Original Research

Diagnostic and prognostic nomograms for newly diagnosed intrahepatic cholangiocarcinoma with brain metastasis: A population-based analysis

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Impact Statement

Intrahepatic cholangiocarcinoma (ICC) with brain metastasis (BM) has a poor prognosis, with a median survival of only 3.7 months. Due to the rarity of BM among ICC patients, studies on such cases are primarily small case reports from a single agency, which lack credible statistical conclusions. Thus, a large-scale study based on the Surveillance, Epidemiology, and End Results (SEER) database is needed to determine the risk and prognostic factors of ICC patients with BM effectively reduce the risk of BM and improve the survival rate of patients. In this study, we used the latest updated data from the SEER database from 2010 to 2018 and established two nomograms for predicting the risk of BM in newly diagnosed ICC patients and the prognosis of ICC patients with BM, respectively. These two nomograms may provide guidelines and a basis for personalized and precise clinical diagnosis and treatment of ICC cases with BM.

Abstract

Brain metastasis (BM) is one of the rare metastatic sites of intrahepatic cholangiocarcinoma (ICC). ICC with BM can seriously affect the quality of life of patients and lead to a poor prognosis. The aim of this study was to establish two nomograms to estimate the risk of BM in ICC patients and the prognosis of ICC patients with BM. Data on 19,166 individuals diagnosed with ICC were retrospectively collected from the Surveillance, Epidemiology, and End Results (SEER) database. Independent risk factors and prognostic factors were identified by the logistic and the Cox regression, respectively. Next, two nomograms were developed, and their discrimination was estimated by concordance index (*C*-index) and calibration plots, while the clinical benefits of the prognostic nomogram were evaluated using the receiver operating characteristic (ROC) curves, the decision curve analysis (DCA), and the Kaplan–Meier analyses. The independent risk factors for BM were T stage, N stage, surgery, alpha-fetoprotein (AFP) level, and tumor size. T stage, surgery, radiotherapy, and bone metastasis were prognostic factors for overall survival (OS). For the prognostic nomogram, the *C*-index was 0.759 (95% confidence interval (CI) = 0.745–0.773) and 0.764 (95% CI = 0.747–0.781) in the training and the validation cohort, respectively. The calibration curves revealed a robust agreement between predictions and actual observations probability. The area under curves (AUCs) for the 3-, 6-, and 9-month OS were 0.721, 0.727, and 0.790 in the training cohort and 0.702, 0.777, and 0.853 in the validation cohort, respectively. The DCA curves yielded remarkable positive net benefits over a wide range of threshold probabilities. The Kaplan–Meier analysis illustrated that the nomogram could significantly distinguish the population with different survival risks. We successfully established the two nomograms for predicting the incidence of BM and the prognosis of ICC patients with BM, which may assist clinicians in choosing more effective treatment strategies.

Keywords: Intrahepatic cholangiocarcinoma, brain metastasis, nomogram, Surveillance, Epidemiology, and End Results, diagnosis, prognosis

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Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from the diverse endothelial cells of the intrahepatic bile duct and accounts for 10–20% of primary liver malignancies.[1,2] The incidence of ICC has significantly increased over the past few decades, being second only to that of hepatocellular carcinoma (HCC).[3] Radical resection remains a unique and potentially curative treatment for patients with ICC. Unfortunately, only 30–40% of patients are eligible for

complete resection.[4,5] Even more concerning, due to its high aggressiveness, ICC is a fatal disease, and the prognosis for these patients is uniformly quite poor, with an overall 5-year survival rate ranging from 15 to 40%.[6,7]

Distant metastasis of ICC commonly includes lung metastasis, lymph nodes metastasis, bone metastasis, intrahepatic metastasis, and brain metastasis (BM). Although the incidence of BM has been reported to be only 0.47–1.6% in newly diagnosed ICC patients,[8–10] it leads to a despondent prognosis with a median overall survival (OS) of 3.7 months.[10] Furthermore, intracranial pressure increase–related symptoms and manifestations induced by BM – such as severe headaches, nausea, vomiting, and papilledema – may seriously affect the patients' quality of life.[11] Therefore, it is of great importance to predict the occurrence of BM among ICC patients and estimate the prognosis in ICC patients with BM. Currently, no studies are focusing on diagnostic and prognostic models for BM in newly diagnosed ICC patients.

Due to the rarity of BM among ICC patients, studies on such cases are primarily case reports from a single agency, which lack credible statistical conclusions. Thus, a large-scale study based on the Surveillance, Epidemiology, and End Results (SEER) database is essential to identify the risk and prognostic factors for ICC patients with BM. Nomogram is a practical, ideal visualization tool for forecasting and calculating the outcome rates of each patient, which has been widely used to aid clinical decision-making.[12,13] Consequently, by analyzing the data from the SEER database, we aimed to establish two nomograms for predicting the BM in patients initially diagnosed with ICC and assessing the prognosis of ICC patients with BM, respectively. This study may assist oncologists in promoting personalized treatment options and medical decision-making for ICC individuals with BM.

Materials and methods

Study patients' selection

The data employed in this study were abstracted from the public SEER database (SEER ID: 13738-Nov2020). The analysis with SEER de-identified data was exempt from medical ethics review, and informed consent was not required. Patients who met the following criteria were included: (1) patients diagnosed with ICC (primary site code = intrahepatic bile duct, along with histologic type the *International Classification of Diseases for Oncology–Third Edition* (ICD-O-3) = 8160.3) between 2000 and 2018; (2) demographic characteristics and tumor variables were available; (3) ICC was the only primary malignancy; and (4) patients aged ⩾18 years old at the time of diagnosis. Individuals with unknown survival time, incomplete stage records, missing tumor grade records, and no information on metastasis were subsequently excluded. Eventually, a cohort of 12,436 patients was formed to explore the risk factors for BM from ICC patients, and 112 patients with BM were used to identify the prognostic factors. A detailed flow chart of the participant selection process is shown in Figure 1.

Data collection

A total of 12 variables were applied to identify the risk factors for BM from ICC, including age, sex, race, grade, T stage, N stage, surgery of the primary site, radiotherapy, chemotherapy, alpha-fetoprotein (AFP) level, fibrosis score, and tumor size. In the survival analysis to select the prognostic factors for ICC with BM, three metastatic features – that is, intrahepatic, lung, and bone metastases – were included. The primary endpoint of our research was OS, which was determined as the time from the date of diagnosis to the date of death (due to any cause) or the date of the last follow-up.

Statistical analysis

All statistical analyses were carried out with SPSS 25.0 and R software (version 4.1.0). The chi-square test or Fisher's exact test was applied to compare the characteristics of the training and validation cohort. In this study, a P value < 0.05 (two sides) was defined as statistically significant. Factors with P value < 0.05 in the univariate logistic analysis or the univariate Cox regression analysis were included in the multivariate logistic regression analysis or multivariate Cox regression analysis to determine the independent risk factors of BM in newly diagnosed ICC patients and the independent prognostic factors of ICC patients with BM. Accordingly, the predictive and prognostic nomograms were established by the "regplot" package in R software, and the *C*-index and calibration plots were used to assess the discriminative and accuracy ability of those nomograms. Both discrimination and calibration were estimated by bootstrapping 1000 times. Meanwhile, the receiver operating characteristic (ROC) and decision curve analysis (DCA) curves were plotted to estimate the clinical application value of the prognostic nomogram; the higher the area under curves (AUCs), the better the predictive power. Moreover, pursuant to the median risk score, all patients were separated into the high-risk and low-risk clusters, and the survival curve with a log-rank test was used to confirm the prognostic value of the nomogram.

