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Nomogram Predicts the Cancer-Specific Survival of Patients with Gastrointestinal Mixed Adenoneuroendocrine Carcinoma

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Mixed adenoneuroendocrine carcinoma; Gastrointestinal; SEER; Prognosis; Nomogram

1. Abstract

1.1. Background: Our study aims to establish a nomogram model to predict Cancer-specific survival of patients with gastrointestinal mixed adenoneuroendocrine carcinoma.

1.2. Methods: Patients diagnosed with MANEC were identified from the Surveillance, Epidemiology and End Results (SEER) database. The patients included after randomization were divided into training cohort and verification cohort. Through the Cox regression analysis of the training cohort, a nomogram model was established. Internal and external validations were conducted to confirm the accuracy of the model.

1.3. Results: A total of 478 patients were included in the study. After randomization, a total of 358 people entered the training cohort, and 120 people entered the validation cohort. The 1-year, 3-year and 5-year Cancer-specific survival (CSS) rates were 81.8%, 60.0% and 52.3% respectively. Multivariate analysis demonstrated that advanced age [(≥60 and <80) Hazard Ratio (HR): 1.596, 95%Confidence Interval (95%CI): 1.100-2.316, P=0.014; (≥80) HR: 2.411, 95%CI: 1.368-4.250, P=0.002], advanced grade [(G3) HR: 3.097, 95%CI: 1.332-7.200, P=0.009; (G4) HR: 3.546, 95%CI: 1.262-9.968, P=0.016] were independent risk factors of CSS, while SEER stage [(localized) HR: 0.204, 95%CI: 0.102-0.407, P<0.001], chemotherapy [HR: 0.541, 95%CI: 0.342-0.773, P=0.001] were independent protective factors. The original and adjusted C-index of nomogram model were 0.793 and 0.778 respectively. Calibration plots showed that the 3-year and 5-year CSS predicted by the model had a high consistency with the actual situation according to both the training and validation cohort.

1.4. Conclusion: The nomogram model has good application value for predicting CSS in MANEC. We still need more study for further validation.

2. Introduction

Mixed Adenoneureoendocrine Carcinoma (MANEC) is a rare pathological type of tumor. It is currently found that MANEC is mainly located in the gastrointestinal tract and other special parts such as the pancreas, gallbladder, bladder and uterus [9, 14, 16]. According to epidemiological studies, the incidence of gastrointestinal MANEC increased from 0.23 cases per 1 million populations in 2000 to 1.16 cases per 1 million populations in 2016 [17, 18]. In 2010, World Health Organization (WHO) defined it as a special tumor type with both adenocarcinomatous and neuroendocrine components, and the proportion of each component was higher than 30% (Fléjou 2011). For diagnosis, it mainly depends on immunohistochemistry. It is generally accepted that when two of the three biomarkers (synaptophysin, chromogranin, and CD56) are positive, the diagnosis is established [6, 12]. Due to the rarity, there is insufficient data to show its clinical and pathological features. Moreover, reported prognostic data are currently quite different [1-2, 17-18]. For its treatment, we still do not have unified standard. From limited pathology reports and retrospective studies, we found that the main treatment strategies were surgery and chemotherapy [8, 11, 13, 20].

The clinical and prognostic characteristics of gastrointestinal MANEC remain unclear, which also limits the relevant decision-making in

clinical practice. Therefore, in order to further research and provide further evidence for clinical practice, we will establish a prognostic prediction model for the gastrointestinal MANEC using the Surveillance, Epidemiology, and End Results (SEER) database. We present the following article in accordance with the STROBE reporting checklist."

3. Materials and Methods

3.1. Ethics Statement

The Surveillance, Epidemiology, and End Results (SEER) Program is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS). After signing the applicable agreement, researchers can legally use the relevant data without ethical approval. We obtained the research related data through the account 10456-Nov2019.

3.2. Patients

Persistent data between 1975 and 2016 were obtained using the SEER * State v8.3.6 tool. Inclusion criteria are: (1) (Site and Morphology. ICD-0-3 Hist / behav, malignant) = 8244/3: Mixed adenoneuroendocrine carcinoma (ICD-O-3 update); (2) Race and age at diagnosis are clearly documented; (3) Diagnostic confirmation is positive histology; (4) Tumor site is the stomach and intestines. After getting the information we screened again to obtain the final data. The main exclusion criteria for secondary screening are: (1) Not first tumor; (2) SEER summary stage does not know; (3) Tumor size is blank. The remaining patients were enrolled in the initial study.

