Original Article

Development and validation of a nomogram to predict overall survival of gastroenteropancreatic neuroendocrine carcinoma: a SEER database analysis

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Background: Gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) is a rare group of diseases with poor prognosis and the assessment of its prognosis is a significant challenge. This study aimed to develop and validate a prognostic nomogram to assess overall survival (OS) in patients with GEP-NEC.

Methods: Patients diagnosed with poorly differentiated GEP-NEC were collected from the Surveillance, Epidemiology, and End Results (SEER) database between 2011 and 2015 and were randomly assigned to the training or validation cohort in a 7:3 ratio. The data included details of clinicopathological characteristics, therapeutic interventions and survival outcomes. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors. Nomogram was used to predict OS at 1 and 2 years. The nomogram was internally validated with validation cohort, and its predictive ability was evaluated using concordance index (C-index), receiver operating characteristic (ROC) curves, calibration plots, decision curve analysis (DCA), and integrated discrimination improvement (IDI) index.

Results: A total of 887 patients were divided into the training group (n=623) and the validation group (n=264). A total of 476 patients (53.66%) were in stage IV. Based on multivariate analysis, a nomogram was constructed with age, gender, N stage, tumor size, primary tumor resection, radiotherapy and chemotherapy ($P<0.05$). The C-index was 0.701 [95% confidential interval (CI): 0.677–0.725] and 0.731 (95% CI: 0.698–0.764) for the training and validation groups, respectively. The C-index, ROC, IDI and DCA results indicated that this nomogram model has a good predictive value.

Conclusions: In this study, a nomogram model based on seven independent prognostic factors provided visualization of the risk and could help clinicians predict the 1-year and 2-year OS for GEP-NEC. This tool can provide personalized survival predictions and improve clinical decision making for the management of GEP-NEC.

Keywords: Gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC); prognosis; Surveillance Epidemiology and End Results (SEER); nomogram; survival

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Introduction

Gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC) is a rare and highly aggressive cancer with poor prognosis and rapid disease progression. The digestive tract is the most common site of extrapulmonary neuroendocrine carcinoma. Despite the increasing incidence of poorly differentiated GEP-NEC, this group of diseases remains relatively rare, accounting for 10–20% of gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) (1,2) and <1% of all digestive system malignancies (3). Over the years, tumor classification has evolved based on a better understanding of disease biology. The 2019 World Health Organization (WHO) classification of tumors of the digestive system has recognized poorly differentiated high-grade neuroendocrine carcinoma (NEC) as a distinct entity from well differentiated high-grade neuroendocrine tumor (NET) (4). Compared with other gastrointestinal tumor types, GEP-NEC has distinct cell origins and displays a unique biological behavior, suggesting that accurate evaluation of its prognosis is essential. However, little is known about prognostic and predictive factors due to the lack of clinical data for GEP-NEC patients. Data indicate that staging, primary tumor site, and histology may be associated with the prognosis of GEP-NEC (5,6). Nevertheless, despite the recognition of these characteristics, an individual prediction model to evaluate the survival based on large sample-GEP-NEC cohorts is yet to be established. The tumor node metastasis (TNM) staging system proposed by American Joint Committee on Cancer (AJCC) is now one of the most important methods for evaluating the prognosis of GEP-NEC. However, the TNM staging system does not involve many other factors, such as age and treatment, which may also affect the survival of GEP-NEC.

Nomograms are graphical calculations with continuous scaling to calculate the probability of a given outcome and have been widely used as a predictive model in recent years, showing a more accurate prediction of prognosis for most cancer types than the TNM staging system. They integrate multiple predictors to help clinicians in prognosis prediction and decision making. Given that GEP-NEC has a relatively low incidence rate, there is a lack of availability of prospective data and large-scale studies. In light of these limitations, we used the Surveillance, Epidemiology, and End Results (SEER) program, which offers a comprehensive dataset encompassing various cancer types among the American population. This extensive dataset was used to investigate the clinical characteristics, treatment outcomes, and prognostic factors. In our study, we aimed to construct a nomogram to predict the prognosis of GEP-NEC patients using a large GEP-NEC dataset from the SEER database. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2215/rc).

Highlight box

Key findings

- This study identified seven independent prognostic factors (age, sex, N stage, tumor size, primary tumor resection, radiotherapy, and chemotherapy) for predicting the prognosis of gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC).
- A prognostic nomogram developed based on these factors demonstrated superior predictive accuracy for 1- and 2-year overall survival in GEP-NEC patients, surpassing the traditional tumor node metastasis (TNM) staging system.

What is known and what is new?

- GEP-NEC is a rare and highly aggressive cancer, posing challenges in prognosis assessment and therapeutic strategy determination.
- The prognostic nomogram presented in this study, based on a large-sample analysis from the Surveillance, Epidemiology, and End Results (SEER) database, provides a more accurate prediction of survival rates in GEP-NEC patients and can offer more targeted clinical treatment suggestions.

What is the implication, and what should change now?