Results

The baseline clinicopathologic features of patients with ICC

After strict screening assessment, 12,436 patients diagnosed with ICC who met the study inclusion criteria were included in this study. All eligible patients were randomly divided into the training cohort (8705 cases) and the validation cohort (3731 cases) at a ratio of approximately 7:3.

The clinicopathologic features of 12,436 patients are presented in Table 1. Generally, 78.3 and 77.7% of the patients were male, and 63.2 and 61.6% of the patients were White in the training and validation cohort, respectively. The majority of the patients were diagnosed through pathological and radiological examination in the training cohort (48.1 and 44.6%) and validation cohort (50.9 and 40.2%), respectively. The AFP level and fibrosis score were predominantly classified as raised (52.5 and 50.8%) and 0–4 (50.4 and 52.7%) in either training or validation cohort, respectively. With reference to therapy, 36.1 and 33.1% of patients chose to undergo surgery of the primary site, 9.0 and 8.8% received radiotherapy, while 49.9 and 49.1% received chemotherapy in the training and validation cohort, respectively. The chi-square test showed no significant difference between the training and validation cohort.

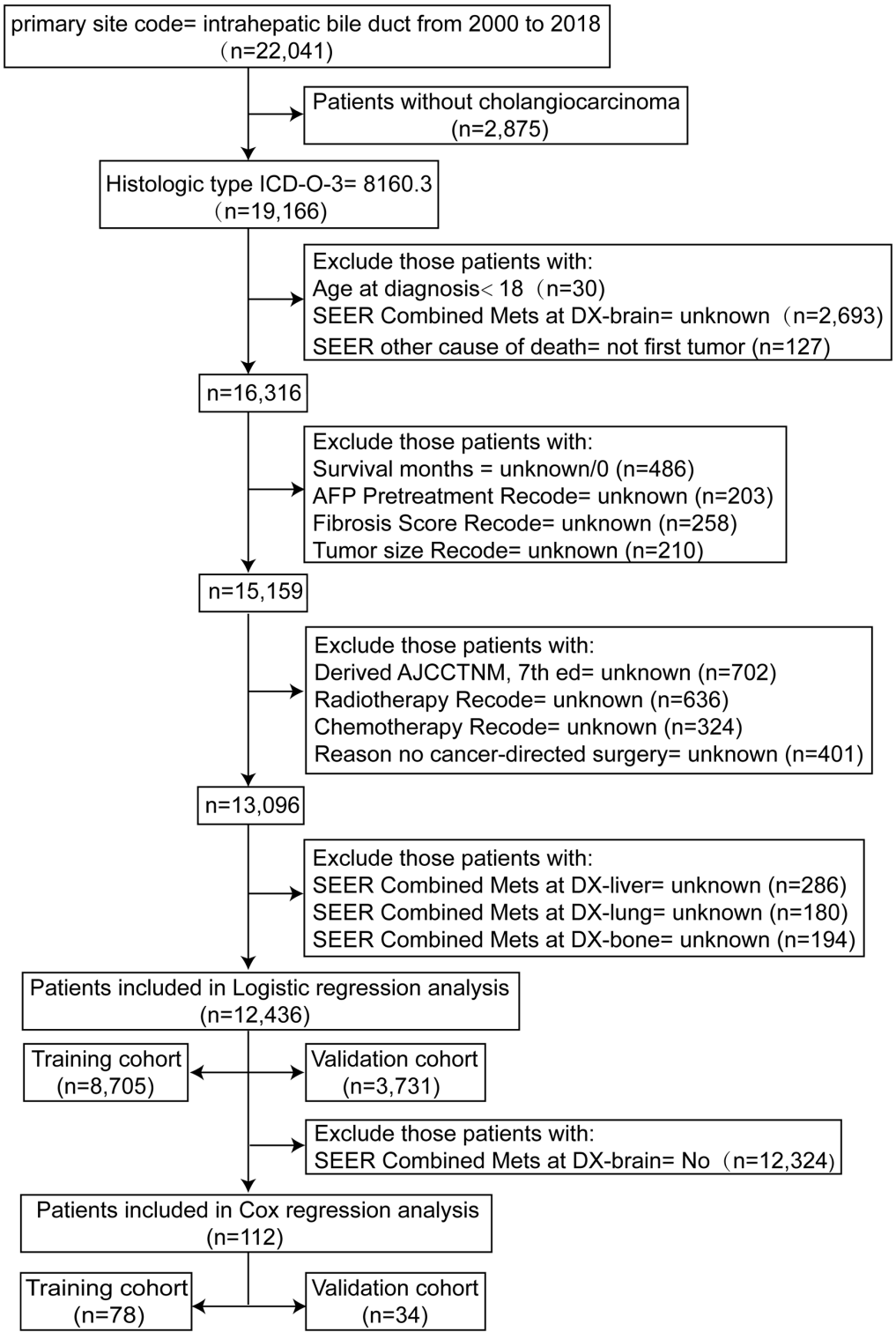

Figure 1. The flow diagram of the study.

Risk factors independently correlated with BM in ICC patients

Among 12,436 ICC patients, 112 (0.90%) were initially diagnosed with BM. In order to find out the independent predictors associated with BM, univariate logistic regression analysis was utilized; the results are shown in Table 2. Five factors were found to be associated with BM in ICC patients, including T stage, N stage, surgery of the primary site, AFP level, and tumor size (all P values < 0.05). Next, multivariate logistic regression analysis was conducted, and those five variables were determined to be independent predictors in BM from newly diagnosed ICC patients, comprising T stage (P value = 0.000), N stage (P value = 0.000), surgery of the primary site (P value = 0.000), AFP level (P value = 0.002), and tumor size (P value = 0.000) (Table 2).

Table 1. Clinicopathologic features of patients newly diagnosed as ICC.

Variables	Training cohort ($n=8705$)	Validation cohort ($n=3731$)	*P* value
Age			0.899
18–64	4118 (47.3%)	1698 (45.5%)	
⩾65	4587 (52.7%)	2033 (54.5%)	
Sex			0.660
Female	1889 (21.7%)	832 (22.3%)	
Male	6816 (78.3%)	2899 (77.7%)	
Race			0.345
American Indian	157 (1.8%)	78 (2.1%)	
Asian	1837 (21.1%)	772 (20.7%)	
Black	1210 (13.9%)	582 (15.6%)	
White	5501 (63.2%)	2299 (61.6%)	
Diagnostic confirmation			0.114
Clinical diagnosis	183 (2.1%)	112 (3.0%)	
Cytology	131 (1.5%)	78 (2.1%)	
Histology	4187 (48.1%)	1899 (50.9%)	
Laboratory test	322 (3.7%)	142 (3.8%)	
Radiography	3882 (44.6%)	1500 (40.2%)	
Grade			0.529
I–II	6329 (72.7%)	2772 (74.3%)	
III–IV	2376 (27.3%)	959 (25.7%)	
T stage			0.646
T1–2	6659 (76.5%)	2914 (78.1%)	
T3–4	2046 (23.5%)	817 (21.9%)	
N stage			0.557
N0	5458 (62.7%)	2358 (63.2%)	
N1	3247 (37.3%)	1373 (36.8%)	
Surgery of the primary site			0.039
No	5562 (63.9%)	2496 (66.9%)	
Yes	3143 (36.1%)	1235 (33.1%)	
Radiotherapy			0.873
No	7921 (91.0%)	3403 (91.2%)	
Yes	784 (9.0%)	328 (8.8%)	
Chemotherapy			0.607
No	4361 (50.1%)	1899 (50.9%)	
Yes	4344 (49.9%)	1832 (49.1%)	
AFP level			0.339
Normal	4135 (47.5%)	1836 (49.2%)	
Raised	4570 (52.5%)	1895 (50.8%)	
Fibrosis score			0.096
0–4	4387 (50.4%)	1966 (52.7%)	
5–6	4318 (49.6%)	1765 (47.3%)	
Tumor size (cm)			0.883
<5	3177 (36.5%)	1321 (35.4%)	
⩾5	5528 (63.5%)	2410 (64.6%)	
Intrahepatic metastasis			0.553
No	8226 (94.5%)	3518 (94.3%)	
Yes	479 (5.5%)	213 (5.7%)	
Lung metastasis			0.417
No	8270 (95.0%)	3537 (94.8%)	
Yes	435 (5.0%)	194 (5.2%)	
Bone metastasis			0.104
No	8348 (95.9%)	3571 (95.7%)	
Yes	357 (4.1%)	160 (4.3%)	

