institute, https://seer.cancer.gov/seerstat/). The "Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975–2016 varying)" database was selected, and the selection criteria were as follows: (i) International Classification of Diseases for Oncology, the 3rd edition (ICD-O-3) was adopted and the following identification codes were used: terrain code C22.0 and morphology codes 8160/8180, histology codes 8000, 8001, 8010, 8020, 8160, and 8140, and behavior code 3 (3 = malignant tumor); (ii) the primary site was from the intrahepatic biliary ducts ; (iii) all patients had detailed TNM staging information, and the pathological staging was classified by the 7th edition of the American Joint Cancer Commission (AJCC) (2010) TNM classification (TNM7) [20]. The exclusion criteria were as follows: (i) unknown age, (ii) unknown race, (iii) unknown tumor grade, (iv) unknown TNM7, (v) unknown tumor type, (vi) unknown tumor size, and (vii) unknown surgical procedures at the primary site and no pathological specimens. Finally, this study included the data of 1,325 ICC patients. As shown in Fig. 1, the step-by-step extraction process of available cases finally yielded 1,325 cases that met the inclusion criteria in this analysis. Data on clinical variables, including age at diagnosis, sex, race, primary tumor site, grade, diagnostic confirmation, ICD-O-3 Hist/behave, TNM7, primary tumor, surgery method, tumor size, vital status recodes, and survival months, were obtained for each patient. In order to observe the long-term survival of patients, we used data before 2018, which did not include records of the 8th edition TNM classification (TNM8). We used the disease severity, collaborative staging code, and TNM7 provided by SEER to derive TNM8 for each patient [21]. Regarding the clinical outcome, OS was chosen as the primary endpoint. Then, the Caret software package of R software was used to divide the patients into 2 groups (929 and 396 cases in the training and verification groups, respectively) at a ratio of 7:3 (SEER Stat Software, ver. 8.3.5). The registration number used to acquire clinical data from the SEER database was 12402-Nov2019. The need for informed consent from the subjects was waived.

Determination of the optimal cutoff points for age and tumor size in intrahepatic cholangiocarcinoma

To study the relationship of age and tumor size with survival, we used the X-tile program to determine the best cutoff points for age and tumor size in ICC patients. The X-tile program is a general method for describing and assessing the best cutoff points for the correlation between risk factors and prognosis