- The prognostic nomogram in this study offers a novel, individualized tool for predicting survival rates in GEP-NEC patients. This tool can assist clinicians in more effectively evaluating patient prognosis and supporting treatment decision-making.
- Future studies should aim to improve the nomogram by incorporating more clinical data and integrating molecular and genetic markers to improve its predictive accuracy and applicability in different clinical settings.

Methods

Data source and patient selection criteria

Data of patients were extracted from SEER*Stat (version 8.4.0.1) database Incidence - SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019) in SEER Program (www.seer.cancer.gov) with reference number 20320-Nov2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

GEP-NEC patients were included based on the following criteria: (I) classification scheme for tumors

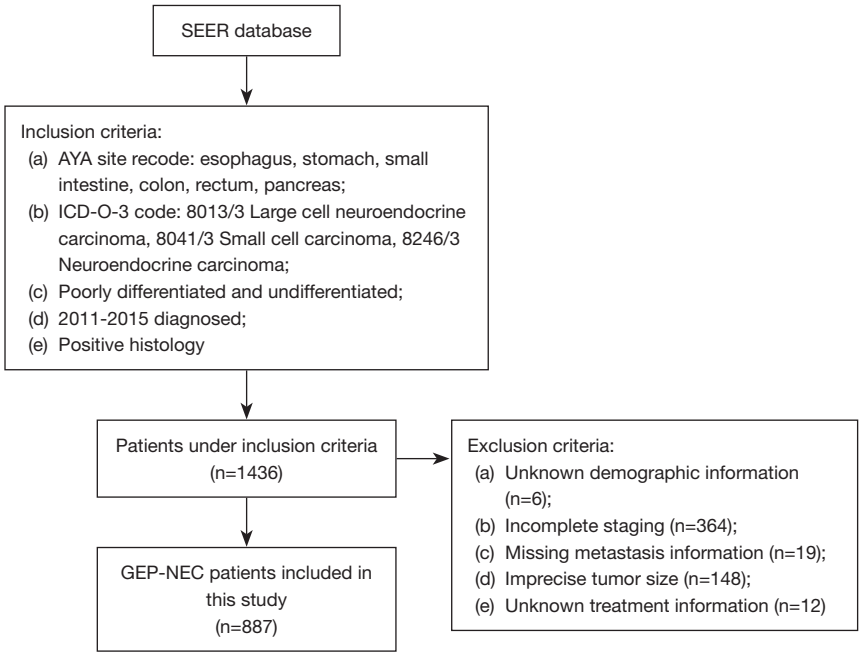

Figure 1 Flowchart of patient selection. SEER, Surveillance, Epidemiology, and End Results; AYA, adolescents and young adults; ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma.

of adolescents and young adults (AYA) site recode 2020 Revision (9.3.1 Esophagus, 9.3.2.1.2 Stomach, 9.3.3.1.2 Small intestine, 9.3.4.1.2 Appendix, 9.3.4.2.1.2 Colon excluding appendix, 9.3.5.1.2 Rectum, 9.3.9.1.2 Pancreas); (II) International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code (8013/3 Large cell neuroendocrine carcinoma, 8041/3 Small cell carcinoma, 8246/3 Neuroendocrine carcinoma); (III) poorly differentiated and undifferentiated in Grade (thru 2017); (IV) diagnosed from 2011 to 2015; (V) positive histology in diagnostic confirmation.

Patients with unknown demographic information, incomplete staging (stage 0 or T stage 0 also excluded), missing metastasis information, imprecise tumor size and unknown treatment information (unknown if surgery/radiotherapy/chemotherapy administered or unknown chemotherapy sequence) were excluded. The well-differentiated NET was excluded. The workflow of patient selection is shown in *Figure 1*.

Clinical variables

Data from the SEER database included variables related to GEP-NEC from previous studies. These variables included age, sex, race, tumor site, histology, AJCC 6th edition stage (I, II, III, IV), T stage (T1, T2, T3, T4), N stage (N0, N1, N2, N3), M stage (M0, M1), tumor size, primary tumor resection, non-primary surgery (to distant site/distant lymph nodes/other regional sites), radiotherapy, chemotherapy and its sequence (adjuvant chemotherapy, neoadjuvant chemotherapy, etc.), metastasis (liver, lung, bone, brain) (as four separate variables). The study endpoint, or overall survival (OS), was defined as the interval between the initial diagnosis of GEP-NEC and either the patient's death from any cause or the date of the patient's last follow-up. The patients who participated in this study had a documented survival status and a documented survival period.

Statistical analysis

We randomly grouped patients using the "caret" package in the R software (version 4.2.1), using 70% as the training cohort and the remaining 30% as the validation cohort. Normally distributed data were described as the mean [standard deviation (SD)] and non-normally distributed data were described as the median [interquartile ranges (IQRs)]. Categorical variables were presented as frequencies and percentages. The chi-squared test using IBM SPSS software (version 25) was conducted to evaluate the clinical characteristics between the two groups. A two-sided $P<0.05$

was recognized as statistically significant.