ICC: intrahepatic cholangiocarcinoma; AFP: alpha-fetoprotein.

A diagnostic nomogram predicting BM among ICC patients was developed and validated

A diagnostic nomogram for predicting the risk of BM from ICC patients was created based on the five independent predictors described above (Figure 2). The total points were calculated by adding the individual points of the corresponding predictors, and each total point then represented the probability of BM in ICC patients. In addition, the *C*-index of the training cohort was 0.716 (95% confidence interval

Table 2. Logic regression analysis of risk factors of BM from ICC patients.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age				
18–64	Reference			
⩾65	1.012 (0.749–1.366)	0.939		
Sex				
Female	Reference			
Male	1.473 (0.997–2.176)	0.052		
Race				
American Indian	Reference			
Asian	2.169 (0.519–9.069)	0.289		
Black	2.494 (0.592–10.515)	0.213		
White	1.616 (0.393–6.644)	0.506		
Grade				
I–II	Reference			
III–IV	1.316 (0.921–1.881)	0.132		
T stage				
T1–2	Reference		Reference	
T3–4	6.639 (4.888–9.017)	0.000	3.922 (2.815–5.463)	0.000
N stage				
N0	Reference		Reference	
N1	4.974 (3.528–7.013)	0.000	2.323 (1.611–3.350)	0.000
Surgery of the primary site				
No	Reference		Reference	
Yes	0.265 (0.173–0.405)	0.000	0.420 (0.267–0.663)	0.000
Radiotherapy				
No	Reference			
Yes	1.409 (0.902–2.202)	0.132		
Chemotherapy				
No	Reference			
Yes	1.289 (0.965–1.723)	0.086		
AFP level				
Normal	Reference		Reference	
Raised	2.991 (1.956–4.572)	0.000	2.033 (1.310–3.155)	0.002
Fibrosis score				
0–4	Reference			
5–6	0.448 (0.328–0.613)	0.212		
Tumor size (cm)				
<5	Reference		Reference	
⩾5	1.772 (0.722–4.350)	0.003	1.213 (0.595–2.576)	0.000

BM: brain metastasis; ICC: intrahepatic cholangiocarcinoma; OR: odds ratio; CI: confidence interval; AFP: alpha-fetoprotein.

(CI) = 0.702–0.730), and that of the validation cohort was 0.723 (95% CI = 0.706–0.740). Meanwhile, in both the training and validation cohort, the favorable calibration curves of the nomogram were shown (Figure 3(A) and (B)), illustrating that the predictions were strongly consistent with the actual observations.

Prognostic factors independently associated with the survival of ICC patients with BM

As shown in Table 3, 112 eligible ICC patients with BM were used to obtain the prognostic factors. The 112 patients were randomly separated into the training cohort (78 cases) and the validation cohort (34 cases) at a 7:3 ratio. In general, 84.6 and 82.4% of the patients were male, and 62.8 and 58.8% of the patients were White in the training and validation cohort, respectively. The chi-square test showed no significant difference between the training and validation cohort.

As shown in Table 4, univariate Cox regression analysis indicated that T stage, surgery of the primary site, radiotherapy, and bone metastasis were prognostic factors. Then, those prognostic variables with a P value < 0.05 in the univariate Cox regression analysis were involved in the multivariate Cox regression analysis to identify the prognostic factors for BM in ICC patients. Finally, four variables, T stage (P value = 0.010), surgery of the primary site (P value = 0.000), radiotherapy (P value = 0.001), and bone metastasis (P value = 0.012) were determined as independent prognostic factors for ICC patients with BM.

A prognostic nomogram for ICC patients with BM was developed and validated

A prognostic nomogram was formulated based on the four independent prognostic factors described above (Figure 4). The *C*-index was 0.759 (95% CI = 0.745–0.773) and 0.764

