Original Article

Risk factors, prognostic factors and nomograms for distant metastasis in colorectal neuroendocrine neoplasms: a SEER-based study

Yuqin Bai[1,2,3], Na Lei[1,2,3], Pan Zhang[1,2,3], Qian Yang[1,2,3], Fei Feng[4], Yue Zhao[2,3]

[1]The First Clinical Medical College, Lanzhou University, Lanzhou, China; [2]Department of Gastroenterology, The First Hospital of Lanzhou University, Lanzhou, China; [3]Gansu Province Clinical Research Center for Digestive Diseases, The First Hospital of Lanzhou University, Lanzhou, China; [4]Department of Ultrasound, The First Hospital of Lanzhou University, Lanzhou, China

Contributions: (I) Conception and design: Y Bai, Y Zhao; (II) Administrative support: Y Zhao; (III) Provision of study materials or patients: Y Bai, N Lei, F Feng; (IV) Collection and assembly of data: Y Bai, P Zhang, Q Yang; (V) Data analysis and interpretation: Y Bai, N Lei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yue Zhao, MD. Department of Gastroenterology, The First Hospital of Lanzhou University, No. 1 Donggang West Road, Chengguan District, Lanzhou 730000, China; Gansu Province Clinical Research Center for Digestive Diseases, The First Hospital of Lanzhou University, Lanzhou, China. Email: zhaoyueldyy@126.com.

Background: Distant metastasis is uncommon in colorectal neuroendocrine neoplasms (CRNENs). However, the prognosis of patients with distant metastasis is often poor, so it is crucial to detect distant metastasis in time. This article aims to study the risk factors and prognostic factors for the development of distant metastasis in patients with CRNENs and to construct two related nomograms.

Methods: Patient data were obtained through the Surveillance, Epidemiology, and End Results (SEER) database, and the inclusion population was identified according to inclusion and exclusion criteria. Logistic regression analysis was used to determine risk factors for distant metastasis in patients with CRNENs. Cox regression analysis was utilized to identify prognostic factors in patients with CRNENs with distant metastasis. Two nomograms were created and the predictive performance of the nomogram was evaluated using receiver operating characteristic (ROC) curves, the calibration curve, and decision curve analysis (DCA) curves.

Results: We included 9,142 patients with CRNENs and 859 patients with distant metastasis. Age, race, marital status, primary site, histological grade, T stage, N stage, and tumor size were independent risk factors. Age, primary site, histological grade, N stage, tumor size, dissected lymph nodes, and surgery were independent prognostic factors. The constructed nomogram can predict the occurrence and prognosis of distant metastasis in patients with CRNENs.

Conclusions: The nomogram developed in this paper may contribute to the diagnosis and prognosis of distant metastasis in patients with CRNENs and may help clinicians make better clinical decisions.

Keywords: Colorectal neuroendocrine neoplasms (CRNENs); distant metastasis; nomogram; Surveillance, Epidemiology, and End Results (SEER)

Submitted Oct 19, 2024. Accepted for publication Jan 27, 2025. Published online Mar 04, 2025.
doi: 10.21037/tcr-24-2018
View this article at: https://dx.doi.org/10.21037/tcr-24-2018

Introduction

Neuroendocrine neoplasms (NENs) are a group of heterogeneous tumors originating from cells of the diffuse neuroendocrine system, including highly or moderately differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed adeno-NECs (MANECs), which mainly occur in the gastrointestinal tract and pancreas (1,2). Between 10.9% and 25.2% of these tumors are located in the colon or rectum (3). Several studies based on the Surveillance, Epidemiology, and End Results (SEER) database suggests that the incidence of colorectal NENs (CRNENs) has increased dramatically over the past 40 years, which may be related to the increased detection rate due to the widespread use of endoscopes (4,5). Most NENs are reported to be malignant, with approximately 30% of colon NENs and 12–20% of rectal NENs already metastasized at diagnosis, and the median survival of patients with distant colorectal NETs is only 10.4 months, with a 5-year survival rate of 15–30% (5-8). Therefore, it is crucial to be able to predict distant metastasis and thus improve the prognosis of patients with CRNENs in clinical practice. In recent years, there have been retrospective studies identifying risk and prognostic factors in patients with liver metastasis (9). However, there is relatively little data on exploring the occurrence of distant metastasis in patients with CRNENs, and the relationship between some clinical factors and distant metastasis has not been adequately investigated.

Highlight box

Key findings

- This study constructed and validated risk prediction nomograms for distant metastasis and survival prognosis in patients with colorectal neuroendocrine neoplasms (CRNENs).

What is known and what is new?

- Age, race, marital status, primary site, histological grade, T stage, N stage, and tumor size were independent risk factors. Age, primary site, histological grade, N stage, tumor size, dissected lymph nodes, and surgery were independent prognostic factors.
- Previous studies have found that older age is more likely to prone to distant metastases. However, our study suggests a higher risk of metastasis in younger age.

What is the implication, and what should change now?

- The findings of this study provide a better understanding of the diagnosis and prognosis of distant metastasis in patients with CRNENs, which can help clinicians make better clinical decisions.

A nomogram is a very important visual prediction tool that plays an important role in clinical practice. At present, there have been studies which have constructed nomograms of the prognosis of gastroenteropancreatic NETs, and they have shown good utility (10). However, at present, no studies have identified clinical or pathological factors and built models to predict the occurrence and prognosis of distant metastasis in CRNENs. Moreover, CRNENs with distant metastasis are rare clinically, and it is difficult to collect multi-center data. We therefore chose a large-scale public database to develop two convenient and accurate models to predict the risk and prognosis of distant metastasis in CRNENs. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2018/rc).

Methods

Study population and data collection

Clinical data on patients with CRNENs from 2010 to 2015 were collected from the SEER database. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The International Classification of Diseases of Oncology, 3rd edition (ICD-O-3 histology/behavior, malignant) codes for CRNENs include 8002/3, 8013/3, 8040–8045/3, 8150–8156/3, 8240–8246/3, 8249/3, 8510/3, 8680/3, 8693/3, 8700/3. Demographic and clinicopathologic characteristics of the included population were collected, including the variables: sex (male, female); age (<57, 57–72, >72 years); race [other (American Indian/Alaska Native, Asian/Pacific Islander), Black, White]; marriage (unmarried, married, unknown); primary site (left colon, right colon, rectum, unknown); grade (I, II, III, IV, unknown); T stage (TX, T1, T2, T3, T4); N stage (NX, N0, N1, N2); M stage (M0, M1); tumor size (≤32 mm, >32 mm, unknown); dissected lymph nodes (no, 1–3, ≥4, unknown); surgery (no/unknown, yes); radiation (no/unknown, yes); chemotherapy (no/unknown, yes); survival time; vital status. The primary endpoint of the study was overall survival (OS), defined as the duration from initial diagnosis to death or last follow-up. The inclusion criteria were as follows: (I) diagnosed from 2010 to 2015; (II) being the 1st primary tumor; (III) primary tumor site of rectum or colon; and (IV) pathologically confirmed. Patients with insufficient clinical information were excluded. The flowchart of the enrollment screening is shown (*Figure 1*).

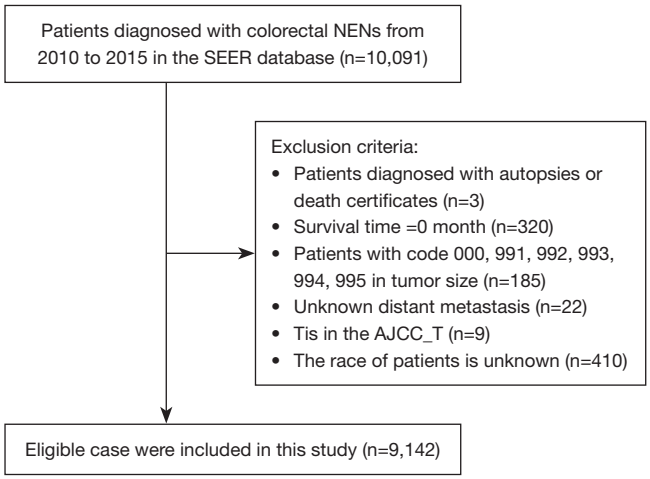

Figure 1 Patient enrollment flowchart. AJCC_T, American Joint Committee on Cancer_Tumor; NENs, neuroendocrine neoplasms; SEER, Surveillance, Epidemiology, and End Results.

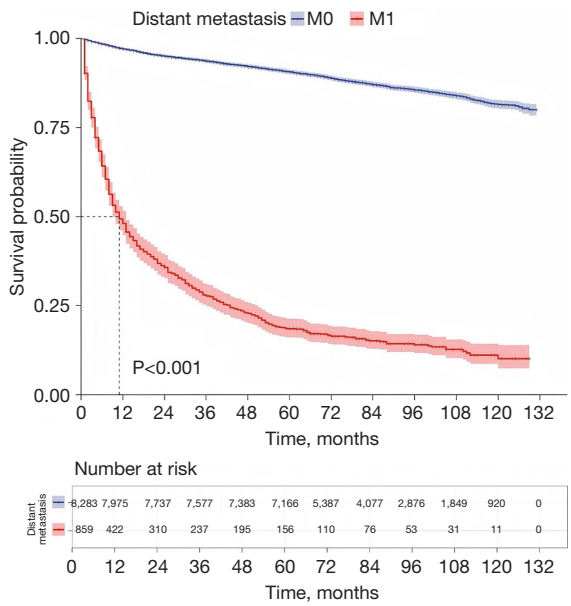

Figure 2 Kaplan-Meier analysis of OS for distant and non-distant metastasis. OS, overall survival.