3.3. Covariates and outcomes

Covariates included sex, age at diagnosis, race, location, differentiation, lymph nodes positive, distant metastasis, tumor size, surgery, chemotherapy, radiotherapy. The principal outcomes included the predicted probability of 1-year, 3-year and 5-year overall Cancer-specific survival (CSS) on the basis of baseline characteristics. CSS was defined as the time interval from diagnosis to the most recent follow-up date or date of death caused by MANEC.

3.4. Statistical Analysis

First, we used IBM SPSS statistics 21 (IBM Corp, Armonk, NY, United States) for data analysis. We randomized the included cases depending on the ratio of 3: 1, of which 3/4 entered the training cohort and 1/4 entered the validation cohort. Univariate analysis of CSS was operated using training set according to the Cox proportional hazards regression model. And covariates with P <0.2 were included into Cox multivariate regression to find independent influencing factors. Then Graphpad Prism 8.0.2 was utilized to generate survival curves. A two-sided test with P-value <0.05 was considered statistically significant.

Finally, according to the Cox regression results, a visual nomogram model of CSS independent risk factors was established with R software (version 3.6.3). Then we adopted the bootstrap method with 1000 boot-strapping resamples for internal and external validation. External validation was executed with the validation cohort. In order to evaluate the accuracy of the model, we calculated the concordance index (C-index) and the estimated calibration curve. The C-index refers to the probability that the results derived from the model for two randomized selected patients are consistent with the results obtained from the actual observation. A C-index of 0.5 means that the model has no predictive power, and a C-index of 1 means that the model's prediction is completely coherent with the actual result.

4. Results

4.1. Patients and Demographics

A total of 478 patients diagnosed with MANEC were chosen from the SEER database between 1973 and 2013. After randomization, 358 people entered the training cohort and 120 people entered the validation cohort. The specific screening process is shown in (Figure 1). Overall, MANEC was more prevalent among white race (83.3%), but there was no significant difference in gender. The median age at diagnosis was 60 years (10-89 years). The most frequent tumor sites were appendix (60.9%) and large intestine (30.1%). In addition, we found that the proportion of positive regional lymph nodes and distant metastasis reached 65.5% and 30.3%, respectively. In terms of treatment, surgery (92.7%) was still the most important treatment, but chemotherapy (46.4%) also played an important part. More specifically, clinicopathological characteristics of training cohort and validation cohort are listed in (Table 1).

4.2. Survival Analysis

In the training cohort, the median survival time was 28 months (0-154 months). The 1-year, 3-year and 5-year CSS rates were 81.8%, 60.0% and 52.3% respectively. Through univariate analysis, we found that age, site, grade, positive lymph node, distant metastasis, SEER stage, surgery, chemotherapy, tumor size were the influencing factors of CSS. After Cox multivariate analysis, we found that advanced age [(≥60 and <80) Hazard Ratio (HR): 1.596, 95% Confidence Interval (95%CI): 1.100-2.316, P=0.014; (≥80) HR: 2.411, 95%CI: 1.368-4.250, P=0.002], advanced grade [(G3) HR: 3.097, 95%CI: 1.332-7.200, P=0.009; (G4) HR: 3.546, 95%CI: 1.262-9.968, P=0.016] were independent risk factors of CSS, while SEER stage [(localized) HR: 0.204, 95%CI: 0.102-0.407, P<0.001], chemotherapy [HR: 0.541, 95%CI: 0.342-0.773, P=0.001] were independent protective factors. Detailed information can be consulted on (Table 2). The survival curve is illustrated in (Figure 2). In addition, when we performed univariate analysis and multivariate analysis, we found that the results of adjuvant chemotherapy were contradictory. Therefore, we further conducted a subgroup analysis based on stage and found that adjuvant chemotherapy is a protective factor for prognosis in patients with distant metastasis (P=0.0021), and a risk factor for prognosis in patients with regional stage (P=0.0065) (Figure 3).

