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Nomograms for predicting survival in patients with gastric carcinoid or neuroendocrine carcinoma based on the SEER database

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Abstract. – OBJECTIVE: The aim of this study was to construct a competent model that can effectively predict the prognosis of patients with gastric carcinoid (GC) or neuroendocrine carcinoma (NEC).

PATIENTS AND METHODS: Data of patients with GC or NEC were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2017. Univariable and multivariable Cox analysis was used to determine the independent factors for patients with GC or NEC. Nomograms were established based on the independent factors and the results were evaluated using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

RESULTS: A total of 214 patients with GC and 65 patients with gastric NEC were extracted from the SEER database. Independent prognostic factors for patients with GC were M stage, gender, age, and chemotherapy. Independent prognostic factors for patients with gastric NEC included age, M stage, and chemotherapy. ROC curves, calibration curves, and DCA confirmed that the nomograms can precisely predict the prognosis of patients with GC and NEC.

CONCLUSIONS: The nomograms can effectively predict survival in patients with GC or NEC, which may assist the clinician in their decision-making and quantitatively judge the prognosis of individual patients.

Key Words:
Gastric neuroendocrine carcinoma, Gastric carcinoid, Nomogram, SEER, Surgery, Chemotherapy, prognosis.

Introduction

Gastric neuroendocrine neoplasms (gNENs) are heterogeneous tumors originating from the diffuse neuroendocrine cell system in the stomach and are characterized by slow progression and metastasis. gNENs are rare cancers and account for 0.3% of all gastric malignancies[1], and 4.1% of all neuroendocrine tumors (NETs)[2]. With the widespread application of gastroscope in clinical practice, more and more gNENs are discovered. According to a recent report[3] from the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of gNENs has grown much faster in the past 40 years, rising to 0.62/100,000 in 2016. This trend has significantly attracted clinicians, especially regarding the prognosis of gNENs.

gNENs can be divided into functional and non-functional categories. Functional gNENs, such as gastrinoma, can secrete hormones and cause corresponding clinical symptoms. Nonfunctional gNENs account for the vast majority of gNENs and are predominantly space-occupying lesions. The classification of gNENs varies in different periods. At present, according to the World Health Organization (WHO) classification[4] of 2010, which is widely used in clinics, gNENs are divided into (1) NET G1 stage (carcinoid), (2) NET G2 stage, (3) neuroendocrine carcinoma (NEC) (large cell type or small cell type) G3 stage, (4) mixed adenoneuroendocrine carcinoma (MANEC), and (5) hyperplasia and precancerous lesions. The differentiation degree of gNENs is higher in G1 and G2 stages (GC and NEC), but lower in the G3 stage. gNENs with high differentiation have less malignancy, a slower proliferation of tumor cells, and a smaller volume compared with gNENs with low differentiation. However, because GC or NEC does not present with overt symptoms in the early stages, the di-

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seases remain highly underdiagnosed and poorly understood. To the best of our knowledge, there are a limited number of studies focusing on the relationship between clinicopathological features and the prognosis of GC or NEC, and no predictive model for patients with GC or NEC has been proposed. This study aims to construct nomograms based on the SEER database that can effectively predict survival in patients with GC or NEC, to assist clinicians in their decision-making and quantitatively judge the prognosis of individual patients.

Patients and Methods

Patient Selection

Data on patients with GC or NEC were retrieved from the SEER Research Plus database from 1975 to 2017. The inclusion criteria were as follows: (1) the primary site of the malignant tumor was the stomach, (2) pathological diagnosis was GC or NEC, (3) active follow-up, (4) one primary only, and (5) availability of specific treatment information, including surgery, and chemotherapy. The exclusion criteria were as follows: (1) unknown TNM stage; (2) unknown or blank American Joint Committee on Cancer (AJCC) stage, (3) unknown tumor size, and (4) survival time unknown or less than 1 month. A patient selection flow chart was shown in Figure 1. The study was approved by the Ethics Committee of the central Hospital of Shaoyang under the protocol KY 2022-002-17.

Variables Collection

Clinical variables including ethnicity, gender, primary site, grade, TNM stage, AJCC stage, the status of surgery, survival time, status of survival, cause of death, tumor size, surgery, and chemotherapy were extracted from the SEER database. The ethnicity was divided into white and non-white categories. Marital status was divided into married and unmarried categories. Unmarried patients include single, separated, divorced, and widowed. The grade was defined by the following codes: well-differentiated (Grade I), moderately differentiated (Grade II), and poorly differentiated (Grade III). Overall survival (OS) was the primary study endpoint. For OS, death from any cause was considered an event and the survivor was regarded as a censored event. For cancer–specific survival (CSS) analysis, death caused by GC or NEC was considered an event, and death from other causes or survivors was considered a censored event.

