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A prognostic nomogram for distal bile duct cancer from Surveillance, Epidemiology, and End Results (SEER) database based on the STROBE compliant

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Abstract

In this study, we aimed to develop a reliable nomogram to estimate individualized prognosis for patients with distal bile duct cancer (DBDC) and compare the predictive value with the American Joint Committee on Cancer staging system.

Data of 1110 patients diagnosed with DBDC were recruited from the Surveillance, Epidemiology, and End Results database between 1973 and 2015. All patients were randomly divided into the training (n = 777) and validation (n = 333) cohorts, respectively. Multivariate Cox regression was performed to identify the independent risk factors. The Akaike information criterion was used to select covariates for constructing a nomogram. The predictive ability of the nomogram was assessed by concordance index (C-index) and area under receiver operating characteristic curve (AUROC) compared to tumor-node-metastasis (TNM) staging system.

A nomogram integrating 8 risk factors was developed with a higher C-index than that of the TNM staging system (training data set, 0.70 vs 0.61; validation data set, 0.71 vs 0.57). The AUROCs of the nomogram for 1-year and 3-year overall survival (OS) predication were 0.76 and 0.78 in the training cohort, 0.78 and 0.77 in the validation cohort. However, AUROCs of the TNM stage for predicting 1-year and 3-year OS were all below 0.60. Calibration curves showed the optimal agreement in predicating OS between nomogram and actual observation. In addition, this nomogram can effectively distinguish the OS between low and high-risk groups divided by the median score ($P < .01$).

Present study was the first one to construct a prognostic nomogram of DBDC patients, which has the potential to provide individual prediction of OS.

Abbreviations: AIC = Akaike information criterion, AJCC = American Joint Committee on Cancer, AUROC = area under receiver operating characteristic curve, CCA = cholangiocarcinoma, CI = confidence interval, C-index = concordance index, DBDC = distal bile duct cancer, HR = hazard ratio, ICD-O-3 = International Classification of Disease for Oncology 3rd edition, LN = lymph node, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results, TNM = tumor-node-metastasis.

Keywords: distal bile duct cancer, nomogram, overall survival, prognostic model, Surveillance, Epidemiology, and End Results

1. Introduction

Cholangiocarcinoma (CCA) is a relatively rare cancer that formed in the biliary duct system and comprised of intrahepatic, hilar and distal subtypes.[1] But the burden of CCA is rapidly increasing worldwide in recent years.[2] CCA has dismal prognosis owing to its aggressiveness and delayed diagnosis with a 5-year survival rate of 5% to 10%.[3,4] Surgical resection provide a chance to improve the probability of long-term survival.[5]

Distal bile duct cancer (DBDC) is the most common type after perihilar bile duct cancer and account for 20% to 30% of all CCA.[6,7] It is defined as a malignancy arising between the junction of the cystic duct–bile duct and the ampulla of Vater.[8] However, due to its rarity, many studies have raised the concern on the prognosis of DBDC combined with either periampullary or perihilar cancer. Thus, prognostic data of patients with DBDC are relative scarce. Nevertheless, accurate assessment of a patient's prognosis informs treatment decisions and is integral to effective communication between physician and patients.

The tumor-node-metastasis (TNM) staging system is an acknowledged way to predict the prognosis of bile duct cancer.[9] However, published data showed that the TNM staging system does not account for many essential factors that can significantly affect DBDC patient survival, including patient characteristics, tumor cell differentiation, and resection margin.[7,10,11] Therefore, it is necessary to develop a predictive tool for assessing survival in individual patients considering both patient status and tumor characteristics.

Prognostic nomogram, as a simple and visual statistical tool to quantify risk, has been widely used in clinical practice for oncologic prognosis.[12] Recently, several prognostic nomograms

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The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

The SEER research data is publicly available for registered users without informed patient consent and our permission number was 16459-Nov2017.

