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ORIGINAL RESEARCH

A nomogram to predict overall survival for biliary tract cancer

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Background: The aim of the study was to develop and validate a nomogram to predict overall survival (OS) in biliary tract cancer (BTC).

Patients and methods: Patients diagnosed with BTC between 2004 and 2014 were selected for the study from the Surveillance, Epidemiology, and End Results (SEER) database. All patients were randomly allocated to 2 sets, the training set (n = 8,869) and the validation set (n = 8,766), for the purposes of validation. The prognostic effects of each variable were examined using univariate and multivariate analyses. Cox regression models and a nomogram were developed based on significant prognostic factors. The predictive and discriminatory capacity of the nomogram was evaluated by Harrell's concordance index (C-index) and calibration plots.

Results: Data of 17,635 patients with BTC were collected from the SEER database. Age; race; tumor site; tumor grade; T, N, and M stage; marital status; and therapy were associated with survival in the multivariate models. All these factors were integrated to construct the nomogram. The nomogram for predicting OS displayed better discrimination power than the tumor-node-metastasis (TNM) stage system 6th edition in the training set and validation set. The calibration curve indicated that the nomogram was able to accurately predict 3- and 5-year OS.

Conclusion: This predictive model has the potential to provide an individualized risk estimate of survival in patients with BTC.

Keywords: nomogram, biliary tract cancer, SEER, prognosis

Introduction

Biliary tract cancer (BTC) comprises a heterogeneous collection of malignant tumors arising from the cells lining the biliary tree, the spectrum of which includes cholangiocarcinoma, ampulla of Vater cancer, and gallbladder cancer.[1,2] Although BTC is a relatively rare malignancy, its incidence and mortality have been increasing globally in recent years.[3,4] A complete surgical resection remains the only curative treatment option, but unfortunately, most of the patients have lost the opportunity for surgery by the time of diagnosis. Moreover, BTC is a relatively chemoresistant and radioresistant disease. Despite improvements in therapeutic strategies, patients with BTC have dismal outcomes, with a 5-year survival rate of 10%–20% and a median survival of < 1 year.[5,6] Therefore, it is essential to estimate the prognosis of the patient with BTC, thus enabling individualization of patient therapy, according to the risk, and facilitating treatment optimization.

At present, the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system has been widely established in patients with BTC. In this

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classification system, patients are stratified according to depth of invasion (T), number of metastasis nodes (N), and presence of distant metastases (M).[7,8] However, other factors such as age, sex, race, tumor size, tumor site, differentiation, marital status, platelet-to-lymphocyte ratio, C-reactive protein, and serum carcinoembryonic antigen level can also influence patient outcomes.[9–11] Therefore, there is an urgent need to develop a staging system considering both patient status and tumor characteristics.

Currently, nomograms, as simple statistical predictive tools, have been widely used in clinical practice for cancer prognosis.[12–14] Compared to the AJCC TNM staging system, nomograms can more accurately estimate survival for individual patients by integrating and illustrating important prognostic factors.[15,16] To date, however, nomograms have rarely been used to assess prognosis of patients with BTC. Using the patient data available in the Surveillance, Epidemiology, and End Results (SEER) database, the purpose of this current study was to develop and validate a new prognosis model for overall survival (OS) based on individual pathologic, demographic, and treatment data.

Patients and methods

Study population

The SEER Program of the US National Cancer Institute is the largest publicly available cancer dataset; SEER is a population-based cancer registry that covers approximately 30% of the US population across several geographic regions.[17] The SEER Program collects tumor-related data, including incidence, prevalence, survival, mortality, and treatment.