Statistical Analysis

The statistical analyses were performed using R software version 4.1.3 (available at: http://www.r-project.org), and a $p < 0.05$ was considered statistically significant. Fisher's test was used to analyze category variables. The Kaplan–Meier (KM) curve was used to estimate the OS and CSS in different groups, and differences between the curves were analyzed using a log–rank test.

Univariate Cox regression analysis was used to determine OS-related factors for GC or NEC patients. Then, significant variables with $p < 0.05$ were incorporated into a multivariate Cox analysis to further determine independent prognostic factors. A prognostic nomogram based on independent prognostic predictors was established to predict the OS of patients with GC or NEC. In addition, time-dependent ROC curves of nomograms and all independent prognostic variables at 6, 12, and 18 months were constructed using the timeROC package[5] in R, and the corresponding time-dependent area under the curve (AUC) was used to assess discrimination. Moreover, calibration curves and decision curve analysis (DCA) were used to evaluate the performance of the nomograms.

Results

Patient Characteristics

A total of 214 patients with GC and 65 patients with gastric NEC were extracted from the SEER database. As shown in Table I, the mean age of patients with GC or NEC was 60.3 and 63.5 years old, respectively. Most patients with GC or NEC were white (77.1% *vs.* 80%), married (52.8% vs. 70.8%), with grade I (79.9% *vs.* 55.4%), N0 (95.8% *vs.* 81.5%) and M0 (97.2% *vs.* 94.6%). Moreover, the vast majority of patients with GC or NEC were treated with surgery (87.9% *vs.* 78.5%) and without chemotherapy (98.1% *vs.* 83.1%). The mean tumor size for GC or NEC was 10.3 and 25.4 mm, respectively.

Univariate Cox Regression Analysis for Patients with Carcinoid or NEC

OS and CSS rates were first compared between patients with GC and NEC using KM curves and the results showed that patients with GC had longer OS ($p = 0.0042$) and CSS ($p < 0.0001$)

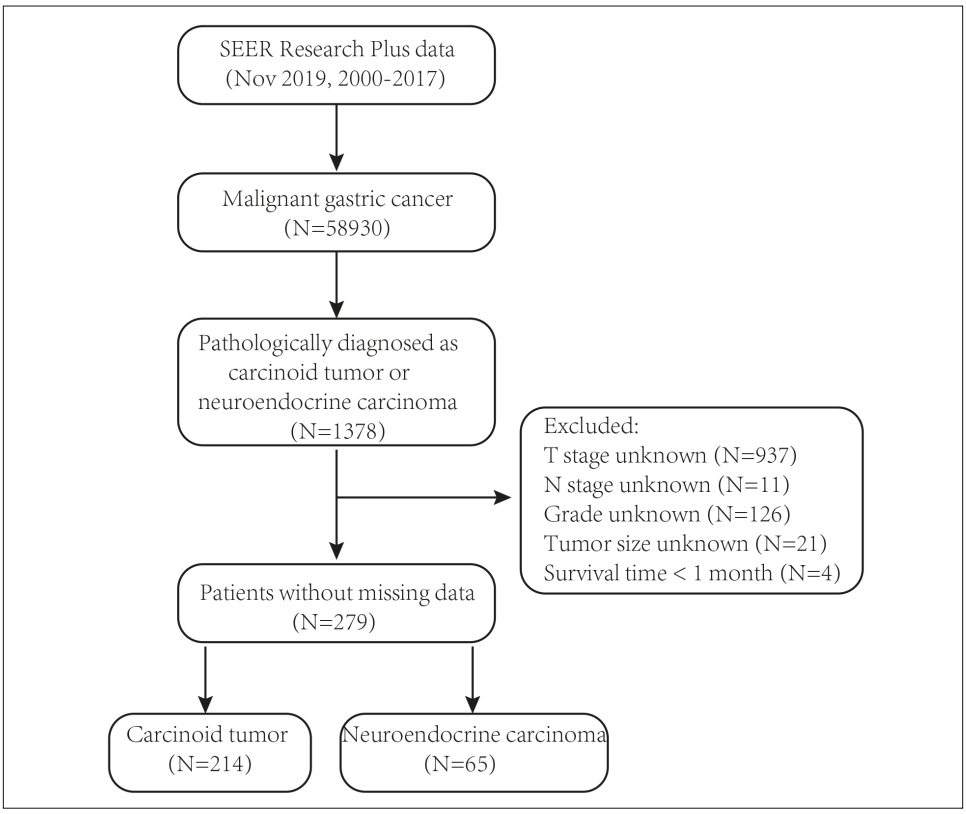

Figure 1. Patient selection flowchart.