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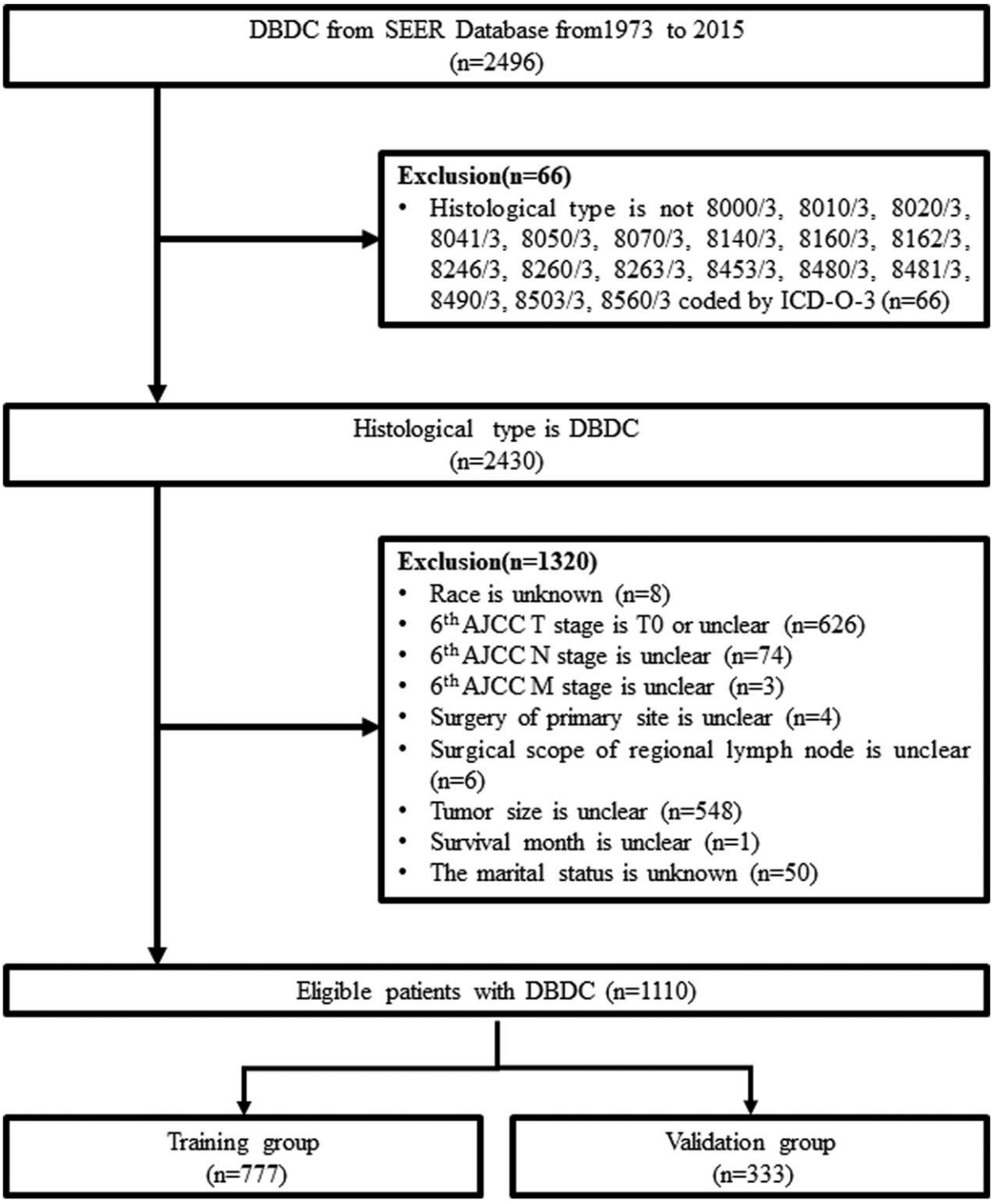

Figure 1. Flow chart of patient selection. AJCC = American Joint Committee on Cancer, DBDC = distal bile duct cancer, ICD-O-3 = International Classification of Disease for Oncology 3rd edition, SEER = the Surveillance, Epidemiology, and End Results database.

have been introduced for numerous malignancies, including gastric cancer, liver cancer, colorectal cancer, breast cancer, and prostate cancer.[13–17] However, until now, no nomogram that predict overall survival (OS) of DBDC has been established.

To more accurately investigate long-term prognosis of DBDC, we interrogated Surveillance, Epidemiology, and End Results (SEER) program database to develop and validate a new prognosis model for individual patients based on demographic,

tumor-dependent characteristics, histological features, and therapeutic regimen.

2. Patients and methods

2.1. Study population

A total of 2496 patients with DBDC between 1973 and 2015 were retrospectively extracted from the SEER database, which was publicly available for registered users without informed patient consent and our permission number was 16459-Nov2017. Covariates of interest extracted for each case were age, race, gender, degree of differentiation, tumor size, surgery of the primary tumor, regional lymph node surgery, surgical procedure of metastasis, marital status, and American Joint Committee on Cancer (AJCC) tumor stage. The inclusion criteria for data screening were the consistency between DBDC diagnosis and International Classification of Disease for Oncology 3rd edition (ICD-O-3). The primary site limited to diagnosis code C24.0, and histology codes were ICD-O-3 8000, 8010, 8020, 8041, 8050, 8070, 8140, 8160, 8162, 8246, 8260, 8263, 8453, 8480, 8481, 8490, 8503, and 8560. The exclusion criteria were as follows: patients with unknown race; inaccessible pathological data including AJCC tumor stage and tumor size; surgical information of primary site and regional lymph node were unclear; and unavailable information about survival data and marital status. After patient identification, 1110 eligible patients were enrolled and made up the primary cohort of DBDC. For further analysis, the primary cohort were randomly allocated into a training group (n = 777) and a validation group (n = 333). The detailed process for patients screening is presented in Figure 1.

2.2. Statistical analysis

Univariate Cox regression analysis was performed to evaluate the association between survival and covariates extracted for each patient. Multivariable Cox proportional regression can be extended to identify the independent prognostic risk factors in DBDC for OS. Using the patients in the training cohort, the final variables included in the nomogram were identified by a backward step-down process based on the smallest Akaike information criterion (AIC) value. The performances of the nomogram and conventional AJCC TNM staging systems were assessed using the concordance index (C-index) and receiver operating characteristic (ROC) curves. The predictive ability of this model was further testified by 333-sample bootstrap validation. Calibration curves were drawn to compare the nomogram-predicted probabilities with actual survival probabilities. According to the median score of patients in training group based the nomogram, we divided the patients into high-risk group and low-risk group. OS probabilities of these 2 groups were analyzed by Kaplan–Meier curves.

