

Nomogram to Predict the Occurrence and Prognosis of Distant Metastasis in T1N0 Colon Cancer: A SEER Data-Based Study

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Purpose: Distant metastasis (DM) is relatively rare in T1 colon cancer (CC) patients, especially in those with negative lymph node metastasis. The aim of this study was to explore the main clinical factors and build nomogram for predicting the occurrence and prognosis of DM in T1N0 colon cancer patients.

Methods: Patients with T1N0 stage CC were collected from the Surveillance, Epidemiology, and End Result (SEER) database. All patients were divided into development and validation cohorts with the 3:1 ratio. Logistic regressions were performed to analyze the clinical risk factors for DM. Cox regression model was used to identify potential prognostic factors for patients with DM. The performance of nomogram was evaluated by concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curves and decision curve analyses (DCAs). Based on cancer-specific survival (CSS), Kaplan–Meier curves were generated and analyzed using Log rank tests.

Results: A total of 6770 patients were enrolled in this study, including 428 patients (6.3%) with DM. Age, size, grade, CEA were independent risk factors associated with DM. Age, grade, CEA, surgery and chemotherapy were independent prognostic factors for CSS. Nomograms were applied and C-index, calibration curves, ROC curves and DCA curves proved good discrimination, calibration and clinical practicability of the nomogram in predicting the occurrence and prognosis of DM in T1N0 CC patients. In the DM nomogram, the AUCs for development and validation cohort were 0.901 (95% CI = 0.879–0.922) and 0.899 (95% CI=0.865–0.940), respectively. The calibration curves (development cohort: S: $p = 0.712$; validation cohort: S: $p = 0.681$) showed the relatively satisfactory prediction accuracy. Similarly, the AUCs of the nomogram at 1-, 2-, and 3-year were 0.763 (95% CI=0.744–0.782), 0.794 (95% CI=0.775–0.813), and 0.822 (95% CI=0.803–0.841) for the development cohort, and 0.785 (95% CI=0.754–0.816), 0.748 (95% CI=0.717–0.779) and 0.896 (95% CI=0.865–0.927) for the validation cohort in the CSS nomogram. The C-indices of the development and validation cohort were 0.718 (95% CI=0.639–0.737) and 0.712 (95% CI=0.681–0.743).

Conclusion: The population-based nomogram could help clinicians predict the occurrence and prognosis of DM in T1N0 CC patients and provide a reference to perform appropriate metastatic screening plans and rational therapeutic options for the special population.

Keywords: T1N0 colon cancer, distant metastasis, nomogram, SEER

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Introduction

Colorectal cancer (CRC) is one of the most common cancers, causing a large number of deaths every year and forming a huge burden on both family and society. In 2019, CRC was estimated to be the highest cancer incidence and death rate in the United

States.¹ In general, surgical resection, endoscopic therapy, and neoadjuvant therapy have become the main treatment methods for different stages of CRC.^{2–5} With the widespread application of endoscopic screening, more CC patients have been identified at an early stage in recent years. According to the American Joint Committee on Cancer (AJCC) staging manual, T1 CC refers to submucosal invasive carcinoma. The 2019 National Comprehensive Cancer Network (NCCN) recommended that endoscopic therapy is considered as the preferred treatment strategy for T1N0 CC patients without DM, which is associated with higher quality of life and less postoperative morbidity compared with extensive surgical resection.⁶ Approximately 10% of T1 CC are stage III or IV after primary endoscopic resection based on population studies.^{7–9} Notwithstanding that the risk of DM in CC patients is relatively rare, the open question that “whether the T1N0 CC patient has developed a metastatic disease” should also be considered in the clinical management for this special population without doubt. However, in some cases, because of the limited manifestations for patients with early-stage CC, although simultaneous DM has occurred in their bodies, they might fail to be diagnosed as stage IV disease and subsequently receive an unreasonable endoscopic therapy. Additionally, although the effects of some multidisciplinary therapeutic strategies for stage IV CC patients have been explored by many scholars in recent years, there is still no consensus on the optimal treatment for these patients. As we know, an accurate prognostic assessment is of vital significance for clinicians to develop personalized treatments for patients. Hence, a further prognostic model is imminently needing to be explored to provide a potential reference for the better treatment of T1N0 CC patients.

Therefore, in the current study, we built a nomogram to predict the probability of T1N0 patients developing DM and also established a nomogram to determine prognosis of T1N0M1 patients using the Surveillance, Epidemiology, and End Result (SEER) database.

Methods

Patients

The data of patients with T1N0Mx CC in the SEER database between January 2004 and December 2015 were extracted with the SEER*Stat software (version 8.3.8; www.seer.cancer.gov) using a private ID (account number: 25213-Nov2019), and treatment data were acquired from SEER custom data via further application.

Informed consent was not required because the SEER database is publicly available.

Inclusion criteria included the following: 1) The patient was diagnosed as T1N0 colon cancer; 2) aged ≥ 18 years; 3) patients with complete records of cancer-specific survival months; 4) colon cancer was the only primary malignancy. Exclusion criteria included the following: 1) patients underwent neoadjuvant therapy; 2) patients with unknown race, histological type, grade, T stage, N stage, tumor size and CEA level and 3) patients without complete follow-up. In SEER, tumor information is confirmed according to histological examination after endoscopic therapy or surgery. For those who did not undergo surgery therapy, information were defined according to clinical staging.

Variables

In this study, the following variables were selected from the SEER database: patient ID, sex, age at diagnosis, TNM stage, tumor size, tumor site, histology, grade, CEA level, surgery, chemotherapy, CCS.

According to our study, age was regrouped into <40, 40–59, 60–79 and ≥ 80 years; sex was classified as male or female; race was recorded as black, white, or other; tumor size was divided into three groups; ≤ 3 cm, ≤ 5 cm ($3 \text{ cm} < \text{tumor size} \leq 5 \text{ cm}$), $> 5 \text{ cm}$. The tumor site was grouped into right-sided colon (cecum, ascending colon, hepatic flexure and transverse colon) and left-sided colon (splenic flexure, descending colon and sigmoid colon). The histology variable was classified as “adenocarcinoma”, “mucinous adenocarcinoma” or “other”; the grade variable was classified as “well differentiated”, “moderately differentiated”, “poorly differentiated” and “undifferentiated” and the CEA level was classified as “positive” ($\geq 5 \text{ ng/mL}$) and “negative” ($< 5 \text{ ng/mL}$). Chemotherapy was classified as “yes” or “no”; surgery was classified as “yes” or “no” according to the SEER database. CSS was defined as the time from diagnosis to the date of death due to CC.