Table 1: The demographic and clinicopathological characteristics of the training cohort and validation cohort.

Characteristic	Training Cohort (n=358)(%)	Validation Cohort (n=120)(%)	*P*
Race			0.325
White	293(81.8)	105(87.5)	
Black	39(10.9)	10(8.3)	
Other	26(7.3)	5(4.2)	
Sex			0.267
Male	191(53.4)	57(47.5)	
Femal	167(46.6)	63(52.5)	
Age			0.277
<60	177(49.4)	51(42.5)	
≥60 and <80	149(41.6)	60(50.0)	
≥80	32(8.9)	9(7.5)	
Site			0.094
Stomach	12(3.4)	10(8.3)	
Appendix	217(60.6)	74(61.7)	
Small intestine	15(4.2)	6(5.0)	
Large intestine	114(31.8)	30(25.0)	
Grade			0.239
G1	35(9.8)	12(10.0)	
G2	53(14.8)	21(17.5)	
G3	124(34.6)	40(33.3)	
G4	22(6.1)	14(11.7)	
Unknown	124(34.6)	33(27.5)	
SEER stage			0.361
Regional	139(38.8)	53(44.2)	
Localized	99(27.7)	35(29.2)	
Distant	120(33.5)	32(26.7)	
Lymph side positive			0.567
No	121(33.8)	44(36.7)	
Yes	237(66.2)	76(63.3)	
Distant metastasis			0.312
No	245(68.4)	88(73.3)	
Yes	113(31.6)	32(26.7)	
Tumor size			0.869
≦3cm	112(31.3)	41(34.2)	
>3cm and ≦5cm	77(21.5)	26(21.7)	
>5cm	66(18.4)	23(19.2)	
Not measured	103(28.4)	30(25.0)	
Surgery			0.067
No	31(8.7)	4(3.3)	
Yes	327(91.3)	116(96.7)	
Chemotherapy			0.489
No	195(54.5)	61(50.8)	
Yes	163(45.5)	59(49.2)	
Radiotherapy			0.738
No	349(97.5)	118(98.3)	
Yes	9(2.5)	2(1.7)	

Table 2: Univariate and multivariate analyses of Cancer-specific Survival (CSS) using training cohort according to the Cox proportional hazards regression model.

Characteristic	Univariable analysis		Multivariable analysis	
	HR [95%CI]	P-value	HR [95%CI]	P-value
Race		0.161		0.353
White	Reference		Reference	
Black	1.304[0.805-2.111]		1.334[0.790-2.253]	0.281
Other	0.584[0.273-1.250]		0.706[0.318-1.563]	0.39
Sex		0.158		0.72
Male	Reference		Reference	
Femal	1.256[0.915-1.722]		0.938[0.663-1.328]	
Age		<0.001		0.003
<60	Reference		Reference	

≥60 and <80	1.621[1.151-2.282]		1.596[1.100-2.316]	0.014
≥80	3.240[1.974-5.318]		2.411[1.368-4.250]	0.002
Site		0.002		0.112
Stomach	Reference		Reference	
Appendix	0.315[0.157-0.630]		0.437[0.182-1.054]	0.065
Small intestine	0.429[0.165-1.121]		0.418[0.132-1.327]	0.139
Large intestine	0.524[0.258-1.063]		0.681[0.300-1.548]	0.359
Grade		<0.001		0.046
G1	Reference		Reference	
G2	1.415[0.636-3.151]		2.018[0.775-5.251]	0.15
G3	3.065[1.524-6.163]		3.097[1.332-7.200]	0.009
G4	3.040[1.232-7.501]		3.546[1.262-9.968]	0.016
Unknown	1.603[0.789-3.258]		2.178[0.941-5.042]	0.069
SEER stage		<0.001		<0.001
Regional	Reference		Reference	
Localized	0.227[0.118-0.436]		0.204[0.102-0.407]	<0.001
Distant	3.800[2.676-5.397]		1.663[0.650-4.255]	0.289
Lymph node positive		<0.001		0.067
No	Reference		Reference	
Yes	4.445[2.827-6.990]		0.560[0.312-1.040]	
Distant metastasis		<0.001		0.059
No	Reference		Reference	
Yes	5.786[4.164-8.040]		2.411[0.966-6.037]	
Tumor size		<0.001		0.186
≦3cm	Reference		Reference	
>3cm and ≦5cm	2.108[1.337-3.322]		1.531[0.927-2.531]	0.096
>5cm	2.726[1.703-4.364]		1.690[1.017-2.809]	0.043
Not measured	1.273[0.819-1.979]		1.488[0.894-2.476]	0.126
Surgery		<0.001		0.067
No	Reference		Reference	
Yes	0.278[0.178-0.436]		0.570[0.312-1.040]	
Chemotherapy		<0.001		0.001
No	Reference		Reference	
Yes	1.898[1.371-2.626]		0.514[0.342-0.773]	
Radiotherapy		0.924		NA
No	Reference		NA	
Yes	0.953[0.353-2.573]		NA	