Data about patients with a diagnosis of BTC were extracted from the SEER Program (2004–2014), using the SEER*Stat software version 8.3.2. The International Classification of Diseases for Oncology 3rd edition was used to identify BTC using site codes (C22.1, C24.0, C24.1, C23.0, and C23.9) and histology codes (8010, 8020, 8040, 8041, 8070, 8140, 8144, 8160, 8161, 8162, 8260, 8310, 8480, 8490, and 8560). Inclusion criteria for the eligible patients were 1) patients older than 18 years old; 2) no history of malignancy; 3) BTC diagnosed as the first and only cancer; and 4) active follow-up complete with dates and known outcome. Patients were excluded if the number of months survived was unknown or if there were multiple primary cancers. In addition, patients were excluded if they had incomplete clinicopathological information for race, T stage, N stage, M stage, and therapy. To establish and validate the nomogram, all patients were randomly allocated to a training set (n = 8,869) and a validation set (n = 8,766). This research was classified as exempt by the Ethical Committee for Human Research at our institute. SEER research data are publicly available and we received permission from SEER to access the research data (accession number: 10091-Nov 2016).

Several variables, including demographics (age, sex, race); tumor grade; marital status; T, N, and M stage; tumor site (cholangiocarcinoma, ampulla of Vater cancer, and gallbladder cancer); and treatment were examined. The primary endpoint was OS. We used the AJCC TNM staging system 6th edition, and we limited our research to between 2004 and 2014, because it was published in 2004.

Statistical analyses

Data were summarized as frequency (percentage) for categorical variables. Chi-squared test was used to compare categorical variables among different groups of patients. Survival curves were generated using Kaplan–Meier method, and log-rank test was used to compare the difference between the groups. Possible prognostic variables from univariate analyses were further included in a multivariate Cox proportional hazards analysis in order to yield independent prognostic variables. We constructed the prognostic nomogram using significant prognostic factors. The nomogram was validated by measuring discrimination and calibration both internally (training set) and externally (validation set). Bootstraps with 1,000 resamples were used for the development of the nomogram and calibration curve to reduce the overfit bias. Discrimination between observed and predicted outcome was assessed using the concordance Index (C-index).[18] Comparison between the nomogram and the AJCC TNM staging system 6th edition was performed with the rcorrp.cens package in Hmisc in R and were evaluated by the C-index. The calibration curves were used to compare the predicted probability with the cohort observed in the study. All statistical analyses were conducted using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) and the R software version 3.13 (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). *P*-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 17,635 patients with BTC diagnosed between 2004 and 2014 were included in the study. Of those, 8,869 patients were in the training set and 8,766 were in the validation set. Among the eligible patients, 7,910 (44.9%) were males and 9,725 (55.1%) were females. The majority of patients in both sets were elderly (>60 years), married, and white. The most

common tumor site was the bile duct (46.2%). In both sets, most patients received surgery and had T3 stage (36.4%), with no node metastasis (67.3%) and no distant metastasis (74.9%). The demographic features and clinicopathological characteristics are summarized in Table 1.

Nomogram construction

For the training set, data on the patients' sex; age at diagnosis; race; tumor grade; marital status; T, N, and M stage; tumor site; and therapy were collected. With the exception of sex, these variables were significantly associated with OS in univariate analyses (Table 2). After adjusting for other risk factors, the multivariate analysis showed that 9 variables were independent predictive factors, including age; race; tumor grade; marital status; T, N, and M stage; tumor site; and therapy.

A nomogram for predicting 3- and 5-year OS was constructed based on the independent variables in the training set