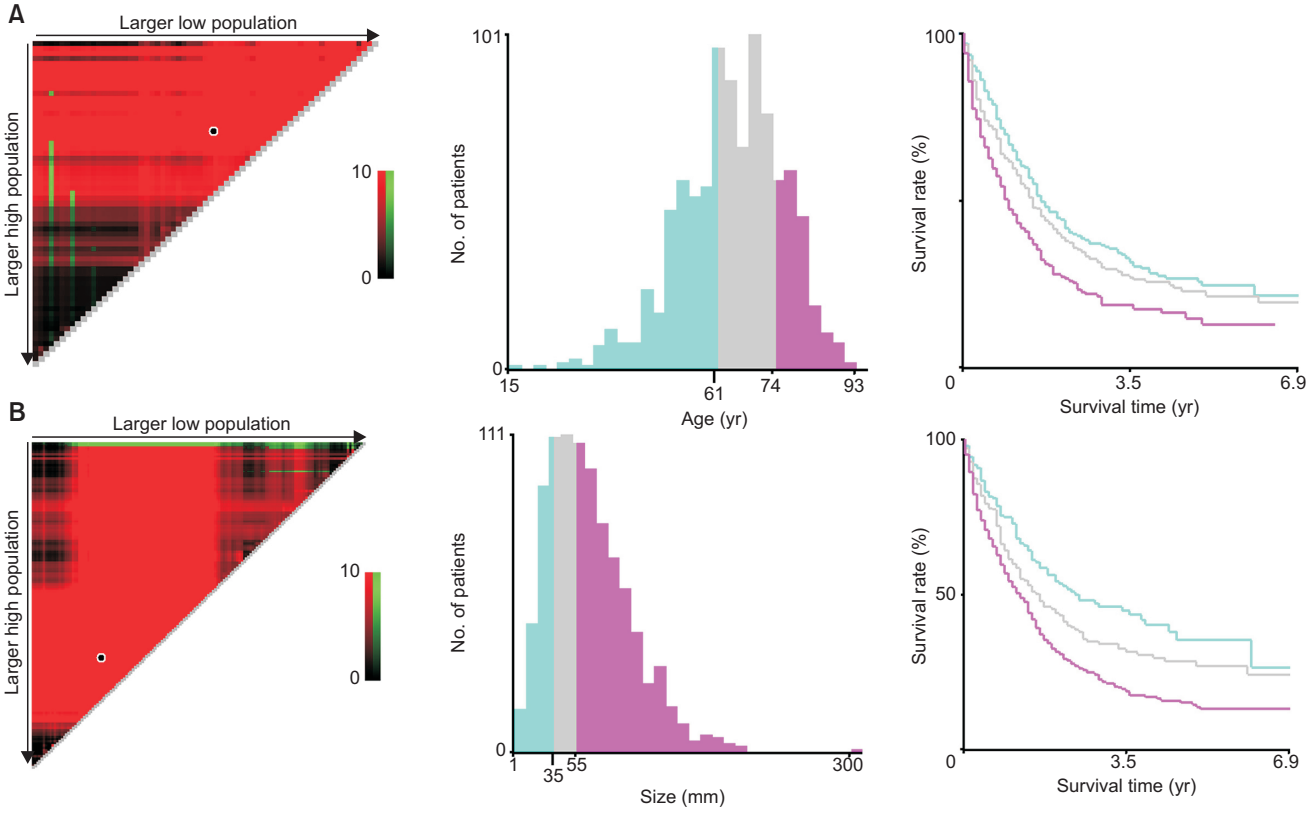

Fig. 2. X-tile analysis of the patient's age and tumor size. (A) The best age cutoff points. (B) The best tumor size cutoff points.

[22]. This tool is currently used to distinguish different subgroups based on tumor size in many prognostic models [23]. The X-tile software was used to divide the tumor size and age of ICC patients in the training cohort into 3 groups.

Statistical analysis

The OS was estimated using the Kaplan-Meier method and compared by the log-rank test. In addition, the Cox proportional hazard model was used to filter important variables, and the independent risk factors selected by multivariate analysis were used to construct a nomogram and predict the 1-, 3-, and 5-year OS rates. As the optimal cutoff point for tumor size was reassessed in this study, we mainly included the TNM7 rather than TNM8 in the Cox proportional hazard model. The C-index and area under the curve (AUC) were used to evaluate the discrimination of the new evaluation model, and a calibration curve was applied to evaluate the fit of the model. The C-index and AUC values of 0.5–0.7, 0.7–0.9, and >0.9 indicate that a given model has low, moderate, and high predictive value, respectively. The calibration curve adopted the bootstrap-free sampling method, and sampling was repeated 100 times. The constructed nomogram was verified internally using the data of 396 patients in the verification group. Furthermore, the AUC values were used to compare the predictive ability based on the new nomogram, TNM7 and TNM8. All statistical analyses were performed using the R software ver. 4.0.2 (The R Foundation). Statistical significance was set at a P-value of ≤0.05.

Table 1. Baseline demographic and clinical characteristics of intrahepatic cholangiocarcinoma patients

Characteristic	All subjects	Training cohort	Validation cohort	P-value
No. of patients	1,325	929	396	
Age (yr)				0.669
≤61	476 (35.9)	327 (35.2)	149 (37.6)	
62–74	564 (42.6)	398 (42.8)	166 (41.9)	
≥75	285 (21.5)	204 (22.0)	81 (20.5)	
Race				0.290
Black	103 (7.8)	66 (7.1)	37 (9.3)	
White	1,052 (79.4)	747 (80.4)	305 (77.0)	
Others	170 (12.8)	116 (12.5)	54 (13.6)	
Sex				0.594
Female	656 (49.5)	455 (49.0)	201 (50.8)	
Male	669 (50.5)	474 (51.0)	195 (49.2)	
Grade (7th)				0.154
I	145 (10.9)	106 (11.4)	39 (9.8)	
II	634 (47.8)	429 (46.2)	205 (51.8)	
III	535 (40.4)	388 (41.8)	147 (37.1)	
IV	11 (0.8)	6 (0.6)	5 (1.3)	
T stage (7th)				0.886
T1	472 (35.6)	328 (35.3)	144 (36.4)	
T2	578 (43.6)	404 (43.5)	174 (43.9)	
T3	179 (13.5)	130 (14.0)	49 (12.4)	
T4	96 (7.2)	67 (7.2)	29 (7.3)	
N stage (7th)				0.531
N0	936 (70.6)	651 (70.1)	285 (72.0)	
N1	389 (29.4)	278 (29.9)	111 (28.0)	
M stage (7th)				0.151
M0	1029 (77.7)	711 (76.5)	318 (80.3)	
M1	296 (22.3)	218 (23.5)	78 (19.7)	
Surgery				0.338
Yes	691 (52.2)	476 (51.2)	215 (54.3)	
No	634 (47.8)	453 (48.8)	181 (45.7)	
Tumor size (mm)				0.999
≤35	281 (21.2)	197 (21.2)	84 (21.2)	
36–55	297 (22.4)	208 (22.4)	89 (22.5)	
≥56	747 (56.4)	524 (56.4)	223 (56.3)	

Values are presented as number (%).