Note: HR, Hazard Ratio; 95%CI, 95% Confidence Interval; NA, Not Analyzed

Table 3:

Characteristic	Localized stage			Regional stage			Distant metastasis stage		
	UA	MA		UA	MA		UA	MA	
	P	HR[95%CI]	*P*	*P*	HR[95%CI]	*P*	*P*	HR[95%CI]	*P*
Race	0.614			0.703			0.185		0.123
White								Reference	
Black								1.908[0.988-3.685]	0.054
Other								0.682[0.161-2.884]	0.603
Sex	0.289			0.356			0.655		
Male									
Femal									
Age	0.216			0.002		0.023	0.033		0.584
<60					Reference			Reference	
≥60 and <80					2.100[1.013-4.352]	0.046		1.133[0.705-1.820]	0.607
≥80					3.593[1.344-9.604]	0.011		1.472[0.705-3.073]	0.304
Site	0.005		0.008	0.001		0.293	0.004		0.004
Stomach		Reference			Reference			Reference	
Appendix		0.039[0.006-0.247]	0.001		0.842[0.201-3.519]	0.814		0.989[0.249-3.923]	0.987
Small intestine					2.476[0.434-14.113]	0.307		0.193[0.027-1.376]	0.101
Large intestine					0.745[0.195-2.844]	0.667		1.866[0.494-7.040]	0.357
Grade	0.671			0.007		0.088	0.369		

G1					Reference				
G2					1.422[0.352-5.740]	0.621			
G3					1.892[0.515-6.953]	0.337			
G4					2.327[0.492-11.008]	0.287			
Unknown					0.614[0.177-2.132]	0.443			
Lymph side positive	0.409			<0.001		0.013	0.013		0.05
No					Reference			Reference	
Yes					3.615[1.317-9.924]			2.044[1.000-4.182]	
Tumor size	0.333			0.05		0.78	0.04		0.112
≦3cm					Reference			Reference	
>3cm and ≦5cm					1.040[0.493-2.193]	0.918		2.400[1.150-5.010]	0.02
>5cm					1.465[0.662-3.242]	0.345		1.884[0.898-3.956]	0.094
Not measured					0.934[0.335-2.604]	0.896		1.453[0.712-2.966]	0.305
Surgery	0.638			0.008		0.016	0.003		0.009
No					Reference			Reference	
Yes					0.167[0.039-0.720]			0.418[0.217-0.806]	
Chemotherapy	0.106		0.401	0.071		0.785	<0.001		<0.001
No		Reference			Reference			Reference	
Yes		1.821[0.449-7.376]			1.111[0.522-2.364]			0.260[0.157-0.428]	
Radiotherapy	0.751			0.821			0.255		
No									
Yes									