Table 1 Patient demographics and pathological characteristics

Variables	All patients (n = 1,7635)	Training set (n = 8,869)	Validation set (n = 8,766)
	N (%)	N (%)	N (%)
Sex			
Male	7,910 (44.9)	3,981 (44.9)	3,929 (44.8)
Female	9,725 (55.1)	4,888 (55.1)	4,837 (55.2)
Age (years)			
≤60	4,858 (27.5)	2,410 (27.2)	2,448 (27.9)
>60	12,777 (72.5)	6,459 (72.8)	6,318 (72.1)
Race			
White	13,482 (76.5)	6,808 (76.8)	6,674 (76.1)
Black	1,739 (9.9)	859 (9.7)	880 (10.0)
Other*	2,414 (13.7)	1,202 (13.6)	1,212 (13.8)
Marital status			
Married	9,736 (55.2)	4,965 (56.0)	4,771 (54.4)
Unmarried	7,229 (41.0)	3,586 (40.4)	3,643 (41.6)
Unknown	670 (3.8)	318 (3.6)	352 (4.0)
Tumor site			
Gallbladder	6,395 (36.3)	3,241 (36.5)	3,154 (36.0)
Bile duct	8,152 (46.2)	4,082 (46.0)	4,070 (46.4)
Ampulla of Vater	3,088 (17.5)	1,546 (17.4)	1,542 (17.6)
T stage			
T1	4,672 (26.5)	2,317 (26.1)	2,355 (26.9)
T2	3,845 (21.8)	1,916 (21.6)	1,929 (22.0)
T3	6,427 (36.4)	3,312 (37.3)	3,115 (35.5)
T4	2,691 (15.3)	1,324 (14.9)	1,367 (15.6)
N stage			
N0	11,866 (67.3)	5,939 (67.0)	5,927 (67.6)
N1	5,769 (32.7)	2,930 (33.0)	2,839 (32.4)
M stage			
M0	13,215 (74.9)	6,657 (75.1)	6,559 (74.8)
M1	4,420 (25.1)	2,212 (24.9)	2,208 (25.2)
Grade			
I	1,558 (8.8)	782 (8.8)	776 (8.9)
II	5,340 (30.3)	2,702 (30.5)	2,638 (30.1)
III	4,416 (25.0)	2,242 (25.3)	2,174 (24.8)
IV	176 (1.0)	81 (0.9)	95 (1.1)
Unknown	6,145 (34.8)	3,062 (34.5)	3,083 (35.2)
Therapy			
Surgery	9,921 (56.3)	5,025 (56.7)	4,896 (55.9)
No surgery	7,714 (43.7)	3,844 (43.3)	3,870 (44.1)

Note: *Other includes American Indian/Alaska native, Asian/Pacific Islander, and unknown.

Table 2 Univariate and multivariate analyses of overall survival in the training set

Variables	Univariate analysis	Multivariate analysis	
	P-value	HR (95% CI)	*P*-value
Sex	0.766		NI
Male			
Female			
Age (years)	< 0.001		
≤60		Reference	
>60		1.475 (1.393–1.563)	< 0.001
Race	< 0.001		
White		Reference	
Black		1.132 (1.041–1.230)	0.004
Other*		0.907 (0.843–0.977)	0.010
Marital status	< 0.001		
Married		Reference	
Unmarried		1.250 (1.187–1.317)	< 0.001
Unknown		0.988 (0.861–1.134)	0.863
Tumor site	< 0.001		
Gallbladder		Reference	
Bile duct		0.813 (0.765–0.864)	< 0.001
Ampulla of Vater		0.570 (0.525–0.618)	< 0.001
T stage	< 0.001		
T1		Reference	
T2		0.926 (0.854–1.003)	0.061
T3		1.315 (1.232–1.403)	< 0.001
T4		1.313 (1.211–1.424)	< 0.001
N stage	< 0.001		
N0		Reference	
N1		1.080 (1.023–1.141)	< 0.001
M stage	< 0.001		
M0		Reference	
M1		1.573 (1.480–1.672)	< 0.001
Grade	< 0.001		
I		Reference	
II		1.312 (1.178–1.461)	< 0.001
III		1.803 (1.617–2.010)	< 0.001
IV		1.950 (1.500–2.536)	< 0.001
Unknown		1.542 (1.380–1.724)	< 0.001
Therapy	< 0.001		
Surgery		Reference	
No surgery		2.481 (2.314–2.660)	< 0.001

Note: *Other includes American Indian/Alaska native, Asian/Pacific Islander, and unknown.

Abbreviation: NI, not included in the multivariate survival analysis.

(Figure 1). This model revealed that therapy contributed most to prognosis, followed by the tumor location, M stage, T stage, age, grade, marital status, N stage, and race. By adding the scores of each selected variable, the likelihood of survival of the individual patient can be easily calculated.