Statistical analysis

In this study, SPSS (version 27.0, IBM Corp, Armonk, NY, USA), R software (version 4.3.2, StataCorp LLC, College Station, TX, USA), and X-tile software (version 3.6.1, Yale University School of Medicine, New Haven, CT, USA) were used for data analysis. X-tile software was used to determine optimal cutoff values for age and tumor size. Categorical variables were expressed as percentages and compared using the Chi-squared test. Independent risk factors for distant metastasis were determined in patients with CRNENs using univariate and multivariate logistic regression analyses. Univariate and multivariate Cox regression analyses were used to determine the independent prognostic factors in patients with CRNENs with distant metastasis. A nomogram was constructed for predicting the probability of distant metastasis and the likelihood of 1-, 3-, and 5-year survival in patients with CRNENs. Patients were risk-scored according to the prognostic nomogram and categorized into low- and high-risk groups, and Kaplan-Meier analysis was performed to evaluate the OS of the two groups. In all statistical analysis results, P<0.05 was considered significant.

Results

Kaplan-Meier survival analysis

Kaplan-Meier survival curves (*Figure 2*) for patients with or without distant metastasis showed that patients with distant metastasis had shorter OS than those without distant metastasis, and the difference in OS was statistically significant (P<0.001). The 1-, 3-, and 5-year survival rates for patients with distant metastasis were 49.1%, 27.6%, and 18.2%. For patients without distant metastasis, the 1-, 3-, and 5-year survival rates were 96.3%, 91.5%, and 86.5%.

Characterization of the population in the diagnostic nomogram

A total of 9,142 patients were included in this study, of whom 859 (9.4%) developed distant metastasis. All included populations were formed into a diagnostic cohort, and they were randomized in a 7:3 ratio into a training group (n=6,399) and a validation group (n=2,743). The baseline characteristics of the patients are shown in *Table 1*, and there were no statistically significant differences in demographic or clinicopathologic characteristics. Patients were predominantly female (52.3%), <57 years (56.7%), White (68.4%), and married (50.6%). More than half of the tumors occurred in the rectum (54.9%). The majority of patients were in grade I (43.5%), N0 (75.4%), T1 (46.2%), and M0 (90.6%). Less than 32 mm (57.1%) was the common tumor size. In terms of treatment, and most of the patients did not undergo lymph node dissection (74.3%), most of the patients underwent surgery (84.8%). In addition, the majority of the patients did not receive

Table 1 Demographic and clinicopathologic characteristics of patients with CRNENs

Variables	Train (n=6,399)	Validation (n=2,743)	Total (n=9,142)	χ^2	P
Sex				1.721	0.19
Male	3,021 (47.2)	1,336 (48.7)	4,357 (47.7)		
Female	3,378 (52.8)	1,407 (51.3)	4,785 (52.3)		
Age (years)				1.344	0.51
<57	3,608 (56.4)	1,578 (57.5)	5,186 (56.7)		
57–72	2,174 (34.0)	917 (33.4)	3,091 (33.8)		
>72	617 (9.6)	248 (9.0)	865 (9.5)		
Race				0.116	0.94
Other	818 (12.8)	347 (12.7)	1,165 (12.7)		
Black	1,209 (18.9)	512 (18.7)	1,721 (18.8)		
White	4,372 (68.3)	1,884 (68.7)	6,256 (68.4)		
Marriage				0.204	0.90
Unmarried	2,267 (35.4)	965 (35.2)	3,232 (35.4)		
Married	3,230 (50.5)	1,398 (51.0)	4,628 (50.6)		
Unknown	902 (14.1)	380 (13.9)	1,282 (14.0)		
Primary site				1.695	0.64
Left colon	510 (8.0)	200 (7.3)	710 (7.8)		
Right colon	2,288 (35.8)	1,007 (36.7)	3,295 (36.0)		
Rectum	3,520 (55.0)	1,500 (54.7)	5,020 (54.9)		
Unknown	81 (1.3)	36 (1.3)	117 (1.3)		
Grade				2.387	0.67
I	2,799 (43.7)	1,182 (43.1)	3,981 (43.5)		
II	590 (9.2)	272 (9.9)	862 (9.4)		
III	532 (8.3)	219 (8.0)	751 (8.2)		
IV	227 (3.5)	109 (4.0)	336 (3.7)		
Unknown	2,251 (35.2)	961 (35.0)	3,212 (35.1)		
T stage				4.930	0.30
TX	1,778 (27.8)	773 (28.2)	2,551 (27.9)		
T1	2,959 (46.2)	1,264 (46.1)	4,223 (46.2)		
T2	400 (6.3)	168 (6.1)	568 (6.2)		
T3	832 (13.0)	383 (14.0)	1,215 (13.3)		
T4	430 (6.7)	155 (5.7)	585 (6.4)		
N stage				2.314	0.51
NX	613 (9.6)	281 (10.2)	894 (9.8)		
N0	4,842 (75.7)	2,055 (74.9)	6,897 (75.4)		
N1	816 (12.8)	361 (13.2)	1,177 (12.9)		
N2	128 (2.0)	46 (1.7)	174 (1.9)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Train (n=6,399)	Validation (n=2,743)	Total (n=9,142)	χ^2	P
M stage				1.618	0.20
M0	5,814 (90.9)	2,469 (90.0)	8,283 (90.6)		
M1	585 (9.1)	274 (10.0)	859 (9.4)		
Tumor size (mm)				0.027	0.99
≤32	3,658 (57.2)	1,563 (57.0)	5,221 (57.1)		
>32	872 (13.6)	375 (13.7)	1,247 (13.6)		
Unknown	1,869 (29.2)	805 (29.3)	2,674 (29.2)		
Dissected lymph nodes				2.088	0.55
No	4,767 (74.5)	2,028 (73.9)	6,795 (74.3)		
1–3	98 (1.5)	53 (1.9)	151 (1.7)		
≥4	1,420 (22.2)	610 (22.2)	2,030 (22.2)		
Unknown	114 (1.8)	52 (1.9)	166 (1.8)		
Surgery				0.067	0.80
No/unknown	977 (15.3)	413 (15.1)	1,390 (15.2)		
Yes	5,422 (84.7)	2,330 (84.9)	7,752 (84.8)		
Radiation				0.641	0.42
No/unknown	6,282 (98.2)	2,686 (97.9)	8,968 (98.1)		
Yes	117 (1.8)	57 (2.1)	174 (1.9)		
Chemotherapy				0.458	0.50
No/unknown	5,789 (90.5)	2,469 (90.0)	8,258 (90.3)		
Yes	610 (9.5)	274 (10.0)	884 (9.7)		

Data are presented as n (%). CRNENs, colorectal neuroendocrine neoplasms.

radiation (98.1%) or chemotherapy (90.3%).

Risk factors for distant metastasis in patients with CRNENs

The univariate logistic analysis was performed with the training group, and statistically significant factors were included in the multivariate logistic analysis. The results showed that age [>72 years: odds ratio (OR) =0.549, 95% confidential interval (CI): 0.397–0.759, reference to <57 years], race (Black: OR =0.644, 95% CI: 0.419–0.990, reference to other races), marital status (unknown: OR =0.252, 95% CI: 0.158–0.403, reference to unmarried), primary site (rectum: OR =0.516, 95% CI: 0.355–0.751, reference to the left colon), histologic grade (II: OR =1.966, 95% CI: 1.322–2.923; III: OR =6.026, 95% CI: 4.246–8.552; IV: OR =6.820, 95% CI: 4.477–10.388; unknown: OR =1.915, 95% CI: 1.402–2.616, reference to I), and T stage (T1: OR =0.186, 95% CI: 0.107–0.322; T3: OR =0.554, 95% CI: 0.360–0.854; T4: OR =1.651, 95% CI: 1.067–2.553, reference to TX), and N stage (N0: OR =0.302, 95% CI: 0.216–0.422; N1: OR =1.631, 95% CI: 1.105–2.407, reference to NX), tumor size (>32 mm: OR =1.643, 95% CI: 1.197–2.256, reference to ≤32 mm) were statistically significant (P<0.05), and were independent risk factors for distant metastasis in patients with CRNENs. The specific results of the logistic analysis of the training group are shown in *Table 2*.