rates than those with NEC (Figure 2A-B). As shown in Figure 2C, univariate Cox regression analysis revealed that age [HR = 1.09, 95% confidence interval (CI): 1.06-1.13, $p < 0.001$], gender (HR = 4.58, 95% CI: 1.82-11.5), M stage (HR = 5.29, 95% CI: 1.21-23.14, $p = 0.027$), surgery (HR = 0.27, 95% CI: 0.11-0.67, $p = 0.004$), chemotherapy (HR = 9.29, 95% CI: 2.75-31.34, $p < 0.001$), and tumor size (HR = 1.03, 95% CI: 1.00-1.04, $p = 0.001$) were associated with OS in patients with GC. As shown in Figure 2D, univariate Cox regression analysis revealed that N stage (HR = 3.59, 95% CI: 1.36-9.44, $p = 0.01$), M stage (HR = 11.29, 95% CI: 4.24-30.02, $p < 0.001$), surgery (HR = 0.29, 95% CI: 0.11-0.75, $p = 0.011$), chemotherapy (HR = 9.64, 95% CI: 3.57-26.04, $p < 0.001$), and tumor size (HR = 1.02, 95% CI: 1.01-1.04, $p < 0.001$) were associated with OS in patients with NEC.

Multivariate Cox Regression Analysis for Patients with GC or NEC

Significant variables ($p < 0.05$) were incorporated into a multivariate Cox analysis to further determine independent prognostic factors. Multivariate Cox regression analysis revealed that age (HR = 1.09, 95% CI: 1.05-1.13, $p < 0.001$), gender (HR = 3.98, 95% CI: 1.52-10.43, $p < 0.001$), M stage (HR = 12.61, 95% CI: 1.59-100.24, $p = 0.016$), and chemotherapy (HR=6.13, 95% CI, 1.55-24.21, $p = 0.009$) were independent prognostic risk factors for patients with GC (Figure 3A). In addition, multivariate Cox regression analysis revealed that M stage (HR = 4.30, 95% CI: 1.05-17.67, $p = 0.042$), and chemotherapy (HR = 5.00, 95% CI: 1.57-15.92, $p = 0.009$) were independent prognostic risk factors for patients with NEC (Figure 3B).

Construction of Prognostic Nomograms

Although the surgery was not a significant factor in multivariate Cox analysis, it was still the only way to cure NENs[6]. Therefore, surgery was incorporated into the nomograms due to its vital role in the treatment of NENs. Finally, prognostic nomograms for patients with GC or NEC were established based on independent risk factors using multivariate Cox regression analysis (Figure 3C-D). The C-index of nomograms predi-

Table I. Characteristics of patients with GC or NEC.

	Carcinoid tumor (N=214)	Neuroendocrine carcinoma (N=65)	Overall (N=279)	*p*
Age				
Mean (SD)	60.3 (12.8)	63.5 (12.0)	61.0 (12.7)	0.0699
Ethinicity				
Non-White	49 (22.9%)	13 (20.0%)	62 (22.2%)	0.734
White	165 (77.1%)	52 (80.0%)	217 (77.8%)	
Gender				
Female	124 (57.9%)	32 (49.2%)	156 (55.9%)	0.254
Male	90 (42.1%)	33 (50.8%)	123 (44.1%)	
Marital status				
Married	113 (52.8%)	46 (70.8%)	159 (57.0%)	0.0105
Unmarried	101 (47.2%)	19 (29.2%)	120 (43.0%)	
Grade				
Grade I	171 (79.9%)	36 (55.4%)	207 (74.2%)	<0.001
Grade II	39 (18.2%)	15 (23.1%)	54 (19.4%)	
Grade III	4 (1.9%)	14 (21.5%)	18 (6.5%)	
AJCC Stage				
Stage I	150 (70.1%)	22 (33.8%)	172 (61.6%)	<0.001
Stage II	49 (22.9%)	26 (40.0%)	75 (26.9%)	
Stage III	9 (4.2%)	8 (12.3%)	17 (6.1%)	
Stage IV	6 (2.8%)	9 (13.8%)	15 (5.4%)	
T				
T1	151 (70.6%)	22 (33.8%)	173 (62.0%)	<0.001
T2	56 (26.2%)	32 (49.2%)	88 (31.5%)	
T3	2 (0.9%)	5 (7.7%)	7 (2.5%)	
T4	5 (2.3%)	6 (9.2%)	11 (3.9%)	
N				
N0	205 (95.8%)	53 (81.5%)	258 (92.5%)	<0.001
N1	9 (4.2%)	12 (18.5%)	21 (7.5%)	
M				
M0	208 (97.2%)	56 (86.2%)	264 (94.6%)	0.00186
M1	6 (2.8%)	9 (13.8%)	15 (5.4%)	
Surgery				
No	26 (12.1%)	14 (21.5%)	40 (14.3%)	0.0694
Yes	188 (87.9%)	51 (78.5%)	239 (85.7%)	
Chemotherapy				
No	210 (98.1%)	54 (83.1%)	264 (94.6%)	<0.001
Yes	4 (1.9%)	11 (16.9%)	15 (5.4%)	
Tumor size				
Mean (SD)	10.3 (14.3)	25.4 (27.0)	13.8 (19.1)	<0.001
OS time				
Mean (SD)	45.8 (21.8)	44.4 (22.3)	45.5 (21.9)	0.672
OS status				
Alive	190 (88.8%)	48 (73.8%)	238 (85.3%)	0.00479
Dead	24 (11.2%)	17 (26.2%)	41 (14.7%)	