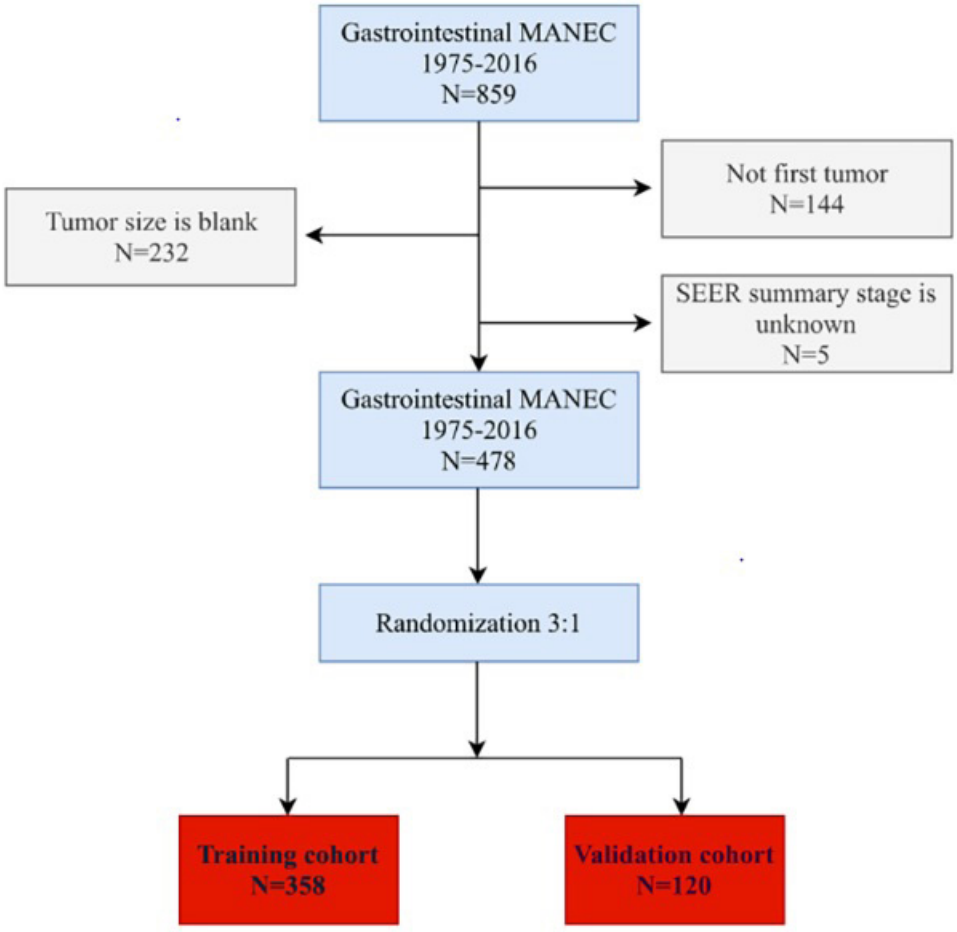

Figure 1: Patient screening flowchart.

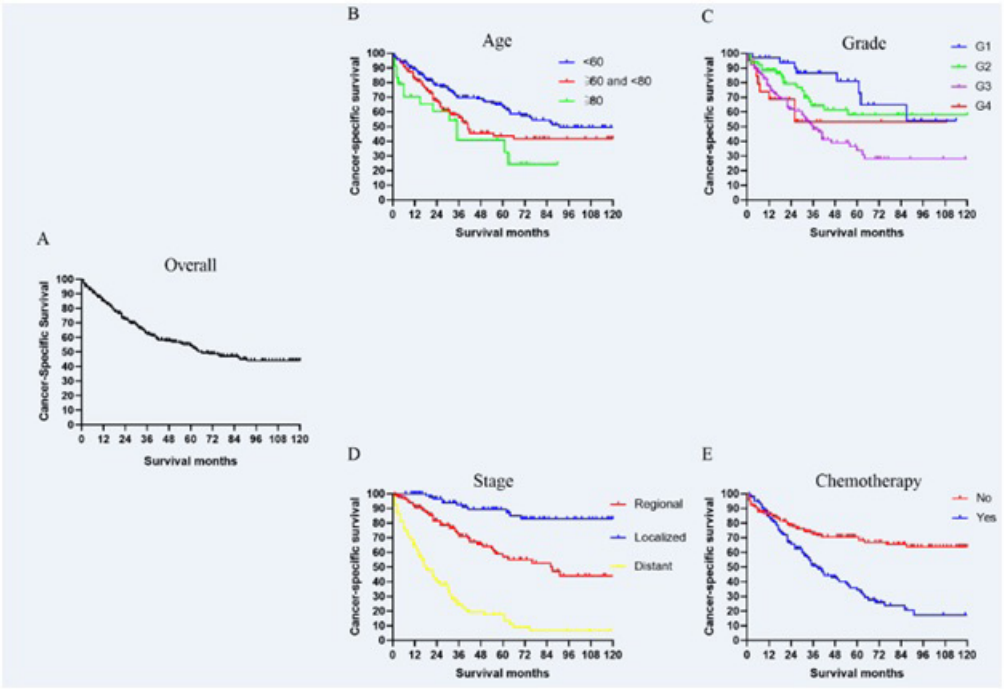

Figure 2: Kaplan–Meier survival curves of Cancer-specific Survival (CSS). (A) Overall; (B) Age; (C) Grade; (D) Stage