Development and validation of a diagnostic nomogram

Based on the eight independent risk factors obtained by multivariate logistic analysis, a nomogram (*Figure 3*) for predicting distant metastasis was established. Due to the lack of external data, we rescreened 1,136 patients from the seer database using the same inclusion and exclusion criteria to form a testing group in order to validate the applicability

Table 2 Univariate and multivariate logistic analysis of patients with CRNENs

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Sex				
Male	Reference			
Female	0.874 (0.738–1.036)	0.12		
Age (years)				
<57	Reference		Reference	
57–72	1.942 (1.612–2.339)	<0.001	1.250 (0.996–1.568)	0.054
>72	2.636 (2.041–3.404)	<0.001	0.549 (0.397–0.759)	<0.001
Race				
Other	Reference		Reference	
Black	0.896 (0.622–1.290)	0.56	0.644 (0.419–0.990)	0.045
White	1.660 (1.239–2.223)	<0.001	0.746 (0.523–1.064)	0.11
Marriage				
Unmarried	Reference		Reference	
Married	0.967 (0.810–1.155)	0.71	0.915 (0.735–1.138)	0.42
Unknown	0.246 (0.162–0.375)	<0.001	0.252 (0.158–0.403)	<0.001
Primary site				
Left colon	Reference		Reference	
Right colon	1.316 (0.988–1.753)	0.06	0.910 (0.627–1.322)	0.62
Rectum	0.294 (0.215–0.402)	<0.001	0.516 (0.355–0.751)	<0.001
Unknown	2.987 (1.732–5.152)	<0.001	1.877 (0.981–3.588)	0.057
Grade				
I	Reference		Reference	
II	3.469 (2.424–4.963)	<0.001	1.966 (1.322–2.923)	<0.001
III	23.352 (17.598–30.987)	<0.001	6.026 (4.246–8.552)	<0.001
IV	27.111 (19.209–38.262)	<0.001	6.820 (4.477–10.388)	<0.001
Unknown	2.231 (1.682–2.960)	<0.001	1.915 (1.402–2.616)	<0.001
T stage				
TX	Reference		Reference	
T1	0.096 (0.063–0.145)	<0.001	0.186 (0.107–0.322)	<0.001
T2	1.682 (1.207–2.343)	0.002	0.995 (0.613–1.616)	0.99
T3	2.389 (1.874–3.045)	<0.001	0.554 (0.360–0.854)	0.008
T4	9.636 (7.487–12.401)	<0.001	1.651 (1.067–2.553)	0.02
N stage				
NX	Reference		Reference	
N0	0.245 (0.184–0.327)	<0.001	0.302 (0.216–0.422)	<0.001
N1	3.955 (2.986–5.238)	<0.001	1.631 (1.105–2.407)	0.01
N2	6.329 (4.147–9.661)	<0.001	1.043 (0.607–1.793)	0.88

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Tumor size (mm)				
≤32	Reference		Reference	
>32	15.575 (12.366–19.616)	<0.001	1.643 (1.197–2.256)	0.002
Unknown	2.982 (2.341–3.799)	<0.001	1.422 (0.963–2.100)	0.08

CI, confidential interval; CRNENs, colorectal neuroendocrine neoplasms; OR, odds ratio.

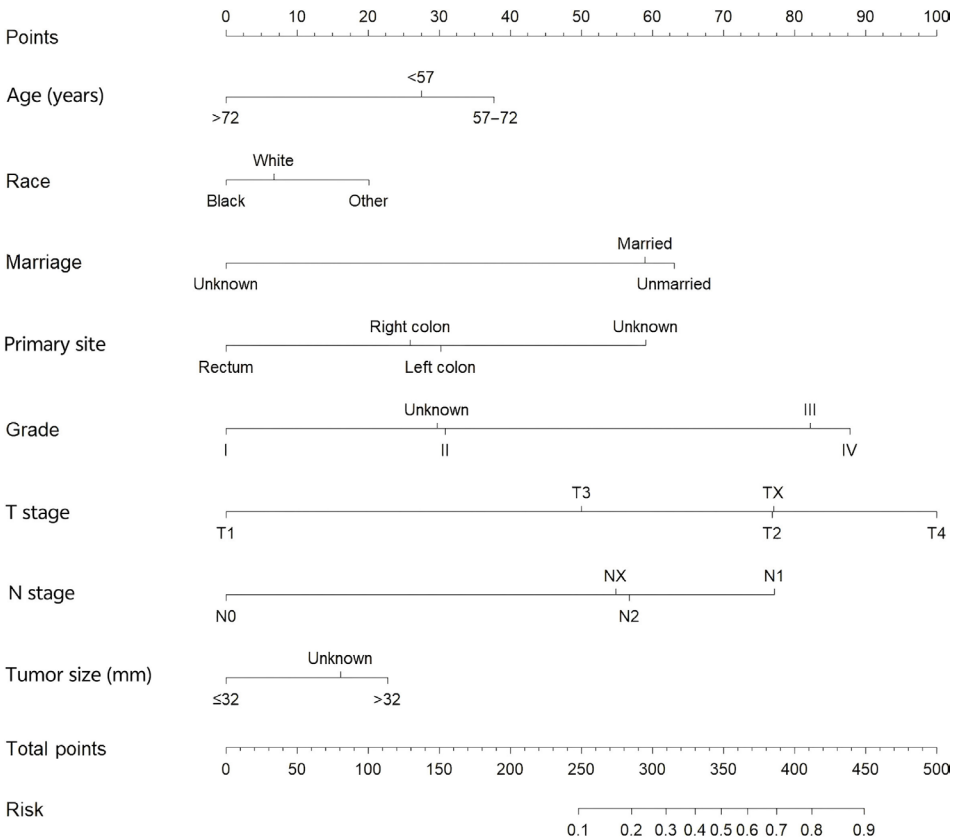

Figure 3 A diagnostic nomogram predicting risk of distant metastasis in patients with CRNENs. CRNENs, colorectal neuroendocrine neoplasms.

of the model. The receiver operating characteristic (ROC) curve was plotted (*Figure 4A-4C*), showing that the area under the ROC curve (AUC) of the training group was 0.904 (95% CI: 0.8923–0.9157), the validation group was 0.911 (95% CI: 0.8944–0.9277), and the testing group was 0.735 (95% CI: 0.7054–0.7636), indicating that the model had a good discriminative ability in predicting metastatic *vs.* non-metastatic patients. Further observation of the calibration curves (*Figure 4D-4F*) showed good agreement between model observations and predictions. Finally, the decision curve analysis (DCA) (*Figure 4G-4I*) was plotted, showing that the model has a good performance in clinical practice for predicting distant metastasis. In addition, we generated ROC curves for each independent risk factor (*Figure 5*), and the AUC for each factor was lower than the nomogram in the training, validation, and testing groups, implying that the predictive accuracy of the model was better than that of a single factor.

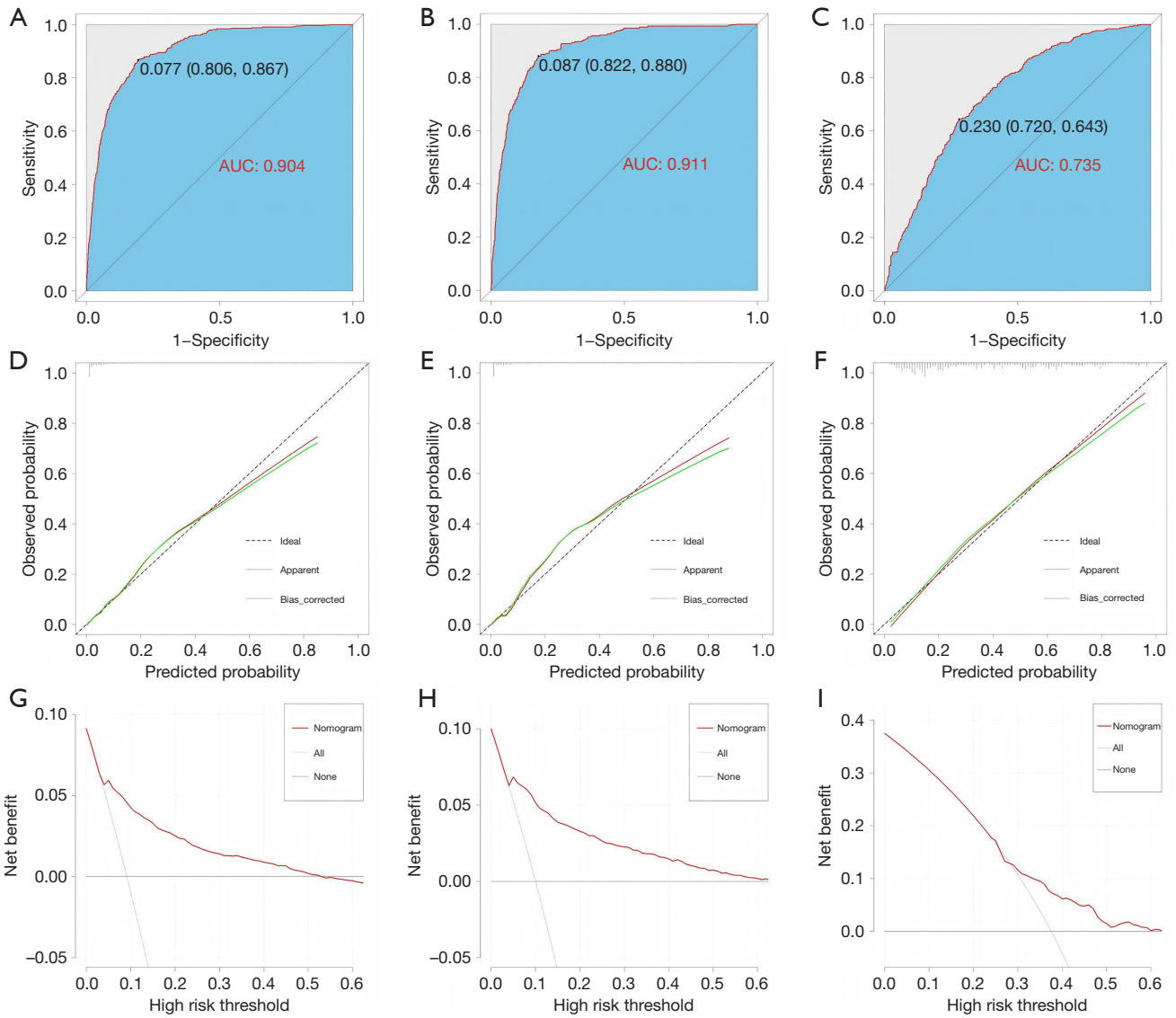

Figure 4 ROC, calibration curves, and DCA of the nomogram for the risk of CRNENs with distant metastasis. ROC of the training (A), validation (B), and testing (C) sets; calibration curve of the training (D), validation (E), and testing (F) sets; DCA curve of the training (G), validation (H), and testing (I) sets. AUC, area under the ROC curve; DCA, decision curve analysis; ROC, receiver operating characteristic.