American Joint Committee on Cancer (AJCC), Overall survival (OS).

cting OS in patients with GC or NEC was 0.84 and 0.79, respectively. Moreover, ROC analysis revealed that the AUC of the nomogram model in predicting 6-, 12-, and 18-month prognosis of GC was 0.75, 0.88, and 0.87, respectively (Figure 4A). The AUC of the nomogram model in predicting 6-, 12-, and 18-month prognosis of NEC patients was 0.67, 0.79, and 0.81, respectively (Figure 4B). The calibration curves of the nomograms for the predicting 6-, 12-, and 18-month OS showed a strong agreement between the predicted and actual outcome (Figure 4C-H). DCA curves also revealed that the nomograms had good performance in clinical practice (Figure 5A-D). Due to the limitation of the study samples, patients were not divided into training and validation groups.

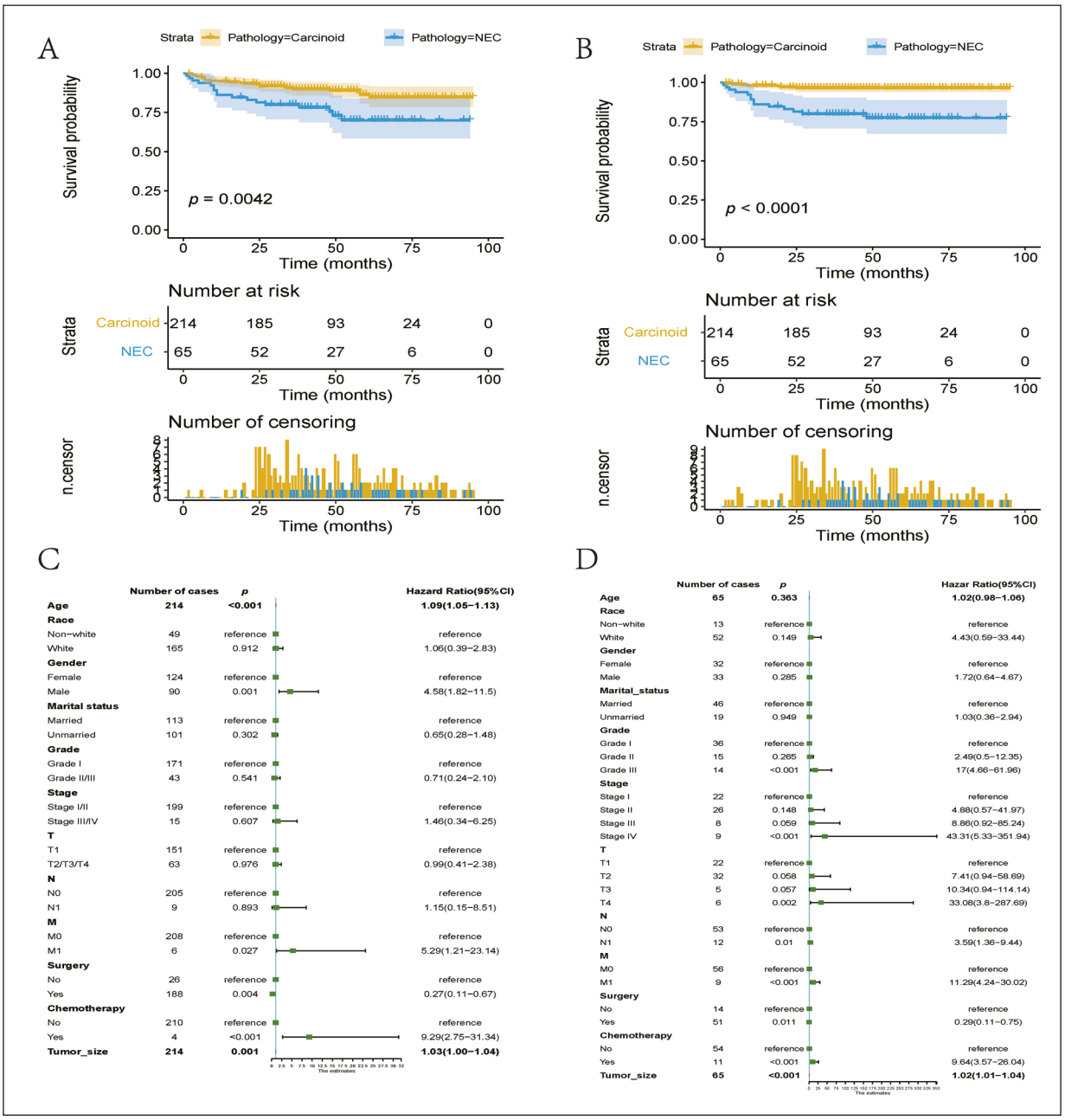

Figure 2. Forrest plots and Kaplan-Meier curves of univariate Cox analysis. Kaplan-Meier curves of overall survival (OS) (**A**) and cancer-specific survival (CSS) (**B**) are stratified by pathology. Forrest plots of univariate Cox analysis in patients with gastric carcinoid (GC) (**C**) and neuroendocrine carcinoma (NEC) (**D**). Significant variables with p <0.05 were incorporated into a multivariate Cox analysis.

Discussion

NETs are neoplasms that originate from Kulchitsky cells of the primitive intestinal mucosa in the embryonic period. In 1907, Oberndorfe[7] officially named it "Cazenoid", namely Carcinoid, which is still used today. NETs are slow-growing tumors with low malignancy, and they can occur in different parts of the body because they originate from different embryonic parts. The organs where the carcinoid originates are the foregut, midgut, and hindgut of the embryo. The gastric NETs belong to the NETs that occur in the foregut. NETs occur throughout the body, and the most common sites include the pulmonary, digestive systems, and the skin[8]. In the digestive