All statistical analyses were carried out using SPSS 25.0 (SPSS Inc, Chicago, IL) and R software (3.5.2). Calibration curve plots, ROC, and Kaplan–Meier curves were drawn by the "rms" and "survivalROC" package. All tests with $P < .05$ in a two-tailed test were considered statistically significant.

3. Results

3.1. Patient baseline characteristics

The baseline characteristics of the primary cohort (1110 patients), training cohort (777 patients), and validation cohort (333 patients) were listed in Table 1. Among the eligible patients, 658 (59%) were males and 452 (41%) were females. The majority of patients in both sets were elderly (>50 years), white and married. In both sets, most patients received surgery and had T3 stage (40%), with no node metastasis (60%) and no distant metastasis (87%). The median OS were 15.6 and 14.9 months for the training and validation group, respectively.

Table 1

Patient demographics and clinical characteristics.

Variables	All patients (n = 1110)	Training set (n = 777)	Validation set (n = 333)
Age, years, n (%)			
20–49	47 (4)	40 (5)	7 (2)
50–79	819 (74)	575 (74)	244 (73)
≥80	244 (22)	162 (21)	82 (25)
Race, n (%)			
Black	88 (8)	59 (8)	29 (9)
White	844 (76)	591 (76)	253 (76)
Other*	178 (16)	127 (16)	51 (15)
Sex, n (%)			
Male	658 (59)	468 (60)	190 (57)
Female	452 (41)	309 (40)	143 (43)
T stage, n (%)			
T1	275 (25)	186 (24)	89 (27)
T2	188 (17)	137 (18)	51 (15)
T3	439 (40)	310 (40)	129 (39)
T4	208 (19)	144 (19)	64 (19)
N stage, n (%)			
N0	667 (60)	468 (60)	199 (60)
N1	443 (40)	309 (40)	134 (40)
Metastases, n (%)			
M0	968 (87)	675 (87)	293 (88)
M1	142 (13)	102 (13)	40 (12)
Therapy, n (%)			
No surgery	389 (35)	266 (34)	123 (37)
Surgery	721 (65)	511 (66)	210 (63)
LN surgery, n (%)			
No	407 (37)	281 (36)	126 (38)
Yes	703 (63)	496 (64)	207 (62)
Metastasectomy, n (%)			
No	1006 (91)	705 (91)	301 (90)
Yes	104 (9)	72 (9)	32 (10)
Tumor size, n (%)			
<1 cm	43 (4)	29 (4)	14 (4)
1–5 cm	993 (89)	698 (90)	295 (89)
>5 cm	74 (7)	50 (6)	24 (7)
Marital status, n (%)			
Married	679 (61)	483 (62)	196 (59)
Unmarried	431 (39)	294 (38)	137 (41)

LN = lymph node.
* The other comprises American Indian/Alaska Native, Asian/Pacific Islander.

3.1.1. Univariate and multivariate Cox regression of the training cohort. In univariate regression analysis, 7 covariates were associated with the OS of DBDC patients. To reduce the potential effect of confounding factors, multivariable Cox proportional regression method was applied to identify the independent prognosis risk factors. As shown in Table 2, age, gender, N stage, metastases, tumor size, marital status, primary tumor, and lymph node surgery were significantly associated with OS.

Table 2

Univariate and multivariate Cox regression analyses of prognostic factors for patients with distal bile duct cancer in the training set.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (years)				
20–49	Reference		Reference	
50–79	1.07 (0.71–1.61)	.740	1.25 (0.82–1.89)	.299
≥80	2.01 (1.31–3.10)	.001†	1.85 (1.17–2.91)	.008†
Race				
Black	Reference		Reference	
White	1.05 (0.76–1.46)	.397	1.01 (0.73–1.41)	.933
Other*	0.85 (0.58–1.24)	.089	0.98 (0.66–1.45)	.926
Sex				
Male	Reference		Reference	
Female	0.99 (0.82–1.18)	.898	0.83 (0.68–1.00)	.047†
T stage				
T1	Reference		Reference	
T2	0.50 (0.37–0.67)	.000†	0.76 (0.55–1.04)	.084
T3	0.76 (0.61–0.94)	.013†	1.01 (0.79–1.29)	.967
T4	0.71 (0.54–0.93)	.012†	0.92 (0.68–1.23)	.565
N stage				
N0	Reference		Reference	
N1	1.03 (0.86–1.24)	.715	1.42 (1.16–1.74)	.001†
Metastases				
M0	Reference		Reference	
M1	2.53 (2.00–3.21)	.000†	1.47 (1.12–1.92)	.005†
Therapy				
No surgery	Reference		Reference	
Surgery	0.30 (0.25–0.36)	.000†	0.54 (0.37–0.78)	.001†
LN surgery				
No	Reference		Reference	
Yes	0.33 (0.28–0.40)	.000†	0.61 (0.42–0.89)	.011†
Metastasectomy				
No	Reference		Reference	
Yes	0.82 (0.59–1.13)	.224	1.09 (0.78–1.54)	.607
Tumor size				
<1 cm	Reference		Reference	
1–5 cm	2.33 (1.24–4.36)	.008	1.72 (0.91–3.25)	.094
>5 cm	4.10 (2.06–8.16)	.000†	2.27 (1.11–4.63)	.024†
Marital status				
Married	Reference		Reference	
Unmarried	1.36 (1.14–1.63)	.001†	1.25 (1.04–1.51)	.019†

CI = confidence interval, LN = lymph node.