Prognostic factors in patients with CRNENs with distant metastasis

A total of 859 patients with CRNENs with distant metastasis formed the prognostic cohort. Patients in the prognostic cohort were randomized in a 7:3 ratio into a training group (n=601) and a validation group (n=258). General clinicopathological characteristics as shown in *Table 3*.

Univariate and multivariate Cox regression analyses were performed on the training group data (*Table 4*), and the results showed that age, primary site, histological grade, N stage, tumor size, dissected lymph nodes, and surgery were statistically significant (P<0.05). Compared with patients aged <57 years, those aged 57–72 years [hazard ratio (HR) =1.349, 95% CI: 1.106–1.646, P=0.003], and >72 years (HR =1.581, 95% CI: 1.229–2.034, P<0.001) had a worse prognosis; compared with other primary sites, the primary site of rectum (HR =0.697, 95% CI: 0.507–0.959, P=0.03) had better prognosis; grade III had the significantly worst prognosis compared to other histologic grades (HR =3.979,

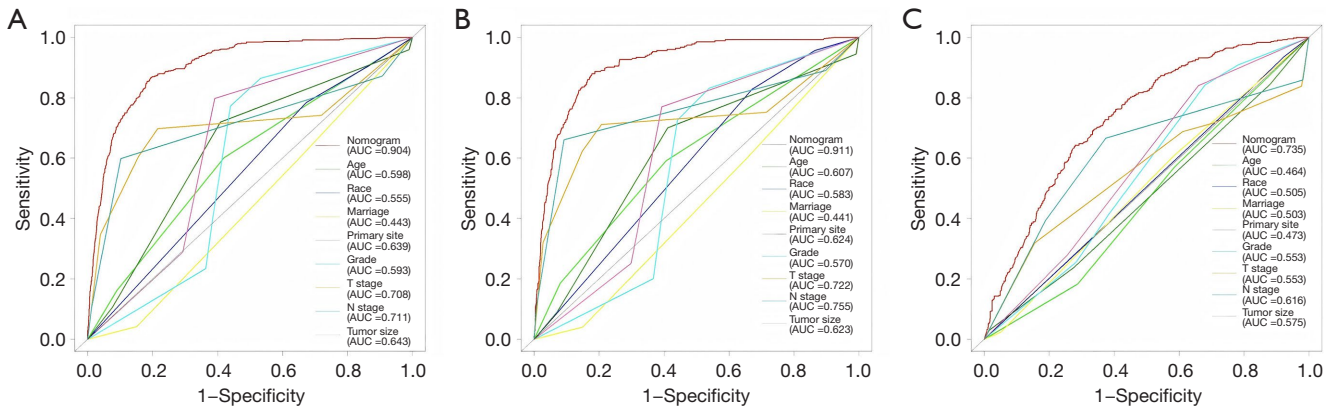

Figure 5 Comparison of AUC between nomogram and all independent factors, including age, race, marriage, primary site, grade, T stage, N stage, and tumor size in the training set (A), validation set (B), and testing set (C). AUC, area under the ROC curve; ROC, receiver operating characteristic.

Table 3 Baseline clinical features of patients diagnosed with CRNENs with distant metastasis

Variables	Train (n=601)	Validation (n=258)	Total (n=859)	χ^2	P
Sex				0.068	0.79
Male	304 (50.6)	128 (49.6)	432 (50.3)		
Female	297 (49.4)	130 (50.4)	427 (49.7)		
Age (years)				3.253	0.20
<57	247 (41.1)	98 (38.0)	345 (40.2)		
57–72	246 (40.9)	122 (47.3)	368 (42.8)		
>72	108 (18.0)	38 (14.7)	146 (17.0)		
Race				0.786	0.68
Other	44 (7.3)	22 (8.5)	66 (7.7)		
Black	78 (13.0)	29 (11.2)	107 (12.5)		
White	479 (79.7)	207 (80.2)	686 (79.9)		
Marriage				2.485	0.29
Unmarried	231 (38.4)	114 (44.2)	345 (40.2)		
Married	344 (57.2)	134 (51.9)	478 (55.6)		
Unknown	26 (4.3)	10 (3.9)	36 (4.2)		
Primary site				2.151	0.54
Left colon	62 (10.3)	26 (10.1)	88 (10.2)		
Right colon	359 (59.7)	166 (64.3)	525 (61.1)		
Rectum	150 (25.0)	57 (22.1)	207 (24.1)		
Unknown	30 (5.0)	9 (3.5)	39 (4.5)		

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Train (n=601)	Validation (n=258)	Total (n=859)	χ^2	P
Grade				6.821	0.15
I	89 (14.8)	36 (14.0)	125 (14.6)		
II	64 (10.6)	19 (7.4)	83 (9.7)		
III	201 (33.4)	107 (41.5)	308 (35.9)		
IV	105 (17.5)	46 (17.8)	151 (17.6)		
Unknown	142 (23.6)	50 (19.4)	192 (22.4)		
T stage				6.440	0.17
TX	156 (26.0)	63 (24.4)	219 (25.5)		
T1	30 (5.0)	7 (2.7)	37 (4.3)		
T2	47 (7.8)	31 (12.0)	78 (9.1)		
T3	160 (26.6)	74 (28.7)	234 (27.2)		
T4	208 (34.6)	83 (32.2)	291 (33.9)		
N stage				7.750	0.051
NX	83 (13.8)	22 (8.5)	105 (12.2)		
N0	163 (27.1)	60 (23.3)	223 (26.0)		
N1	297 (49.4)	145 (56.2)	442 (51.5)		
N2	58 (9.7)	31 (12.0)	89 (10.4)		
Tumor size (mm)				3.621	0.16
≤32	136 (22.6)	45 (17.4)	181 (21.1)		
>32	297 (49.4)	143 (55.4)	440 (51.2)		
Unknown	168 (28.0)	70 (27.1)	238 (27.7)		
Dissected lymph nodes				2.499	0.48
No	307 (51.1)	118 (45.7)	425 (49.5)		
1–3	19 (3.2)	7 (2.7)	26 (3.0)		
≥4	264 (43.9)	127 (49.2)	391 (45.5)		
Unknown	11 (1.8)	6 (2.3)	17 (2.0)		
Surgery				2.950	0.09
No/unknown	271 (45.1)	100 (38.8)	371 (43.2)		
Yes	330 (54.9)	158 (61.2)	488 (56.8)		
Radiation				0.084	0.77
No/unknown	542 (90.2)	231 (89.5)	773 (90.0)		
Yes	59 (9.8)	27 (10.5)	86 (10.0)		
Chemotherapy				1.273	0.26
No/unknown	243 (40.4)	115 (44.6)	358 (41.7)		
Yes	358 (59.6)	143 (55.4)	501 (58.3)		

Data are presented as n (%). CRNENs, colorectal neuroendocrine neoplasms.

Table 4 Univariate and multivariate Cox analysis in patients diagnosed with CRNENs with distant metastasis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex				
Male	Reference		Reference	
Female	0.821 (0.691–0.977)	0.03	0.849 (0.708–1.017)	0.08
Age (years)				
<57	Reference		Reference	
57–72	1.174 (0.968–1.425)	0.10	1.349 (1.106–1.646)	0.003
>72	1.731 (1.360–2.202)	<0.001	1.581 (1.229–2.034)	<0.001
Race				
Other	Reference			
Black	0.812 (0.548–1.202)	0.30		
White	0.894 (0.648–1.233)	0.50		
Marriage				
Unmarried	Reference			
Married	0.883 (0.737–1.059)	0.18		
Unknown	1.500 (0.981–2.294)	0.06		
Primary site				
Left colon	Reference		Reference	
Right colon	0.556 (0.420–0.736)	<0.001	0.783 (0.584–1.050)	0.10
Rectum	0.771 (0.569–1.045)	0.09	0.697 (0.507–0.959)	0.03
Unknown	0.673 (0.425–1.068)	0.09	0.771 (0.469–1.267)	0.31
Grade				
I	Reference		Reference	
II	1.558 (1.050–2.311)	0.03	1.327 (0.884–1.993)	0.17
III	4.403 (3.202–6.054)	<0.001	3.979 (2.768–5.722)	<0.001
IV	5.028 (3.552–7.117)	<0.001	3.746 (2.540–5.524)	<0.001
Unknown	3.372 (2.426–4.687)	<0.001	2.293 (1.596–3.295)	<0.001
T stage				
TX	Reference		Reference	
T1	0.670 (0.435–1.032)	0.07	1.475 (0.913–2.383)	0.11
T2	0.643 (0.449–0.921)	0.02	0.914 (0.613–1.362)	0.66
T3	0.561 (0.441–0.715)	<0.001	1.057 (0.776–1.440)	0.73
T4	0.682 (0.548–0.848)	<0.001	1.292 (0.961–1.738)	0.09
N stage				
NX	Reference		Reference	
N0	0.705 (0.534–0.930)	0.01	0.754 (0.558–1.018)	0.07
N1	0.673 (0.521–0.870)	0.002	1.100 (0.809–1.495)	0.55
N2	1.154 (0.819–1.625)	0.41	1.622 (1.056–2.490)	0.03

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Tumor size (mm)				
≤32	Reference		Reference	
>32	2.135 (1.683–2.708)	<0.001	1.424 (1.093–1.855)	0.009
Unknown	2.391 (1.847–3.095)	<0.001	1.112 (0.811–1.525)	0.51
Dissected lymph nodes				
No	Reference		Reference	
1–3	0.354 (0.193–0.647)	<0.001	0.488 (0.247–0.965)	0.04
≥4	0.465 (0.386–0.559)	<0.001	0.422 (0.280–0.635)	<0.001
Unknown	0.709 (0.377–1.334)	0.29	0.577 (0.298–1.120)	0.10
Surgery				
No/unknown	Reference		Reference	
Yes	0.382 (0.319–0.459)	<0.001	0.581 (0.400–0.846)	0.005
Radiation				
No/unknown	Reference			
Yes	1.150 (0.863–1.532)	0.34		
Chemotherapy				
No/unknown	Reference		Reference	
Yes	1.667 (1.384–2.007)	<0.001	0.878 (0.703–1.096)	0.25

CI, confidential interval; CRNENs, colorectal neuroendocrine neoplasms; HR, hazard ratio.