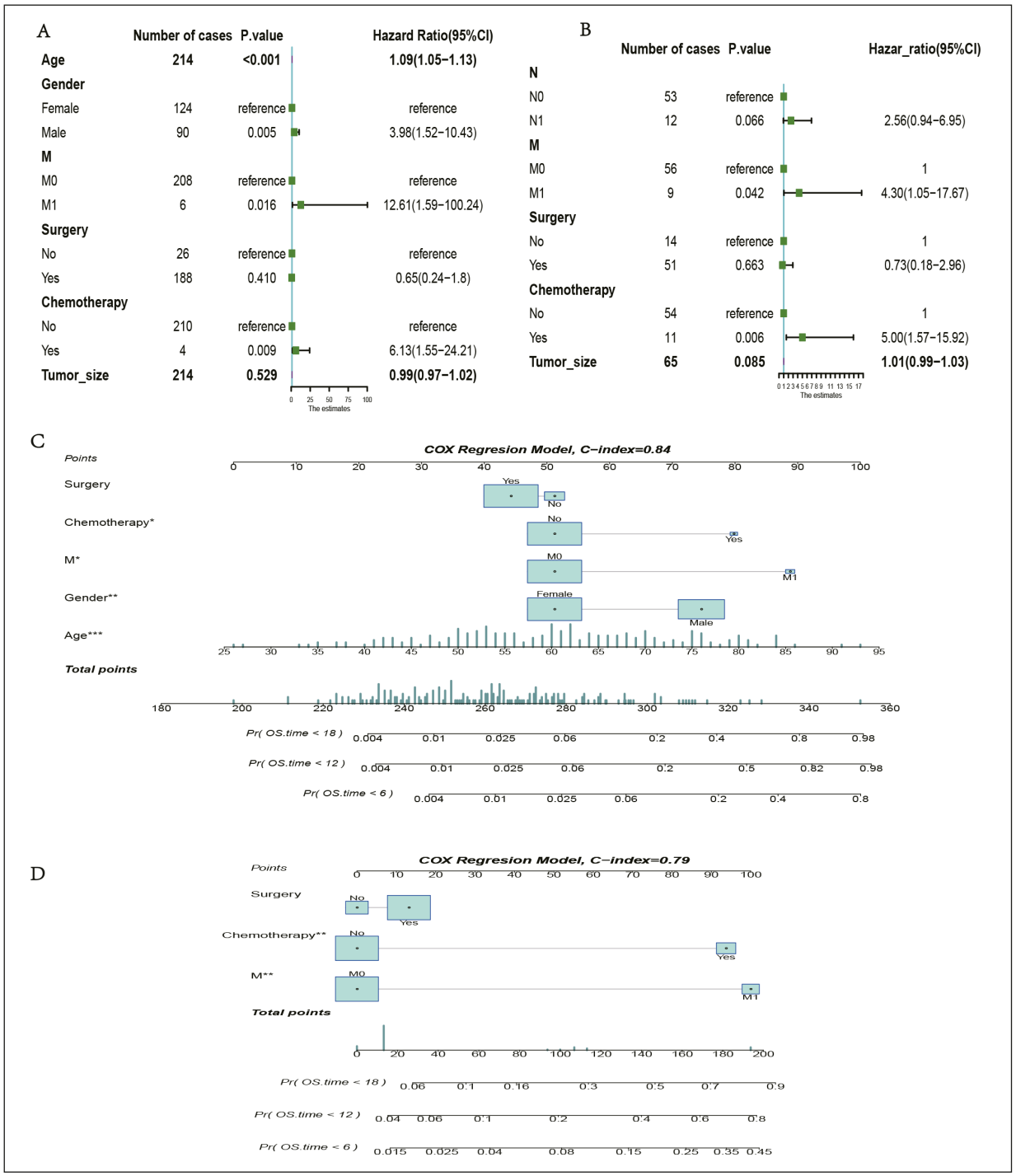

Figure 3. Forrest plots of multivariate Cox analysis and nomograms for predicting the OS of patients. Forrest plots of multivariate Cox analysis in patients with GC (**A**) and NEC (**B**). Significant variables with p <0.05 were incorporated into the construction of the nomograms. Nomograms for predicting 6-, 12-, and 18-month OS for patients with GC (**C**) and NEC (**D**) C-index for GC and NEC were 0.84 and 0.79, respectively.

system, NETs often occurred in the gastrointestinal tract[9-11]. In our study, a total of 214 GC patients and 65 gastric NEC patients with complete clinical information were extracted from the SEER database, and appropriate nomograms were established to predict OS for these patients based on univariate and multivariate Cox regression analysis, and vital clinicopathologic variables.