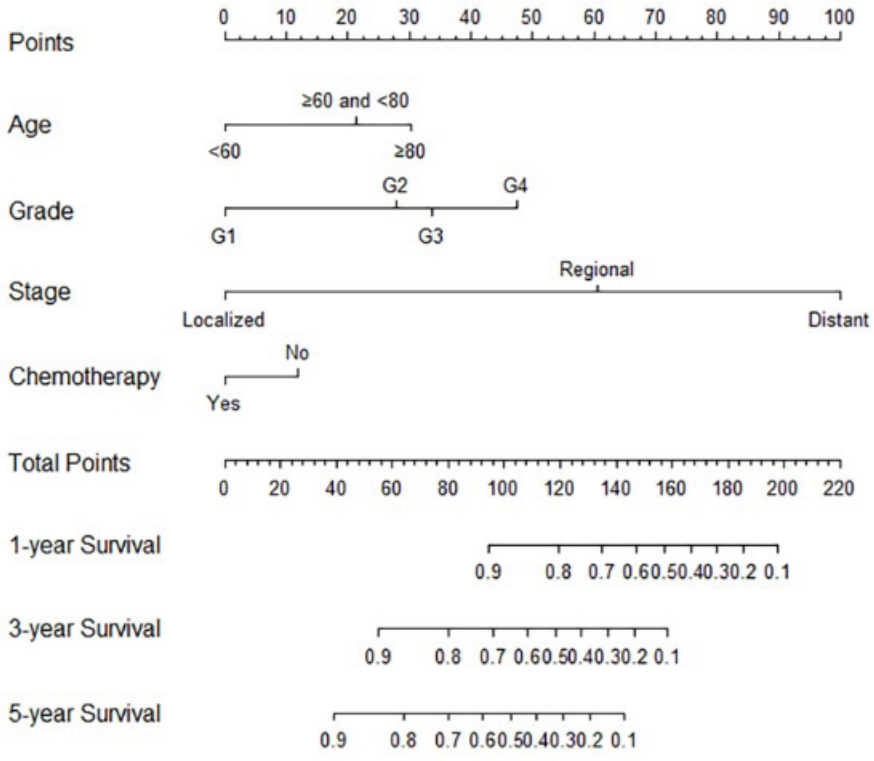

Figure 3: The impact of chemotherapy on the survival of patients with different stages. NC: non-chemotherapy; C: chemotherapy

4.3. Nomogram and Validations

Based on the Cox regression results, the MANEC survival prediction nomogram model was established (Figure 4). With the help of validation cohort data, we conducted external validation of the model. Through internal and external validation, we calculated that the original and adjusted C-index were 0.793 and 0.778. The calibration plots were utilized to verify the similarity between the predicted survival rate of the nomogram and the actual survival rate. The x axis represents the survival rate predicted by the nomogram, whereas the y axis presents the actual survival rate obtained using the Kaplan–Meier method. The results demonstrated that the 3-year and 5-year CSS predicted by the model had a high consistency with the actual situation according to both the training and validation cohort (Figure 5).