Statistical Analysis

All the statistical analyses were calculated in statistical software package SPSS 22.0 (IBM Corp, Armonk, NY, USA) and R software (version 3.6.1, <https://www.r-project.org/>). In this study, in order to ensure the accuracy of the nomogram, patients were randomly (3:1 ratio) divided into development and validation cohorts. Univariate and multivariate Logistic regression analyses were performed to determine the risk factors for DM in T1N0Mx patients and Cox regression models were utilized

to analyze prognostic factors in T1N0 patients with DM. Nomogram was constructed based on the results of multivariate regression, and its performance was further evaluated by C index, calibration and AUC. Calibration is performed graphically by plotting the correlation between predicted probabilities and actual results. In addition, clinical impact curves were drawn based on DCA to help us more intuitively understand the significant value of the nomogram. Besides, with the X-tile program,¹⁰ T0N0M1 patients were classified into low-risk and high-risk groups according to their total scores derived from the survival nomogram. Kaplan–Meier curves were generated and analyzed using Log rank tests. The difference was considered statistically significant for a two-sided $P < 0.05$ and the calibration chart is considered meaningful for a two-sided $P > 0.1$.

Results

Patient Characteristics

According to the screening criteria, a total of 6770 T1N0Mx patients were in the study predicting DM and 428 T1N0 patients with DM were in the study predicting CSS. In all T1N0 patients, most proportions were found in 60–79 years old, white, male, right colon, tumor size ≤ 3 cm, moderately differentiated, adenocarcinoma, CEA negative and absence of DM. And in patients with DM, most cases were found to be associated with 60–79 years old, white, male, right colon, $3 <$ tumor size ≤ 5 cm, moderately differentiated, adenocarcinoma, CEA positive, absence of surgery and presence of chemotherapy. The baseline characteristics of patients after 3:1 ratio randomly stratification were calculated in Tables 1 and 2.

Construction and Validation of Nomogram to Predict DM Probability

In order to further explore the risk factors for DM in T1N0 patients, univariate and multivariate logistic regression analyses were performed to determine the independent risk factors for DM. In univariate analysis, the candidate predictors for the model were age, race, sex, tumor size, tumor site, grade, histology and CEA. All the predictors except for sex, tumor site and histology were significantly different between subgroups in the development cohorts, which were then further analyzed by multivariate logistic regression model. And the results indicated that age (OR = 0.647, 95% CI = 0.243–1.719 for 40–59 years old, $P = 0.382$; OR = 0.332, 95% CI = 0.126–0.874 for 60–79 years

Table 1 Baseline Clinical Characteristics of T1N0 Patients in Our Study

Characteristics	Development Cohort (n = 5077)	Validation Cohort (n = 1693)	P-value
Age (years), n(%)			0.076
<40	67(1.3)	16(0.9)	
40–59	1374(27.1)	419(24.7)	
60–79	2770(54.6)	980(57.9)	
≥ 80	866(17.1)	278(16.4)	
Race, n(%)			0.869
Black	655(12.9)	210(12.4)	
White	3921(77.2)	1315(77.7)	
Other	501(9.9)	168(9.9)	
Sex, n(%)			0.528
Male	2609(51.4)	885(52.3)	
Female	2468(48.6)	808(47.7)	
Tumor site, n(%)			0.663
Right colon	2830(55.7)	954(56.3)	
Left colon	2247(44.3)	739(43.7)	
Tumor size (cm), n(%)			0.283
≤ 3	4066(80.1)	1344(79.4)	
≤ 5	694(13.7)	254(15.0)	
> 5	317(6.2)	95(5.6)	
Grade, n(%)			0.175
Well differentiated	1054(20.8)	347(20.5)	
Moderately differentiated	3632(71.5)	1206(71.2)	
Poorly differentiated	341(6.7)	131(7.7)	
Undifferentiated	50(1.0)	9(0.5)	
Histology, n(%)			0.752
Adenocarcinoma	4896(96.4)	1632(96.4)	
Mucinous	166(3.3)	54(3.2)	
Other	15(0.3)	7(0.4)	
CEA, n(%)			0.205
Positive	987(19.4)	313(18.5)	
Negative	4090(80.6)	1380(81.5)	
Distant metastasis, n(%)			0.567
Yes	316(6.2)	112(6.6)	
No	4761(93.8)	1581(93.4)	

old, $P = 0.026$; OR = 0.202, 95% CI = 0.073–0.557, $P = 0.002$ for ≥ 80 years old; using < 40 years old as the reference), tumor size (OR = 0.092, 95% CI = 0.064–

Table 2 Baseline Clinical Characteristics of T1N0 Patients with DM in Our Study

Characteristics	Development Cohort (n = 321)	Validation Cohort (n = 107)	P-value
Age (years), n (%)			0.080
<40	9(2.8)	3(2.8)	
40–59	110(34.3)	43(40.2)	
60–79	149(46.4)	54(50.5)	
≥80	53(16.5)	7(6.5)	
Race, n(%)			0.335
Black	70(21.8)	18(16.8)	
White	224(69.8)	76(71.0)	
Other	27(8.4)	13(12.1)	
Sex, n(%)			0.911
Male	175(54.5)	59(55.1)	
Female	146(45.5)	48(44.9)	
Tumor site, n(%)			0.615
Right colon	165(51.4)	58(54.2)	
Left colon	156(48.6)	49(45.8)	
Tumor size (cm), n(%)			0.169
≤3	110(34.3)	30(28.0)	
≤5	120(37.4)	51(47.7)	
>5	91(28.3)	26(24.3)	
Grade, n(%)			0.483
Well differentiated	32(10.0)	7(6.5)	
Moderately differentiated	230(71.7)	84(78.5)	
Poorly differentiated	52(16.2)	15(14.0)	
Undifferentiated	7(2.2)	1(0.9)	
Histology, n(%)			0.590
Adenocarcinoma	302(94.1)	98(91.6)	
Mucinous	15(4.7)	7(6.5)	
Other	4(1.2)	2(1.9)	
CEA, n(%)			1.000
Positive	261(81.3)	87(81.3)	
Negative	60(18.7)	20(18.7)	
Surgery, n(%)			0.160
Yes	68(21.2)	16(15.0)	
No	253(78.8)	91(85.0)	
Chemotherapy, n(%)			0.418
Yes	199(62.0)	71(66.4)	
No	122(38.0)	36(33.6)	