95% CI: 2.768–5.722, P<0.001); in N stage, patients with N2 stage had the worst prognosis (HR =1.622, 95% CI: 1.056–2.490, P=0.03); the risk of death was higher for >32 mm compared to tumor size ≤32 mm (HR =1.424, 95% CI: 1.093–1.855, P=0.009); in terms of the number of lymph node dissection, patients with a number of dissection ≥4 patients had a higher survival rate (HR =0.422, 95% CI: 0.280–0.635, P<0.001); as for surgery, operated patients (HR =0.581, 95% CI: 0.400–0.846, P=0.005) had a higher survival rate than those who were not operated.

Development and validation of a prognostic nomogram

A prognostic nomogram (*Figure 6*) was constructed based on the seven prognostic factors derived above. To further validate its applicability, we used 426 patients who developed distant metastasis out of the 1,136 patients with complete information included above as the testing group. The ROC (*Figure 7*) analysis showed that the AUCs of 1-, 3-, and 5-year OS of the training group were 0.833, 0.863, and 0.868, the validation group were 0.782, 0.833, and 0.803, the testing group were 0.728, 0.827, and 0.844, respectively, meaning that the nomogram showed a better differentiation ability. Moreover, the calibration curves (*Figure 8*) for OS at 1, 3, and 5 years in the training, validation, and testing groups showed that the nomogram predictions and the actual observations were in general agreement, which indicated good calibration. DCA (*Figure 9*) further demonstrated that the nomogram has good clinical benefits. In addition, the ROC curves for the prognostic column charts and their constituent risk variables are shown in *Figure 10*, and the results indicated that the AUC of the nomogram is superior to the AUC of the individual risk variables in predicting 1-, 3-, and 5-year survival. All these results suggest that the nomogram shows good performance in predicting the prognosis of patients with CRNENs with distant metastasis.

Risk stratification by nomogram

Each patient in the training group in the prognostic cohort

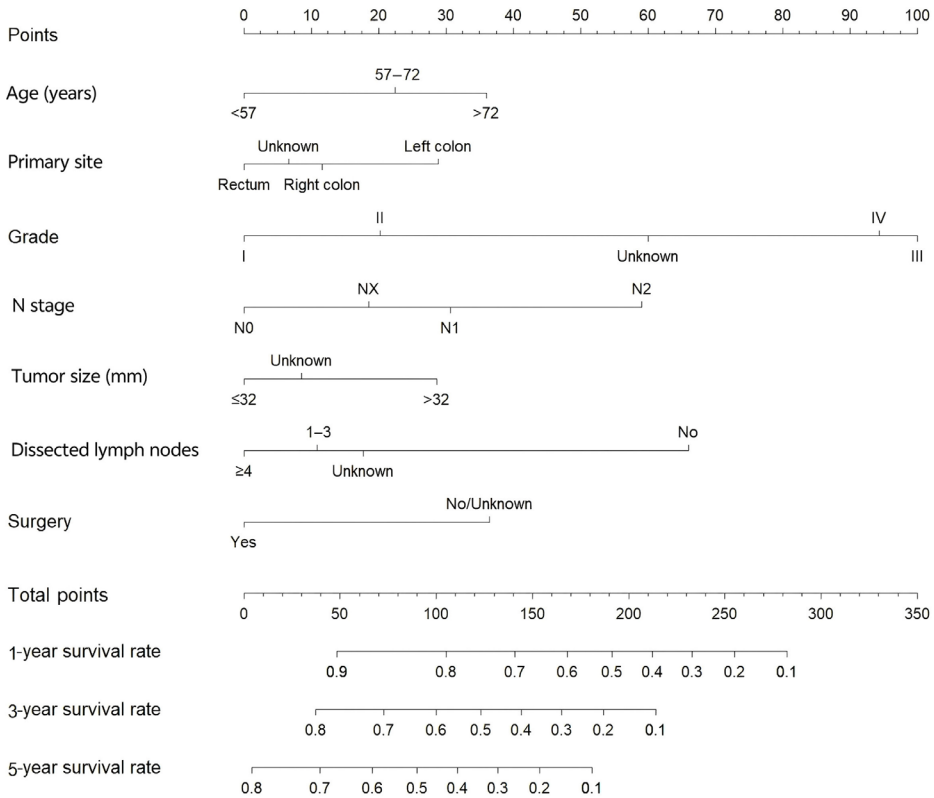

Figure 6 Nomogram for 1-, 3-, and 5-year OS in patients with CRNENs with distant metastasis. CRNENs, colorectal neuroendocrine neoplasms; OS, overall survival.

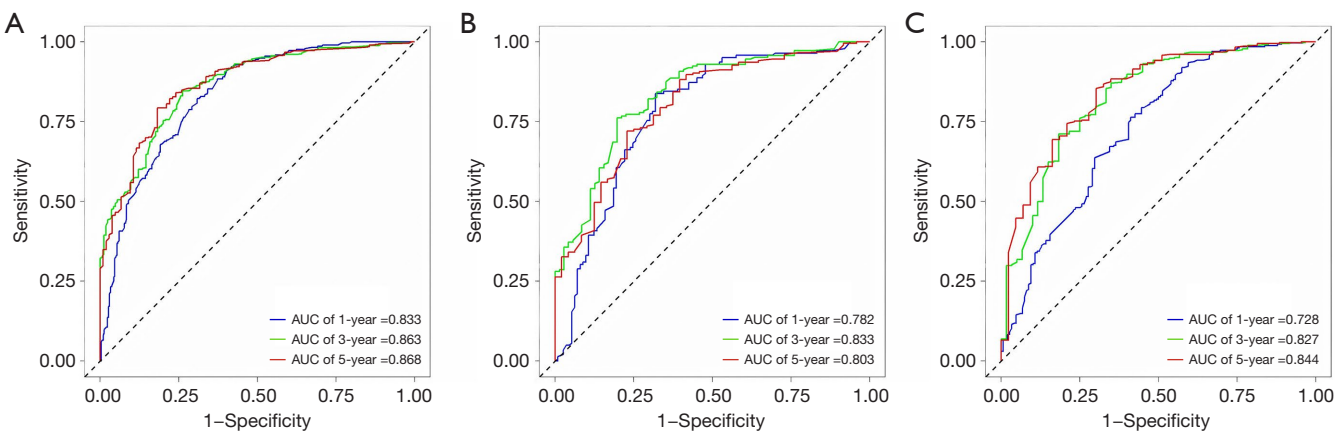

Figure 7 The ROC of 1-, 3-, and 5-year of the training (A), validation (B), and testing (C) sets. AUC, area under the ROC curve; ROC, receiver operating characteristic.

was given a risk score based on the constructed prognostic nomogram, and X-tile software was used to determine the optimal cut-off value of the score (198 points), which was divided into low-risk and high-risk groups. We utilized the Kaplan-Meier method to evaluate the OS of both the low-risk and high-risk groups, as shown in *Figure 11A,11B*. The median survival time in the low-risk group was 41 months (95% CI: 33.0–51.0), with 1-, 3-, and 5-year survival rates