RESULTS

Determination of optimal age, tumor size cutoff points, and prognosis

As shown in Fig. 2, age, tumor size, vital status recodes, and survival months were inputted into the X-tile software. The critical point for age was "3," and the patients were divided into 3 groups: ≤61, 62–74, and ≥75 years; the critical point for tumor size was "3," and the patients were divided into 3 groups: ≤35, 36–55, and ≥56 mm.

Patient characteristics

This study included 1,325 eligible patients who were diagnosed with ICC as the only primary cancer. Of these, 929 and 396 were included in the training and testing cohorts, respectively. The descriptive and clinical characteristics of the patients are presented in Table 1. Among all patients, 476 (35.9%) were aged ≤61 years old, 564 (42.6%) were aged between 62 and 74 years, and 285 (21.5%) were aged ≥75 years. Regarding race, 1,054 people (79.4%) were white, and 103 (7.8%) were black. Further, 656 were female (49.5%) and 669 were male (50.5%). There were no statistically significant differences between the clinical characteristics of the training and testing cohorts.

Independent prognostic factors of overall survival in the training cohort

The prognostic factors for ICC were calculated using univariate and multivariate Cox proportional hazard

Table 2. Univariate and multivariate analysis of overall survival rates in training cohort

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)				
≤61	Reference		Reference	
62–74	1.157 (0.9642–1.388)	0.117	1.412 (1.1711–1.702)	<0.001
≥75	1.627 (1.3226–2.000)	<0.001	1.896 (1.5330–2.345)	<0.001
Race				
White	Reference		Reference	
Black	1.408 (1.0523–1.883)	0.021	1.678 (1.2464–2.259)	<0.001
Others	1.025 (0.8061–1.303)	0.841	1.101 (0.8620–1.407)	0.441
Sex				
Female	Reference		Reference	
Male	1.266 (1.082–1.481)	<0.001	1.242 (1.0596–1.456)	<0.001
Grade (7th)				
I	Reference		Reference	
II	1.140 (0.8646–1.503)	0.353	1.113 (0.8415–1.473)	0.453
III	1.933 (1.4681–2.545)	<0.001	1.680 (1.2708–2.221)	<0.001
IV	0.609 (0.5970–4.516)	0.337	1.580 (0.5548–4.503)	0.392
T stage (7th)				
T1	Reference		Reference	
T2	1.741 (1.444–2.099)	<0.001	1.386 (1.1431–1.680)	<0.001
T3	1.897 (1.485–2.424)	<0.001	1.609 (1.2475–2.075)	<0.001
T4	1.738 (1.279–2.362)	<0.001	1.827 (1.3376–2.496)	<0.001
N stage (7th)				
N0	Reference		Reference	
N1	1.881 (1.594–2.220)	<0.001	1.352 (1.1316–1.616)	<0.001
M stage (7th)				
M0	Reference		Reference	
M1	2.545 (2.141–3.024)	<0.001	1.385 (1.1388–1.685)	<0.001
Surgery				
Yes	Reference		Reference	
No	3.839 (3.241–4.547)	<0.001	3.041 (2.5099–3.685)	<0.001
Tumor size (mm)				
≤35	Reference		Reference	
36–55	1.364 (1.053–1.768)	0.019	1.309 (1.0062–1.703)	0.045
≥56	1.908 (1.531–2.377)	<0.001	1.265 (1.0049–1.592)	0.045

HR, hazard ratio; CI, confidence interval.

regressions, and the results showed that in addition to age and tumor size, sex, race, grade, TNM7, and surgery were all independent prognostic factors (Table 2). The forest plot generated intuitive results (Fig. 3). In addition, survival curves were drawn using a Kaplan-Meier estimator to investigate the influence of certain single factors on the OS (Fig. 4). We found (Fig. 4) that with an increase in age and tumor size, the patient's survival rate showed a downward trend. Moreover, the survival rate of surgical patients was significantly higher than that of nonsurgical patients. Nonsurgical patients had a 3.839-fold higher risk of death than surgical patients.