0.134 for 3cm< tumor size ≤5 cm, $P < 0.001$; OR = 0.654, 95% CI = 0.446–0.958 for tumor size >5cm, $P = 0.029$; using tumor size ≤3 cm as the reference), grade (OR = 2.323, 95% CI = 1.511–3.574 for moderately differentiated, $P < 0.001$; OR = 5.686, 95% CI = 3.236–9.99 for poorly differentiated, $P < 0.001$; OR = 7.159, 95% CI = 2.462–20.821 for undifferentiated, $P < 0.001$; using well differentiated as the reference), CEA level (OR = 0.054, 95% CI = 0.040–0.074 for CEA negative, $P < 0.001$, using CEA positive as the reference) were independent risk factors in predicting the occurrence of DM (Table 3).

Based on the independent risk factors in the multivariate analysis, we construct a nomogram to predict DM in T1N0Mx patients (Figure 1). The AUCs for the development and validation cohorts were 0.901 (95% CI = 0.879–0.922) and 0.899 (95% CI = 0.865–0.940), respectively (Figure 2). The calibration curves (development cohort: S: $p = 0.712$; validation cohort: S: $p = 0.681$) showed the relatively satisfactory prediction accuracy of the nomogram (Figure 3). In addition, the DCA curve also indicated good clinical practicability in both cohorts (Figure 4).

Construction and Validation of Nomogram to Predict CSS in T1N0 Patients with DM

After analyzing the risk factors of DM in T1N0Mx patients, we also explored CSS in DM patients using Kaplan–Meier method and Cox regression model. Univariate analysis revealed that sex and grade were not important factors for CSS in DM patients. The risk factors in the univariate analysis were further analyzed by Cox multivariate regression model. And the results indicated that age (HR = 0.587, 95% CI = 0.272–11.264 for <40 years old, $P = 0.174$; HR = 0.439, 95% CI = 0.296–0.651 for 40–59 years old, $P < 0.001$; HR = 0.603, 95% CI = 0.418–0.871 for 60–79 years old, $P = 0.007$; using ≥80 years old as the reference), histology (HR = 1.487, 95% CI = 0.794–2.784 for mucinous, $P = 0.215$; HR = 4.682, 95% CI = 1.672–13.115 for other, $P = 0.003$; using adenocarcinoma as the reference), surgery (HR = 3.450, 95% CI = 2.313–5.145 for no, $P < 0.001$; using yes as the reference), chemotherapy (HR = 2.032, 95% CI = 1.512–2731 for no, $P < 0.001$; using yes as the reference), CEA level (HR = 0.454, 95% CI = 0.293–0.703 for CEA negative, $P < 0.001$, using CEA positive as

Table 3 Logistic Regression Analysis of the Risk Factors for DM in T1N0 Patients

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR [95% CI]	P-value	OR [95% CI]	P-value
Age (years)				
<40	Ref		Ref	
40–59	0.600[0.290–1.241]	0.168	0.647[0.243–1.719]	0.382
60–79	0.359[0.174–0.738]	0.005	0.332[0.126–0.874]	0.026
≥80	0.345[0.161–0.741]	0.006	0.202[0.073–0.557]	0.002
Race				
Black	Ref		Ref	
White	0.547[0.410–0.731]	<0.001	0.880[0.612–1.265]	0.489
Other	0.537[0.339–0.851]	0.008	0.709[0.403–1.248]	0.223
Sex				
Male	Ref			
Female	0.866[0.689–1.089]	0.218		
Tumor site				
Right colon	Ref			
Left colon	1.245[0.991–1.564]	0.059		
Tumor size (cm)				
≤3	Ref		Ref	
≤5	8.543[6.469–11.282]	<0.001	0.092[0.064–0.134]	<0.001
>5	16.466[12.043–22.513]	<0.001	0.654[0.446–0.958]	0.029
Grade				
Well differentiated	Ref		Ref	
Moderately differentiated	2.149[1.475–3.132]	<0.001	2.323[1.511–3.574]	<0.001
Poorly differentiated	5.232[3.284–8.336]	<0.001	5.686[3.236–9.99.]	<0.001
Undifferentiated	5.199[2.172–12.446]	<0.001	7.159[2.462–20.821]	<0.001
Histology				
Adenocarcinoma	Ref			
Mucinous	1.185[0.651–2.157]	0.578		
Other	2.340[0.526–10.418]	0.264		
CEA				
Positive	Ref		Ref	
Negative	0.043[0.033–0.058]	<0.001	0.054[0.040–0.074]	<0.001

the reference) were independent prognosticators in predicting CSS with DM patients (Table 4).

We constructed a nomogram to predict 1-, 2- and 3-year survival in DM patients with T1N0 colon cancer, incorporating age, histology, CEA, surgery and chemotherapy (Figure 5). The C-indices of the development and validation cohort were 0.718 (95% CI=0.639–0.737) and 0.712 (95% CI=0.681–0.743). The area under the ROC curves of the CSS nomogram were shown in Figure 6. The AUCs of the nomogram at 1-, 2-, and 3-year were 0.763 (95% CI=0.744–0.782), 0.794 (95% CI=0.775–0.813), and

0.822 (95% CI=0.803–0.841) for the development cohort, and 0.785 (95% CI=0.754–0.816), 0.748 (95% CI=0.717–0.779) and 0.896 (95% CI=0.865–0.927) for the validation cohort. The calibration plot showed a satisfactory predictive accuracy between 1-, 2-, and 3-year predicted CSS and observed CSS in both cohorts (Figure 7). In addition, clinical impact curves were drawn based on DCA to help us more intuitively understand the significant value of the nomogram model (Figure 8).