Nomogram validation

Internal validation via the training set demonstrated that the C-index for the nomogram to predict OS was 0.715, which was in excellent agreement with actual OS. Likewise, the C-index for prediction of OS in the external validation was also 0.710. As shown in Figures 2 and 3, there is an excellent agreement between prediction by the nomogram and actual observation in both the training and validation sets. In addition, we compared the discrimination of the nomogram with that of the AJCC TNM staging system 6th edition in the training set. The C-index of the nomogram for predicting OS was 0.715, which was significantly higher than the TNM staging (0.646). Moreover, the nomogram established in this study also displayed more powerful efficiency of discrimination for OS prediction in the validation set compared with the TNM staging (C-index = 0.710 vs 0.652). The results suggest that the nomogram discrimination for OS prediction was superior to that of the AJCC TNM staging.

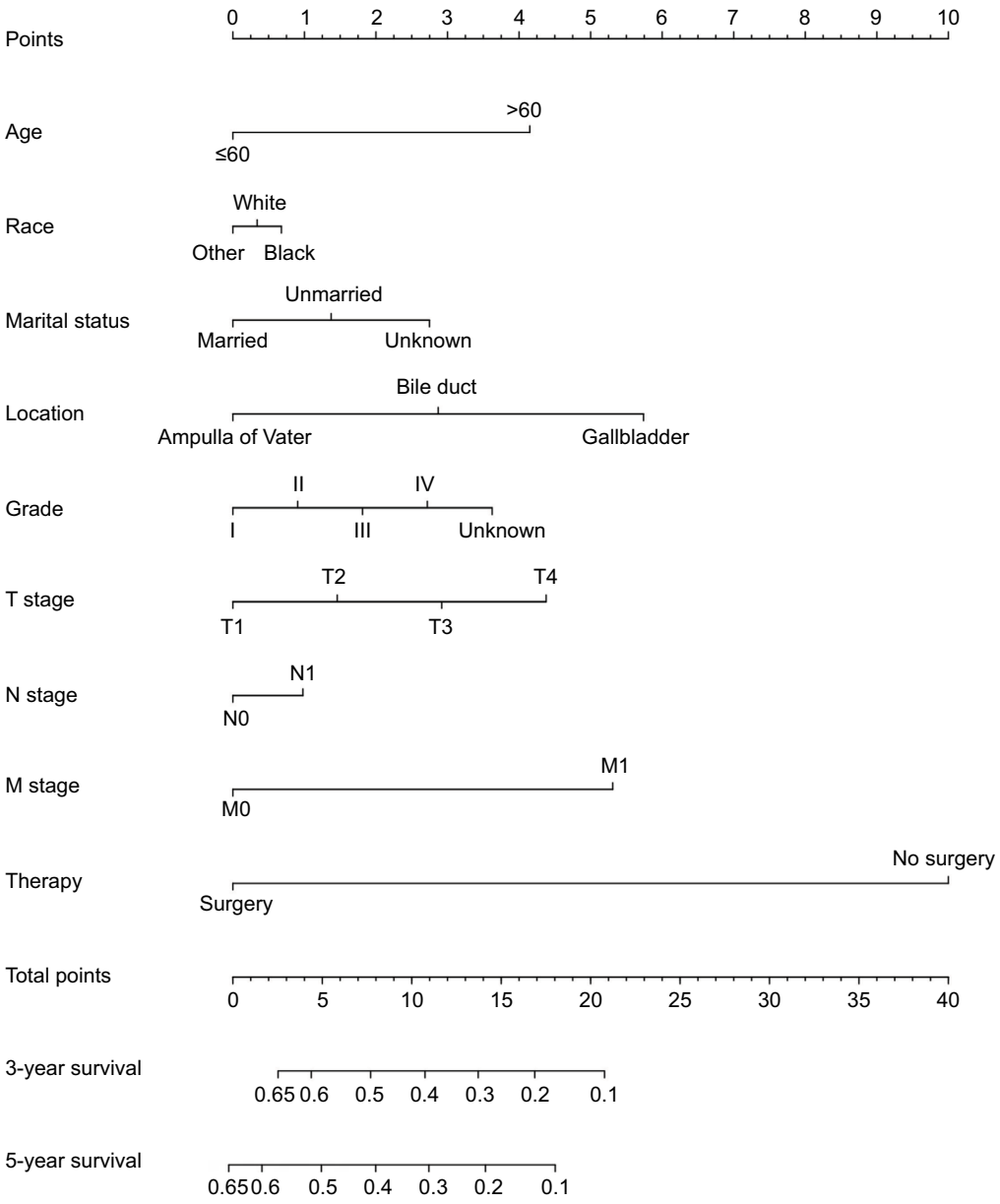

Figure 1 Nomogram for predicting 3-year and 5-year overall survival.