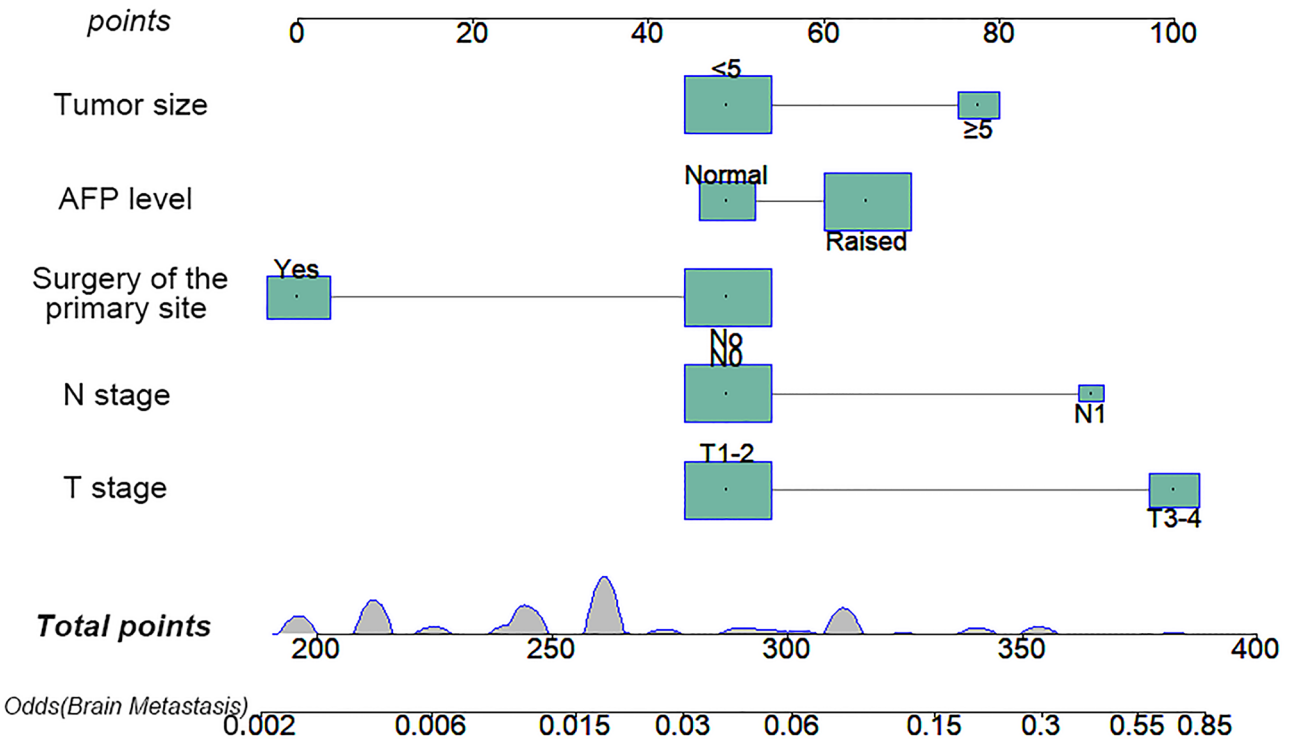

Figure 2. Diagnostic nomogram for predicting BM among ICC patients. When using the nomogram for an individual ICC patient, each risk factor is assigned a point value by drawing a vertical line from the corresponding value to the first point line. The total points are calculated by adding the individual points of the corresponding predictors, and each total point corresponds to a probability of brain metastasis among ICC patients in the bottom row. (A color version of this figure is available in the online journal.)
BM: brain metastasis; ICC: intrahepatic cholangiocarcinoma.

(95% CI = 0.747–0.781) in the training cohort and validation cohort, respectively. The calibration curves of the nomogram for the 3-, 6-, and 9-month OS also revealed a robust agreement between predictions and actual observations (Figure 5). Moreover, ROC analysis showed that the AUCs of the nomogram for the 3-, 6-, and 9-month OS were 0.721, 0.727, and 0.790 in the training cohort and 0.702, 0.777, and 0.853 in the validation cohort, respectively (Figure 6(A) and (B)). More importantly, we further compared the differences between the nomogram and individual prognostic factors, finding that the AUC of the nomogram was higher than that of all individual factors at 3-, 6-, and 9-months, regardless of training and validation cohorts, which implied that the merged model showed the highest prediction ability for survival in ICC patients with BM (Figure 7). The worth of the nomogram in the clinical application was estimated by DCA. As shown in Figure 8, the DCA curves manifested remarkable positive net benefits over a wide range of threshold probabilities, implying that the nomogram had strong clinical utility in predicting the OS for ICC patients with BM. Besides, the Kaplan–Meier survival analysis was carried out on the training and validation cohort, which suggested that patients in the high-risk cluster had a worse prognosis than those in the low-risk cluster (Figure 9).

Discussion

ICC is an aggressive malignancy with a relatively insidious onset. Most patients with ICC are initially diagnosed at an advanced stage and are often accompanied by extrahepatic metastasis.[14,15] Brain is a rare site of extrahepatic metastasis, being affected in 0.47–1.6% of ICC cases.[8–10] In their study, D'Andrea *et al.*[9] reported that the incidence of BM in ICC cases was 0.47% based on hospitalized population from Mount Sinai Hospital between 2000 and 2017. Frega *et al.*[10] revealed that 1.4% of 419 ICC patients were diagnosed with BM at Sant'Orsola-Malpighi Hospital between January 2000 and December 2015. In this study, we used the most recently updated data from the SEER database containing data from 2000 to 2018, and ultimately formed a study cohort of 12,436 individuals based on the inclusion and exclusion criteria. A total of 112 cases were initially diagnosed with BM, with an incidence of 0.90% (112/12,436).

Despite its low incidence, BM has a poor prognosis compared to other extrahepatic metastasis, with a median survival of only 3.7 months.[10] Therefore, screening and identifying independent risk factors for BM in ICC patients and applying them for early detection and prevention of clinically high-risk populations can effectively reduce the risk of BM. Shi *et al.*[16] noted that gender, grade, N stage, tumor size, and intrahepatic metastasis were significantly associated with lung metastasis in ICC. Lin *et al.*[17] found that age, grade, surgery, radiotherapy, chemotherapy, bone metastasis, and lung metastasis were independently positively associated with BM in the HCC cohort. These factors also reflect the invasion ability of the primary tumor to varying degrees, thus suggesting that these indicators can be used as risk factors for extrahepatic metastasis. In this study,

Table 3. Clinicopathologic features of patients newly diagnosed as ICC with BM.

Variables	Training cohort ($n=78$)	Validation cohort ($n=34$)	*P* value
Age			0.624
18–64	38 (48.7%)	16 (47.1%)	
⩾65	40 (51.3%)	18 (52.9%)	
Sex			0.832
Female	12 (15.4%)	6 (17.6%)	
Male	66 (84.6%)	28 (82.4%)	
Race			0.136
American Indian	1 (1.3%)	0 (0.0%)	
Asian	18 (23.1%)	10 (29.4%)	
Black	10 (12.8%)	4 (11.8%)	
White	49 (62.8%)	20 (58.8%)	
Diagnostic confirmation			0.990
Clinical diagnosis	2 (2.6%)	1 (2.9%)	
Cytology	1 (1.3%)	1 (2.9%)	
Histology	38 (48.7%)	17 (50.0%)	
Laboratory test	6 (7.7%)	3 (8.8%)	
Radiography	31 (39.7%)	12 (35.3%)	
Grade			0.051
I–II	60 (76.9%)	27 (79.4%)	
III–IV	18 (23.1%)	7 (20.6%)	
T stage			0.319
T1–2	54 (69.2%)	24 (70.6%)	
T3–4	24 (30.8%)	10 (29.4%)	
N stage			0.995
N0	55 (70.5%)	24 (70.6%)	
N1	23 (29.5%)	10 (29.4%)	
Surgery of the primary site			0.492
No	50 (64.1%)	22 (64.7%)	
Yes	28 (35.9%)	12 (35.3%)	
Radiotherapy			0.752
No	67 (85.9%)	30 (88.2%)	
Yes	11 (14.1%)	4 (11.8%)	
Chemotherapy			0.632
No	40 (51.3%)	18 (52.9%)	
Yes	38 (48.7%)	16 (47.1%)	
AFP level			0.819
Normal	34 (43.6%)	15 (44.1%)	
Raised	44 (56.4%)	19 (55.9%)	
Fibrosis score			0.311
0–4	42 (53.8%)	19 (55.9%)	
5–6	36 (46.2%)	15 (44.1%)	
Tumor size (cm)			0.995
<5	33 (42.3%)	14 (41.2%)	
⩾5	45 (57.7%)	20 (58.8%)	
Intrahepatic metastasis			0.865
No	73 (93.6%)	31 (91.2%)	
Yes	5 (6.4%)	3 (8.8%)	
Lung metastasis			0.181
No	74 (94.9%)	32 (94.1%)	
Yes	4 (5.1%)	2 (5.9%)	
Bone metastasis			0.994
No	75 (96.2%)	33 (97.1%)	
Yes	3 (3.8%)	1 (2.9%)	

ICC: intrahepatic cholangiocarcinoma; BM: brain metastasis; AFP: alpha-fetoprotein.

we found that higher T stage, higher N stage, no surgery of the primary site, raised AFP, and larger tumor size were significant predictors for BM. Notably, our data suggested that surveillance neuroimaging should be routinely recommended for ICC patients with the above characteristics, even if they are without obvious clinical symptoms.