Using the nomogram derived scores, all DM patients were classified into two subgroup low-risk (risk score

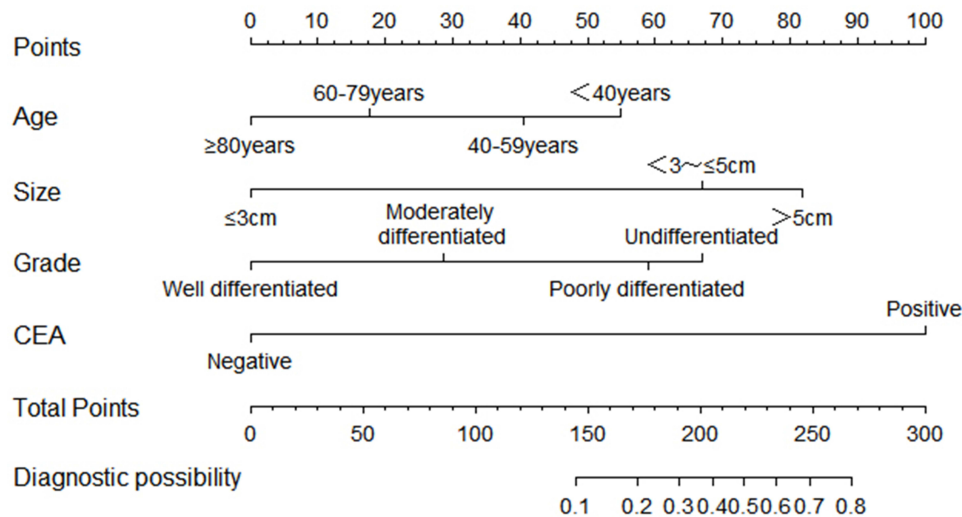


Figure 1 Nomogram for predicting the probability of distant metastasis.

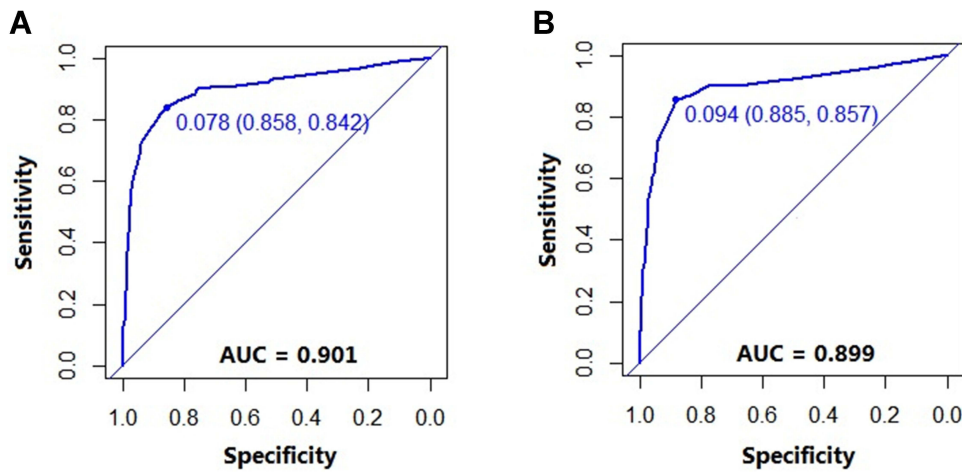


Figure 2 The ROC curves of nomogram for predicting DM in the development cohort (A) and validation cohort (B).

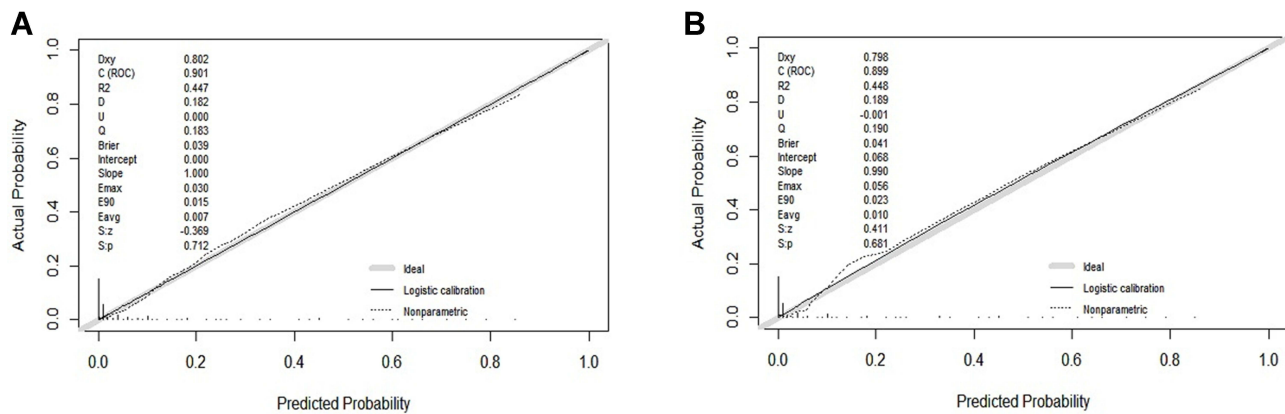


Figure 3 The calibration curves of the nomogram for predicting DM in the development cohort (A) and validation cohort (B).

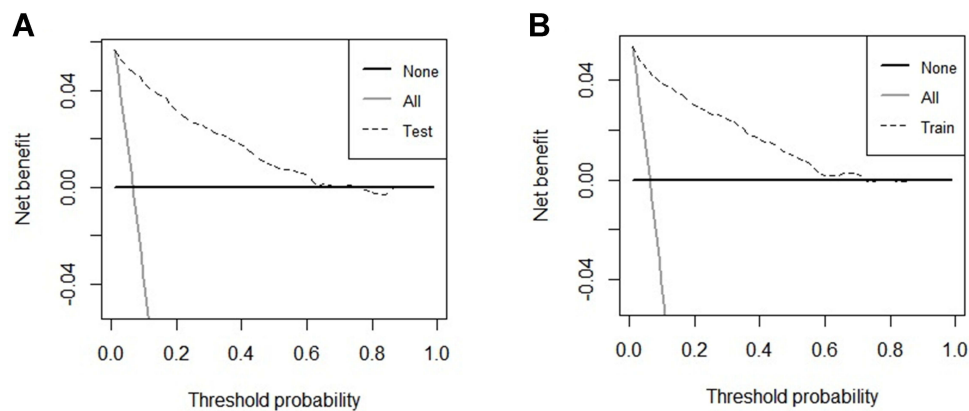


Figure 4 The DCA curves of the nomogram for predicting the occurrence of DM in the development cohort (**A**) and validation cohort (**B**).