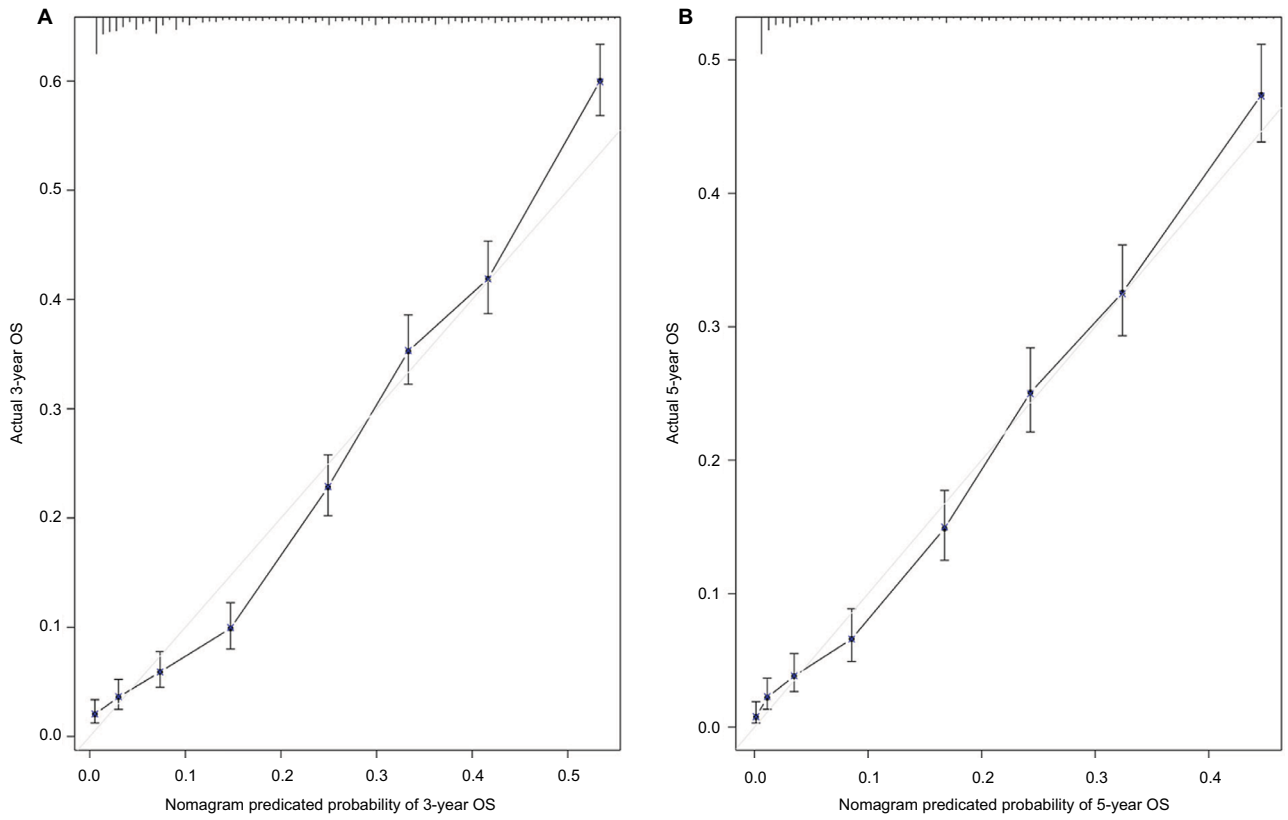

Figure 2 Internal calibration plot. (**A**) 3-Year and (**B**) 5-year overall survival (OS) nomogram calibration curves.