Construction and validation of nomogram for overall survival

The prognostic nomogram of ICC combined all the important independent factors of OS in the training cohort, as shown in Fig. 5. The prognostic nomogram C-indexes for predicting the OS were 0.738 (95% confidence interval [CI], 0.718–0.758) and 0.750 (95% CI, 0.72–0.78) in the training cohort and testing cohort, respectively. The AUC was used to compare the results based on the new nomogram, the TNM7 and TNM8 staging systems. In the training set, the nomogram-based AUCs of 1, 3, and 5 years were 0.792, 0.853, and 0.838, respectively, whereas the AUCs were 0.677, 0.745, and 0.777, respectively for the TNM7 stage system, and were 0.678, 0.751, and 0.784, respectively for the TNM8 (Fig. 6A–C). In the validation set, the AUCs of the nomogram for predicting 1, 3, and 5 years were 0.839, 0.79, and 0.813, respectively, while the AUCs of the TNM7 were 0.675, 0.694, and 0.711, respectively and the AUCs of the TNM8 staging were 0.688, 0.706, and 0.73, respectively (Fig. 6D–F). The calibration plots of the 1-, 3-, and 5-year OS rates of ICC patients showed that there was optimal consistency between the nomogram predictions and actual observations in the training (Fig. 7A–C) and testing (Fig. 7D–F) cohorts.

DISCUSSION

Globally, ICC is the second most common primary liver malignant tumor [1]. In recent years, the prevalence of metabolic diseases such as type 2 diabetes mellitus and metabolic-associated fatty liver disease has been continuously increasing. These diseases not only increase the risk of cardiovascular

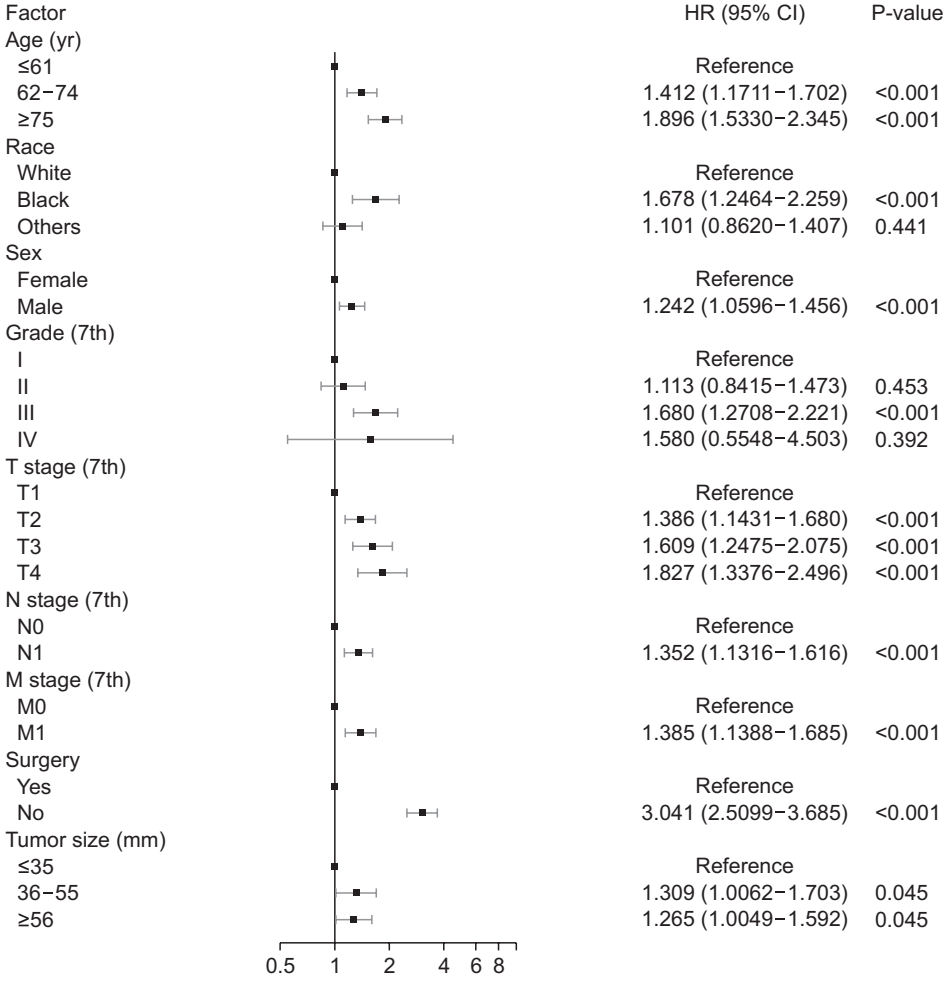

Fig. 3. Forest plot of hazard ratio of independent prognostic factors for overall survival of intrahepatic cholangiocarcinoma patients.