≤ 171) and high-risk groups (risk score > 171) by the X-tile program (Figure 9). And we found there were significant differences in Kaplan–Meier curves between the high-risk and low-risk groups in the development cohort ($P < 0.001$) and the validation cohort ($P < 0.001$) (Figure 10).

Discussion

CC is one of the most common cancers worldwide and the major causes of cancer-related mortality.^{1,11} Thanks to the prevalence of screening programs and advancement of endoscopic techniques, more and more CC patients are diagnosed at an early stage (T1).¹² About 90% of T1 CC patients have been diagnosed at stage I, and endoscopic resection of the lesion is an attractive therapeutic strategy for these patients, which allows comparable prognosis to surgery less surgical complications, better functional recovery and improved quality of life. However, it is important to note that DM is the key component in considering reasonable treatment of T1N0 patients. To our knowledge, our study is the first to identify the major clinical risk indicators and prognosticators for DM in patients with T1N0 CC.

In the current study, we found age, tumor size, tumor grade and CEA level were associated with the development of DM in T1N0 patients. Compared with elderly patients, young patients are related to more aggressive histopathologic features and advanced stage, so age has been always deemed as an important factor of metastasis.¹³ Mostly, large tumor size is usually associated with stronger potential to develop metastasis.¹⁴ Poor histological grade is linked to more invasive ability of tumor cells and would be prone to DM. Luo et al revealed that CEA level is a significant serum tumor marker of metastasis in T1 patients.¹⁵ Subsequently, the

aforementioned factors were used to build the nomogram to predict the probability of DM. The AUCs were 0.901 and 0.899 for the development and validation cohorts, respectively. The clinical power was also proved by the calibration and DCA curves in the two cohorts. Previously, some studies have analyzed the risk of lymph node metastasis in T1 CC in order to conduct a reasonable endoscopic treatment.⁶ But DM in this special population has been described rarely. T1 stage tumors seldom present with DM, especially in the absence of lymph node metastasis. CC could metastasize in several ways, including lymphatic and hematology. The latter is a pattern in which tumor cells invade blood vessels and travel directly to distant organs. Patients with and without metastasis (stage I and stage IV) have completely different treatment concept and dramatically varied prognosis. Stage I patients can be given priority to endoscopic therapy or surgical treatment to achieve radical effect. The treatment of stage IV patients is currently controversial, with some people advocating palliative surgery first followed by adjuvant chemotherapy and others say stage IV patients have lost the chance of surgery and are being treated only with chemotherapy. Most DM are detected by routine imaging studies, such as computed tomography, and small lesions can be easily missed. For this particular group of patients, enhanced computed tomography or positron emission tomography computed tomography (PET-CT) are more reliable method for screening the DM in CC, especially in detecting micro metastases. However, the cost and availability limit their application. Therefore, we constructed an economical and convenient nomogram to help clinicians early identify T1N0 patients at high risk for distant metastasis and conduct targeted imaging examinations

Table 4 COX Regression Analysis of the Prognostic Factors for CSS in T1N0 Patients with DM

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	P-value	HR [95% CI]	P-value
Age (years)				
<40	0.578[0.272–1.229]	0.154	0.587[0.272–1.264]	0.174
40–59	0.438[0.305–0.630]	<0.001	0.439[0.296–0.651]	<0.001
60–79	0.535[0.377–0.760]	< 0.001	0.603[0.418–0.871]	0.007
≥80	Ref		Ref	
Race				
Black	Ref		Ref	
White	0.669[0.496–0.903]	0.009	0.801[0.584–1.098]	0.168
Other	0.585[0.348–0.982]	0.043	0.645[0.377–1.102]	0.109
Sex				
Male	Ref		Ref	
Female	0.786[0.610–1.012]	0.061		
Tumor site				
Right colon	Ref		Ref	
Left colon	0.737[0.573–0.948]	0.017	0.857[0.659–1.114]	0.249
Tumor size (cm)				
≤3	Ref		Ref	
≤5	1.588[1.172–2.154]	0.003	1.101[0.789–1.536]	0.573
>5	1.978[1.420–2.756]	<0.001	1.366[0.960–1.945]	0.083
Grade				
Well differentiated	Ref			
Moderately differentiated	1.168[0.741–1.840]	0.504		
Poorly differentiated	1.587[0.934–2.694]	0.088		
Undifferentiated	1.709[0.643–4.541]	0.282		
Histology				
Adenocarcinoma	Ref		Ref	
Mucinous	1.590[0.866–2.917]	0.135	1.487[0.794–2.784]	0.215
Other	4.846[1.785–13.153]	0.002	4.682[1.672–13.115]	0.003
CEA				
Positive	Ref		Ref	
Negative	0.428[0.287–0.638]	<0.001	0.454[0.293–0.703]	<0.001
Surgery				
Yes	Ref		Ref	
No	3.671[2.543–5.299]	<0.001	3.450[2.313–5.145]	<0.001
Chemotherapy				
Yes	Ref		Ref	
No	1.341[1.027–1.751]	0.031	2.032[1.512–2.731]	<0.001

for this particular population, which can not only reduce the missed detection caused by incomplete examination but also be of eminent importance for the reasonable treatment plan of patients. For example, a 40–59 years (40 points) CC patient with tumor size \leq 3cm (0 points),

grade for poorly differentiated (58 points) and CEA level positive (100 points) has a total of 198 points, resulting the diagnostic possibility is 0.36. Therefore, for this high-risk patient, more aggressive imaging could be performed to avoid the missed diagnosis in clinical practice.

