Original Article

Development and validation of a diagnostic and prognostic model for bone metastasis of intrahepatic cholangiocarcinoma: a population-based analysis

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Background: Bone metastasis (BM) is a common site of metastasis in patients with intrahepatic cholangiocarcinoma (ICC), significantly impacting the quality of life and prognosis of affected individuals. This investigation aimed to assess the risk of BM development in ICC patients and to prognosticate for patients with ICC-associated BM (ICCBM) through the construction of two nomograms.

Methods: We conducted a retrospective analysis of data from 2,651 ICC patients, including 148 cases of BM, documented in the Surveillance, Epidemiology, and End Results (SEER) database spanning 2010 to 2017. Independent predictors for the occurrence of BM in ICC patients were identified via univariate and multivariate logistic regression analyses; simultaneously, independent prognostic indicators for ICCBM patients were ascertained through univariate and multivariate Cox regression analyses. The utility of the nomograms was evaluated through calibration curves, receiver operating characteristic (ROC) curves, decision curve analysis (DCA), and Kaplan-Meier (KM) analysis.

Results: Independent risk factors for BM in ICC included sex, tumor size, lung metastasis, brain metastasis, and intrahepatic metastasis. For ICCBM patients, independent prognostic factors comprised age, chemotherapy, and radiotherapy. The prognostic nomogram exhibited C-indexes of 0.737 [95% confidential interval (CI): 0.682–0.792] for the training cohort and 0.696 (95% CI: 0.623–0.769) for the validation cohort. Calibration curves demonstrated strong concordance between predicted outcomes and observed events. The areas under the curve (AUC) for 3-, 6-, and 12-month cancer-specific survival (CSS) were 0.853, 0.781, and 0.739, respectively, in the training cohort, and 0.794, 0.822, and 0.780 in the validation cohort. DCA illustrated significant net benefits across a broad spectrum of threshold probabilities. KM analysis revealed 1-, 2-, and 3-year CSS rates of 23.91%, 7.55%, and 2.35%, respectively, with a median CSS of 6 months, underscoring the nomograms' capacity to distinctly stratify patients according to survival risk.

Conclusions: The development of these nomograms offers substantial clinical utility in forecasting BM risk among ICC patients and prognosticating for those with ICCBM, thereby facilitating the formulation of more efficacious treatment modalities.

Keywords: Intrahepatic cholangiocarcinoma (ICC); bone metastasis (BM); nomogram; Surveillance, Epidemiology, and End Results (SEER); cancer-specific survival (CSS)

Submitted Apr 06, 2024. Accepted for publication Jul 11, 2024. Published online Aug 27, 2024.
doi: 10.21037/tcr-24-567
View this article at: https://dx.doi.org/10.21037/tcr-24-567

Introduction

Intrahepatic cholangiocarcinoma (ICC), situated between the bile ducts within the liver and the secondary bile ducts, ranks as the second most common primary liver cancer following hepatocellular carcinoma (HCC) (1). Recent years have witnessed a global increase in both the incidence and mortality rates of ICC (2,3). Regrettably, patients with ICC generally face low survival rates and high risks of recurrence. Even after curative surgery, the 5-year overall survival (OS) rates fluctuate between 20% and 35%, with recurrence rates soaring to 40–80% (4-7). Moreover, approximately 70%-80% of patients are ineligible for surgery due to either local unresectability or distant metastasis (4).

Bone metastasis (BM) represents a typical metastatic pattern in ICC patients, with an incidence rate of 29.7% and a median OS of merely about 4 months (8). The traditional tumor-lymph node-metastasis (TNM) staging system primarily focuses on tumor size, lymph node metastasis, and distant metastasis, overlooking other crucial patient attributes such as age, sex, and treatment modalities (9,10). Therefore, developing predictive models to estimate the risk of BM in ICC patients and the prognosis of ICC-associated BM (ICCBM) patients is of paramount importance. However, a lack of research specifically aimed at this objective has resulted in an inability to quantify these prognostic probabilities.

Nomograms, as practical and ideal visual tools, have been extensively utilized in supporting clinical decision-making by predicting and calculating the probability of outcomes for each patient (11,12). Given the relative rarity of ICCBM patients, this study aims to develop and validate two nomograms by analyzing data from the Surveillance, Epidemiology, and End Results (SEER) database, intended to predict the risk of BM occurrence in newly diagnosed ICC patients and the cancer-specific survival (CSS) for ICCBM patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-567/rc).

Highlight box

Key findings

- In this study, two new nomograms were successfully created to predict the risk of bone metastasis (BM) in patients with intrahepatic cholangiocarcinoma (ICC) and the cancer-specific survival (CSS) of 1, 2 and 3 years in patients with ICC-associated BM (ICCBM).

What is known and what is new?

- ICC patients generally face low survival rates and a high risk of recurrence, with even poorer survival outcomes when BM is present, with a median overall survival (OS) of approximately 4 months.
- This study presents a practical and real-world nomogram based on clinicopathological variables from a large-scale database to predict CSS in patients with ICCBM.

What is the implication, and what should change now?

- The utilization of our nomograms will enable clinicians to identify risk factors for BM in ICC patients. At the same time, the clinical treatment strategies of patients with ICCBM may tend to use radiotherapy and chemotherapy. Using nomograms enables them to make more complex and personalized treatment and management decisions.

Methods

Patients and data selection

Utilizing SEER*Stat software (version 8.4.2), we retrieved clinical, pathological, and prognostic data for patients diagnosed with ICC from the SEER database spanning 2010 to 2017. As the SEER database constitutes an anonymized public resource, this investigation did not necessitate patient informed consent or ethical approval. Data collection encompassed variables such as the year of diagnosis, age, sex, race, marital status, histological grade, tumor staging, tumor size, fibrosis score, and the presence of liver, bone, and brain metastases, in addition to interventions including surgery, chemotherapy, and radiotherapy. The primary outcome measure was CSS, delineated as the interval from diagnosis to cancer-attributable mortality. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Inclusion criteria were as follows: (I) diagnosis within the 2010 to 2017 timeframe; (II) ICC diagnosis confirmed by ICD-O-3 code 8160 and ICD site code C22.1. Exclusion criteria comprised: (I) diagnoses established via autopsy or death certificate; (II) absence of essential clinical-pathological details (e.g., age, sex, race, marital status, tumor stage, tumor size); (III) missing information on surgical, chemotherapeutic, or radiotherapeutic interventions; (IV) indeterminate data on distant metastases (bone, brain, liver); (V) ambiguous cause of death or indeterminate survival duration; (VI) presence of primary tumors at other anatomical sites. Ultimately, 2,651 ICC patients were selected for analytical purposes.