Table 4. Cox proportional hazards regression analysis in ICC patients with BM.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
18–64	Reference			
⩾65	1.034 (0.758–1.409)	0.834		
Sex				
Female	Reference			
Male	1.023 (0.683–1.534)	0.911		
Race				
American Indian	Reference			
Asian	0.633 (0.153–2.622)	0.528		
Black	0.658 (0.157–2.756)	0.567		
White	0.647 (0.159–2.630)	0.542		
Grade				
I–II	Reference			
III–IV	1.418 (0.970–2.073)	0.072		
T stage				
T1–2	Reference		Reference	
T3–4	1.757 (1.268–2.435)	0.001	1.582 (1.116–2.244)	0.010
N stage				
N0	Reference			
N1	1.207 (0.861–1.693)	0.275		
Surgery of the primary site				
No	Reference		Reference	
Yes	0.239 (0.138–0.415)	0.000	0.307 (0.173–0.545)	0.000
Radiotherapy				
No	Reference		Reference	
Yes	0.658 (0.487–0.889)	0.006	0.588 (0.427–0.810)	0.001
Chemotherapy				
No	Reference			
Yes	0.911 (0.582–1.427)	0.684		
AFP level				
Normal	Reference			
Raised	1.388 (0.879–2.192)	0.160		
Fibrosis score				
0–4	Reference			
5–6	1.212 (0.878–1.673)	0.242		
Tumor size (cm)				
<5	Reference			
⩾5	2.354 (0.749–7.391)	0.143		
Intrahepatic metastasis				
No	Reference			
Yes	1.314 (0.759–2.277)	0.330		
Lung metastasis				
No	Reference			
Yes	1.060 (0.435–2.584)	0.898		
Bone metastasis				
No	Reference		Reference	
Yes	1.827 (1.329–2.511)	0.000	1.503 (1.092–2.069)	0.012

ICC: intrahepatic cholangiocarcinoma; BM: brain metastasis; HR: hazard ratio; CI: confidence interval; AFP: alpha-fetoprotein.

We further analyzed the prognosis of ICC patients with BM, finding that ICC patients with BM at a higher T stage, no surgery of the primary site, no radiotherapy, and with bone metastasis had an unfavorable prognosis. Yuan *et al.*[18] identified that T stage was strongly associated with the OS of ICC patients. Chen *et al.*[19] also revealed that T stage was an independent prognostic factor for ICC patients. In general, their results suggested that the prognosis of ICC patients gradually deteriorated as the T stage increased. In our research, we found that a higher T stage was negatively associated with OS in ICC patients with newly diagnosed BM. A higher T stage indicates that the primary tumor has a robust ability for vascular invasion and distant metastasis, which may be the reason why a higher T stage leads to poorer prognosis. Furthermore, Chen *et al.*[20] reported that HCC patients with BM who simultaneously developed bone metastasis were at increased risk of tumor-related deaths. Huang *et al.*[21] also identified bone metastasis as a critical independent

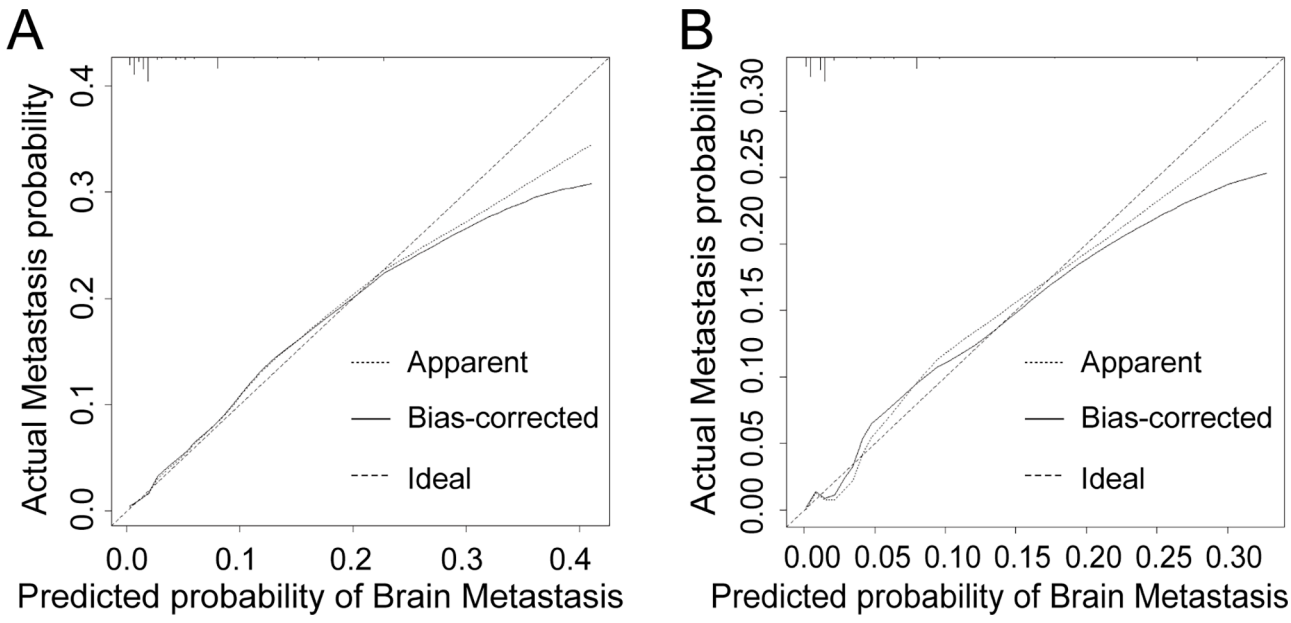

Figure 3. The calibration curves in the training cohort (A) and the validation cohort (B).