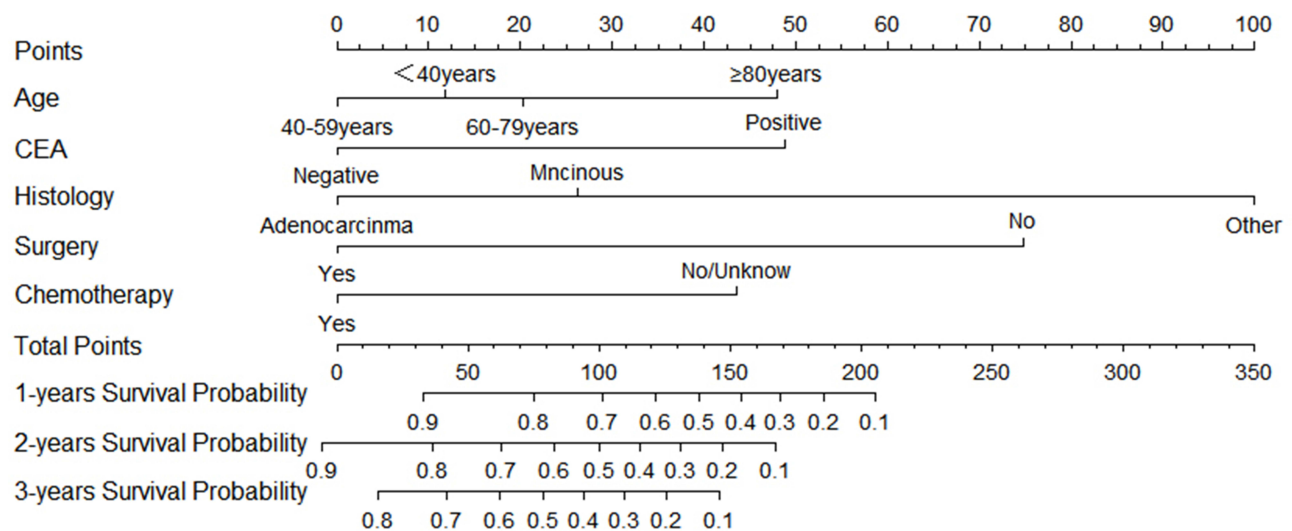


Figure 5 Nomogram for predicting 1-, 2- and 3-year CSS of T1N0 patients with DM.

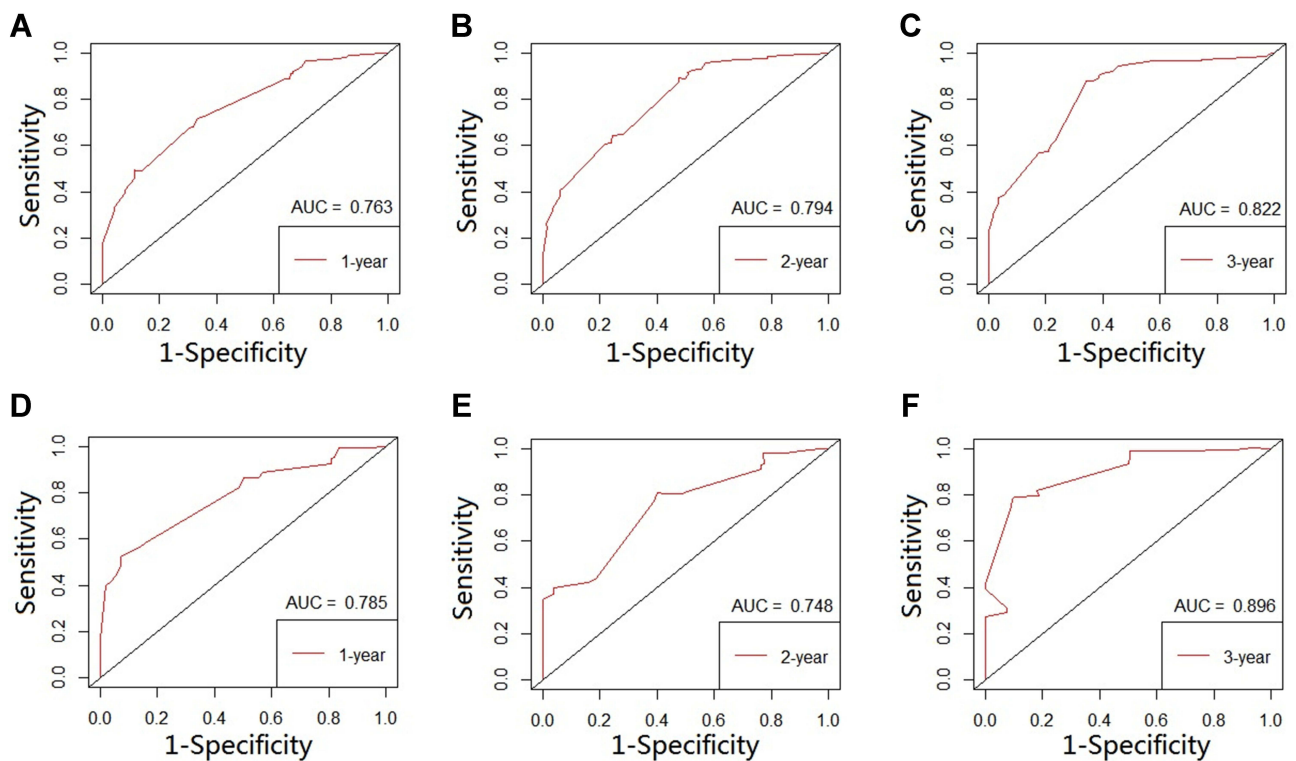


Figure 6 The ROC curves of nomogram for predicting 1-, 2- and 3-year CSS in the development cohort (A-C) and validation cohort (D-F).