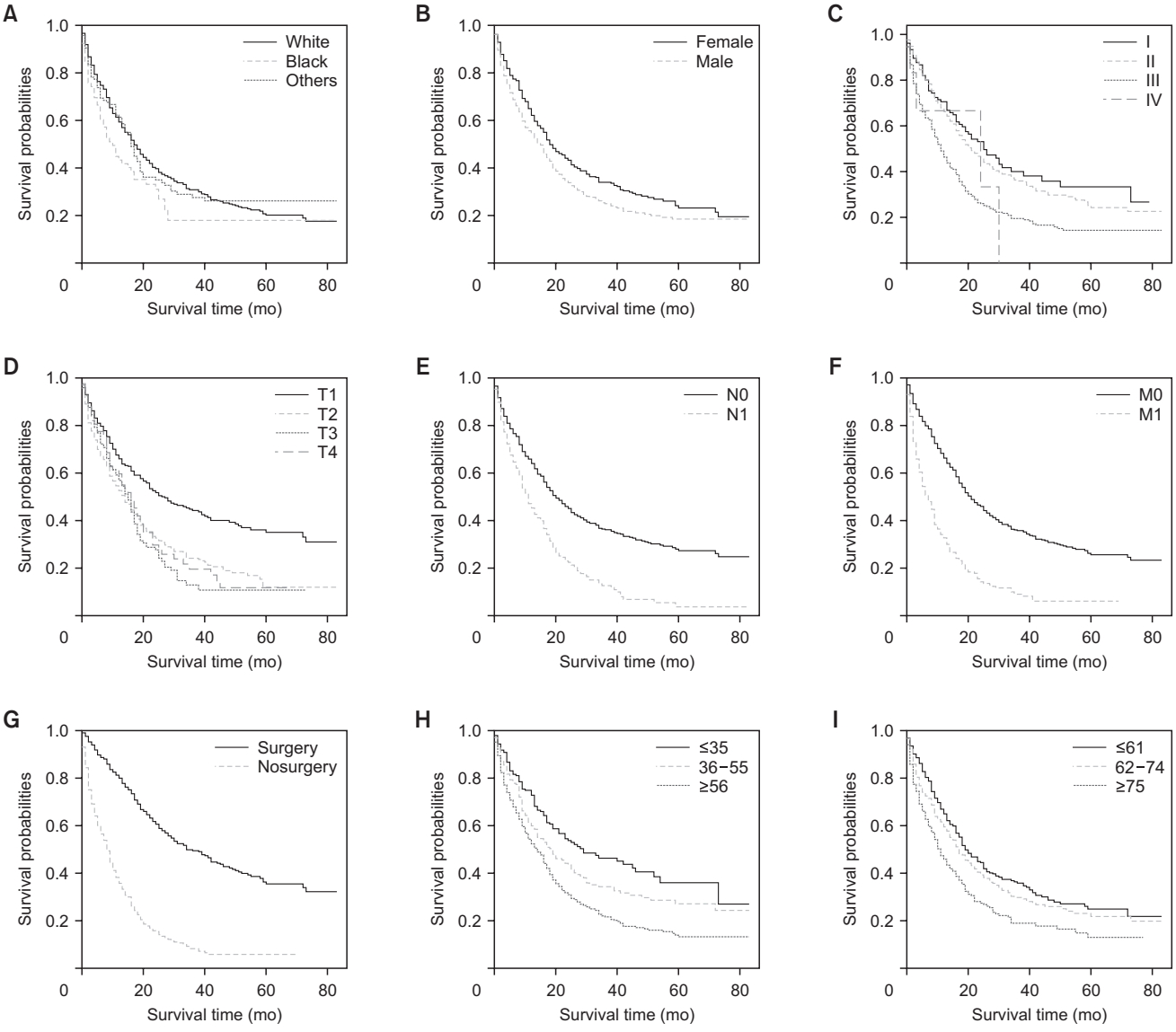

Fig. 4. The Kaplan-Meier curves of overall survival rates stratified by patient characteristics. (A) race, (B) sex, (C) grade, (D) T stage, (E) N stage, (F) M stage, (G) surgery, (H) size, and (I) age.

diseases but also elevate the risk of developing extrahepatic cancers, including ICC [24]. Moreover, the long-term survival rate of ICC patients remains relatively low. In this study, we constructed a more comprehensive model than the TNM staging system based on a combination of various risk factors to better predict the prognosis of ICC patients. We first determined the optimal cutoff values for age and tumor size. Our study showed that race, sex, AJCC T stage, AJCC N stage, AJCC M stage, surgery, and grade were independent prognostic factors of ICC after single-factor (univariate) and multivariate analyses. A nomogram was constructed based on these 9 factors. The factors included race, sex, age, surgery, grade, and tumor size in the traditional AJCC staging system. On continuing internal verification of the new nomogram and comparing its C-index and AUC with those based on the traditional TNM staging system, we found that the new predictive model improved the discriminative ability of the traditional TNM staging system.