* The other comprises American Indian/Alaska Native, Asian/Pacific Islander.

† *P*-value significant (<.05).

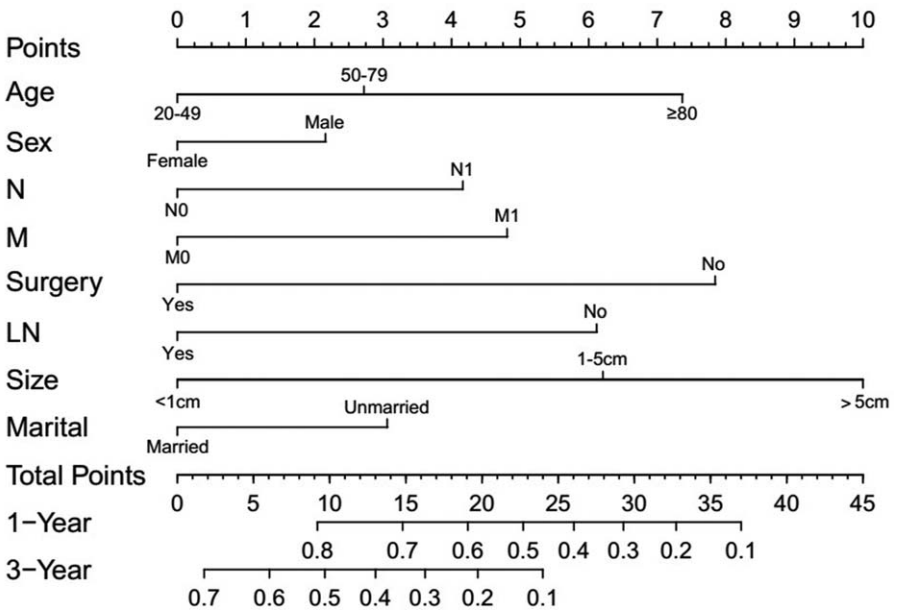

Figure 2. A nomogram to predict 1-year and 3-year overall survival in patients with DBDC. LN = lymph node surgery, M = M stage of TNM classification system, N = N stage of TNM classification system.