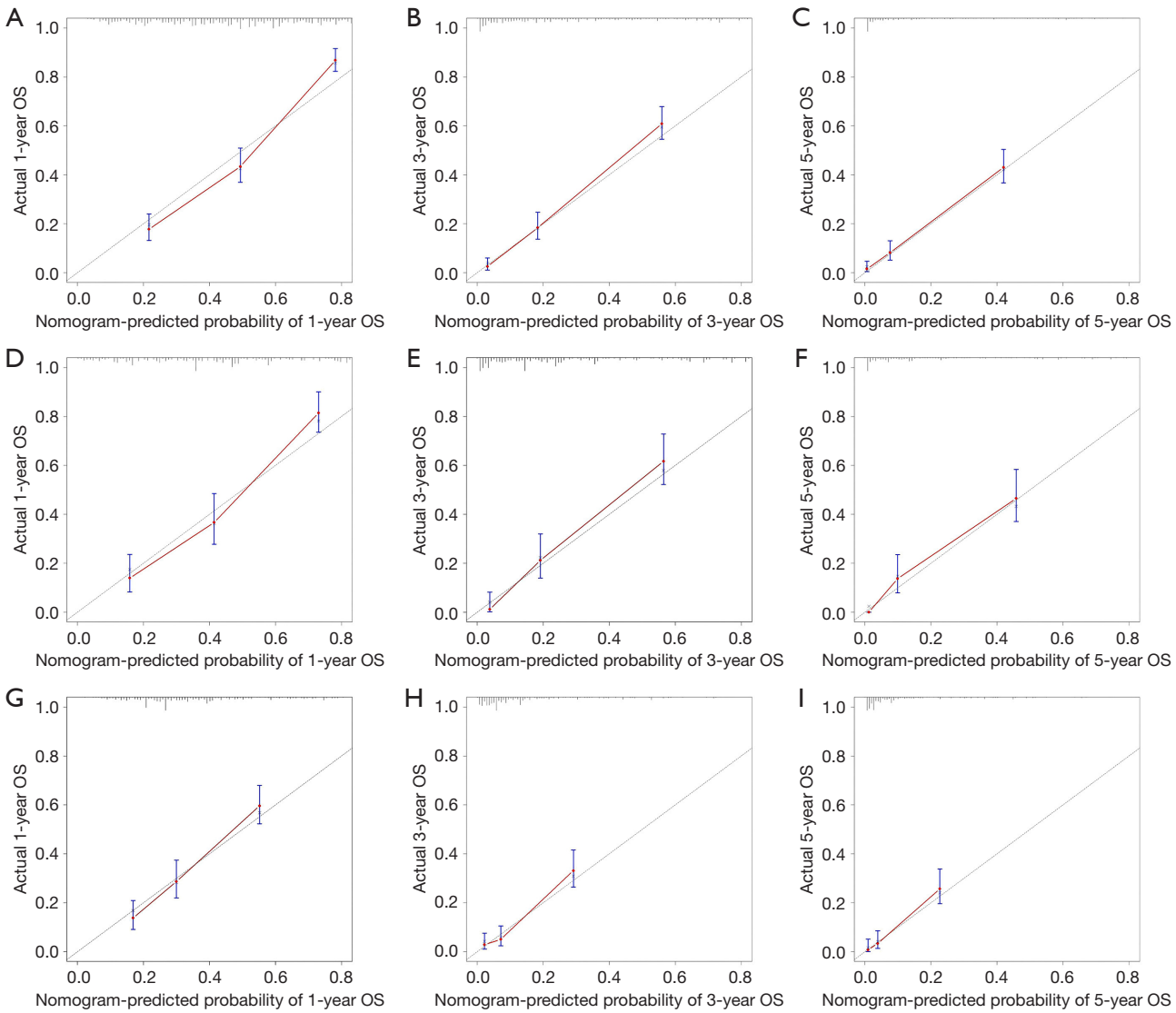

Figure 8 Calibration curve of the nomogram. (A-C) For 1-, 3-, and 5-year OS in the training set; (D-F) for 1-, 3-, and 5-year OS in the validation set; (G-I) for 1-, 3-, and 5-year OS in the testing set. OS, overall survival.

of 77.4%, 52.7%, and 37.4%, respectively. The median survival time in the high-risk group was 7 months (95% CI: 6.0–8.0), and the 1-, 3-, and 5-year survival rates were 33.2%, 10.6%, and 3.9%, respectively. Patients in the validation group were similarly categorized into low-risk and high-risk groups using the same cutoff values. The median survival time in the low-risk group was 44.5 months (95% CI: 27.0–88.0), with 1-, 3-, and 5-year survival rates of 72.4%, 55.3%, and 44.7%, respectively, and in the high-risk group, the median survival time was 7 months (95% CI: 6.0–9.0), with 1-, 3-, and 5-year survival rates of 33.0%, 15.9%, and 9.3%, respectively. Similarly, we grouped the testing set (*Figure 11C*) as well, with a median survival time of 30.5 months (95% CI: 17.0–58.0) and 1-, 3-, and 5-year survival rates of 66.7%, 45.5%, and 34.8% in the low-risk group, and 7 months (95% CI: 7.0–8.0) and 1-, 3-, and 5-year survival rates in the high-risk group of 33.1%, 8.3%, and 5.6%. KM analysis showed that the difference in OS was significant in both the training and validation sets as well as in the low and high-risk groups in the test set, indicating that the predictive scores of the model were related to the prognosis of the patients, and it

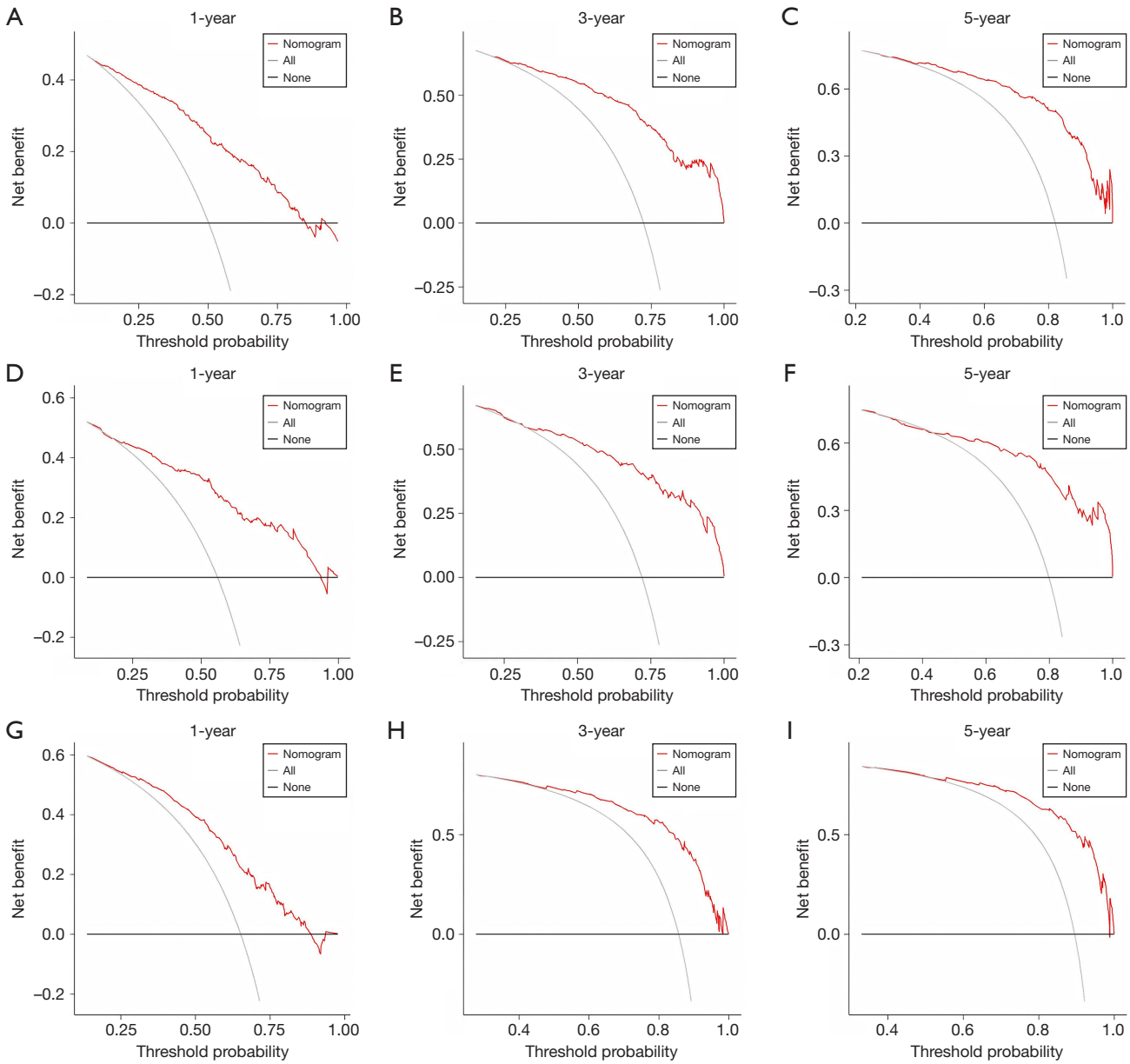

Figure 9 The DCA curves at 1 (A), 3 (B), and 5 years (C) in the training set, 1 (D), 3 (E), and 5 years (F) in the validation set, and 1 (G), 3 (H), and 5 years (I) in the testing set were used to evaluate the reliability of the prognostic nomogram. DCA, decision curve analysis.

was hypothesized that our constructed prognostic columnar plots could be an effective tool for stratifying patients with colorectal NETs with distant metastasis based on the estimated risk of death.