If T1N0 patients are detected with DM, how should we plan treatment? The following results give us a reference. Then, we analyzed CSS in 428 patients with DM. In the CSS nomogram, we included patients' basic information (age, histological type and CEA) and treatment information such as surgery and chemotherapy. The CSS nomogram would be interpreted in a similar way to the DM

nomogram, which would give a survival possibility of 1, 2, 3 years. As a palliative treatment modality for CC patients with M1 stage, the potential benefit of primary tumor resection is diffusely discussed by many scholars. Some people argue that stage IV patients have lost the chance of surgery, and recommend systemic chemotherapy alone to prolong survival. Ichikawa et al and Shimomura et al

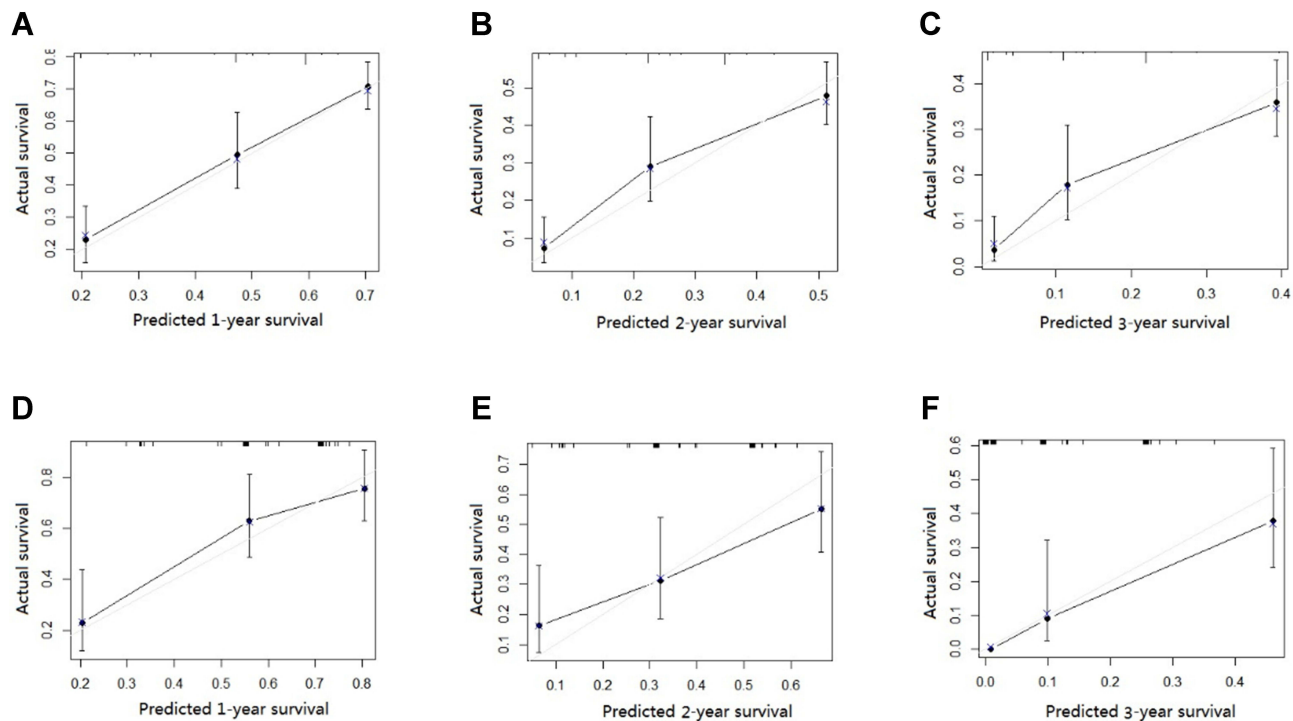


Figure 7 The calibration curves of the nomogram for predicting 1-, 2- and 3-year CSS in the development cohort (A–C) and validation cohort (D–F).

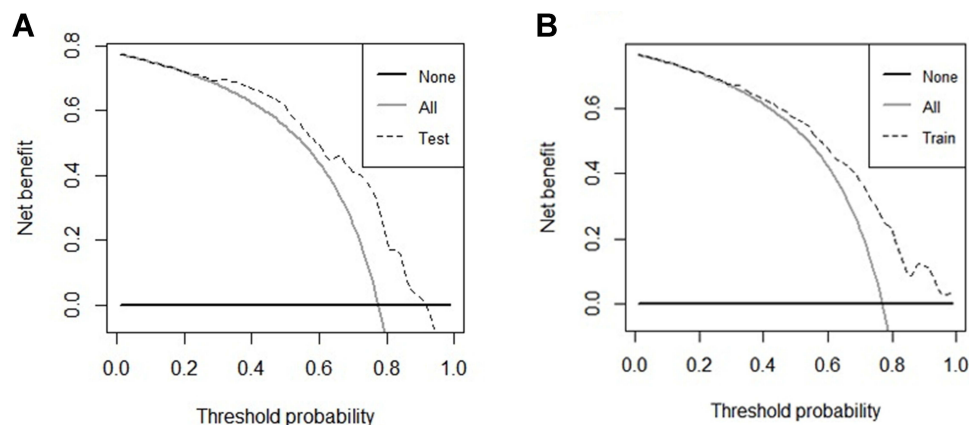


Figure 8 The DCA curves of the nomogram for predicting 1-, 2- and 3-year CSS in the development cohort (A) and validation cohort (B).

suggested that the benefit of primary tumor resection was unclear and needing to be explored by more clinical works.^{16–18} By contrast, Park et al conducted an analysis on 1015 stage IV CRC patients and found that patients receiving palliative surgery without residual disease and chemotherapy harbored better prognosis compared those with chemotherapy alone.¹⁹ Yeom et al also found that the survival time of patients receiving surgery and adjuvant therapy was significantly longer than that of patients receiving adjuvant therapy alone.²⁰ Similar results were achieved by some other reports.^{21–23} In the current

research, primary tumor resection was associated with improved survival time according to the multivariate analyses. The potential reasons might be that the surgery of primary tumor could avoid tumor-related symptoms and alleviate tumor load of the patients, thus prolonging the patients' survival time. Besides, age, histological type, CEA and chemotherapy were also determined as important factors for CSS of T1N0M1 patients, which have been linked with considerable importance in predicting survival of CC patients in recent years.^{24–26} Therefore, a nomogram was built to determine cancer-specific