This research initially focused on identifying risk factors for BM among these 2,651 ICC patients and subsequently

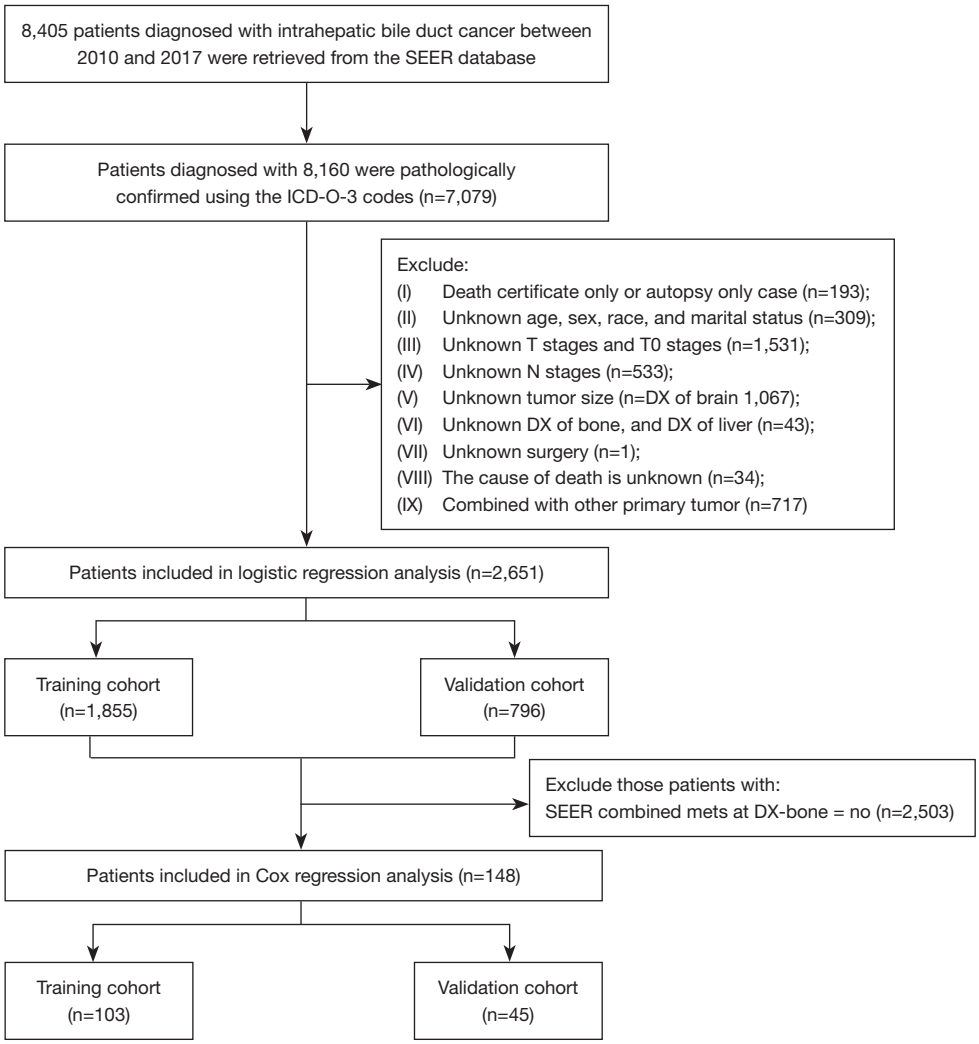

Figure 1 Flow chart of patient screening. SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; DX, diagnosis.

developed corresponding predictive nomograms. A subset of 148 patients with BM was then isolated to examine prognostic factors specific to ICCBM and to formulate prognostic nomograms. For the purpose of nomogram development and validation, patients were randomly allocated to a training cohort (70%) and a validation cohort (30%). The nomograms were constructed based on data from the training cohort and underwent validation using the validation cohort data (*Figure 1*).

Statistical analysis

Univariate logistic regression analysis was utilized to identify factors associated with BM. Variables demonstrating significance (P<0.05) in the univariate logistic regression were subsequently included in a multivariate binary logistic regression analysis to delineate independent risk factors for BM in patients newly diagnosed with ICC. For prognostic factors, initial screening was conducted using univariate Cox regression analysis. Variables with a P<0.05 in this screening were then entered into a multivariate Cox regression analysis to identify independent prognostic factors for ICCBM patients.

A prognostic model for ICCBM patients was developed using the RMS package within R software, and the receiver operating characteristic (ROC) curves for the nomograms were plotted to evaluate their discriminative capacity via the area under the curve (AUC). The discriminative efficacy of

the nomograms was compared against other independent risk factors through ROC curve analysis. Furthermore, calibration curves and decision curve analysis (DCA) were employed to comprehensively assess the performance of the model. Patients were stratified into high-risk and low-risk groups based on the median risk score, and the prognostic accuracy of the nomograms was validated using survival curves and the log-rank test. All statistical analyses were executed using R software (version 4.3.1), considering P<0.05 as statistically significant.

Results

The characteristics of the study population

Following the aforementioned screening criteria, a total of 2,651 patients were included in this study. In accordance with a 7:3 ratio, these eligible patients were randomly assigned to either the training cohort (n=1,855) or the validation cohort (n=796). The baseline characteristics of the 2,651 patients are presented in *Table 1*.

Risk factors of BM in ICC patients

Among the 2,651 patients included in this study, 148 (5.585%) were diagnosed with BM at the time of initial diagnosis. To identify independent predictive factors associated with the occurrence of BM, univariate logistic regression analysis was conducted on 13 potential predictors. The analysis revealed that six factors were significantly associated with the occurrence of BM in ICC patients, including sex, N stage, tumor size, lung metastasis, brain metastasis, and liver metastasis (*Table 2*). Further multivariate logistic regression analysis indicated that being male (P=0.005), larger tumor size (P<0.001), lung metastasis (P<0.001), brain metastasis (P=0.029), and liver metastasis (P<0.001) served as independent predictors for BM in newly diagnosed ICC patients (*Table 2*).

Development and validation of a diagnostic nomogram for BM in newly diagnosed ICC patients