Discussion

CRNENs are tumors with neuroendocrine function and malignant potential (11). In recent years, surgery, traditional chemotherapy, targeted therapy, and immunotherapy have made good development and progress, and the survival of patients with CRNENs has been greatly improved (12-15). However, distant metastasis in patients is still a challenge for treatment and has a great impact on survival time. Identifying distant metastasis is crucial and key to timely treatment, and we urgently need individualized prediction of the probability and prognosis of distant metastasis. Most of the time, positron emission tomography/computed

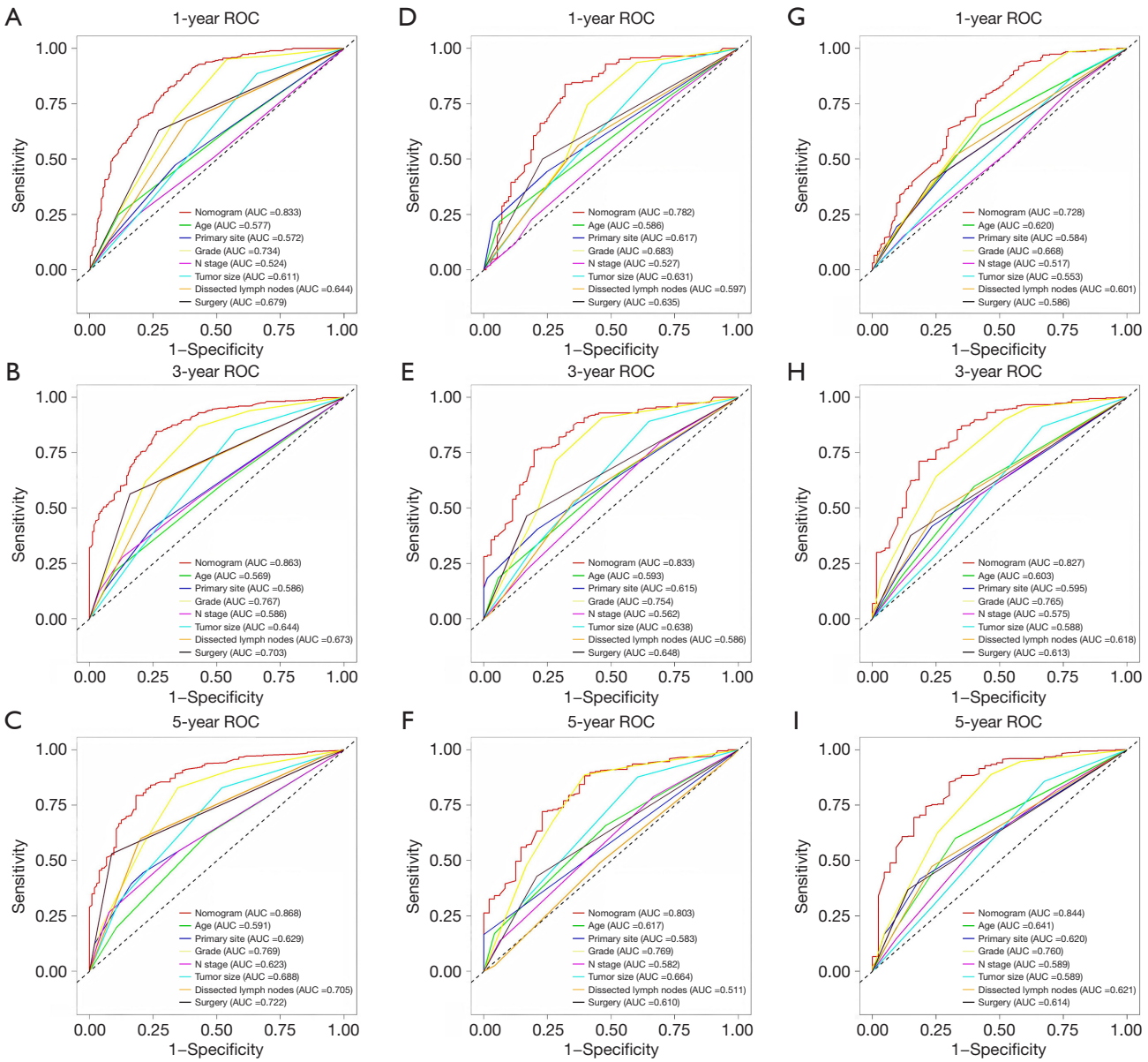

Figure 10 The AUCs were compared for the prognostic nomogram in the training, validation, and testing sets with all independent variables, including age, primary site, grade, N stage, tumor size, dissected lymph nodes, and surgery at 1 (A,D,G), 3 (B,E,H), and 5 years (C,F,I). AUC, area under the ROC curve; ROC, receiver operating characteristic.

tomography (PET/CT) is a diagnostic method for distant metastasis, but it is expensive and may cause radiation damage, studies have found that ionizing radiation can promote tumor metastasis, so it is not suitable for routine screening of distant metastasis (16,17). Therefore, the development of predictive models for screening high-risk and poor-prognosis patients with distant metastasis of CRNENs is crucial, and it can help physicians to adjust the treatment regimen and improve the prognosis of the patients in clinical setting.

According to our findings, several clinical factors may be associated with the occurrence of distant metastasis, including age, race, marriage, primary site, histological grade, T stage, N stage, and tumor size. A similar study of CRNENs found that greater age and tumor size, as well as higher T and N stages, were associated with an increased

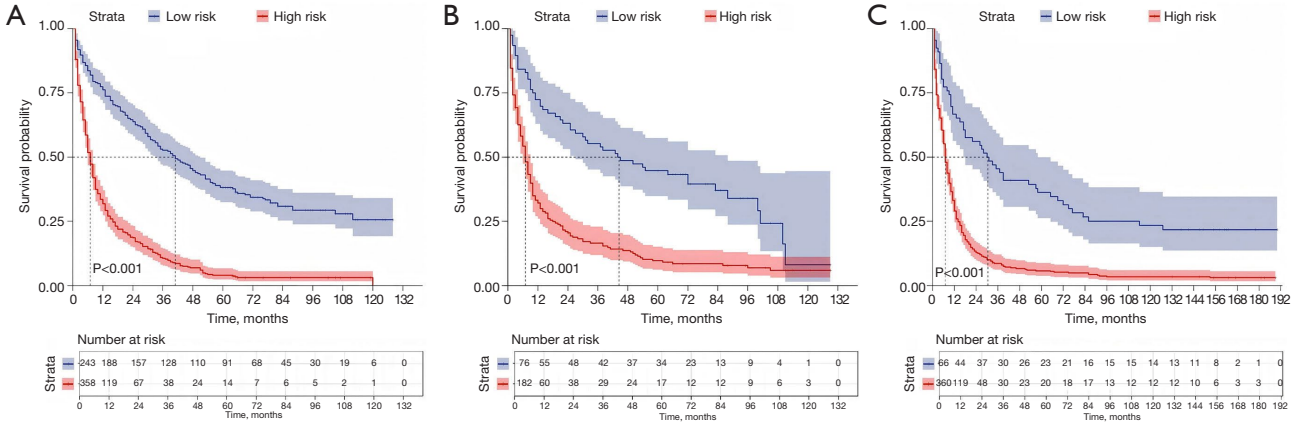

Figure 11 Survival outcomes in the training set (A), validation set (B), and testing set (C) for the high-risk and low-risk groups (according to the prognostic nomogram).

risk of distant metastasis (18). According to Mani *et al.*, patients with rectal NETs greater than 2 cm exhibited a higher risk of metastasis, with 60–80%, compared to patients with tumors less than 1 cm, of only 2% for tumors less than 1 cm (19). Another study also showed that ≥1.15 cm tumors were more likely to have distant metastasis (20). In this study, our results also showed that a higher rate of distant metastasis should be considered for patients with tumors larger than 32 mm and a T stage of T4, presumably because the larger the tumor, the higher the chance of invasion of blood vessels, resulting in a higher probability of cancer cells entering the blood for distant metastasis. In addition, we were surprised to find that patients with CRNENs younger than 57 years of age were more likely to have distant metastasis than patients older than 72 years of age. Wang *et al.* studied the relationship between age and distant metastasis of CRNENs, but the results showed that the risk of metastasis was significantly increased in patients 60 years of age and older compared with those under 60 years of age (18). One study suggests that it may have something to do with the immune system (21). Histologic grade is also a key factor in distant metastasis. Patients with grade IV had a significantly higher risk of developing distant metastasis compared with grade I patients, which is similar to a previous study (20). We hypothesized that this may be because of the highly aggressive and metastatic biological behavior of poorly histologically graded tumors. Our study also found that the risk of distant metastasis was also related to tumor location, with the left colon being more likely to have distant metastasis than the rectum. Previous studies have also shown that colonic NETs metastasize more frequently than rectal NETs (22,23). As a previous study have shown, married cancer patients have better survival rates (24). This may be due to the fact that married patients have a better socio-economic status than unmarried patients and thus have better access to health care (25). It has also been shown that married patients receive psychological and physical support and encouragement from their spouses, leading to better adherence to treatment (26). This may also explain why unmarried patients with CRNENs are more likely to develop distant metastasis. In addition, our study found that the likelihood of distant metastasis in patients with CRNENs was related to race, with Whites having a lower risk of developing distant metastases compared to other (American Indian/Alaska Native, Asian/Pacific Islander) races, which requires more further research. In conclusion, patients with these risk factors should be closely tested during follow-up.