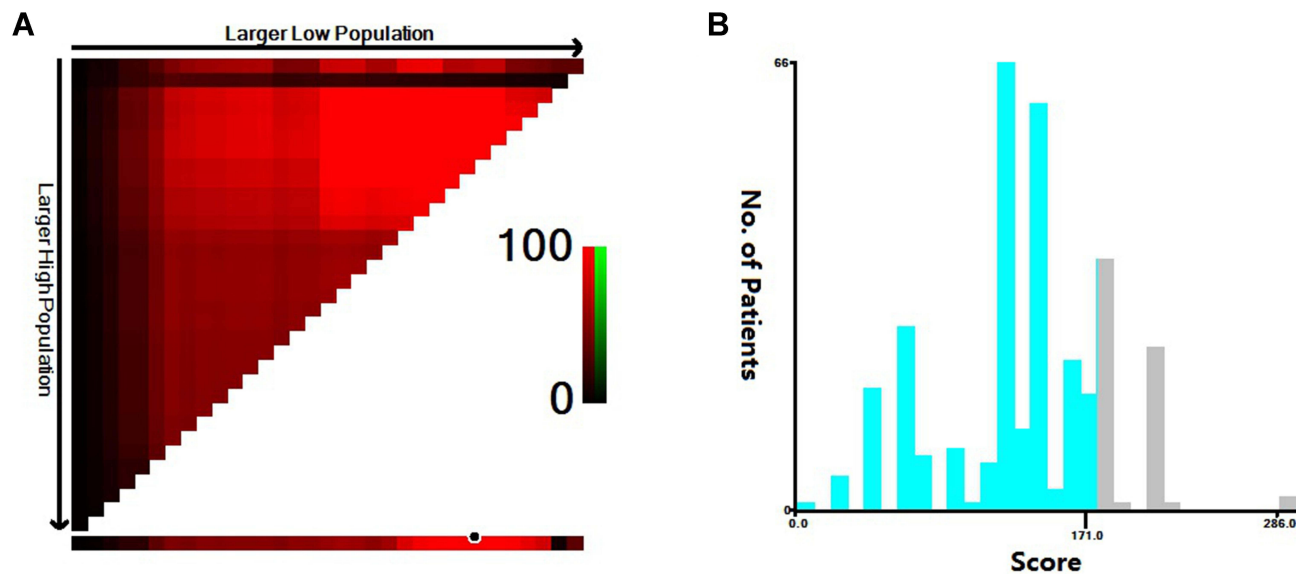


Figure 9 Calculate the cutoff value in DM patients by X-tile program (A and B).

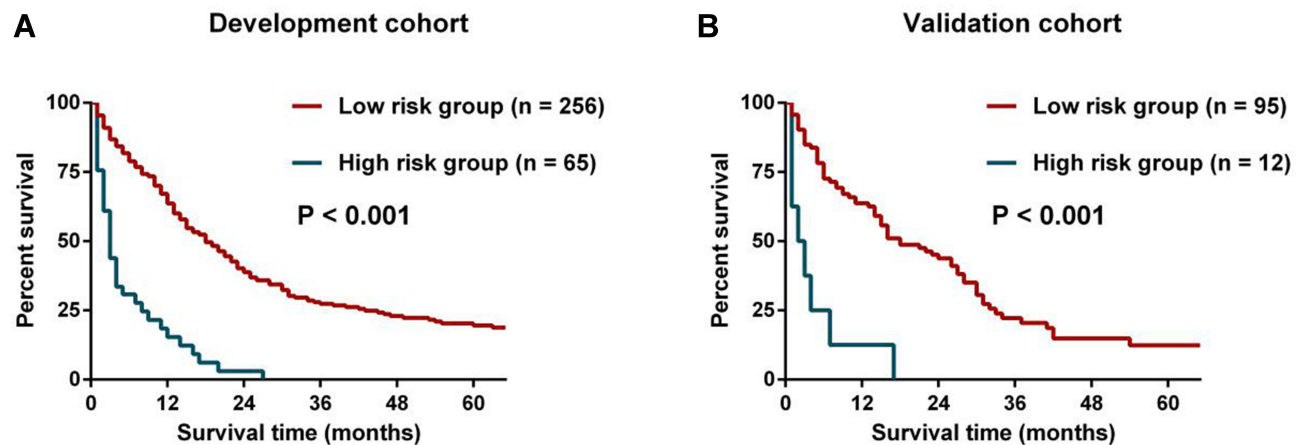


Figure 10 Kaplan–Meier curves for DM patients in the low- and high-risk groups in the development cohort (A) and validation cohort (B).

survival using these five factors (age, histological type, CEA, chemotherapy and surgery) and we found similar results — patients who underwent surgery and chemotherapy had longer survival. The C-indices of the development and validation cohort were 0.718 and 0.712. Moreover, patients were stratified into low- and high-risk groups according to their total scores and we found that the high-risk group had significantly improved survival times than the low-risk group. The proposed results could provide a potential reference to better manage T1N0M1 patients and guide the rational application of medical treatment resource. If the patient's basic conditions permit, surgery plus chemotherapy could be used to

pursue the highest possible survival rate with informed consent. Besides, some novel regimens such as conversion and targeted therapeutic strategies should also be investigated in the near future.

So if DM are not detected on routine imaging and the patient is identified as a high-risk patient by nomogram, the patient should be given more aggressive imaging to determine the presence of micro metastases. For patients who have been diagnosed with DM, surgery combined with adjuvant chemotherapy is preferred to achieve an improved survival time.

This study has several limitations. Firstly, because our study was a retrospective study including patients from

2004 to 2015, there may be the possibility of inaccurate data and it is inevitable to have observer and confusion bias. The current result requires further validation by some prospective clinical researches. Secondly, despite the internal validation of our model, there is a lack of external validation to further determine the accuracy of the model. Thirdly, some potential prognosticators such as BRAF and RAS mutational status, surgical methods, and more detailed information about chemotherapy protocols are not available in the SEER database. Incorporating these important factors may further improve the validity of nomograms. Finally, due to the limited number of cases and missing data in the SEER database, further stratification of metastatic sites was not possible.

In conclusion, this study performed prediction of DM and survival analysis in patients with stage T1N0 CC. Age, histology, tumor size, and CEA were independent predictors of DM. Age, grade, CEA, surgery and chemotherapy were independent prognostic factors for CSS. DM nomogram and CSS nomogram based on the above factors has favorable accuracy and superior predictive power. The proposed nomogram could help clinicians predict the risk and prognosis of DM in T1N0 CC patients and provide a reference to perform appropriate metastatic screening plans and rational therapeutic options for the special population.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the SEER database.

Ethical Statements

This study was approved by the Second Affiliated Hospital of Harbin Medical University and Zhejiang Cancer Hospital. The study used de-identified data and adhered to World Medical Association's Declaration of Helsinki for Ethical Human Research. The informed consent was not required according to personal identifying information was not included.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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