Based on five independent variables significantly associated

Table 1 The baseline clinical characteristics of the ICC patients

Variable	Training cohort (n=1,855)	Validation cohort (n=796)	Overall (n=2,651)	P
Age (years)				0.68
<65	859 (46.3)	361 (45.4)	1,220 (46.0)	
≥65	996 (53.7)	435 (54.6)	1,431 (54.0)	
Sex				0.98
Female	897 (48.4)	386 (48.5)	1,283 (48.4)	
Male	958 (51.6)	410 (51.5)	1,368 (51.6)	
Race				0.12
Black	145 (7.8)	80 (10.1)	225 (8.5)	
White	254 (13.7)	116 (14.6)	370 (14.0)	
Other	1,456 (78.5)	600 (75.4)	2,056 (77.6)	
Marital status				0.89
Married	1,129 (60.9)	492 (61.8)	1,621 (61.1)	
Single	433 (23.3)	180 (22.6)	613 (23.1)	
Other	293 (15.8)	124 (15.6)	417 (15.7)	
Grade				0.62
G1 + G2	543 (29.3)	220 (27.6)	763 (28.8)	
G3 + G4	418 (22.5)	190 (23.9)	608 (22.9)	
Unknown	894 (48.2)	386 (48.5)	1,280 (48.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Training cohort (n=1,855)	Validation cohort (n=796)	Overall (n=2,651)	P
T stage				0.79
T1 + T2	1,439 (77.6)	622 (78.1)	2,061 (77.7)	
T3 + T4	416 (22.4)	174 (21.9)	590 (22.3)	
N stage				0.11
N0	1,204 (64.9)	490 (61.6)	1,694 (63.9)	
N1	651 (35.1)	306 (38.4)	957 (36.1)	
Tumor size (cm)				0.77
>5	1,176 (63.4)	510 (64.1)	1,686 (63.6)	
≤5	679 (36.6)	286 (35.9)	965 (36.4)	
Fibrosis score				0.07
0–4	170 (9.2)	80 (10.1)	250 (9.4)	
5–6	118 (6.4)	33 (4.1)	151 (5.7)	
Unknown	1,567 (84.5)	683 (85.8)	2,250 (84.9)	
Lung metastasis				0.36
No	1,689 (91.1)	715 (89.8)	2,404 (90.7)	
Yes	166 (8.9)	81 (10.2)	247 (9.3)	
Brain metastasis				<0.01
No	1,850 (99.7)	794 (99.7)	2,644 (99.7)	
Yes	5 (0.3)	2 (0.3)	7 (0.3)	
Live metastasis				0.63
No	1,679 (90.5)	715 (89.8)	2,394 (90.3)	
Yes	176 (9.5)	81 (10.2)	257 (9.7)	
Bone metastasis				
No	1,748 (94.2)	755 (94.8)	2,503 (94.4)	
Yes	107 (5.8)	41 (5.2)	148 (5.6)	
Surgery				0.16
No	1,329 (71.6)	592 (74.4)	1,921 (72.5)	
Yes	526 (28.4)	204 (25.6)	730 (27.5)	
Chemotherapy				0.99
No	804 (43.3)	344 (43.2)	1,148 (43.3)	
Yes	1,051 (56.7)	452 (56.8)	1,503 (56.7)	
Radiotherapy				0.50
No	804 (43.3)	344 (43.2)	1,148 (43.3)	
Yes	1,051 (56.7)	452 (56.8)	1,503 (56.7)	

ICC, intrahepatic cholangiocarcinoma.

Table 2 Logistic analysis of risk factor of BM in ICC patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
<65	Reference			
≥65	0.755 (0.586–1.024)	0.13		
Sex				
Female	Reference		Reference	
Male	1.619 (1.225–2.179)	<0.01	1.652 (1.233–2.228)	<0.01
Race				
Black	Reference			
White	1.206 (0.732–2.134)	0.56		
Other	0.937 (0.492–1.833)	0.87		
Marital status				
Married	Reference			
Single	0.959 (0.643–1.395)	0.86		
Other	0.724 (0.495–1.034)	0.15		
Grade				
I + II	Reference			
III + IV	1.353 (0.894–2.054)	0.23		
Unknown	1.564 (1.108–2.054)	0.04		
T stage				
T1 + T2	Reference			
T3 + T4	0.844 (0.588–1.184)	0.42		
N stage				
N0	Reference		Reference	
N1	1.683 (1.272–2.225)	<0.01	1.251 (0.932–1.676)	0.21
Tumor size (cm)				
>5	Reference		Reference	
≤5	0.372 (2.351–4.248)	<0.01	0.449 (0.308–0.641)	<0.01
Fibrosis score				
0–4	Reference			
5–6	2.462 (1.083–5.810)	0.07		
Unknown	2.146 (1.184–4.385)	0.053		
Lung metastasis				
No	Reference		Reference	
Yes	1.086 (0.824–1.431)	<0.01	3.266 (2.305–4.581)	<0.01

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Brain metastasis				
No	Reference		Reference	
Yes	12.926 (3.370–45.887)	<0.01	6.508 (1.485–26.276)	0.03
Liver metastasis				
No	Reference		Reference	
Yes	3.603 (2.570–4.985)	<0.01	2.364 (1.636–3.369)	<0.01

BM, bone metastasis; ICC, intrahepatic cholangiocarcinoma; HR, hazard ratio; CI, confidential interval.

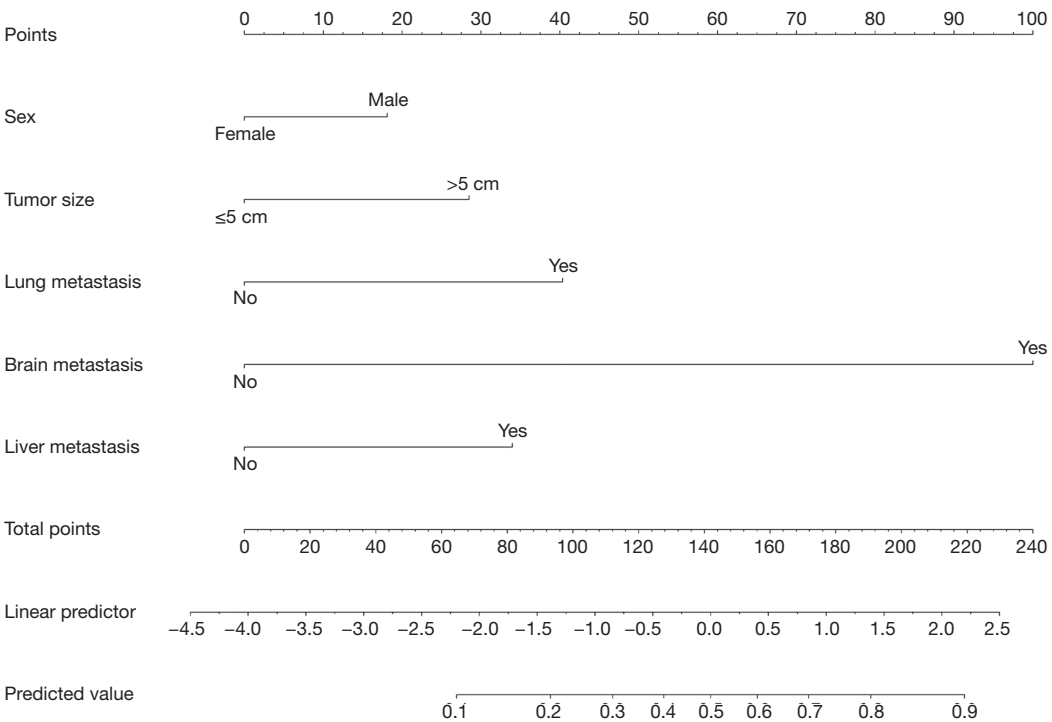

Figure 2 Nomogram for predicting BM from ICC patients. BM, bone metastasis; ICC, intrahepatic cholangiocarcinoma.

with BM, we developed a diagnostic nomogram aimed at assessing the risk of BM in newly diagnosed ICC patients (*Figure 2*). Furthermore, to validate the predictive performance of the nomogram, ROC curves were plotted for both the training and validation cohorts. The results indicated that the AUC for the nomogram was 0.730 [95% confidential interval (CI): 0.679–0.782] in the training cohort and 0.717 (95% CI: 0.626–0.807) in the validation cohort (*Figure 3*). Additionally, calibration curves demonstrated good calibration of the nomogram in both the training and validation cohorts (*Figure 3*). DCA further confirmed the effectiveness of this nomogram in assessing the risk of BM in newly diagnosed ICC patients (*Figure 3*).

Prognostic factors for ICC patients with BM

As *Table 3* demonstrates, this study included 148 eligible ICC patients with BM for prognostic factor analysis.