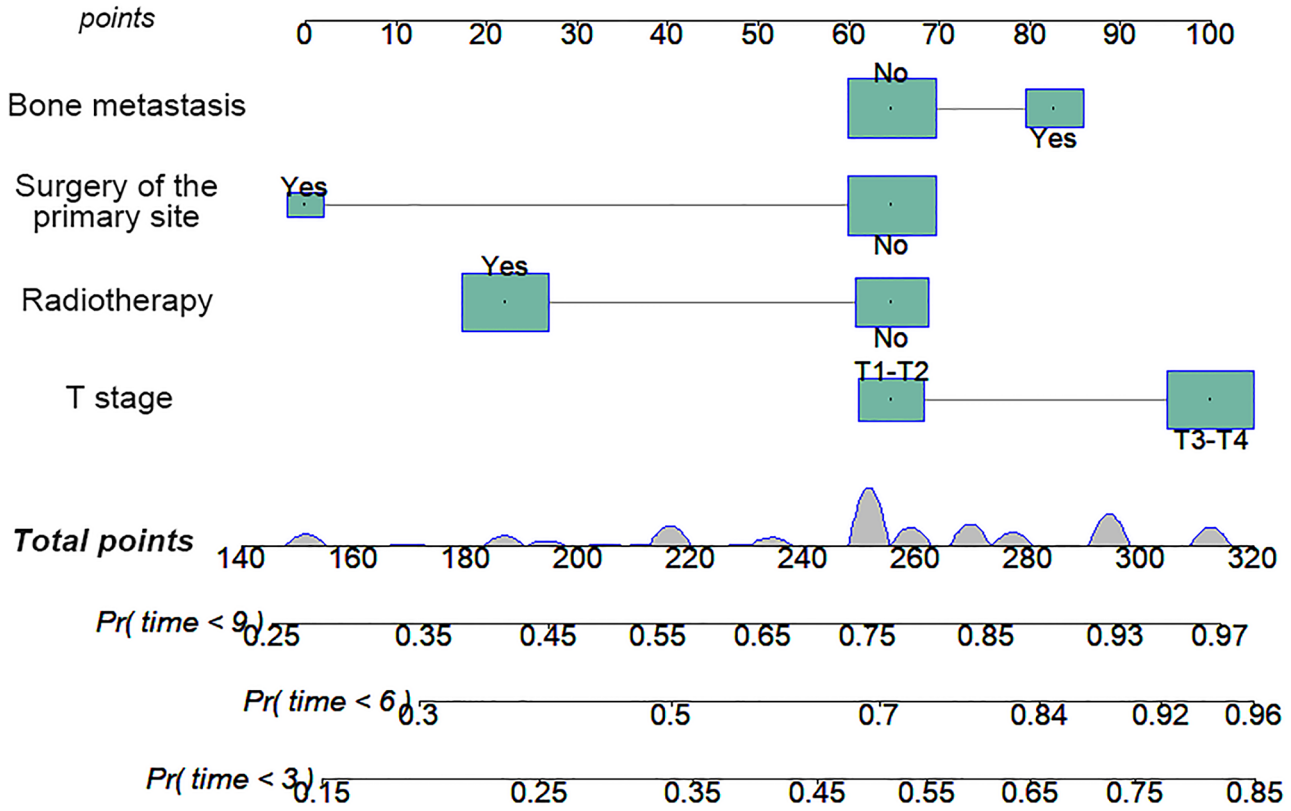

Figure 4. Prognostic nomogram for predicting the 3-, 6-, and 9-month overall survival of ICC patients with BM. When using the nomogram for an individual ICC patient with brain metastasis, each prognostic factor is assigned a point value by drawing a vertical line from the corresponding value to the first point line. The total points are calculated by adding the individual points of the corresponding predictors, and each total point corresponds to the 3-, 6-, and 9-month survival probabilities in the bottom row. (A color version of this figure is available in the online journal.)
ICC: intrahepatic cholangiocarcinoma; BM: brain metastasis.

prognostic factor for lung adenocarcinoma patients with BM. Therefore, it is worth investigating whether other distance metastases affect the outcome of ICC patients with BM in a synergistic manner. Our data showed that ICC patients with BM developed secondary bone metastasis, leading to a sharp decline in survival.

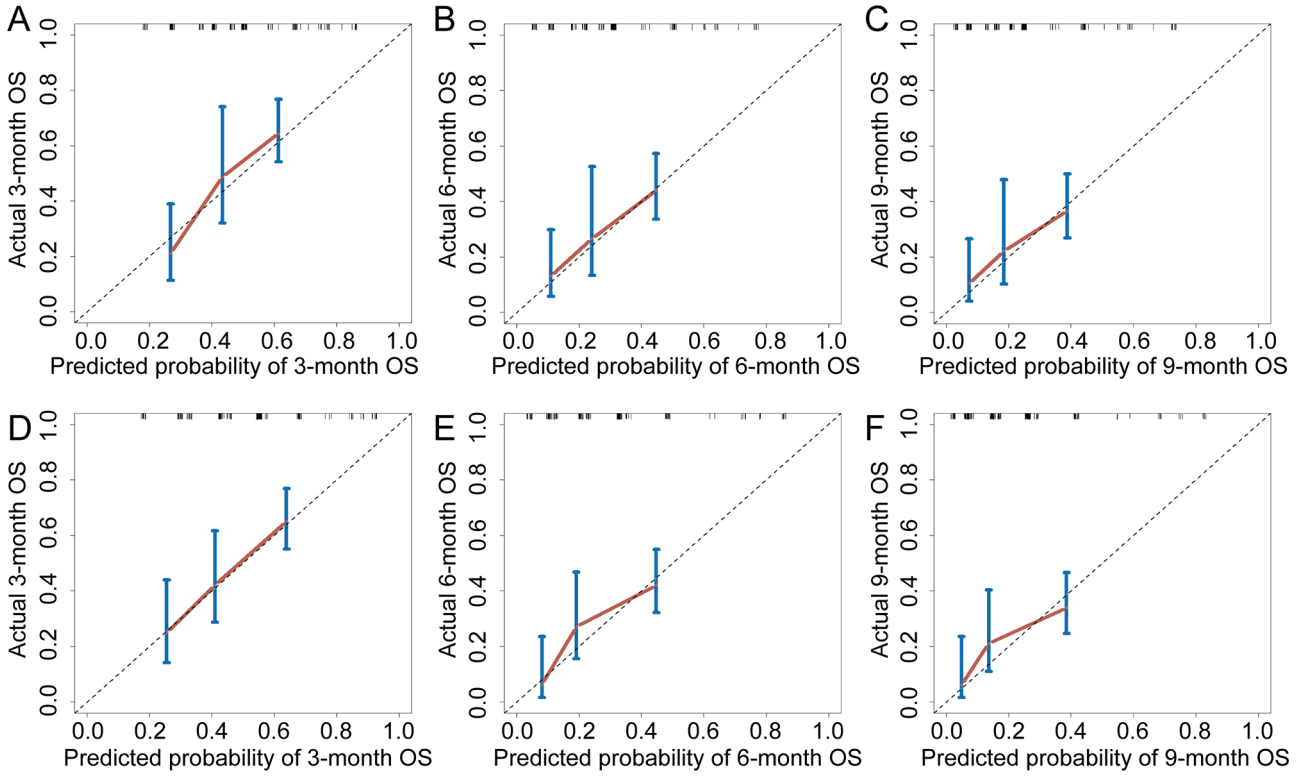

Figure 5. The calibration curves of the nomogram for the (A) 3-, (B) 6-, and (C) 9-month OS prediction in the training cohort. The calibration curves of the nomogram for predicting the (D) 3-, (E) 6-, and (F) 9-month OS in the validation cohort. (A color version of this figure is available in the online journal.)
OS: overall survival.

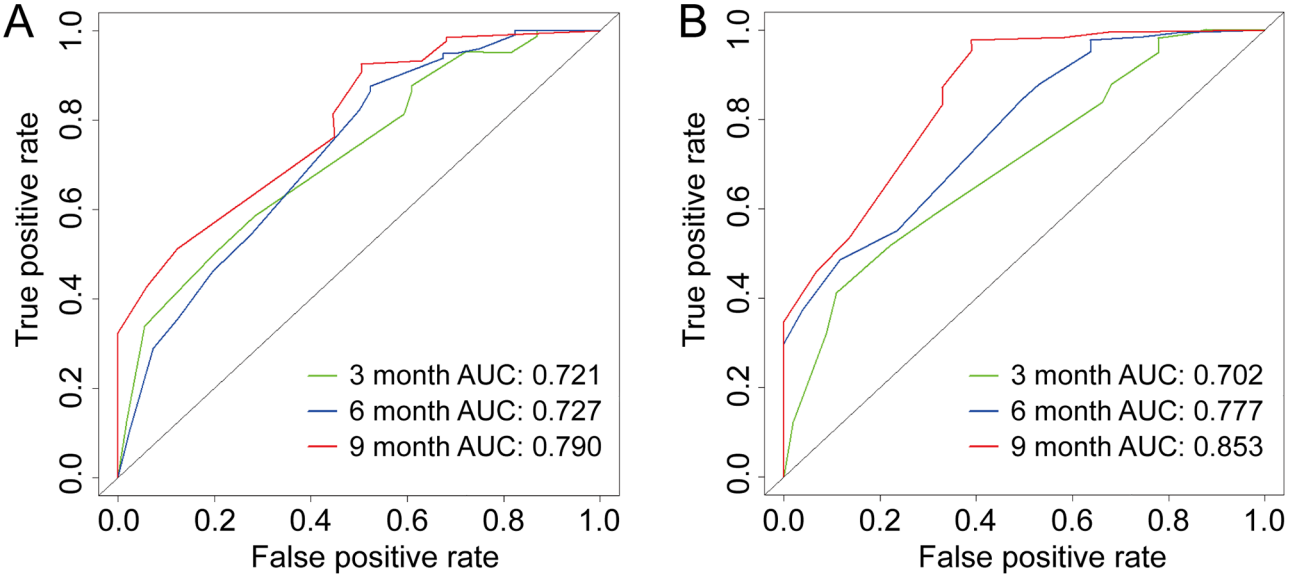

Figure 6. The receiver operating characteristic curves for the 3-, 6-, and 9-month OS in (A) the training cohort and (B) the validation cohort. (A color version of this figure is available in the online journal.)
OS: overall survival.