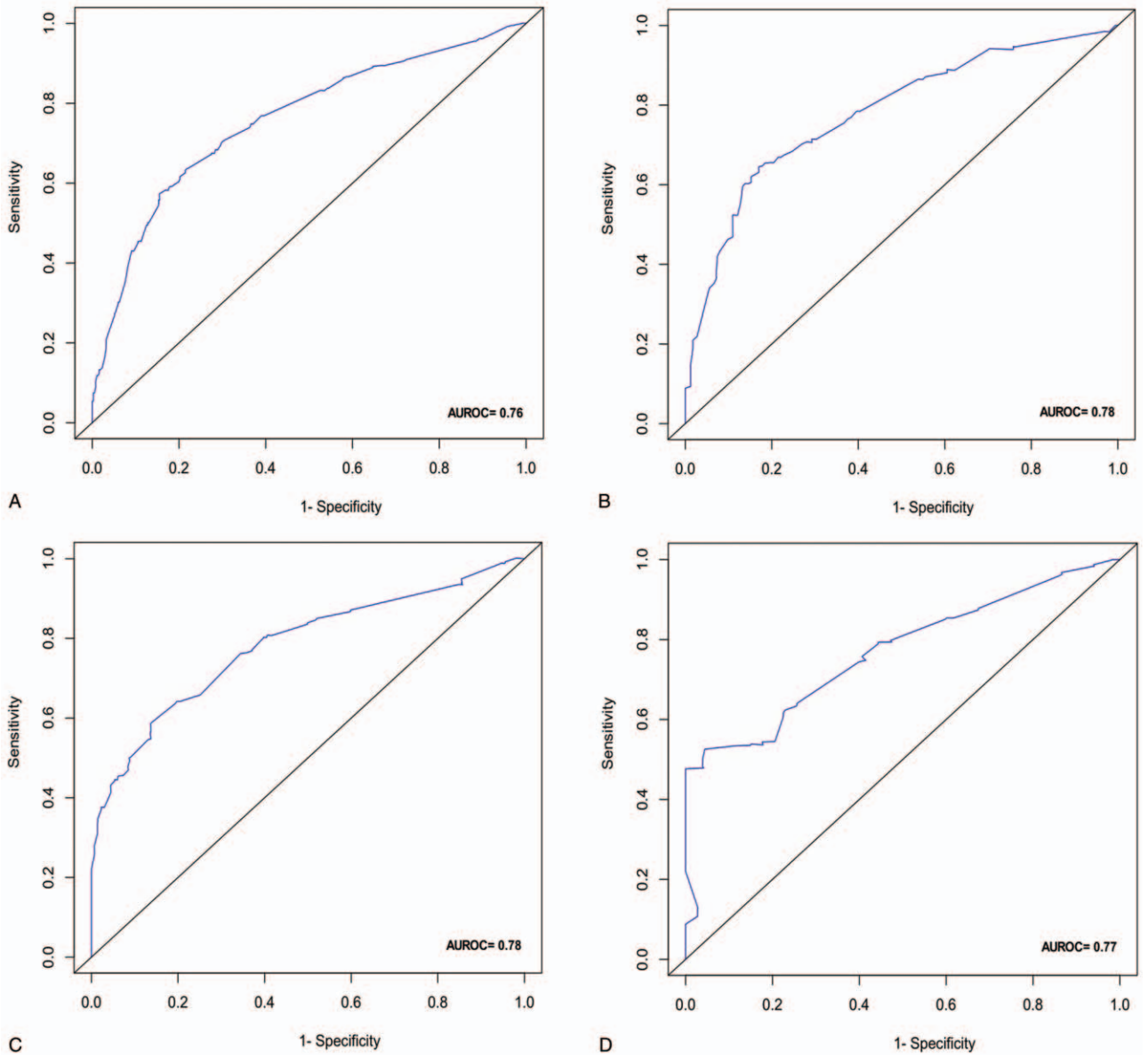

Figure 3. ROC curves of the nomogram for the prognostic prediction of DBDC. (A) The AUROC for 1-year OS was 0.76 in the training group. (B) The AUROC for 1-year OS was 0.78 in the validation group. (C) The AUROC for 3-year OS was 0.78 in the training group. (D) The AUROC for 3-year OS was 0.77 in the validation group. AUROC = area under the receiver operating characteristic curve, DBDC = distal bile duct cancer, OS = overall survival, ROC = receiver operating characteristic curve.

3.1.2. Nomogram construction. Based on the AIC, 8 covariates (age, gender, M stage, N stage, marital status, tumor size, primary tumor, and lymph node surgery) were employed in the nomogram for predicting 1 and 3-year OS (Fig. 2). This model showed that tumor size contributed most to OS, followed by the therapy, age, M stage, N stage, marital status, and gender. We can easily acquire the points of each variable by drawing a vertical line from each variable to points scale. Then we calculated a total score by adding up scores of each selected variable on the scale. In the end, vertical line between total points scale and OS scale can be drawn to acquire the survival rate of the individual patients.

3.1.3. Nomogram validation. The areas under receiver operating characteristic curves (AUROCs) of the nomogram for 1-year and 3-year OS predication were 0.76 and 0.78 in the training cohort (Fig. 3A and C). It also has a very good concordance in validation cohort with the AUROCs of 0.78 and 0.77 to predicate 1-year and 3-year OS (Fig. 3B and D). AUROCs of the TNM stage for predicting 1-year and 3-year OS were respectively 0.57 and 0.59 in the training (Fig. 4A and C), and respectively 0.52 and 0.52 in the validation groups (Fig. 4B and D). In addition, the nomogram has a higher C-index than TNM staging respectively in the training (0.70, 95% confidence interval [CI]: 0.67–0.72 vs 0.61, 95% CI: 0.58–0.63) and validation group (0.71, 95% CI: 0.67–0.75 vs 0.57, 95% CI: 0.53–0.62). The results indicate that the nomogram has adequate ability of discrimination, which is better than the AJCC TNM staging.