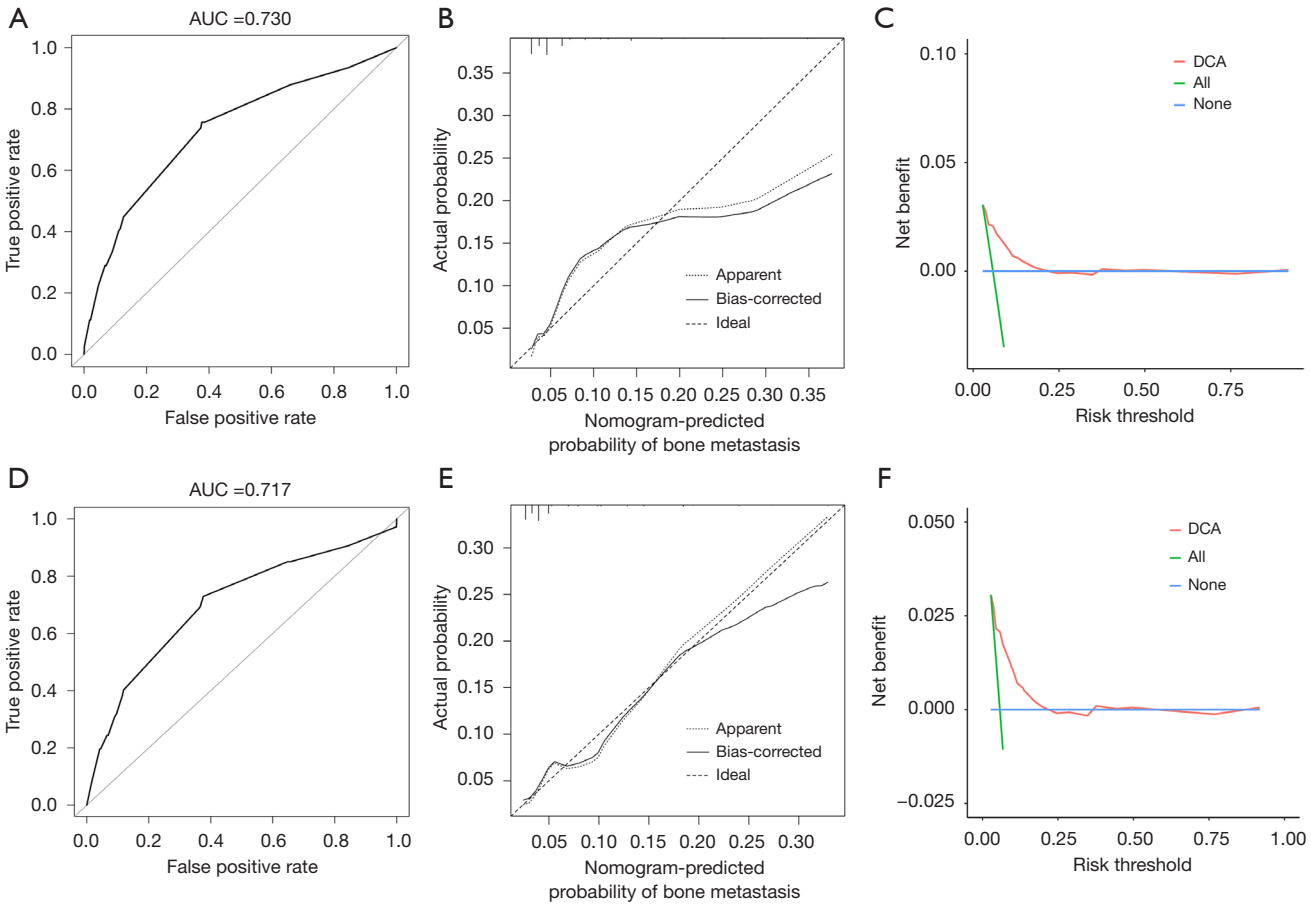

Figure 3 Validation of the nomogram. (A) The ROC curve of the training cohort. (B) The calibration curve of the training cohort. (C) The DCA of the training cohort. (D) The ROC curve of the validation cohort. (E) The calibration curve of the validation cohort. (F) The DCA of the validation cohort. AUC, area under the curve; ROC, receiver operating characteristic; DCA, decision curve analysis.

Among these patients, 62.8% were male, and 37.2% were female. In terms of racial distribution, 81.1% were Caucasian, 7.4% were African American, and 11.5% belonged to other races. These patients were randomly assigned to the training (n=103) and validation (n=45) cohorts in a 7:3 ratio. Chi-squared test results indicated no significant differences between the training and validation cohorts (*Table 3*). To explore various prognostic factors, univariate and multivariate Cox regression analyses were performed (*Table 4*). Univariate Cox regression analysis revealed that age, chemotherapy, and radiotherapy were significantly associated with patient prognosis. Multivariate Cox regression analysis further confirmed that age (P=0.02), chemotherapy (P<0.01), and radiotherapy (P<0.01) were independent prognostic factors for ICCBM patients.

Prognostic nomogram development and validation

Based on three independent prognostic factors, we developed a prognostic nomogram (*Figure 4*). The nomogram showed that chemotherapy made the greatest contribution to prognosis. Each level of each variable is assigned a score on the rating scale. The total score is obtained by adding the scores for each selected variable. Predictions corresponding to this total score help estimate the 3-, 6-, and 12-month CSS for each ICCBM patient. The model exhibited C-indexes of 0.737 (95% CI: 0.682–0.792) in the training cohort and 0.696 (95% CI: 0.623–0.769) in the validation cohort, validating the prognostic model's satisfactory prediction accuracy. Moreover, ROC analysis revealed that the AUC values for 3-, 6-, and

Table 3 The baseline clinical characteristics of the ICCBM patients

Variable	Training cohort (n=103)	Validation cohort (n=45)	Overall (n=148)	P value
Age (years)				0.74
<65	55 (53.4)	22 (48.9)	77 (52.0)	
≥65	48 (46.6)	23 (51.1)	71 (48.0)	
Sex				0.77
Female	37 (35.9)	18 (40.0)	55 (37.2)	
Male	66 (64.1)	27 (60.0)	93 (62.8)	
Race				0.46
Black	6 (5.8)	5 (11.1)	11 (7.4)	
White	84 (81.6)	36 (80.0)	120 (81.1)	
Other	13 (12.6)	4 (8.9)	17 (11.5)	
Marital status				0.28
Married	65 (63.1)	32 (71.1)	97 (65.5)	
Single	20 (19.4)	4 (8.9)	24 (16.2)	
Other	18 (17.5)	9 (20.0)	27 (18.2)	
Grade				0.48
G1 + G2	24 (23.3)	8 (17.8)	32 (21.6)	
G3 + G4	21 (20.4)	13 (28.9)	34 (23.0)	
Unknown	58 (56.3)	24 (53.3)	82 (55.4)	
T stage				0.76
T1 + T2	84 (81.6)	35 (77.8)	119 (80.4)	
T3 + T4	19 (18.4)	10 (22.2)	29 (19.6)	
N stage				0.27
N0	50 (48.5)	27 (60.0)	77 (52.0)	
N1	53 (51.5)	18 (40.0)	71 (48.0)	
Tumor size (cm)				0.55
>5	86 (83.5)	35 (77.8)	121 (81.8)	
≤5	17 (16.5)	10 (22.2)	27 (18.2)	
Fibrosis score				0.054
0–4	6 (5.8)	1 (2.2)	7 (4.7)	
5–6	10 (9.7)	0 (0)	10 (6.8)	
Unknown	87 (84.5)	44 (97.8)	131 (88.5)	
Lung metastasis				<0.01
No	72 (69.9)	32 (71.1)	104 (70.3)	
Yes	31 (30.1)	13 (28.9)	44 (29.7)	