We performed univariate and multivariate Cox proportional hazard regression analyses in the training group to obtain the hazard ratio (HR) and 95% confidential interval (CI) for independent prognostic variables. Nomogram was constructed with "rms", "foreign" and "survival" packages of the R software. Patients were scored by variables in the nomogram and total scores summed up were used to predict 1- and 2-year OS rates.

We validated the nomogram model using an internal cohort. Discrimination of the model was assessed by the concordance index (C-index) and the area under the curve (AUC) of receiver operating characteristic (ROC) curve. Calibration of the model was evaluated using calibration plots, to assess the agreement between the predicted risk and the actual risk. The proximity of the calibration curve to the diagonal indicates the strong predictive capability of the model. The clinical usefulness of the model was evaluated by decision curve analysis (DCA). In general, the model curve further from the axis has a higher net benefit with a certain threshold probability and is shown to be more clinically useful. The overall comparison between the new model and the TNM staging system was conducted by calculating the integrated discrimination improvement (IDI) index. It is suggested that the higher IDI of the new model indicating better predictive power. Z test was used in the IDI calculation to examine the difference.

Patients were divided into high- and low-risk groups with the cutoff point being the median risk score of the whole cohort calculated by the nomogram. Kaplan-Meier survival curves were applied to fit the correlation between survival time and risk scores and to show the potential differences in OS between the high- and low-risk groups. Kaplan-Meier survival curves were applied to perform survival analysis and stratified according to the risk level.

This study used time-to-event data to develop a nomogram, and the sample size should be based on events-per-variable (EPV) greater than or equal to 10. There were 19 variables, which made it necessary to include at least 190 samples (19×10=190) to construct a nomogram.

Results

Patient characteristics

A total of 887 patients were included in our study, of which 623 patients were used as training cohort, and the remaining 264 cases were used as validation cohort. Data of training cohort and validation set of this study are shown in website: https://cdn.amegroups.cn/static/public/10.21037tcr-23-2215-1.xlsx. The median age of the entire cohort was 66 years (IQR: 57–75 years). 56.26% (n=499) were male, and nearly four fifths were white (n=711, 80.16%). More patients had tumor in colon (n=330, 37.20%), followed by pancreas (n=196, 22.10%) and rectum (n=132, 14.88%). As for histology, 69.56% (n=617) were neuroendocrine carcinoma, and the other patients are classified as large cell neuroendocrine carcinoma (n=143, 16.12%) and small cell carcinoma (n=127, 14.32%). As for the AJCC staging system, more than half of the patients were in stage IV (n=476, 53.66%). Most patients were in T3 (n=384, 43.29%) or T4 (n=259, 29.20%) stage. Patients tend to have lymph node metastases (N1 n=391, 44.08%; N2 n=215, 24.24%) or distant metastases (M1 n=473, 53.33%). The median tumor size was 50 mm (IQR: 35–75 mm). 64.49% (n=572) had primary tumor resection surgery, and only 10.37% (n=92) had non-primary surgery. A small number of patients received radiotherapy (n=166, 18.71%) and more than half received chemotherapy (n=503, 56.71%), with more of them receiving adjuvant chemotherapy (n=239, 26.94%) than neoadjuvant chemotherapy (n=37, 4.17%). Liver was the most common metastatic site (n=378, 42.62%). There was no significant difference in characteristics between the two groups (P>0.05). The patient clinicodemographic characteristics are presented in *Table 1*.

Nomogram construction

In multivariate Cox regression analysis, the independent prognostic factors of OS were age, sex, N stage, tumor size, primary tumor resection, radiotherapy and chemotherapy (P<0.05). The HR and P value of each variable in the multivariate Cox risk models are shown in *Table 2*. We used the seven variables identified in the multivariate Cox regression analysis to construct the nomogram, to predict 1- and 2-year OS in patients with GEP-NEC (*Figure 2*). The corresponding scores of each variable were added to get the total score and its 1- and 2-year OS.

Nomogram validation

C-index and ROC curve were used to assess the discrimination of the model. C-index of the nomogram was higher than that of the TNM staging system, 0.701 (95% CI: 0.677–0.725) *vs.* 0.635 (95% CI: 0.611–0.659)