More importantly, to the best of our knowledge, no previous study has defined the critical value for age and tumor size of ICC patients. While only the Hyder nomogram [25] and MEGNA score [11] were included in the ICC nomogram, the critical value for age was not calculated. We used the X-tile software to calculate the optimal critical value for age and found that age was an independent risk factor for ICC patients, as revealed by single-factor (univariate) and multivariate analyses. This result is consistent with that of the study by Ji et al. [26], who found that age is an independent factor affecting the prognosis of ICC after hepatectomy. The impact of age on the prognosis of cancer

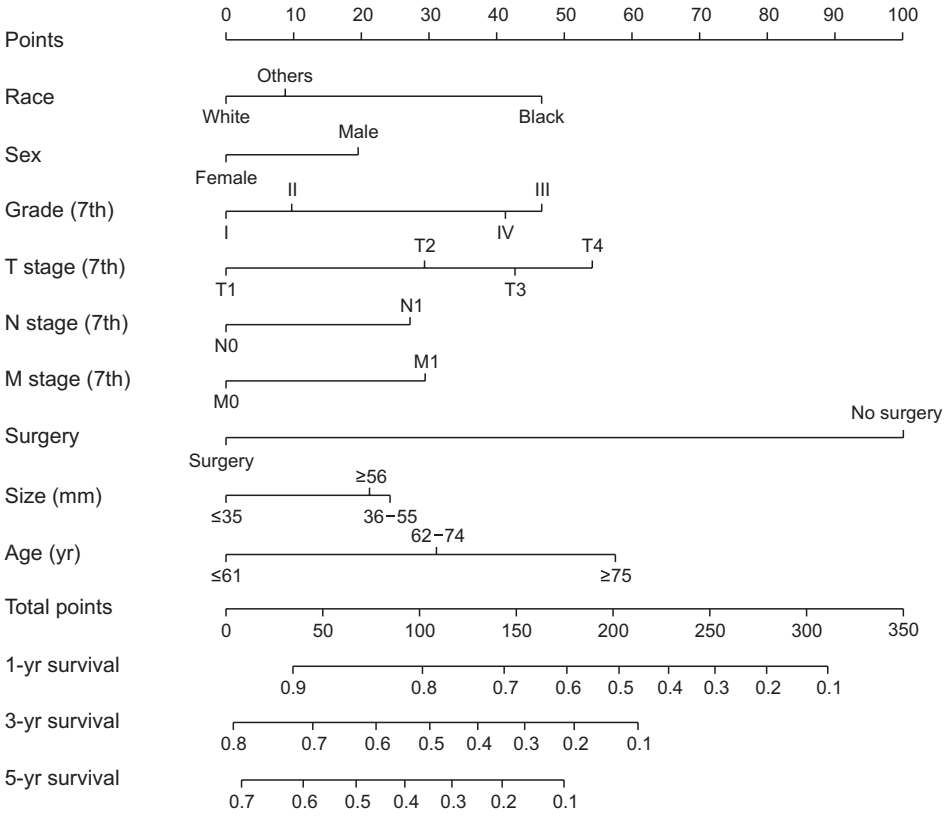

Fig. 5. The nomogram contains independent prognostic factors for the 1-, 3-, and 5-year overall survival of intrahepatic cholangiocarcinoma patients.