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Training cohort (n=103)	Validation cohort (n=45)	Overall (n=148)	P value
Brain metastasis				<0.01
No	101 (98.1)	44 (97.8)	145 (98.0)	
Yes	2 (1.9)	1 (2.2)	3 (2.0)	
Live metastasis				0.70
No	78 (75.7)	32 (71.1)	110 (74.3)	
Yes	25 (24.3)	13 (28.9)	38 (25.7)	
Surgery				0.67
No	103 (100.0)	44 (97.8)	147 (99.3)	
Yes	0 (0.0)	1 (2.2)	1 (0.7)	
Chemotherapy				0.06
No	30 (29.1)	21 (46.7)	51 (34.5)	
Yes	73 (70.9)	24 (53.3)	97 (65.5)	
Radiotherapy				0.69
No	67 (65.0)	27 (60.0)	94 (63.5)	
Yes	36 (35.0)	18 (40.0)	54 (36.5)	

ICCBM, intrahepatic cholangiocarcinoma-associated bone metastasis.

Table 4 Univariate and multivariate analyses of ICCBM patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
<65	Reference		Reference	
≥65	1.890 (1.342–2.661)	<0.01	1.563 (1.088–2.246)	0.02
Sex				
Female	Reference			
Male	0.896 (0.630–1.263)	0.53		
Race				
Black	Reference			
White	0.731 (0.393–1.363)	0.33		
Other	0.507 (0.228–1.127)	0.10		
Marital status				
Married	Reference			
Single	1.074 (0.676–1.705)	0.76		
Other	0.928 (0.594–1.449)	0.74		

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Grade				
I + II	Reference			
III + IV	1.162 (0.687–1.965)	0.58		
Unknown	1.542 (1.002–2.373)	0.049		
T stage				
T1 + T2	Reference			
T3 + T4	0.918 (0.598–1.411)	0.70		
N stage				
N0	Reference			
N1	0.904 (0.645–1.267)	0.56		
Tumor size (cm)				
>5	Reference			
≤5	1.422 (0.922–2.192)	0.11		
Fibrosis score				
0–4	Reference			
5–6	0.985 (0.365–2.660)	0.98		
Unknown	0.853 (0.395–1.839)	0.69		
Lung metastasis				
No	Reference			
Yes	1.068 (0.736–1.548)	0.73		
Brain metastasis				
No	Reference			
Yes	0.769 (0.244–2.423)	0.65		
Liver metastasis				
No	Reference			
Yes	1.031 (0.709–1.500)	0.87		
Surgery				
No	Reference			
Yes	0.531 (0.074–3.814)	0.53		
Chemotherapy				
No	Reference		Reference	
Yes	0.247 (0.168–0.362)	<0.01	0.265 (0.178–0.396)	<0.01
Radiotherapy				
No	Reference		Reference	
Yes	0.652 (0.458–0.928)	0.02	0.566 (0.393–0.813)	<0.01

ICCBM, intrahepatic cholangiocarcinoma-associated bone metastasis; HR hazard ratio; CI confidential interval.

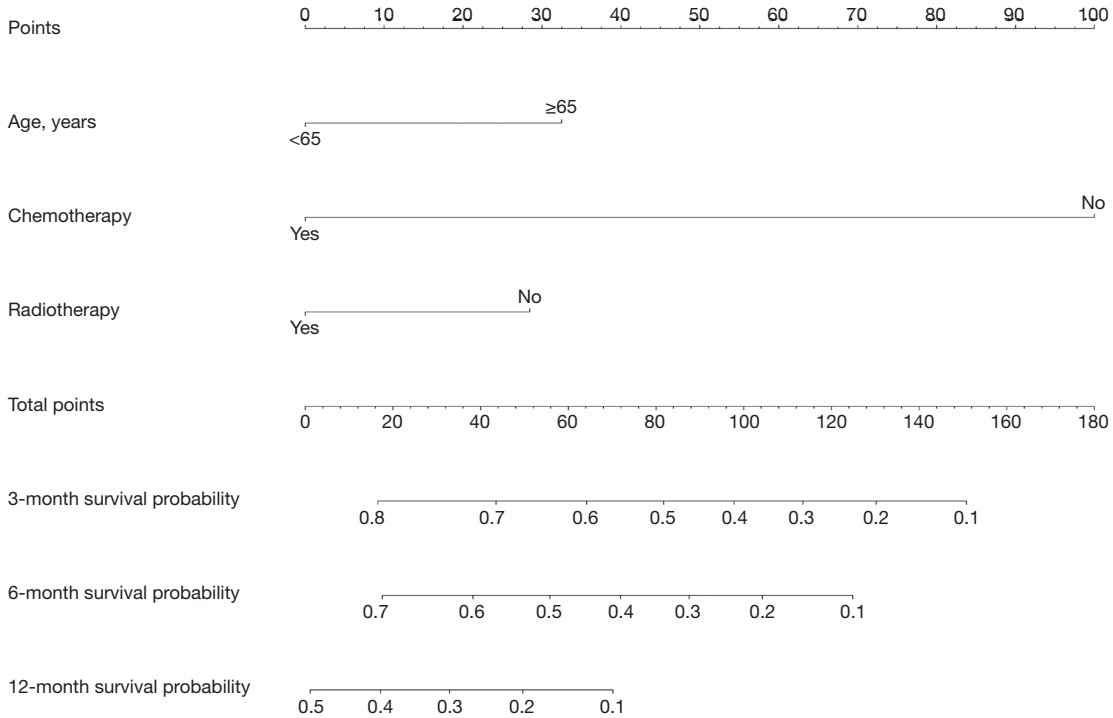

Figure 4 Nomogram predict CSS in patients with ICCBM for 3-, 6-, and 12-month. CSS, cancer-specific survival; ICCBM, intrahepatic cholangiocarcinoma-associated bone metastasis.