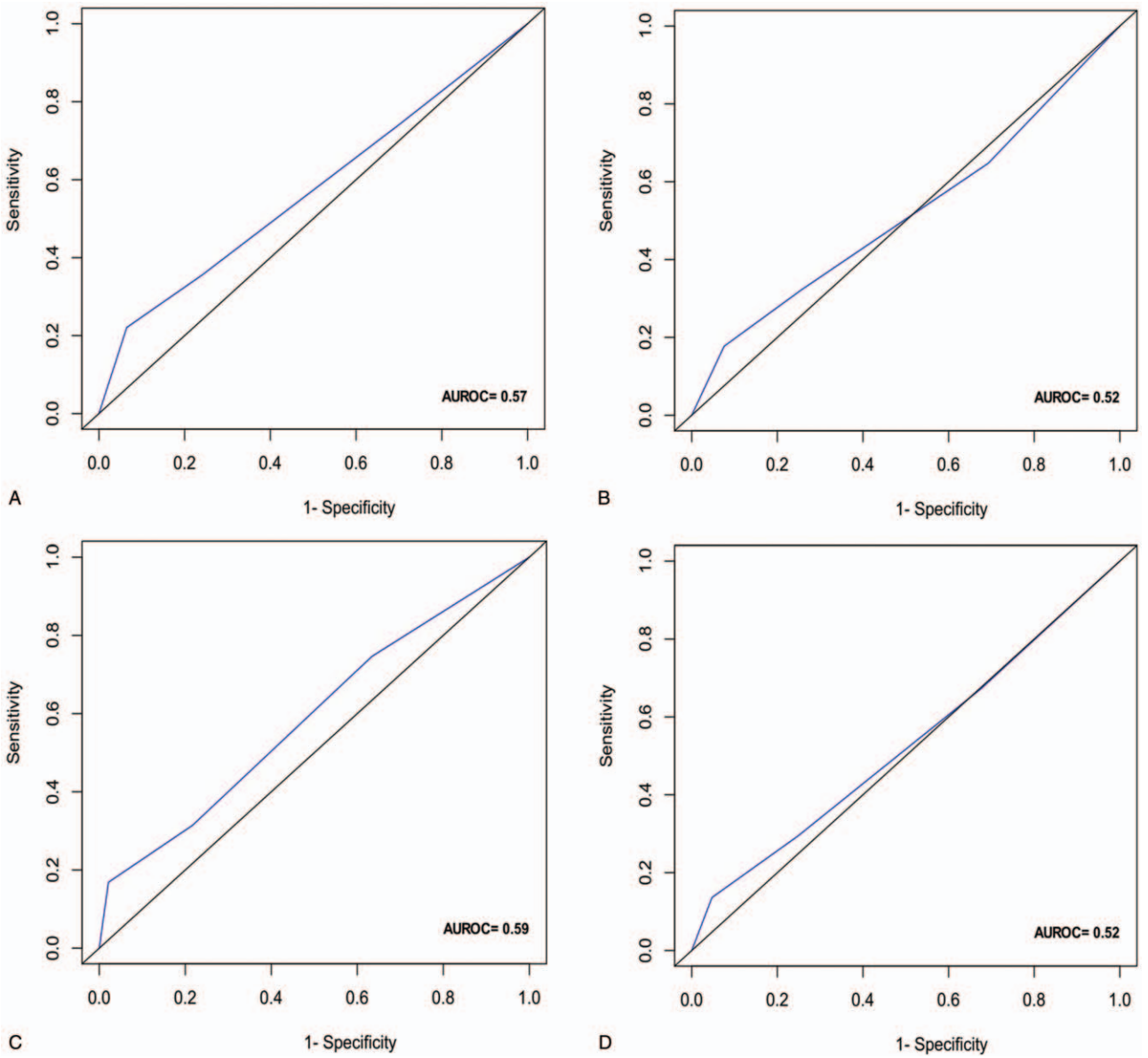

Figure 4. ROC curves of the TNM stage for the prognostic prediction of DBDC. (A) The AUROC for 1-year OS was 0.57 in the training group. (B) The AUROC for 1-year OS was 0.52 in the validation group. (C) The AUROC for 3-year OS was 0.59 in the training group. (D) The AUROC for 3-year OS was 0.52 in the validation group. AUROC = area under the receiver operating characteristic curve, DBDC = distal bile duct cancer, OS = overall survival, ROC = receiver operating characteristic curve, TNM = tumor-node-metastasis.

In order to evaluate the ability of this model, the calibration plots were performed to compare the consistency of predictions (blue line) and actual observed outcomes (dashed diagonal line) for 1-year and 3-year OS (Fig. 5). The figure showed a minor fluctuated above and below the diagonal line indicating a good fit for nomogram model.

3.1.4. Survival comparison in low and high-risk patients. Based on median score (16 point) of patients in training group, patients in the training and validation cohorts were stratified into low and high-risk groups. Each group represented a longer survival time in low-risk patients than that in high-risk patients ($P < .01$) (Fig. 6). The results indicating that the nomogram has a favorable discrimination performance.

4. Discussion

DBDC is relatively uncommon cancer but fatal with a poor prognosis.[18] Although potential prognostic risk factors, such as tumor markers, tumor differentiation, surgical radicality, preoperative cholangitis, and lymph node metastasis have been reported for extrahepatic bile duct cancer.[19–23] However, up till now, there are few studies evaluating the prognosis for DBDC as a separate entity and no available clinical data to guide clinical decision-making. In our analysis, age, lymph node metastasis, distant metastasis, primary site surgery, lymph node surgery, tumor size, and marital status were indeed found to be significant prognostic factors.

In the present study, younger patients have a longer OS (50–79 years: hazard ratio [HR] = 1.07 [95% CI: 0.71–1.61], $P < .05$,