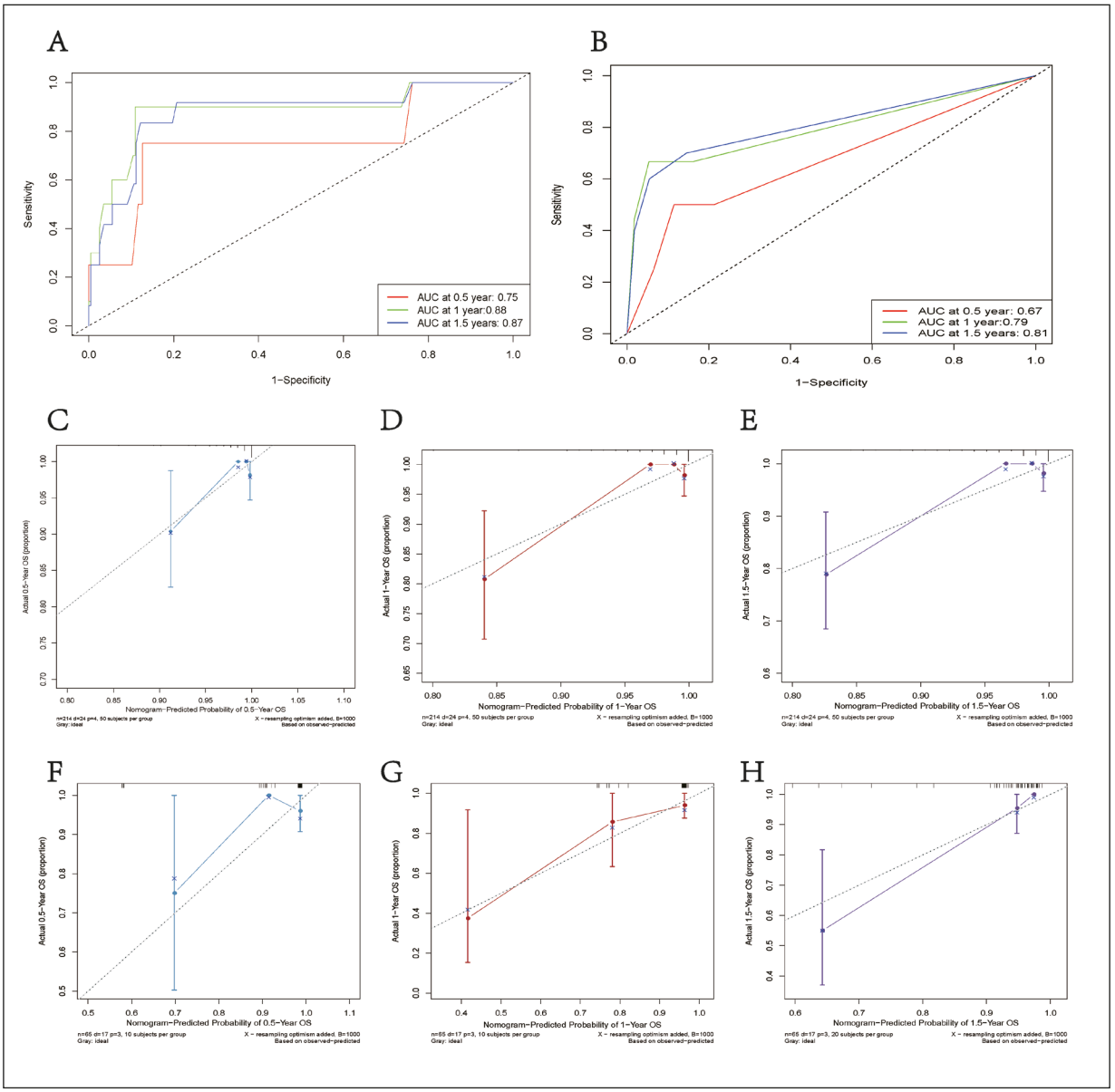

Figure 4. ROC and calibration curves of the nomograms. **A**, ROC curve of the nomogram in patients with GC; AUC values for predicting 6-. 12-, and 18- month were 0.75, 0.88, and 0.87, respectively. **B**, ROC curve of the nomogram in patients with NEC, and the AUC values for 6-. 12-, and 18- month prognosis were 0.67, 0.79, and 0.81, respectively. **C-E**, Calibration curves of the nomogram for predicting the 6-, 12-, and 18-month OS in patients with GC. **F-H**, Calibration curves of the nomogram for predicting the 6-, 12-, and 18-month OS in patients with NEC.

Five (surgery, chemotherapy, M stage, gender, and age) and three (surgery, chemotherapy, and M stage) risk factors could be used by clinicians to evaluate individual survival probability in patients with GC or NEC, respectively. Moreover, the results of ROC curves, calibration curves, and DCA confirmed that the nomograms can precisely predict the prognosis of patients with GC and NEC.

Nomograms transformed complex regression equations into visual graphs, making the results of the prediction model more readable and convenient for the evaluation of patients. Nomograms have attracted considerable attention and application in clinical practice and cancer prognosis[12] due to their intuitionistic and easy-to-understand feature. Zhang et al[13] investigated 260 patients diagnosed with gastric NENs and found that age,