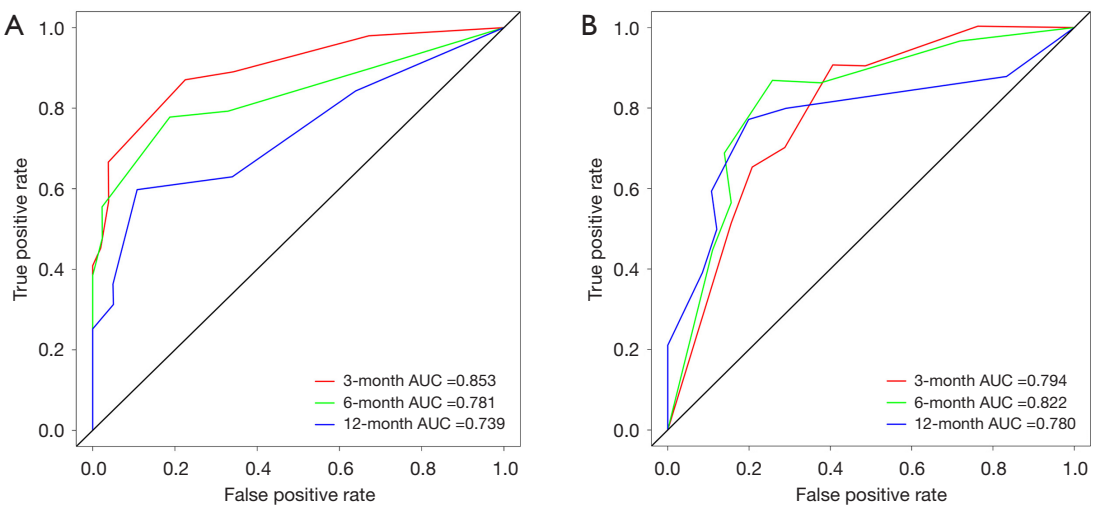

Figure 5 ROC curve for predicting 3-, 6-, and 12-month CSS of ICCBM patients in the training cohort (A), the validation cohort (B). AUC, areas under the curve; ROC, receiver operating characteristic; CSS, cancer-specific survival; ICCBM, intrahepatic cholangiocarcinoma-associated bone metastasis.

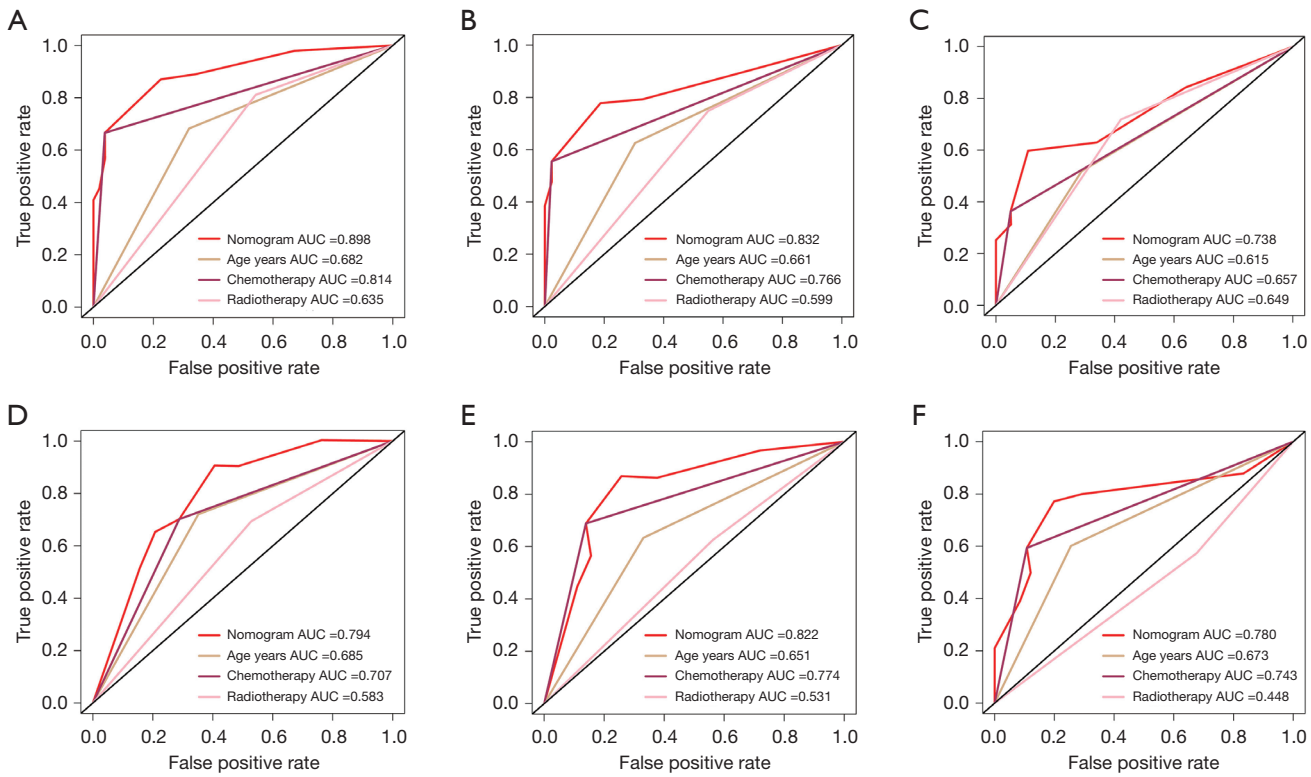

Figure 6 Comparative illustration of predictive accuracy between the nomogram model and independent prognostic factors. This encompasses predictions for 3- (A,D), 6- (B,E), and 12-month (C,F) CSS across the training and validation cohorts, respectively. AUC, areas under the curve; CSS, cancer-specific survival.

12-month CSS in the training cohort were 0.853, 0.781, and 0.739, respectively; in the validation cohort, these values were 0.794, 0.822, and 0.780, as shown in *Figure 5A,5B*. More importantly, by comparing the nomogram with each independent prognostic factor, we found that at 3-, 6-, and 12-month, the AUC values of the nomogram were higher than those of all individual factors, indicating that the comprehensive model has the highest predictive capability for the survival of ICCBM patients (*Figure 6*).

Furthermore, we plotted calibration curves for 3-, 6-, and 12-month CSS for each cohort, demonstrating high consistency between the nomogram's predictions and the actual observations (*Figure 7*). The clinical utility of the nomogram was assessed through DCA. As shown in *Figure 8*, the DCA curves displayed significant net benefits across a wide range of threshold probabilities, indicating the nomogram's strong clinical applicability in predicting CSS for ICCBM patients.

Establish a risk stratification system based on the nomogram model

In this study, Kaplan-Meier (KM) survival analysis conducted on 148 patients revealed 1-, 2-, and 3-year survival rates of 23.91%, 7.55%, and 2.35%, respectively, with a median CSS of 6 months (*Figure 9A*). By applying the Cox proportional hazards model, scores were assigned to each independent prognostic factor, and a total risk score was calculated for each patient based on these scores. Patients in both the training and validation cohorts were stratified into risk categories based on the median total risk score. The results consistently demonstrated that patients in the high-risk group had significantly worse prognosis than those in the low-risk group in both the training and validation cohorts (*Figure 9B,9C*). This finding underscores the importance and practical value of risk stratification in predicting survival outcomes for ICCBM patients.