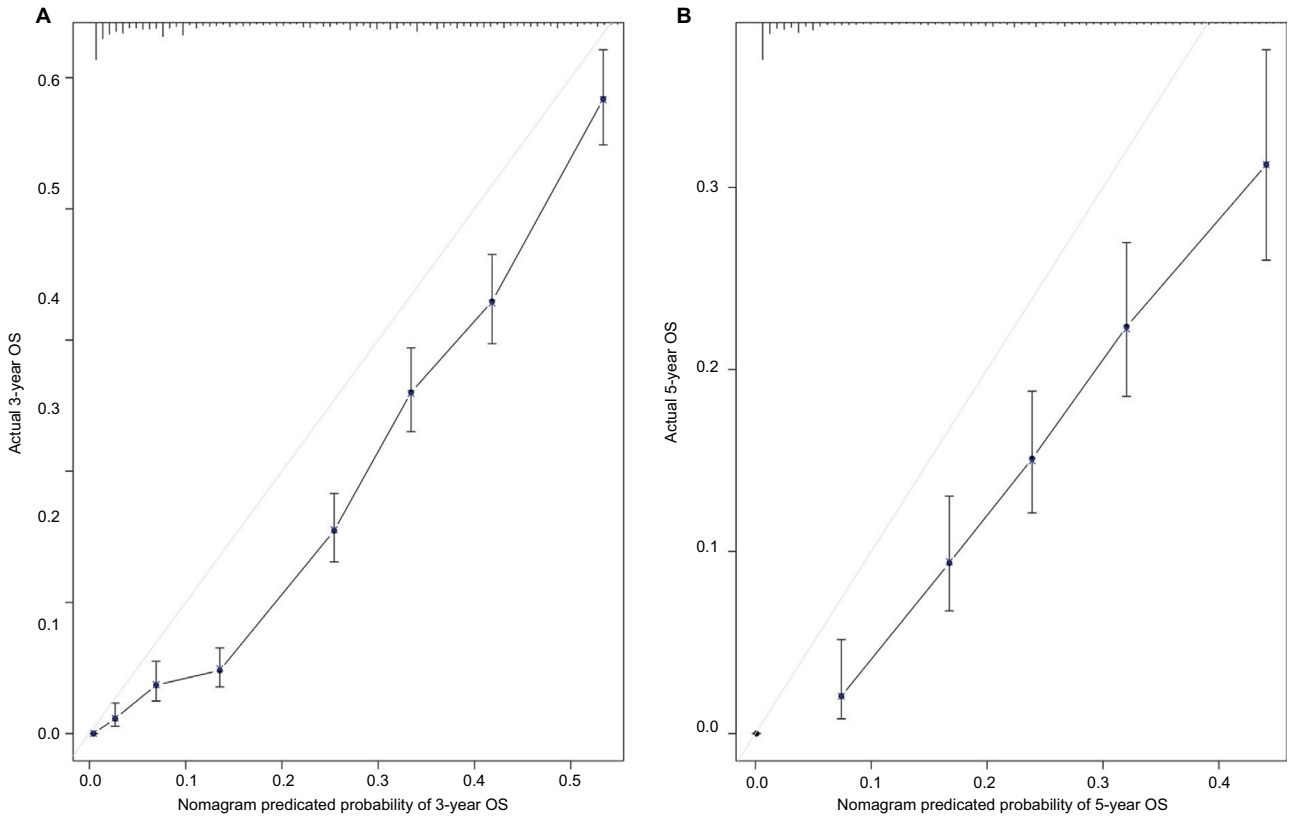

Figure 3 External calibration plot. (**A**) 3-Year and (**B**) 5-year overall survival (OS) nomogram calibration curves.

Discussion

In the present study, a total of 17,635 patients with BTC from the SEER database were analyzed. Based on individual pathologic, demographic, and treatment data, we first developed and validated a new prognosis model to predict OS. The nomogram showed good discrimination in both internal and external validation. In addition, the nomogram displayed more powerful predictive ability than the AJCC TNM staging system 6th edition. Moreover, the calibration plots indicated that the nomogram was able to accurately predict OS.