Table 1 Patient clinicodemographic characteristics

Variables	Training cohort (n=623)	Validation cohort (n=264)	Total (n=887)	P value
Age (years)	65 [57–75]	68 [58–76]	66 [57–75]	0.08
Sex				0.71
Male	353 (56.66)	146 (55.30)	499 (56.26)	
Female	270 (43.34)	118 (44.70)	388 (43.74)	
Race				0.28
White	504 (80.90)	207 (78.41)	711 (80.16)	
Black	77 (12.36)	31 (11.74)	108 (12.18)	
Other	42 (6.74)	26 (9.85)	68 (7.67)	
Tumor site				0.85
Colon	238 (38.20)	92 (34.85)	330 (37.20)	
Pancreas	136 (21.83)	60 (22.73)	196 (22.10)	
Rectum	93 (14.93)	39 (14.77)	132 (14.88)	
Stomach	67 (10.75)	33 (12.50)	100 (11.27)	
Small intestine	44 (7.06)	23 (8.71)	67 (7.55)	
Esophagus	45 (7.22)	17 (6.44)	62 (6.99)	
Histology				0.37
Neuroendocrine carcinoma	441 (70.79)	176 (66.67)	617 (69.56)	
Large cell neuroendocrine carcinoma	99 (15.89)	44 (16.67)	143 (16.12)	
Small cell carcinoma	83 (13.32)	44 (16.67)	127 (14.32)	
Stage				0.09
IV	342 (54.90)	134 (50.76)	476 (53.66)	
III	158 (25.36)	58 (21.97)	216 (24.35)	
II	90 (14.45)	50 (18.94)	140 (15.78)	
I	33 (5.30)	22 (8.33)	55 (6.20)	
T stage				0.32
T3	265 (42.54)	119 (45.08)	384 (43.29)	
T4	187 (30.02)	72 (27.27)	259 (29.20)	
T2	88 (14.13)	46 (17.42)	134 (15.11)	
T1	83 (13.32)	27 (10.23)	110 (12.40)	
N stage				0.32
N1	278 (44.62)	113 (42.80)	391 (44.08)	
N0	186 (29.86)	93 (35.23)	279 (31.45)	
N2	157 (25.20)	58 (21.97)	215 (24.24)	
N3	2 (0.32)	0 (0.00)	2 (0.23)	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Training cohort (n=623)	Validation cohort (n=264)	Total (n=887)	P value
M stage				0.25
M1	340 (54.57)	133 (50.38)	473 (53.33)	
M0	283 (45.43)	131 (49.62)	414 (46.67)	
Tumor size (mm)	50 [35–78]	50 [35–70.75]	50 [35–75]	0.43
Primary tumor resection				0.97
Yes	402 (64.53)	170 (64.39)	572 (64.49)	
No	221 (35.47)	94 (35.61)	315 (35.51)	
Non-primary surgery				0.70
No	560 (89.89)	235 (89.02)	795 (89.63)	
Yes	63 (10.11)	29 (10.98)	92 (10.37)	
Radiotherapy				0.52
None/unknown	503 (80.74)	218 (82.58)	721 (81.29)	
Yes	120 (19.26)	46 (17.42)	166 (18.71)	
Chemotherapy				0.08
Yes	365 (58.59)	138 (52.27)	503 (56.71)	
No/unknown	258 (41.41)	126 (47.73)	384 (43.29)	
Chemotherapy sequence				0.17
No chemotherapy and/or surgery	408 (65.49)	189 (71.59)	597 (67.31)	
Adjuvant chemotherapy	181 (29.05)	58 (21.97)	239 (26.94)	
Neoadjuvant chemotherapy	24 (3.85)	13 (4.92)	37 (4.17)	
Other sequences	10 (1.61)	4 (1.52)	14 (1.58)	
Metastasis				
Liver metastasis	271 (43.50)	107 (40.53)	378 (42.62)	0.41
Lung metastasis	42 (6.74)	20 (7.58)	62 (6.99)	0.66
Bone metastasis	40 (6.42)	16 (6.06)	56 (6.31)	0.84
Brain metastasis	13 (2.09)	3 (1.14)	16 (1.80)	0.33

Data are presented as median [interquartile range] or number (percentage).

respectively in the training cohort and 0.731 (95% CI: 0.698–0.764) *vs.* 0.645 (95% CI: 0.610–0.680) respectively in the validation cohort. In the training cohort, the 1- and 2-year survival AUC of ROC curve calculated from the nomogram were 0.768 and 0.776, respectively, while the 1- and 2-year survival AUC values calculated from the TNM staging system were 0.690 and 0.726, respectively (*Figure 3A*,*3B*). In the validation cohort, the 1- and 2-year survival AUC of the nomogram were 0.805 and 0.817, respectively, while the 1- and 2-year AUC of the TNM staging system were 0.700 and 0.742, respectively (*Figure 3C*,*3D*).

The calibration plots in the training and the internal validation cohorts showed a strong consistency between the nomogram-predicted survival probabilities and actual survival (*Figure 4*). In addition, the DCA showed a better performance in nomogram than the traditional TNM staging system in clinical usefulness in both groups

Table 2 The univariate analysis and multivariate Cox regression analysis of variables affecting OS