In this study, we identified independent prognostic factors for OS in distant metastasis of CRNENs. The results suggest that older age, left-sided colon site, low histological grade, stage N2, larger tumor, fewer number of lymph nodes cleared, and patients who did not undergo surgery at the primary site may be associated with poorer prognosis, which suggests that we should pay great attention to these patients, consider the condition comprehensively and choose the treatment plan carefully. The older the person, the worse the prognosis, which may be related to poor health, comorbidities, and an inability to tolerate the side effects of surgeries, medications, and so on. In this study, we sought to explore the impact of different primary sites on the survival of patients with distant metastasis, and our

results suggest that the rectum is associated with a better prognosis compared to the left colon. Similar results were reported in a previous study, in which the survival of patients with rectal NECs was significantly better than that of patients with colonic NECs for patients with metastasis (27). A higher risk of death has also been reported for right-sided colonic neuroendocrine neoplasms than for left-sided colonic neuroendocrine neoplasms (28). However, this difference did not occur in our findings and may be related to selection bias. Furthermore, the results of our analysis showed that clearing a greater number of lymph nodes was associated with better survival, which is in general agreement with the findings of Bernick *et al.* (7). Our study found that patients with CRENEs with distant metastases could benefit from surgery, probably because surgical resection can effectively break up the tumor. Wang *et al.* reported that surgical resection of the primary site and clearance of a greater number of lymph nodes resulted in a survival benefit for patients with CRNEC (29). A study also showed a significant prolongation of overall median survival in patients who underwent surgical resection of the primary site (30). However, some studies have also shown that surgery and non-surgery do not result in a significant survival difference for metastatic patients (31,32). So, the efficacy of the surgery needs to be evaluated with further studies. In addition, a retrospective study by Zhang *et al.* that included 49 cases found that tumor size was not associated with survival time in patients with CRNENs (33). Instead, our analysis showed that the larger the tumor, the worse the prognosis, a difference that needs to be further confirmed by more studies. A study based on the National Cancer Database (NCDB) found that the 5-year survival rate for patients with stage N2 NETs of the colon was 15.7%, compared to 63.9% for stage N1a patients (34). This is in agreement with our findings. In most tumors, stage and histological grade are considered to be relatively consistent prognostic factors, and likewise in our study, they remain important predictors of prognosis. However, to date, few studies have fully explored this point for CRNENs. In addition, our study showed that marital status was not associated with patients' prognosis. However, the results of Xiao *et al.* showed that the survival rate of married patients with CRNENs was significantly higher than that of unmarried patients, and the prognosis of widowed patients was the worst, presumably because spousal support improves prognosis (35). The prognosis of patients with distant metastasis from CRNENs cannot be determined by any one factor and needs to be considered comprehensively, especially the factors mentioned above.

To more easily identify patients with high-risk CRNENs with poor prognoses for distant metastasis, we divided patients into two groups based on the best cutoff value of the column line graph score. Among them, patients with a score of 198 or more are at high risk. For these patients, attention should be focused.

In this study, we investigated the factors for the occurrence and prognosis of distant metastasis of CRNENs, and we constructed two models using these risk and prognostic factors, and the nomograms showed good predictive performance in both the training cohort and the validation cohort. The predictive model can provide a practical theoretical basis for clinical decision-making and follow-up of patients.

There are some limitations in this study. This study was retrospective, and some cases were excluded due to some missing information, which caused some bias; The study data were obtained from U.S. populations, and the findings may not represent other regions, especially Asia and Europe. In addition, the SEER database does not provide information on clinical markers such as chromogranin A (CgA), synaptophysin (SYP), and neuron-specific enolase (NSE) that may be associated with distant metastasis. Therefore, the nomograms constructed in this study will require further validation with multi-center and large-sample external data in the future.

Conclusions

In this paper, we investigated the risk factors and prognostic factors for distant metastasis in patients with CRNENs, and successfully constructed two nomograms for predicting distant metastasis and prognosis, which can help clinical staff make better clinical decisions.

Acknowledgments

The authors are grateful to the SEER database, which provides publicly available data used in this study.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2018/rc

Peer Review File: Available at https://tcr.amegroups.com/

article/view/10.21037/tcr-24-2018/prf

Funding: This work was supported by the Science and Technology Program of Gansu Province (No. 22JR5RA922) and the Intramural Fund of The First Hospital of Lanzhou University (No. ldyyyn2018-63).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2018/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Zhang Y, Shang L, Zhang PP, et al. Clinicopathological features and prognostic validity of the European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) 8th staging systems in colonic neuroendocrine neoplasms. Cancer Med 2019;8:5000-11.
2. Mandair D, Caplin ME. Colonic and rectal NET's. Best Pract Res Clin Gastroenterol 2012;26:775-89.
3. Kooyker AI, Verbeek WH, van den Berg JG, et al. Change in incidence, characteristics and management of colorectal neuroendocrine tumours in the Netherlands in the last decade. United European Gastroenterol J 2020;8:59-67.
4. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017;3:1335-42.
5. Basuroy R, Haji A, Ramage JK, et al. Review article: the investigation and management of rectal neuroendocrine tumours. Aliment Pharmacol Ther 2016;44:332-45.
6. Starzyńska T, Londzin-Olesik M, Bałdys-Waligórska A, et al. Colorectal neuroendocrine neoplasms - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol 2017;68:250-60.
7. Bernick PE, Klimstra DS, Shia J, et al. Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum 2004;47:163-9.
8. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934-59.
9. Ding X, Tian S, Hu J, et al. Risk and prognostic nomograms for colorectal neuroendocrine neoplasm with liver metastasis: a population-based study. Int J Colorectal Dis 2021;36:1915-27.
10. Fang C, Wang W, Feng X, et al. Nomogram individually predicts the overall survival of patients with gastroenteropancreatic neuroendocrine neoplasms. Br J Cancer 2017;117:1544-50.
11. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-72.
12. Zhu H, Zhao S, Zhang C, et al. Endoscopic and surgical treatment of T1N0M0 colorectal neuroendocrine tumors: a population-based comparative study. Surg Endosc 2022;36:2488-98.
13. Nakano M, Shimada Y, Matsumoto Y, et al. Efficacy of BRAF inhibitor and anti-EGFR antibody in colorectal neuroendocrine carcinoma. Clin J Gastroenterol 2022;15:413-8.
14. Xing J, Ying H, Li J, et al. Immune Checkpoint Markers in Neuroendocrine Carcinoma of the Digestive System. Front Oncol 2020;10:132.
15. Chen X, Wang X, Abadi M, et al. Colorectal Large-Cell Neuroendocrine Carcinoma: Case Report and Literature Review for Potential Novel Therapeutic Options. Clin Colorectal Cancer 2020;19:61-4.
16. Sundahl N, Duprez F, Ost P, et al. Effects of radiation on the metastatic process. Mol Med 2018;24:16.
17. Rodríguez-Fraile M, Cózar-Santiago MP, Sabaté-Llobera A, et al. FDG PET/CT in colorectal cancer. Rev Esp Med Nucl Imagen Mol (Engl Ed) 2020;39:57-66.
18. Wang Z, Liu Q. Development of novel prediction models for nodal and distant metastasis in G1 and G2 colorectal neuroendocrine tumors. Int J Colorectal Dis 2023;38:37.
19. Mani S, Modlin IM, Ballantyne G, et al. Carcinoids of the

rectum. J Am Coll Surg 1994;179:231-48.
20. Concors SJ, Sinnamon AJ, Folkert IW, et al. Predictors of Metastases in Rectal Neuroendocrine Tumors: Results of a National Cohort Study. Dis Colon Rectum 2018;61:1372-9.
21. Purushotham A, Shamil E, Cariati M, et al. Age at diagnosis and distant metastasis in breast cancer--a surprising inverse relationship. Eur J Cancer 2014;50:1697-705.
22. Madani A, Thomassen I, van Gestel YRBM, et al. Peritoneal Metastases from Gastroenteropancreatic Neuroendocrine Tumors: Incidence, Risk Factors and Prognosis. Ann Surg Oncol 2017;24:2199-205.
23. Jiang M, Tan Y, Li X, et al. Clinicopathological Features and Prognostic Factors of Colorectal Neuroendocrine Neoplasms. Gastroenterol Res Pract 2017;2017:4206172.
24. Krajc K, Miroševič Š, Sajovic J, et al. Marital status and survival in cancer patients: A systematic review and meta-analysis. Cancer Med 2023;12:1685-708.
25. Mihor A, Tomsic S, Zagar T, et al. Socioeconomic inequalities in cancer incidence in Europe: a comprehensive review of population-based epidemiological studies. Radiol Oncol 2020;54:1-13.
26. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31:3869-76.
27. Patta A, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. Anticancer Res 2011;31:975-8.
28. Xu GH, Zou HW, Grossman AB. Difference in survival between right- versus left-sided colorectal neuroendocrine neoplasms. J Zhejiang Univ Sci B 2019;20:933-9.
29. Wang Q, Yin R, Tang W, et al. Resection of primary lesion with chemotherapy improves the survival of patients with metastatic colorectal neuroendocrine carcinoma. Zhejiang Da Xue Xue Bao Yi Xue Ban 2022;51:594-602.
30. Tierney JF, Chivukula SV, Wang X, et al. Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors. Surgery 2019;165:644-51.
31. Wu Z, Yu D, Zhao S, et al. The efficacy of chemotherapy and operation in patients with colorectal neuroendocrine carcinoma. J Surg Res 2018;225:54-67.
32. Yu G, Liu S, Wang Z, et al. Palliative primary tumor resection may not offer survival benefits for patients with unresectable metastatic colorectal neuroendocrine neoplasms, one multicenter retrospective cohort study. BMC Surg 2024;24:85.
33. Zhang Y, Xie J, Wang J, et al. Clinicopathological and Prognostic Analysis of Neuroendocrine Carcinoma of the Colorectum. Adv Clin Exp Med 2016;25:719-24.
34. Fields AC, McCarty JC, Lu P, et al. Colon Neuroendocrine Tumors: A New Lymph Node Staging Classification. Ann Surg Oncol 2019;26:2028-36.
35. Xiao K, Zhao Y, Cai Y, et al. The effect of marital status on the survival of patients with colorectal neuroendocrine neoplasms: an analysis of the SEER database. Rev Esp Enferm Dig 2020;112:109-17.

Cite this article as: Bai Y, Lei N, Zhang P, Yang Q, Feng F, Zhao Y. Risk factors, prognostic factors and nomograms for distant metastasis in colorectal neuroendocrine neoplasms: a SEER-based study. Transl Cancer Res 2025;14(3):1576-1595. doi: 10.21037/tcr-24-2018