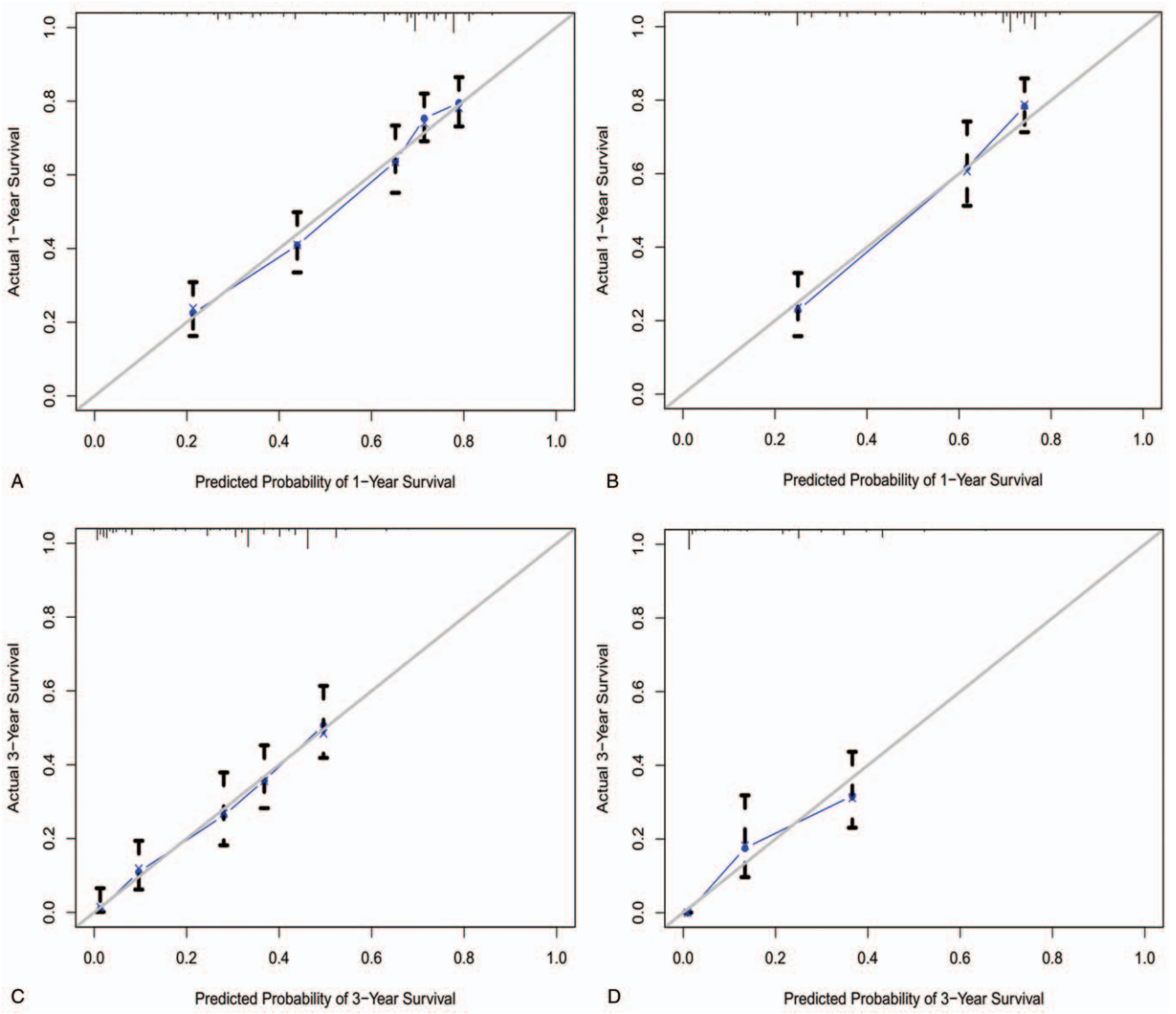

Figure 5. The calibration curves of the nomogram for1-year (A and C) and 3-year (B and D) overall survival probabilities in the training group (A and B) and validation group (C and D). OS = overall survival.

≥80 years: HR = 2.01 [95% CI: 1.31–3.10], $P < .05$) than older patients. As much studies shown, age at diagnosis has been identified as a major influence factor of survival in cancer patients. Utada et al[24] demonstrated that higher mortality rates of intra and extrahepatic bile cancer were observed in older patients. Kim et al[25] also found age >65 years (HR 1.32, 95% CI 1.09–1.60) had a significantly poorer survival than the younger.

Gender was an independent prognostic factor in our study. Female had marginally better prognoses than male with an HR of 0.83 (95% CI 0.68–1.00). The result was consistent with other relevant articles. Kim et al[26] analyzed the prognosis of subsequent CCA in patients with hepatic resection for bile duct stones. The cases of male were associated with shorter survival times (HR 1.28, 95% CI 1.05–1.57) than female ones. Higher risks of mortality were also observed in male patients in each cancer of intrahepatic bile duct (HR = 1.038, $P = .002$), extrahepatic bile duct cancer (HR = 1.12, $P < .001$), and gallbladder cancer (HR = 1.05, $P = .003$) after adjusting for age and year of diagnosis.[27]

Nodal and distance metastasis are poor prognostic factors for DBDC. Compared with no metastasis patients, the HR of lymph vessel and distance invasion were 1.42 (95% CI: 1.16–1.74, $P < .01$) and 1.47 (95% CI: 1.12–1.92, $P < .01$), respectively. Our results were consistent with previous reports. Kiriyama et al[28] reported the poor prognostic value of the increasing number of involved nodes in distal CCA. With respect to hilar CCA, 5-year OS of N1 patients was significantly lower than that of N0 patients (9.0% vs 46.6%).[29] Survival benefit was observed in the patients with primary tumor and lymph node dissection.[30] Likewise, our results showed that patients who received primary tumor or lymph node surgery survived longer than those who did not (primary tumor surgery: HR = 0.54 [95% CI: 0.37–0.78], $P < .05$, lymph node surgery: HR = 0.61 [95% CI: 0.42–0.89], $P < .05$).