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (1.00–1.01)	0.11	1.01 (1.00–1.02)	0.004*
Sex				
Female	Reference		Reference	
Male	1.17 (0.98–1.40)	0.08	1.22 (1.01–1.47)	0.040*
Race				
Black	Reference		Reference	
Other	0.95 (0.63–1.44)	0.82	0.99 (0.64–1.53)	0.97
White	0.92 (0.71–1.19)	0.52	0.88 (0.67–1.16)	0.36
Tumor site				
Colon	Reference		Reference	
Esophagus	0.96 (0.68–1.36)	0.83	1.29 (0.81–2.03)	0.28
Pancreas	0.75 (0.59–0.94)	0.01*	0.80 (0.58–1.10)	0.18
Rectum	0.97 (0.75–1.26)	0.84	1.14 (0.81–1.61)	0.44
Small intestine	0.51 (0.35–0.75)	0.001*	0.81 (0.52–1.25)	0.34
Stomach	0.89 (0.67–1.20)	0.46	1.06 (0.72–1.57)	0.75
Histology				
Large cell neuroendocrine carcinoma	Reference		Reference	
Neuroendocrine carcinoma	1.08 (0.84–1.38)	0.55	1.08 (0.83–1.42)	0.55
Small cell carcinoma	1.27 (0.93–1.75)	0.14	0.99 (0.70–1.40)	0.97
Stage				
I	Reference		Reference	
II	1.81 (1.05–3.13)	0.03*	1.44 (0.79–2.62)	0.24
III	2.02 (1.19–3.40)	0.009	1.09 (0.60–2.01)	0.77
IV	4.59 (2.77–7.60)	<0.001*	0.62 (0.08–5.11)	0.66
T stage				
T1	Reference		Reference	
T2	0.71 (0.51–0.99)	0.045*	0.88 (0.61–1.28)	0.51
T3	0.79 (0.60–1.03)	0.09	1.04 (0.75–1.44)	0.83
T4	1.25 (0.95–1.66)	0.12	1.23 (0.88–1.73)	0.23
N stage				
N4	Reference		Reference	
N1	1.27 (1.03–1.57)	0.03*	1.43 (1.12–1.82)	0.004*
N2	1.97 (1.55–2.49)	<0.001*	2.78 (1.99–3.89)	<0.001*
N3	10.8 (2.63–44.28)	0.001*	5.33 (1.14–4.83)	0.03*

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
M stage				
M0	Reference		Reference	
M1	2.56 (2.14–3.08)	<0.001*	4.01 (0.52–0.95)	0.18
Tumor size	1.01 (1.00–1.01)	<0.001*	1.01 (1.00–1.01)	0.002*
Primary tumor resection				
No	Reference		Reference	
Yes	0.55 (0.46–0.65)	<0.001*	0.28 (0.19–0.41)	<0.001*
Non-primary surgery				
No	Reference		Reference	
Yes	0.89 (0.66–1.19)	0.43	0.76 (0.55–1.06)	0.11
Radiotherapy				
None/unknown	Reference		Reference	
Yes	0.77 (0.62–0.96)	0.02*	0.65 (0.49–0.87)	0.004*
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.84 (0.71–1.01)	0.06	0.40 (0.29–0.55)	<0.001*
Chemotherapy sequence				
Adjuvant chemotherapy	Reference		Reference	
Neoadjuvant chemotherapy	0.56 (0.32–0.98)	0.04*	0.99 (0.55–1.81)	0.98
No chemotherapy and/or surgery	1.48 (1.22–1.79)	<0.001*	0.71 (0.50–1.00)	0.051
Other sequences	1.29 (0.68–2.45)	0.43	1.55 (0.79–3.01)	0.20
Metastasis				
Liver metastasis	2.31 (1.93–2.75)	<0.001*	1.20 (0.89–1.61)	0.23
Lung metastasis	1.78 (1.29–2.45)	<0.001*	0.95 (0.67–1.34)	0.77
Bone metastasis	2.07 (1.49–2.86)	<0.001*	0.99 (0.70–1.41)	0.96
Brain metastasis	1.73 (1.00–3.01)	0.05	1.58 (0.83–3.01)	0.16

*, P<0.05. OS, overall survival; HR, hazard ratio; CI, confidence interval.

median OS of 10 months. The 1- and 2-year survival rates were 43.9% and 27.1%, respectively. Even for patients with localized disease treated with surgery, long-term survival was short, at 22 months, suggesting that micrometastases may have been present at diagnosis. According to our nomogram, patients with the higher age or larger tumor size would likely have poorer prognosis. Sex was associated with survival as a prognostic factor. The nomogram also illustrated that patients with lymph node metastases were more likely to die than N0 stage patients. N stage contributed significantly to the prognosis prediction of GEP-NEC patients, which may have the potential to help identify high-risk individuals for treatment enhancement. That is generally consistent with what Erstad *et al.* found, that a high positive lymph node ratio (LNR) was described as a prognostic marker associated with an increased risk