Nomograms are an important component of modern medical decision-making.[19] The nomogram is a graphical presentation of a statistical prediction model.[20,21] Thus, the parameters to consider should be easily available and measurable. Accumulating evidence has shown that the nomogram shows a better predictive ability than the classic AJCC TNM staging system in multiple malignancies, and thus they have been identified as an alternative or even a new standard.[22–24] Moreover, the nomogram enables individualized predictions that clinicians can use for assessing their patients for participation in clinical trials. Several studies have documented the predictive ability of nomograms regarding gallbladder cancer, and perihilar and intrahepatic cholangiocarcinoma.[25–27] Taken together, nomograms can accurately display the prognosis of patients with BTC. However, those nomograms were based on limited numbers of cases or lacked external validation. As a result, the universal applicability of nomograms to BTC required further validation, with the added benefit that the additional data included would improve the accuracy of the nomogram. To our knowledge, this is the first population-based analysis for developing a new prognostic nomogram for BTC based on a large population from the SEER database. Because this population was racially diverse and included patients from a number of departments, this nomogram may be suitable for universal application.

The model consisted of 9 independent prognostic factors from routine clinical practice: age; race; tumor site; T, N, and M stage; tumor grade; marital status; and therapy. Age was identified as an important prognostic marker for OS in several studies,[28–30] although the precise mechanism remains unclear. Our results indicated that patients older than 60 years have a lower OS than younger patients. Evidence also shows that the risk of mortality of black patients with BTC is significantly higher than that of other patients, and black patients are associated with poor prognosis.[31] Our study of racial differences among all BTC patients showed that the OS of black patients is lowest.

Compared to the widely used TNM staging, our model is not only easy to use but it also provides a quantitative prognosis for individual patients. For instance, consider 2 patients with BTC (T2N1M0, 2.5 points): case A) A patient aged 64 years (4.2 points), with tumor location of the gallbladder (5.75 points), grade III (1.75 points) and case B) A patient aged 58 years (0 points), with tumor location of the bile duct (2.8 points), grade I (0 point). Using our nomogram, the 2 patients have 3-year OS probabilities of 27% and 48%, respectively. By contrast, both patients would be considered to be stage II according to the traditional TNM staging system, which indicates identical outcomes. In addition, the clinician may recommend certain instructions based on the total score. For example, patients with well-differentiated histology might receive surgery because of their good prognosis. On the other hand, those with poorly differentiated histology have low life expectancy, and so palliative chemotherapy could be chosen. However, the selection of patients based solely on the TNM staging may be ambiguous and the physicians have to rely on their clinical experience. Therefore, using the nomogram we constructed, which consists of a large number of clinicopathological parameters, doctors will be better able to select patients with higher survival rates who will be more likely to benefit from palliative resection. Our study has several advantages over earlier ones. In contrast to earlier BTC models, our nomogram was constructed based on a large, diverse, population-based cohort that improves the accuracy of nomograms. The presentation and validity of the nomogram were confirmed by discrimination and calibration. Moreover, the present study utilized 9 easily accessible clinical variables that reflect the patient status and tumor characteristics, thereby providing clinically relevant information about BTC.

This study has several limitations that should be noted. First, the calibration was suboptimal in the external validation set, while the discrimination was good. Second, some important clinicopathological parameters, such as surgical margin status and vascular invasion, were unavailable in the SEER database. In addition, data for radiotherapy or chemotherapy were also unavailable. Third, the information of serum carbohydrate antigen 19-9, the most widely used tumor biomarker for BTC, was unavailable due to missing data.

Conclusion

The proposed nomogram predicts OS for patients with BTC based on 9 variables. The C-index was good in both the internal and external validation. The predictive model has the potential to inform patients, guide adjuvant treatment decisions, and provide individualized survival risk assessments for BTC patients.

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Disclosure

The authors declare no conflicts of interest in this work.

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