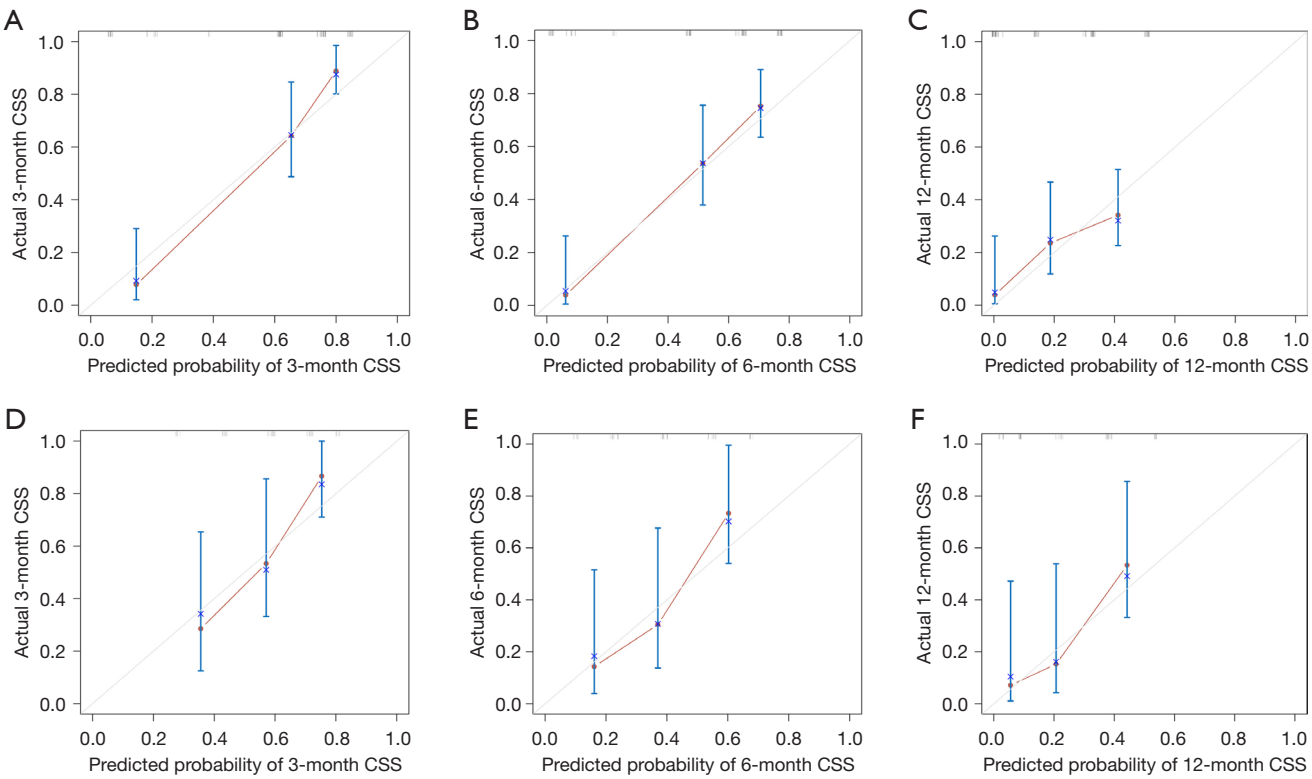

Figure 7 Calibration curves comparing model-predicted survival against observed outcomes for 3- (A,D), 6- (B,E), and 12-month (C,F) CSS across the training and validation cohorts, respectively. CSS, cancer-specific survival.

Discussion

Globally, the incidence of ICC is on the rise. However, due to the lack of specific symptoms in the early stages, most patients are diagnosed at an advanced stage of the disease. Additionally, the high invasiveness of ICC and its resistance to treatment further contribute to a higher mortality rate (1). Bone is a common site for extrahepatic metastasis, with an incidence rate of 11.0–29.7% in ICC patients (8,13). Utilizing data from the SEER database from 2010 to 2017 and following strict inclusion and exclusion criteria, a cohort of 2,651 patients was formed. Among these, 148 patients (5.6%) were diagnosed with BM at the initial diagnosis. This study developed two nomograms: one for predicting BM in newly diagnosed ICC patients and another for assessing the prognosis of ICCBM patients. By collecting data on several easily obtainable variables on the nomograms, a total score can be calculated for each patient, thereby easily identifying the risk of BM and providing guidance for further clinical management. Similarly, the prognosis of ICCBM patients can also be assessed through the prognostic nomogram. In this study, the two nomograms demonstrated excellent performance in assessing BM risk and predicting survival in ICCBM patients, both in the training and validation cohorts, offering a more precise basis for individualized clinical decision-making and monitoring. Furthermore, KM survival analysis revealed that among the included 148 ICC patients, the 1-, 2-, and 3-year CSS were 23.91%, 7.55%, and 2.35%, respectively, with a median CSS of 6 months. Further analysis showed significant differences in CSS between the low-risk and high-risk groups, further confirming the reliability and practicality of our model.

The prognosis for ICCBM patients is poor, with a median OS of only 4 months (13). Therefore, screening and identifying independent risk factors for BM in ICC patients are crucial for early detection and prevention of high-risk individuals in clinical practice, helping to effectively reduce the risk of BM. Shi *et al.* (14) noted that sex, tumor size, and intrahepatic metastasis are significantly associated with BM in ICC. Liu *et al.* (15) study found that T stage, N stage, surgical treatment, alpha-fetoprotein levels, and tumor size are independently positively correlated with