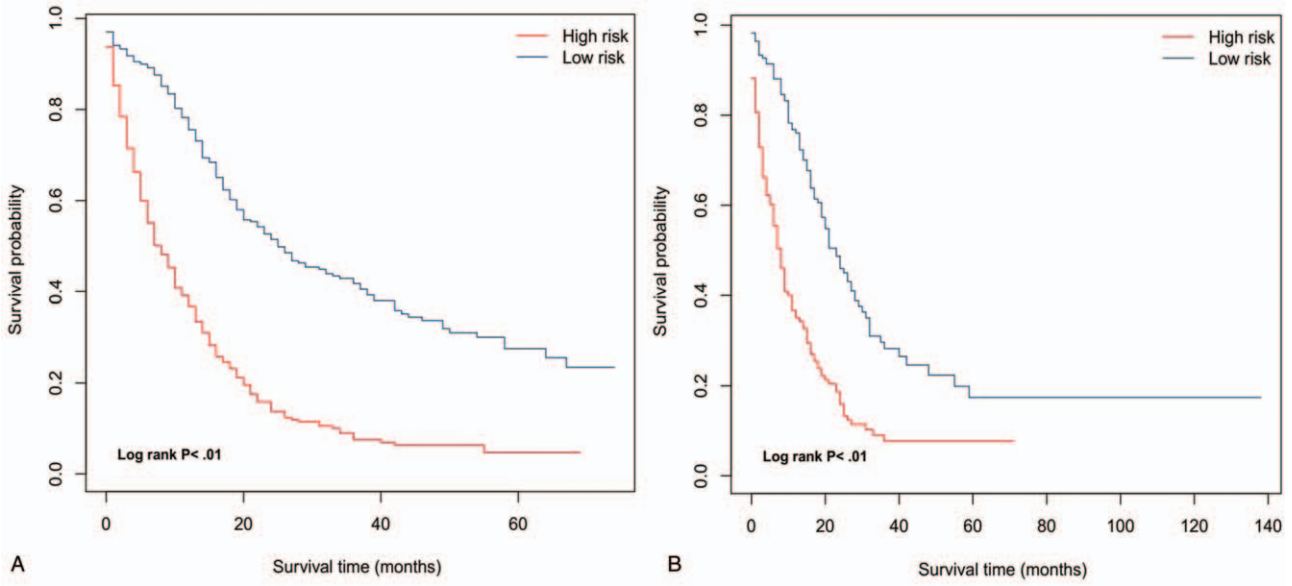

Figure 6. Kaplan–Meier survival curves of DBDC patients with high risk and low risk stratified by the median score of nomogram. (A) Training group. (B) Validation group.

In recently years, an emerging number of studies had found the prognostic significance of marriage in various digestive system malignancies. In patients with gastric cancer, unmarried group, especially widowed ones had an increased risk of cancer mortality.[31] In patients with gallbladder cancer treated with surgical resection, marital status was also an independent prognostic factor for survival.[32] Our study and the research of Chen et al[33] demonstrated the survival benefit associated with married status in CCA. The possible explanations for the high risk of unmarried people in cancer mortality may be as follows. Spouse may encourage patients to seek medical attention for worrying symptoms, which is conducive to early detection and treatment of cancer. The companionship from spouse can provide positive moral support and consequently reduce the psychological stress of patients during treatment. Spouse can provide financially support to patients that is beneficial for patients to have better adherence with prescribed treatments than unmarried patients.

AJCC TNM system is considered the gold standard of staging in oncology. However, the shortcoming of this staging is only include the anatomic extent of the tumor without clinical information, patient factors, and predictive power.[34,35] The nomogram is a graphical presentation of a statistical prediction model that can estimate individualized risk.[36,37] Furthermore, nomograms integrating important prognostic variables into a single model are of higher predictive accuracy and discrimination to predict survival compared to traditional TNM staging systems.[38–40]

In this study, we constructed a nomogram permitting the integration of independent prognostic factors abovementioned with a better predictive performance for predicting OS over the AJCC staging system. Moreover, the nomogram consisting simply of 8 easily accessible variables has the following advantages to estimate individual survival of DBDC patients. First, it is a user-friendly statistical method that can conveniently provide a precise estimation of the survival or a specific outcome to all healthcare providers.[40] Second, it can facilitate the choice of postoperative treatment decision-making such as radiation, chemotherapy, or novel immunotherapy. Third, it can give us assistance to formulate and adjust the follow-up intervals in order to individuality concerned monitor the disease. Fourth, a reliable prognostic tool may be helpful for providing patient's future outcome so that they can make decision about their work, life, money, and therapeutic strategies.

Although our nomogram has good accuracy, we acknowledge several limitations. First, retrospective data and the ethnically homogeneous patient population were the method limitations of our study that can lead to inevitable selection bias. Second, information regarding chemotherapy, which was an important prognostic factor for resected biliary tract cancers,[41] is not available in the SEER database. Third, there are many factors that possible influence the outcomes of our study. The amount and character of comorbidities significantly impact on prognostic outcomes in extrahepatic CCA.[42] Preoperative cholangitis was an independent prognostic factor related to worse prognosis of extrahepatic bile duct cancer.[43] An elevated postoperative CA19–9 level (HR, 7.30; 95% CI 2.04–26.04) was significantly associated with worse OS.[44] Ahn et al[45] suggested the possibility of poor outcomes in extrapancreatic bile duct cancer compared with the intrapancreatic bile duct cancer. However, these clinical information are inaccessible in the SEER database. Finally, although the nomogram showed good performance in the validation group, further validation in additional cohorts is also needed to make the nomogram more reliable. However, it can be challenging to implement a multicenter large-scale prospective clinical study of this rarity disease. Therefore, the nomogram in our study may be interpreted with caution to predicate individual prognosis and facilitate medical decision-making.

5. Conclusion

We developed and validated a satisfactory nomogram for predicting individual prognosis of patients with DBDC. Based

on 8 objective variables, our nomogram improved the ability to predict individual patient survival compared with the current AJCC classification, and showed consistently reliability and clinically practicality for patient counseling and clinical assessments. Further researches are still required to confirm our findings.

Author contributions

Conceptualization: Qin-Si Wan.
Data curation: Ye-Yu Zhao.
Formal analysis: Ye-Yu Zhao.
Methodology: Si-Hai Chen.
Supervision: Qin-Si Wan.
Writing – original draft: Ye-Yu Zhao.
Writing – review & editing: Qin-Si Wan.

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