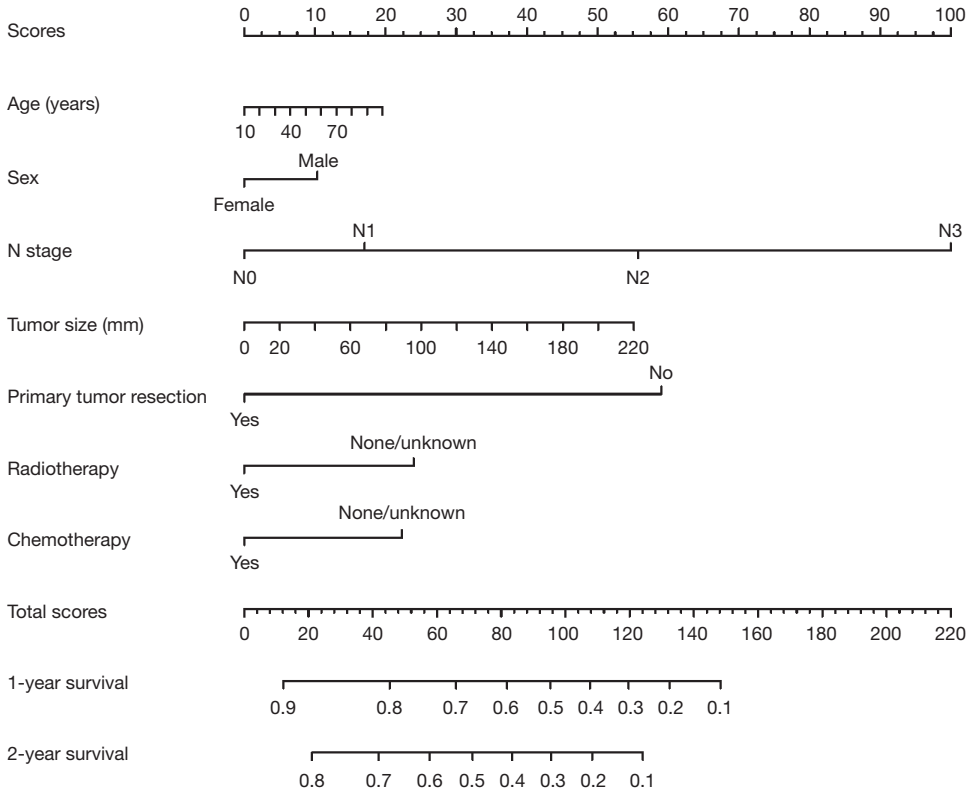

Figure 2 Prognostic nomograms of 1- and 2-year OS for GEP-NEC patients. OS, overall survival; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma.

(*Figure 5*). Furthermore, the 1- and 2-year IDI of nomogram compared with the TNM staging system was 9.66% (P<0.001) and 7.34% (P=0.01) in the validation cohort, which showed the overall improvement of the model. Overall, the nomogram exhibited better survival predictive ability than that of the TNM staging system.

Survival analysis

We used the Kaplan-Meier method to perform survival analysis. In the training cohort, the overall median OS was 10 months (95% CI: 9–11). The overall 1- and 2-year survival rates were 43.9% (95% CI: 40.2–48.0%) and 27.1% (95% CI: 23.8–30.9%), respectively (Figure S1A). Patients were divided into high-risk and low-risk groups based on the median score of the nomogram. Kaplan-Meier analysis showed that the median OS in the high-risk group was significantly lower than that of patients in the low-risk group [5 (95% CI: 4–6) *vs.* 19 months (95% CI: 16–24)], which was consistent with the use of the nomogram (P<0.001) (*Figure 6A*). Patients who underwent primary tumor surgery had longer survival than the patients who did not, with median survival of 14 (95% CI: 11–16) *vs.* 7 months (95% CI: 6–9), 1-year survival of 52.5% (95% CI: 47.8–57.6%) *vs.* 28.51% (95% CI: 23.14–35.1%) and 2-year survival of 36.3% (95% CI: 31.9–41.3%) *vs.* 10.58% (95% CI: 7.19–15.5%), respectively (P<0.001) (*Figure 6B*). The verification cohort also suggested similar results (*Figure 6C*,*6D*).

We performed a subgroup analysis using the training group. Among patients with localized disease who underwent resection of primary tumor (n=229, 36.76%), the median OS was 22 months (95% CI: 17–31). The 1- and 2-year survival rates were 66.3% (95% CI: 60.4–72.7%) and 49.0% (95% CI: 43.0–56.0%), respectively (Figure S1B). For all patients undergoing surgery (n=402, 64.53%), we observed that the median OS was prolonged in patients who received adjuvant chemotherapy compared to those who did not [16 (95% CI: 13–20) *vs.* 8 months (95% CI: 5–15)] (Figure S1C). For patients with advanced disease (n=342, 54.90%), the median OS was 9 months (95% CI: 8–11) and 2 months (95% CI: 1–2) for patients who received palliative chemotherapy and those who did not, respectively