Generally, once a patient with ICC is diagnosed with BM, the best timing for radical treatment is missed, and the therapeutic recommendation at this stage is only alleviative surgical treatment and palliative head radiation therapy.[22] Chan *et al.*[23] reported that the 1- and 3-year survival rates of patients who underwent surgical resection of extrahepatic metastasis were 24 and 7%, respectively, compared with 8 and 0%, respectively, in the non-surgical group. Han *et al.*[24] showed that hepatectomy led to relatively prolonged survival time among HCC patients with BM. Both studies suggested that patients could benefit from the early surgical intervention in primary and metastatic tumors. This study also revealed

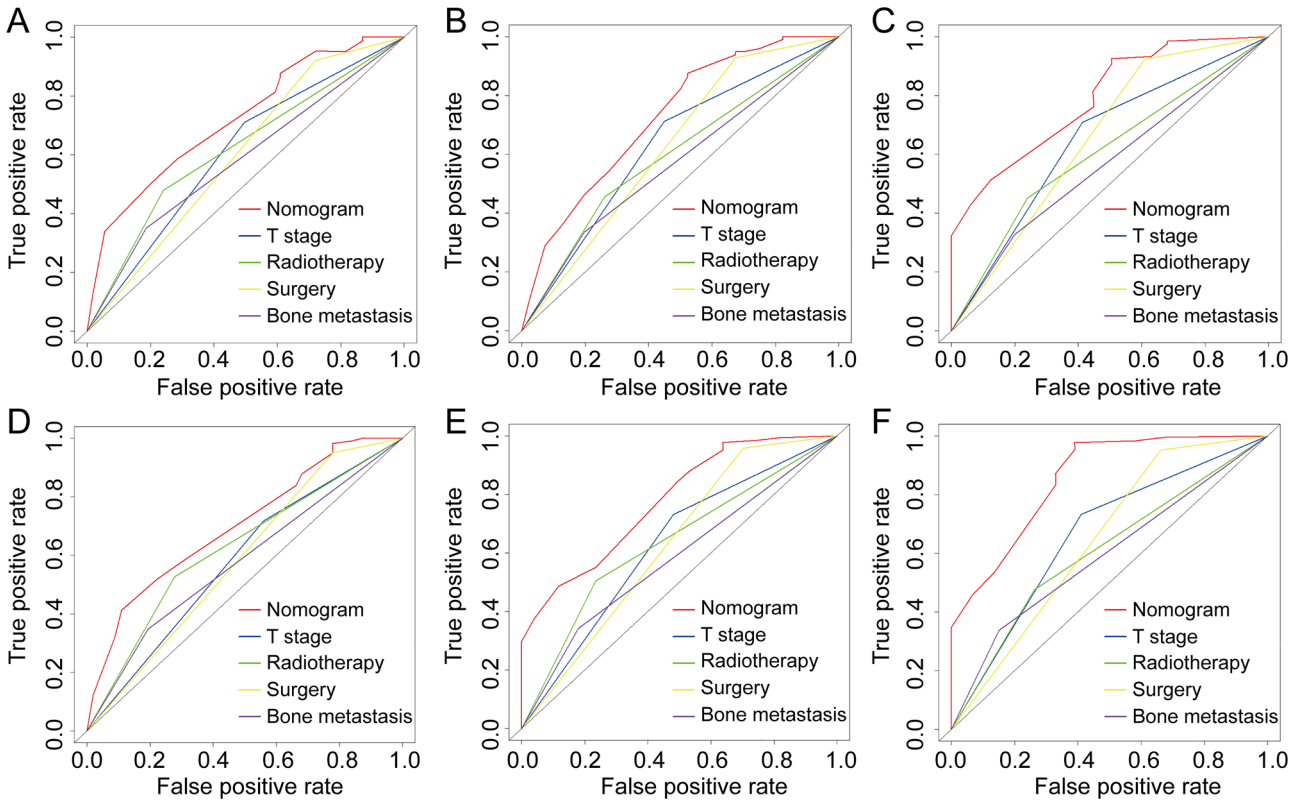

Figure 7. The receiver operating characteristic curves of the prognostic nomogram and each independent indicator at (A) 3-, (B) 6-, and (C) 9-month points in the training cohort and at (D) 3-, (E) 6-, and (F) 9-month points in the validation cohort. (A color version of this figure is available in the online journal.)
Surgery: surgery of the primary site.