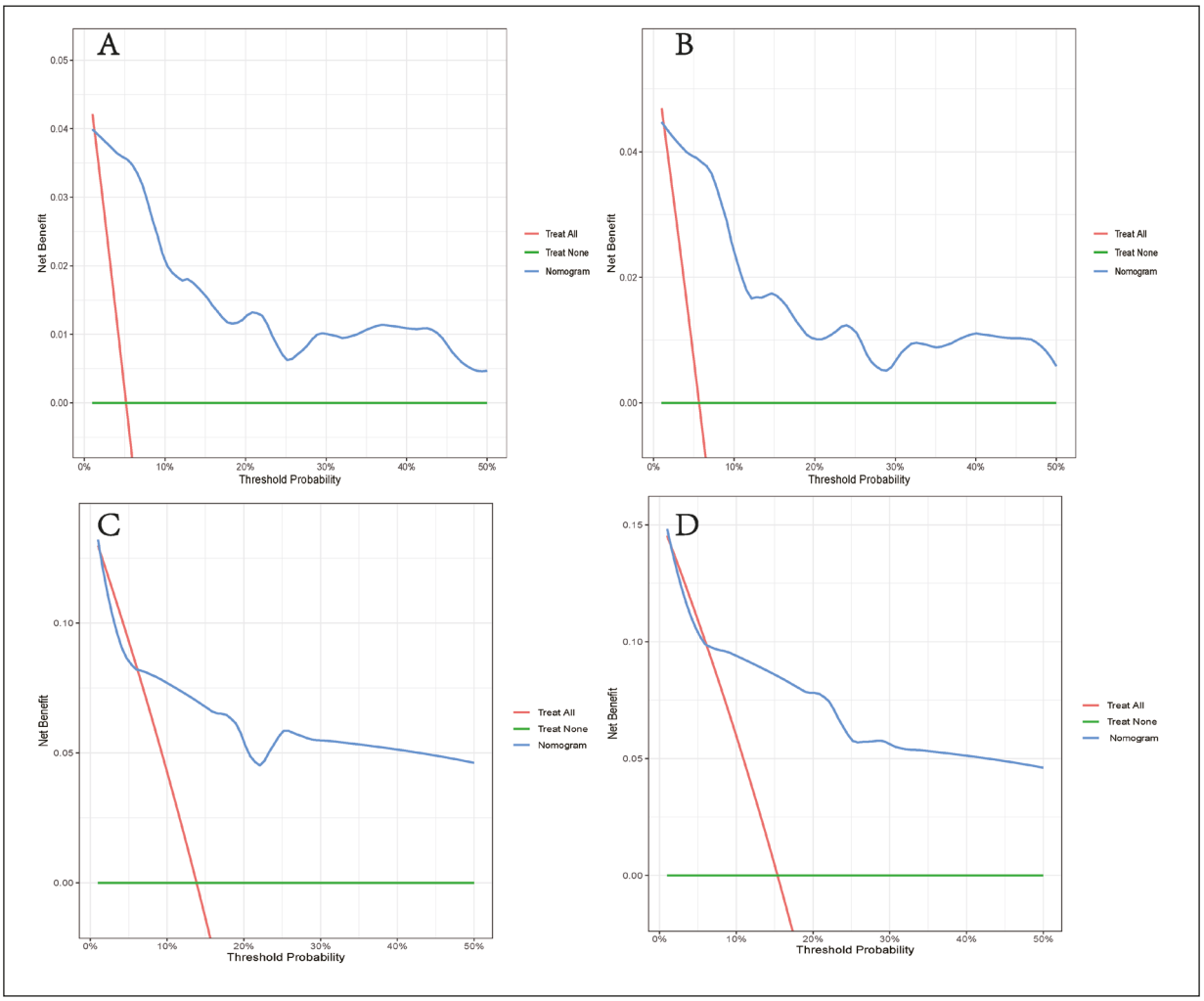

Figure 5. Decision curve analysis of the nomograms. Decision curve analysis of the nomogram for predicting 12- and 18-month OS in patients with GC (**A-B**) and NEC (**C-D**), respectively.

Ki-67, mitoses, neutrophil to lymphocyte ratio, serum tumor marker, and distant metastasis were significantly associated with the OS based on multivariate Cox analysis. However, as the most important treatment option for gastric NETs, surgery was not included in the clinical variables of their study, and a similar deficiency occurred in the study of Cao et al[14].

Surgical resection is the cornerstone of the NET treatment[15], and gastric resection also plays an important role in the treatment of gastric NENs[16,17]. According to the North American Neuroendocrine Tumor Associations (NANETS) consensus guideline[18], well-differentiated NETs of the stomach less than 2 cm (up to 6) should be resected endoscopically, with subsequent interval follow-up, and patients with tumors measuring more than 2 cm require more aggressive management, and local surgical resection is recommended[19,20]. According to the clinical practice guideline[21] of NCCN in neuroendocrine, patients with locoregional disease and favorable biology should undergo regional lymphadenectomy, and patients with metastatic disease should also undergo resection of primary and metastatic sites if feasible. In our study, univariate Cox analysis showed that surgery can prolong the survival time of patients with GC or NEC. These results were in line with the above-mentioned guidelines.

Interestingly, chemotherapy did not prolong the survival time of patients with GC or NEC but was negatively correlated with the survival time based on univariate and multivariate Cox analysis. Chemotherapy was a vital cancer treatment[22-24] and is the only treatment for nonsolid tumors[25,26]. According to the NANETS consensus18, cytotoxic chemotherapy such as 5-fluorouracil, streptozocin, or doxorubicin was considered to be the