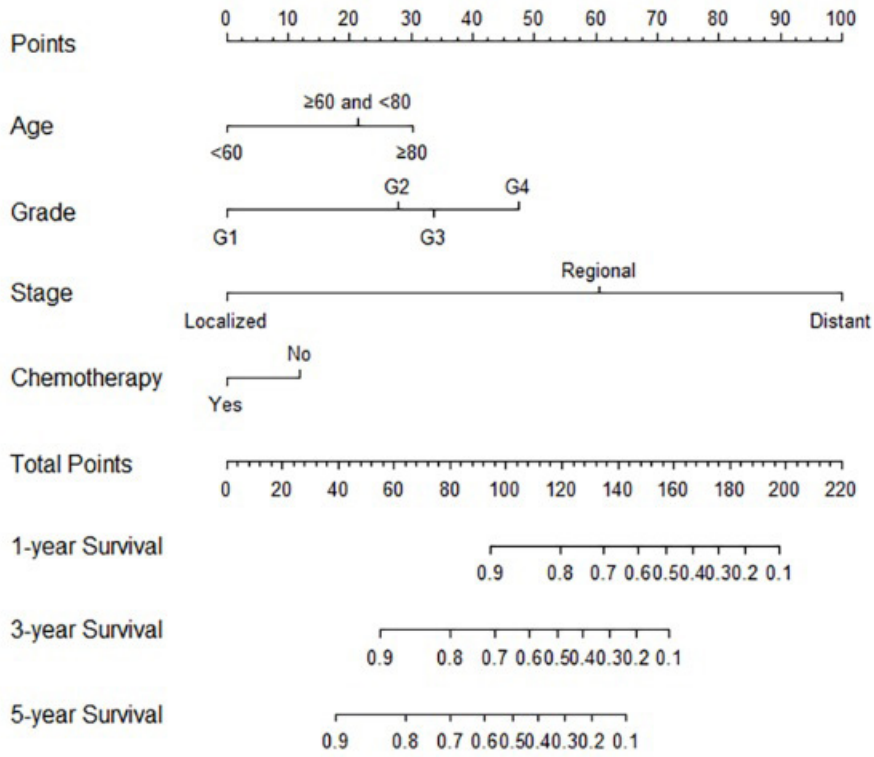

Figure 4: The nomogram predicts the probability of CSS in 1 -year, 3-years and 5-years.