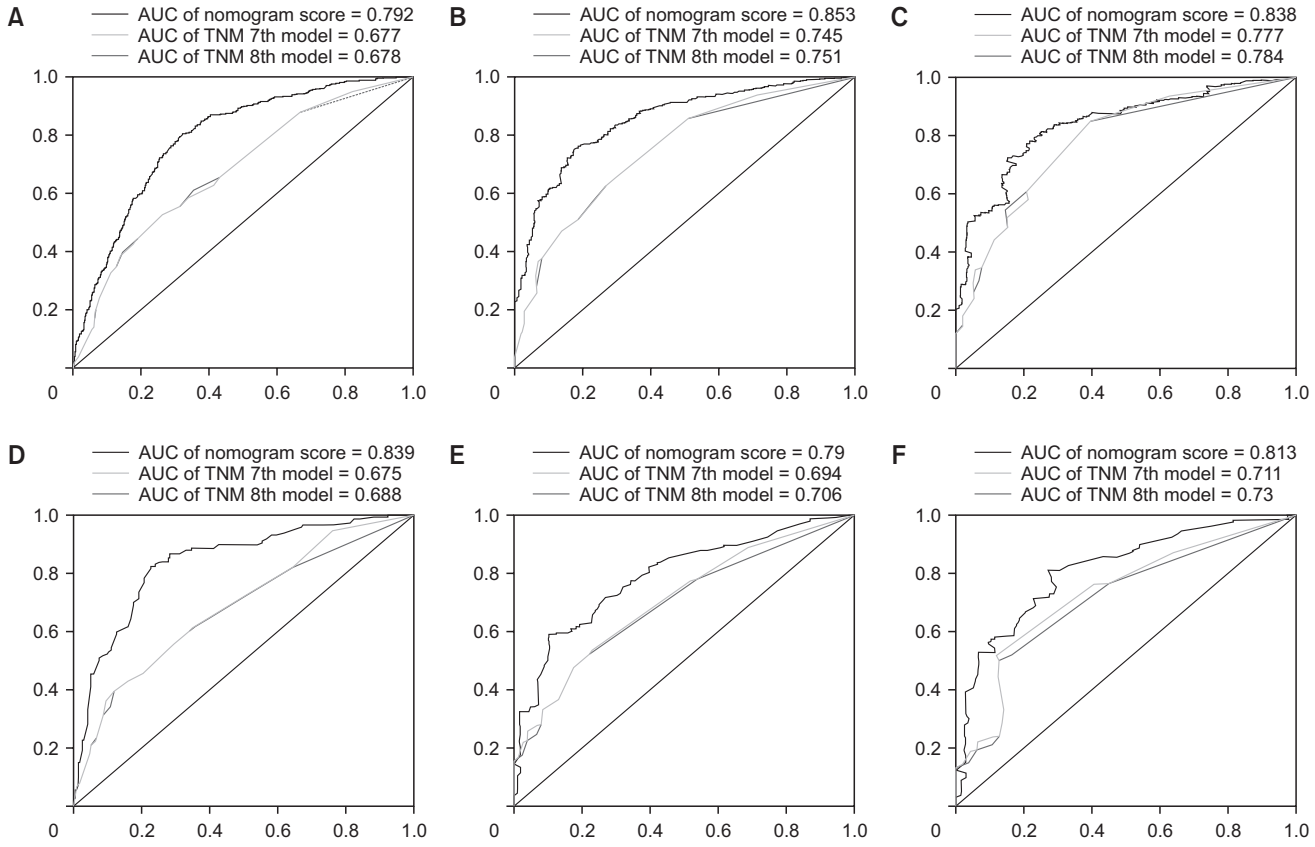

Fig. 6. The receiver operating characteristic (ROC) curves of the nomogram and TNM stage for predicting prognosis in the training and testing cohorts. (A–C) The area under the ROC curve (AUC) of overall survival (OS) in the training cohort at 1 year (A), 3 years (B), and 5 years (C). (D–F) ROC of OS in the testing cohort at 1 year (D), 3 years (E), and 5 years (F).