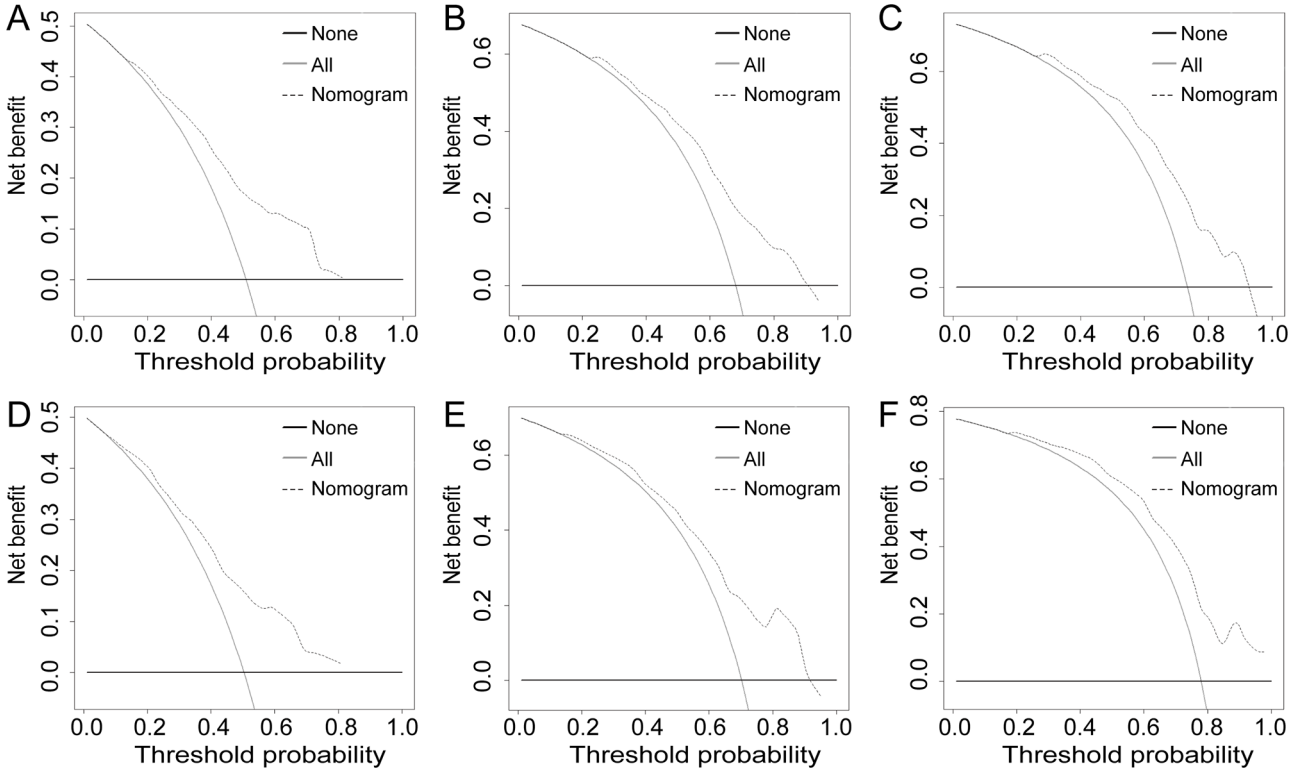

Figure 8. The decision curve analysis of the nomogram for the (A) 3-, (B) 6-, and (C) 9-month OS prediction in the training cohort. The decision curve analysis of the nomogram for predicting the (D) 3-, (E) 6-, and (F) 9-month OS in the validation cohort.
OS: overall survival.

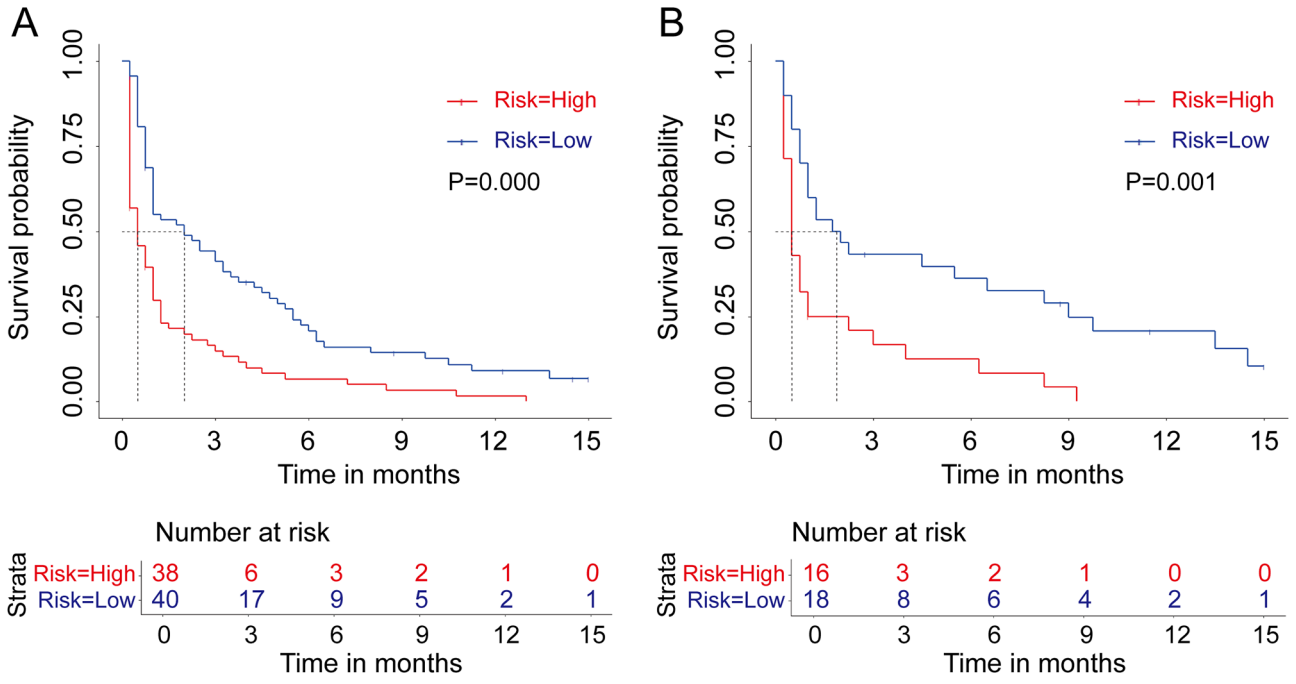

Figure 9. Kaplan–Meier curves for patients in the low-risk (blue) and high-risk (red) clusters: (A) training cohort and (B) validation cohort. (A color version of this figure is available in the online journal.)

that ICC cases with BM achieved a greater OS rate following surgical treatment. Likewise, patients with BM who received radiotherapy had significantly improved outcomes. Chen *et al.*[25] proposed that the addition of radiotherapy to the brain could improve intracranial progression-free survival and OS among lung adenocarcinoma patients with asymptomatic BM. Ou *et al.*[26] found that upfront brain radiotherapy was strongly associated with increased median OS in breast cancer BM patients with Breast-Graded Prognostic Assessment (GPA) 0–2.0. Even in the absence of detailed radiotherapy dosage, our results clearly showed that the prognosis of ICC patients with BM who received radiotherapy significantly improved. Consequently, greater attention should be paid to the possibility of higher T stage and bone metastasis in ICC patients with BM. In order to obtain a satisfactory prognosis, surgery and radiotherapy could become preferred clinical treatments for ICC patients with BM.

For better clinical application, we constructed and verified two nomograms to predict the BM in patients initially diagnosed with ICC and assess the prognosis in ICC patients with BM. The results showed that those nomograms had excellent performance in predicting the risk of BM and assessing the prognosis of ICC cases with BM separately. Meanwhile, the survival curve showed that our prognostic nomogram had the robust potential for clinical application. Thus, these two nomograms could provide guidelines and a basis for personalized and precise clinical diagnosis and treatment of ICC cases with BM.

This study has some limitations that should be acknowledged. Although this is a large population–based study, the use of a retrospective database inevitably leads to selection bias in this analysis. First, the information collected from the SEER database was about the disease at the time of initial diagnosis, which means that the BM occurred later throughout the disease could not be exactly recorded. Second, several patients with BM had no symptoms, resulting in fewer newly diagnosed BM cases than the actual number of cases was. Third, the specific information on detailed treatment was not available in the SEER database, such as the absence of the dosage of radiation and the chemotherapy regimens. After considering these limitations, more rigorous validation through multicenter prospective clinical trials is warranted to confirm these initial evaluations of the established nomograms.

Conclusions

This study demonstrated that T stage, N stage, surgery of the primary site, AFP level, and tumor size were the independent risk factors for BM in ICC. Furthermore, nomogram with independent prognostic factors – including T stage, surgery of the primary site, radiotherapy, and bone metastasis – can be applied to clinically evaluate survival among ICC patients with BM.

AUTHORS' CONTRIBUTIONS

All authors participated in the design, interpretation of the studies and analysis of the data, and review of the manuscript. SL designed the research. ZL and JY performed the statistical analyses and wrote the manuscript. JY, XZ, and LW extracted the data and checked the figures and tables. All authors contributed to the article and approved the submitted version. ZL, JY, and JY contributed equally to this article.

DECLARATION OF CONFLICTING INTERESTS

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DATA AVAILABILITY

Publicly available SEER data sets were analyzed in this study. The data can be found from here: https://seer.cancer.gov/.

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