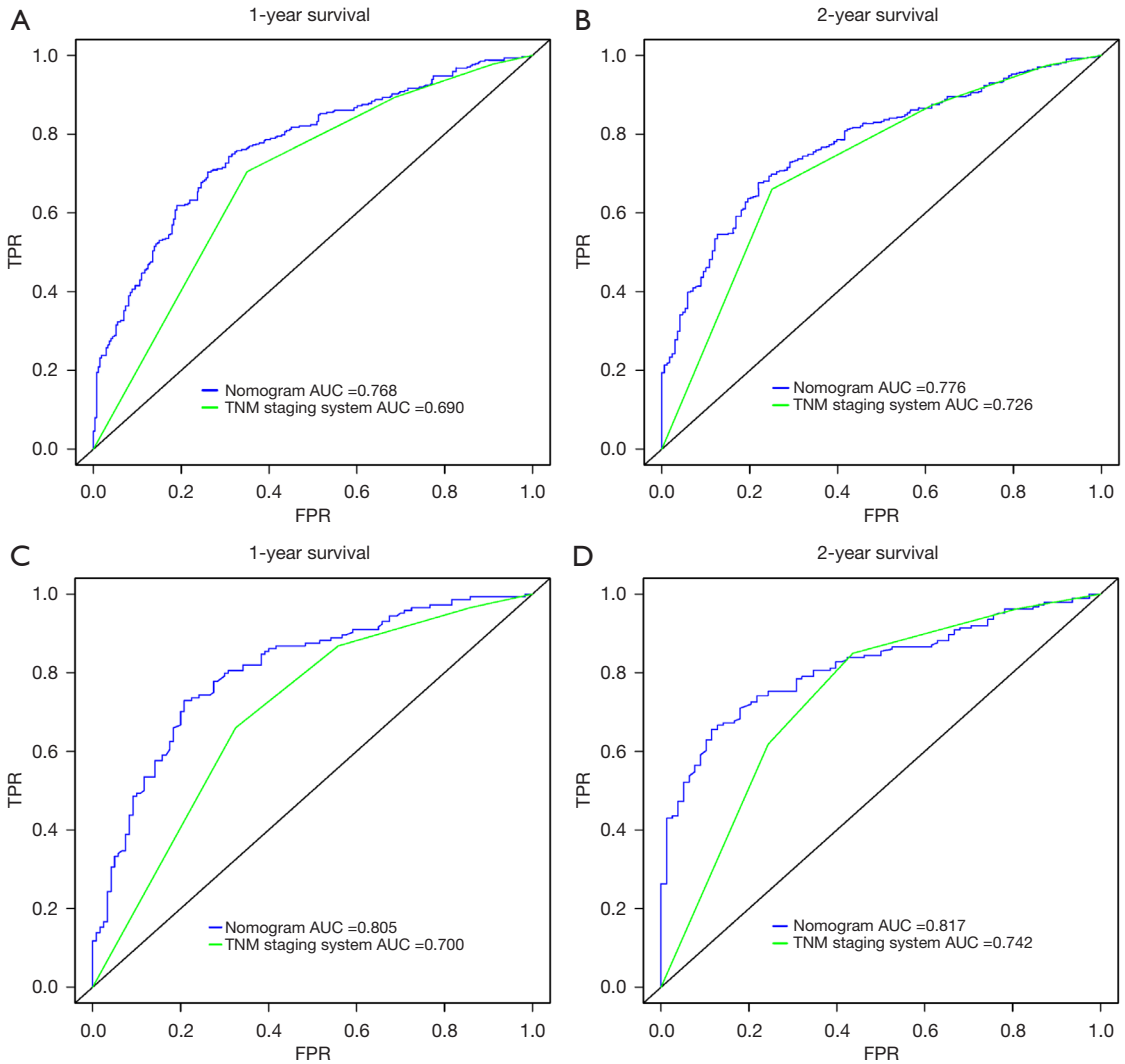

Figure 3 The 1- and 2-year survival ROC curves of nomogram and TNM staging system for GEP-NEC patients in the training cohort (A,B) and the validation cohort (C,D). FPR, false positive rate; TPR, true positive rate; AUC, area under the curve; TNM, tumor node metastasis; ROC, receiver operating characteristic; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma.

(Figure S1D). In terms of tumor primary site, patients with small intestine origin tended to have better survival with median OS of 29.0 months (95% CI: 16–65). The median OS of patients with colon NEC was the worst at 7.0 months (95% CI: 6–9) (Figure S2).

Discussion

GEP-NEC is a distinctive part of neuroendocrine neoplasm and has prognosis different from gastrointestinal neuroendocrine tumor and other types of cancer. Because of the rarity of GEP-NEC, there are few data on the clinicopathological characteristics and prognosis of GEP-NEC. It is still an unsolved challenge for clinicians to make prognostic stratifications and predict the survival outcome of GEP-NEC. As far as we know, nomogram models have been applied to predict the survival status of various tumors and show better predictive value compared with other traditional staging systems. However, there are no nomograms that quantify and visualize risk by various prognostic factors to predict the prognosis of GEP-NEC.

In our study, a total of 887 GEP-NEC patients from the SEER database were analyzed. Age, sex, N stage, tumor size, primary tumor resection, radiotherapy and