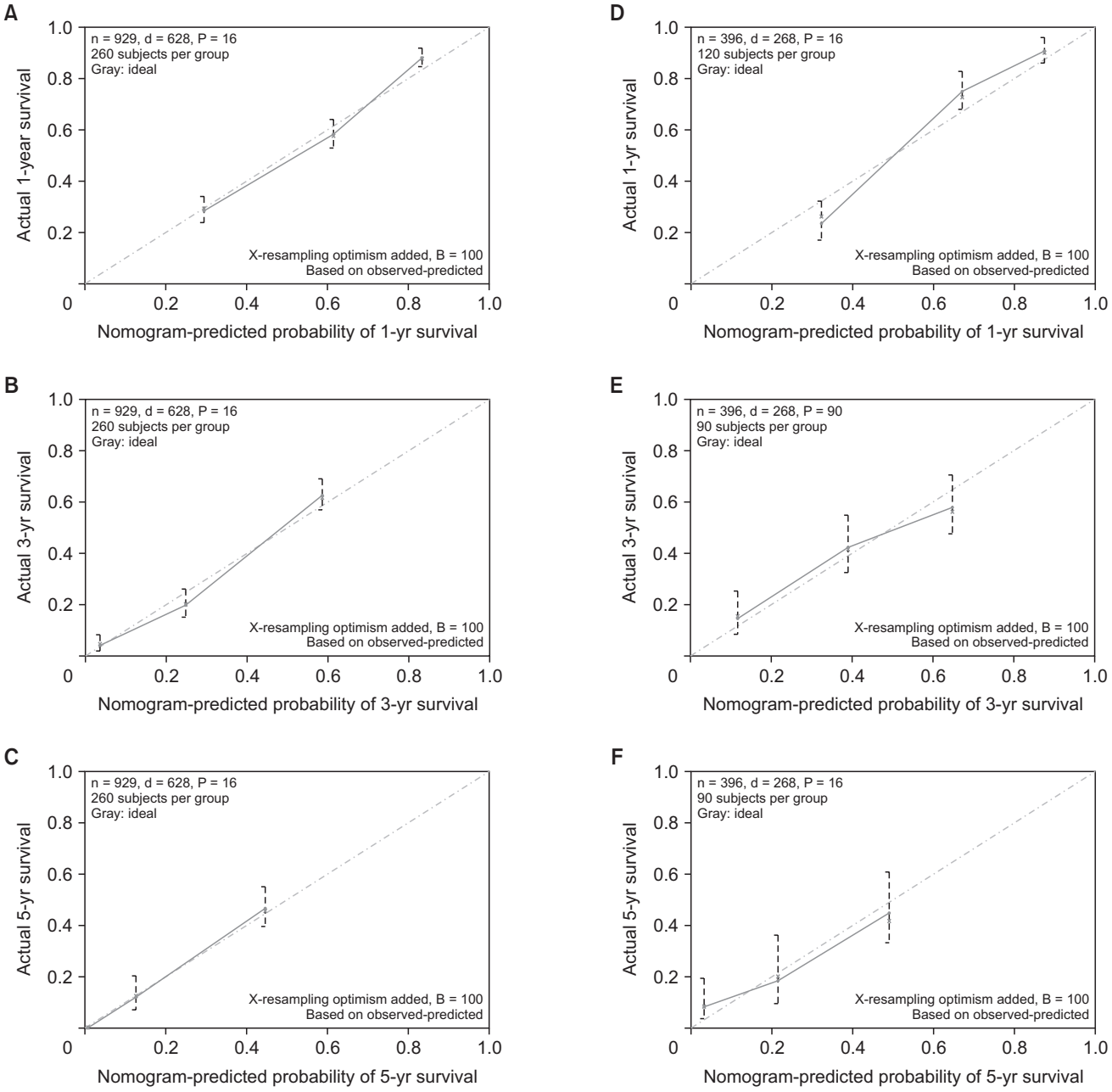

Fig. 7. Calibration plot of the 1-, 3-, and 5-year overall survival (OS) nomogram in the training (A–C) and testing cohorts (D–F).

patients is complex, as the older the patient, the higher the risk of death, which has terrifying significance in the current aging world [7]. Research has shown that advanced age is an obstacle to obtaining professional cancer treatment [27], which may also be a reason for the high risk of death in older people. In addition, in clinical practice, some ICC patients, especially older patients, give up treatment due to general circumstances, but in young patients, the treatment effect is often limited and disease progression is faster [28]. Although older patients with ICC can benefit from active treatment, they prefer relatively conservative treatment [28]. This phenomenon is more obvious in patients ≥75 years old, which may also be the reason for the low survival rate of older patients [29].

At the same time, large tumor sizes increase the risk of death in ICC patients. Although, as per the current research, tumor size is the most important feature of the ICC prediction model [26], it is difficult to determine the critical tumor size initially because the incidence rate of ICC is still relatively low, and there is no consensus on whether tumor size should be included in TNM staging. Nathan et al. [13] developed an ICC staging system that ignored tumor size. The TNM7 manual first confirmed the TNM staging system for ICC but did not include tumor size

[20]. Subsequently, the TNM8 T classification included tumor size (≤5 and >5 cm) as a new staging parameter [15]. However, the critical value of tumor size is controversial. Ruzzenente et al. [30] found that the OS of ICC patients with tumors ≤3 cm was better than that of patients with larger tumors. However, the classification of tumor size thresholds is mostly binary, and our research provides a classification method for 3 tumor size thresholds, and the nomogram showed that dividing the tumor size into 3 subgroups can improve the predictive ability of the TNM staging system.

Although this study was based on a large population, it has some potential limitations. First, the SEER database does not record detailed information about other cancer treatment methods (palliative therapy, radiotherapy, and chemotherapy) that play an important role in the prognosis of ICC. Second, this study only used SEER data for internal verification; external data are needed for in-depth research. Third, although the results of this study include multiple risk factors, they are very similar to the traditional AJCC staging system; therefore, further studies with large-scale, multicenter research samples are needed. Finally, although we have determined the optimal cutoff point for ICC tumor size, it is imperative to acknowledge that our findings are primarily derived from CT or MRI rather than the actual tumor size, and there may be disparities between the tumor sizes determined radiologically and those observed in pathological examinations. These disparities have the potential to impact the predictive performance of the nomogram. Therefore, more clinical data are needed in the future to explore the relationship between imaging tumor size and pathological tumor size in ICC.

In conclusion, based on the SEER database, this study determined, for the first time, the best cutoff points for age and tumor size in ICC patients, both of which are independent factors predicting OS in these patients. The nomogram that we constructed and verified externally can help clinicians predict the prognosis of patients of different ages and tumor sizes, thereby aiding the development of personalized patient treatment and follow-up plans.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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