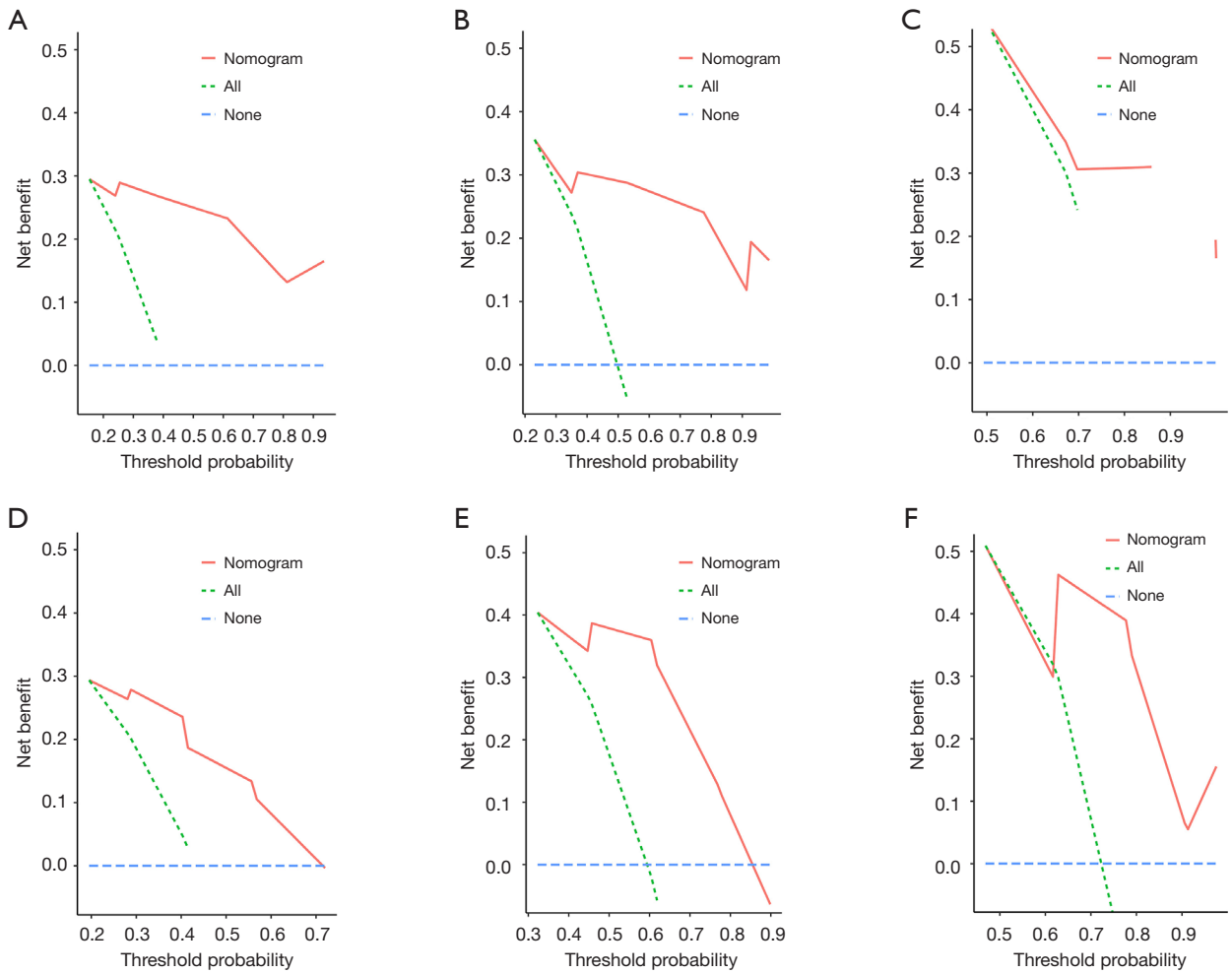

Figure 8 DCA curves for the nomogram across different cohorts and timeframes: 3- (A,D), 6- (B,E), and 12-month (C,F) CSS across the training and validation cohorts, respectively. The Y-axis depicts the net benefit, while the X-axis represents the threshold probability. The blue line signifies scenarios where no patients died, while the green line portrays scenarios with all patient deaths. DCA, decision curve analysis; CSS, cancer-specific survival.

brain metastasis in the ICC cohort. These factors reflect the invasiveness of the primary tumor to varying degrees, suggesting these indicators as potential risk factors for extrahepatic metastasis. However, to date, no predictive model integrating all independent BM-related predictive factors has been established to identify an individual's BM risk. In this study, we found that being male, having a larger tumor, lung metastasis, brain metastasis, and intrahepatic metastasis were important predictors of BM. The model was validated using the C-index, ROC curves, calibration curves, and DCA curves, showing good accuracy and high reliability. We further analyzed the prognosis of ICCBM patients, finding that older age (≥65 years), not receiving chemotherapy, and not receiving radiotherapy were associated with poor prognosis. Based on these three independent prognostic factors, we developed a nomogram. The results show that this nomogram can be an effective tool for identifying high-risk patients.

It has been reported that the incidence of ICC increases with age, with a median age of patients being 62 years (16-18). Ye *et al.* (19) study found that significant prognostic factors affecting the OS of HCC patients with lung metastasis include age, T stage, surgical approach, and chemotherapy. Both radiotherapy and chemotherapy play key roles in tumor treatment (20). Systemic treatments, such as chemotherapy and targeted therapy, are generally

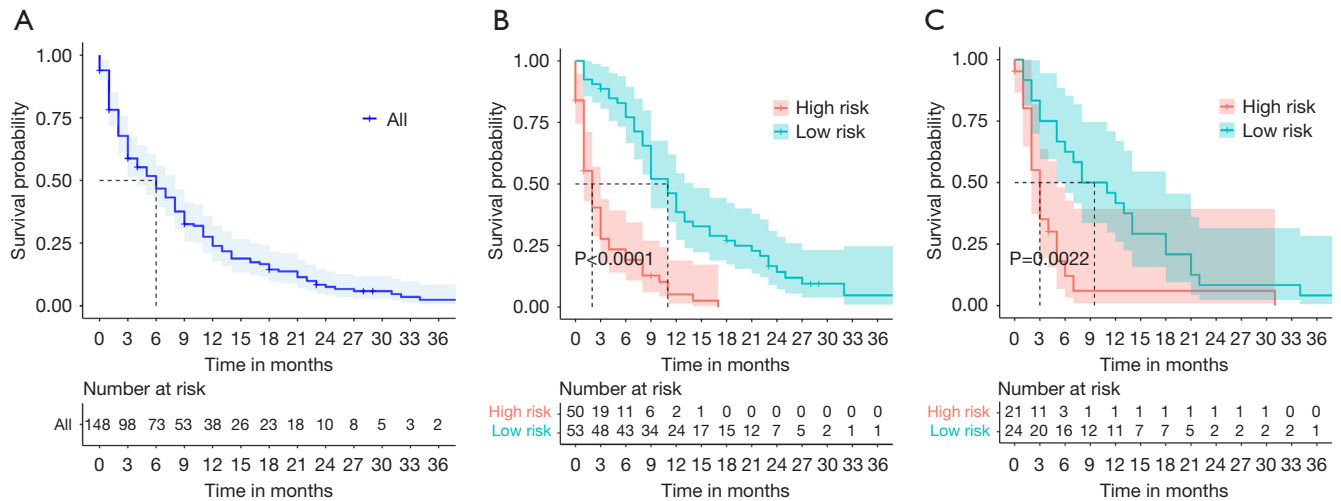

Figure 9 KM survival curves depicting CSS for ICCBM patients across various cohorts: overall (A), training (B) and validation (C). KM, Kaplan-Meier; CSS, cancer-specific survival; ICCBM, intrahepatic cholangiocarcinoma-associated bone metastasis.

recommended for patients with distant metastases (21). The combination chemotherapy regimen of gemcitabine and cisplatin is considered as the most effective first-line treatment strategy for patients with distant metastasis of ICC (3,8,21). Radiotherapy has also been shown to extend the survival of ICC patients and reduce the risk of death from tumor-related liver failure (22,23). For better prognosis, clinical treatment strategies for ICCBM patients may favor the use of radiotherapy and chemotherapy.

While our study provides valuable insights, it also has some notable limitations. First, the data source relied upon is limited to the SEER database, so the study results may not fully reflect situations outside the United States, such as in Asia, Africa, and South America. Second, the SEER database does not include some key factors closely related to patient prognosis, such as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection status, CA19-9 levels, vascular invasion, and detailed treatment information. Lastly, given that the SEER database collects only information at the time of initial diagnosis, it is not possible to track subsequent occurrences of BM in patients.

Conclusions

This study identified sex, tumor size, lung metastasis, brain metastasis, and liver metastasis as independent risk factors of BM from ICC. Age, chemotherapy, and radiotherapy were found to be independent prognostic factors for CSS in patients with ICCBM. The two nomograms we developed provide a standalone, convenient, and intuitively visual tool for assessing risk and predicting prognosis in ICCBM patients.

Acknowledgments

SEER database is an open database. We thank the staff at the SEER database.

Funding: This study was supported by grants from the National Natural Sciences Foundation of China (81974442), and Guangdong Basic and Applied Basic Research Foundation (2021A1515011261).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-567/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-567/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-567/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Zhu SF, Mao BL, Zhuang RY, Huang JY, Wu F, Wang BL, Yan Y. Development and validation of a diagnostic and prognostic model for bone metastasis of intrahepatic cholangiocarcinoma: a population-based analysis. Transl Cancer Res 2024;13(8):4010-4027. doi: 10.21037/tcr-24-567