first-line treatment of NENs with poor differentiation and rapid progress; however, the effect of chemotherapy was not significant[27-29]. Thus, we cautiously conclude that chemotherapy shortened the survival time of patients with GC or NEC because of the limitation of the study samples. In addition to chemotherapy, various studies[30-32] have suggested that agents inhibiting vascular endothelial growth factor pathways, including bevacizumab, sunitinib, and sorafenib, may be effective in preventing tumor growth. Everolimus, an mTOR inhibitor, also appears to be effective in patients with advanced carcinoid[33]. In patients with advanced carcinoid tumors, radiolabeled somatostatin analogs represent another investigational treatment option[34].

Limitations

The present study has several limitations. First, internal verification was not conducted because of the relatively small sample size, and the results are prone to bias. Second, the SEER database does not provide specific drugs for chemotherapy; therefore, the findings of the relationship between chemotherapy and the survival time in patients with GC or NEC should be considered with caution. Third, our prognostic models did not include some potential prognostic factors such as serum chromogranin A (CgA)[35] and important characteristics such as the Ki-67 index.

Conclusions

We have developed reliable nomograms that can effectively predict the prognosis of GC or NEC patients. These nomograms could help clinicians to more accurately and conveniently predict the 6-, 12-and 18-month OS of individual patients. Further prospective multicenter studies with a larger sample size are needed to validate our nomograms.

Authors' Contributions

HS acquired, analyzed and interpreted the data, and drafted the article; QP acquired the data, and analyzed and interpreted the data; SL, XL, and YS wrote the sections of the manuscript. All authors critically revised the manuscript and provided final approval.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Ethics Approval

The study was approved by the Ethics Committee of the Central Hospital of Shaoyang under the protocol KY 2022-002-17.

Informed Consent

Informed consent from subjects was waived due to the database containing anonymized data that cannot identify study subjects.

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Availability of Data and Materials

All data are available in the SEER database (available at: https://seer.cancer.gov/).

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