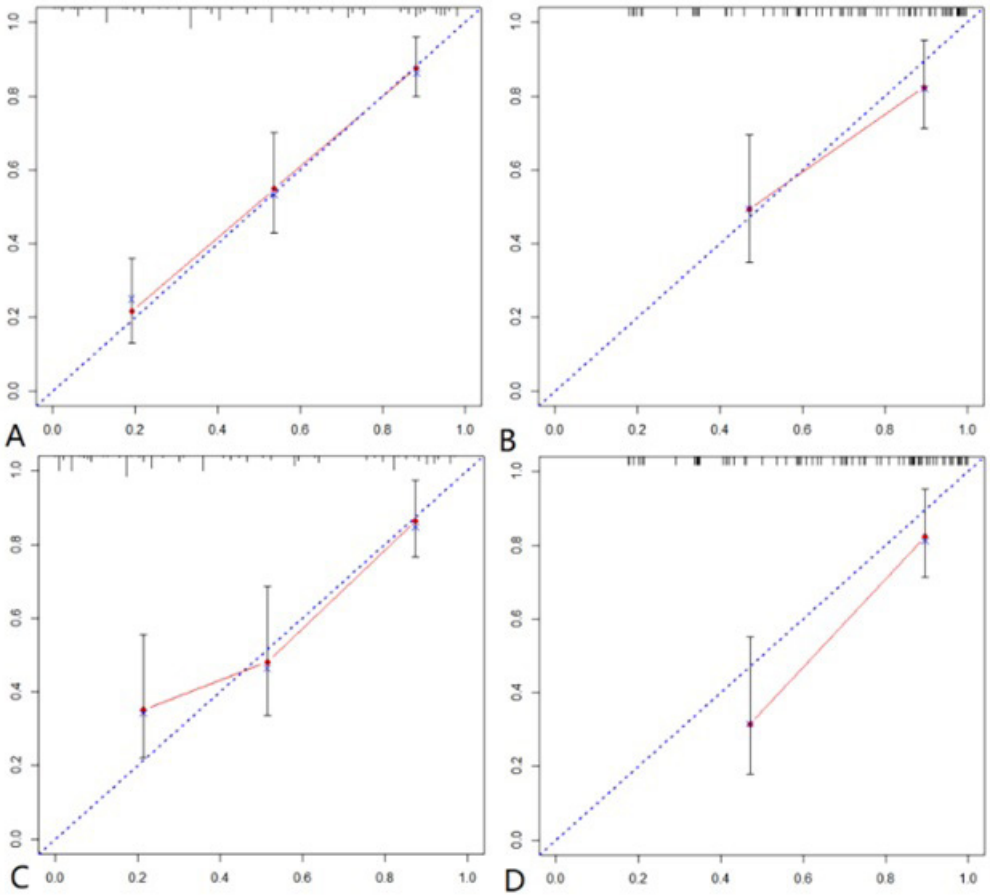

Figure 5: The calibration of the nomograms using the training cohort and validation cohort. The x axis represents the survival rate predicted by the nomogram, whereas the y axis presents the actual survival rate obtained using the Kaplan–Meier method. (A) 3-year survival rate according to the training cohort; (B) 3-year survival rate according to the validation cohort; (C) 5-year survival rate according to the training cohort; (D) 5-year survival rate according to the validation cohort.

5. Discussion

MANEC is a rare type of tumor. At present, most of the studies are case reports, and there lacks clinical studies with a sufficient number of cases. The prevalence of gastrointestinal MANEC based on the population has been reported [17]. There are likewise some reports on the study of prognostic characteristics and influencing factors [2, 4, 17]. But until now, we still lack effective methods to predict the survival of MANEC. Therefore, our study established the survival prediction model of gastrointestinal MANEC based on the SEER database, which is also the first survival prediction model of MANEC.

The incidence of gastrointestinal MANEC continues to rise in the US population, with an annual growth rate of approximately 8% [17]. This shows that the research needs of MANEC are very urgent. In our research, we found that white people are also the main race of MANEC. However, the origin of this tumor remains unclear. At present, two hypotheses have been formed. One believes that both tissue components originate from multipotent stem cells, and another believes that adenocarcinoma cells differentiate into neuroendocrine cancer cells [3, 7, 10]. In the past, we thought that surgery may have a more important role in the treatment of MANEC, and we did not afford enough attention to the role of chemotherapy. But our research found that chemotherapy is an independent protective factor of CSS, especially in patients with metastasis stage. In early patients, univariate analysis showed that chemotherapy was an independent risk factor for CSS, but in multivariate analysis, chemotherapy was an independent and protective factor. This may be because adjuvant chemotherapy is rarely done for early patients. Overall, MANEC's lymph node metastasis rate and distant metastasis rate were 65.5% and 30.3%, respectively. Consistent with previous research results, patients with distant metastasis have a relatively better prognosis than patients confined to the gastrointestinal tract [2, 17]. But unlike some studies, we believe that MANEC is a moderately aggressive clinical entity [1].

Our research uses CSS as the main outcome of the study rather than the overall survival time. The purpose is to eliminate some confounding factors, so as to reflect the clinical characteristics of the tumor more intuitively. We found no significant statistical correlation between the location of the tumor and survival, although some studies have found that the survival time of the tumor in the appendix is longer than that of the cecum [17]. In addition, studies have reported that the median overall survival of colorectal MANEC is 18.1 months and 12.5 months, which is somewhat different from our results [4, 19]. This may be explained by the insufficient number of cases involved in the study.

As a visual prediction model, the nomogram can build a survival model based on the Cox model, which performs better than the TNM stage and has become an essential tool in clinical practice [16, 18]. For gastrointestinal neuroendocrine tumors, nomogram is already available and shows high clinical value [5]. In our study, we analyzed 478 cases of MANEC patients in the SEER database, and finally determined the four independent factors of age, grade, SEER stage, and chemotherapy. Further, we constructed a nomogram model to predict the probability of CSS in 1-year, 3-year, and 5-year. The predictive power and accuracy of the model are essential to clinical decision-making. According to the calculated C-index and calibration curves, we can find that our model has good predictive value and therefore has high feasible in clinical practice.

Our research also has certain limitations. First of all, the data of our research derived from SEER database and some important clinical data such as Ki-67 was not to be clearly recorded, which caused originate bias. Secondly, our nomogram model lacked validation of external data, despite the fact that we artificially randomized the data under study.

6. Conclusion

In conclusion, MANEC is a rare type of gastrointestinal cancer. Age, grade, stage and chemotherapy are independent influence factors of CSS. Moreover, we developed a nomogram to predict the 1-year, 3-year and 5-year survival probability of MANEC. After validation, the model showed good predictive value. Therefore, the model can be used for individualized survival prediction and provide some help for clinical practice.

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