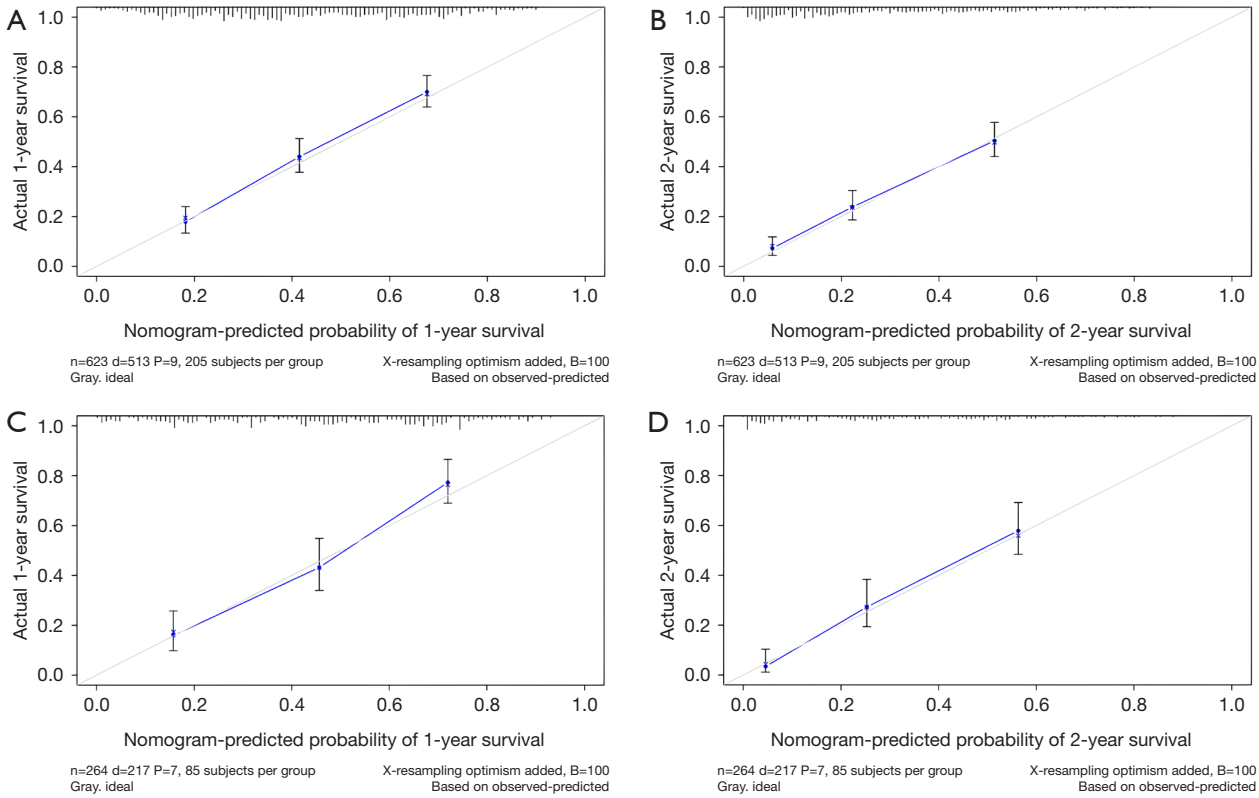

Figure 4 Nomogram calibration plots to predict 1- and 2-year OS in the training cohort (A,B) and the validation cohort (C,D). OS, overall survival.

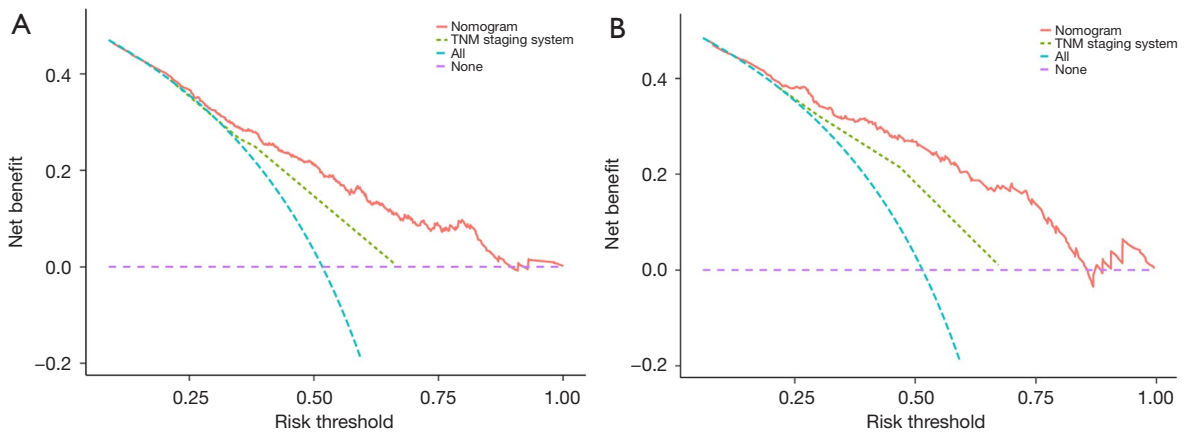

Figure 5 DCA of nomogram and TNM staging system predicting OS in the training cohort (A) and the validation cohort (B). OS, overall survival; DCA, decision curve analysis; TNM, tumor node metastasis.

chemotherapy were independent prognostic factors of OS in GEP-NEC patients. The nomogram was built based on these prognostic factors and was used to predict the 1- and 2-year survival rates in GEP-NEC patients. The nomogram showed better predictive performance than the TNM staging system for OS both in the training and validation cohorts.

Patients with GEP-NEC had a poor prognosis with a

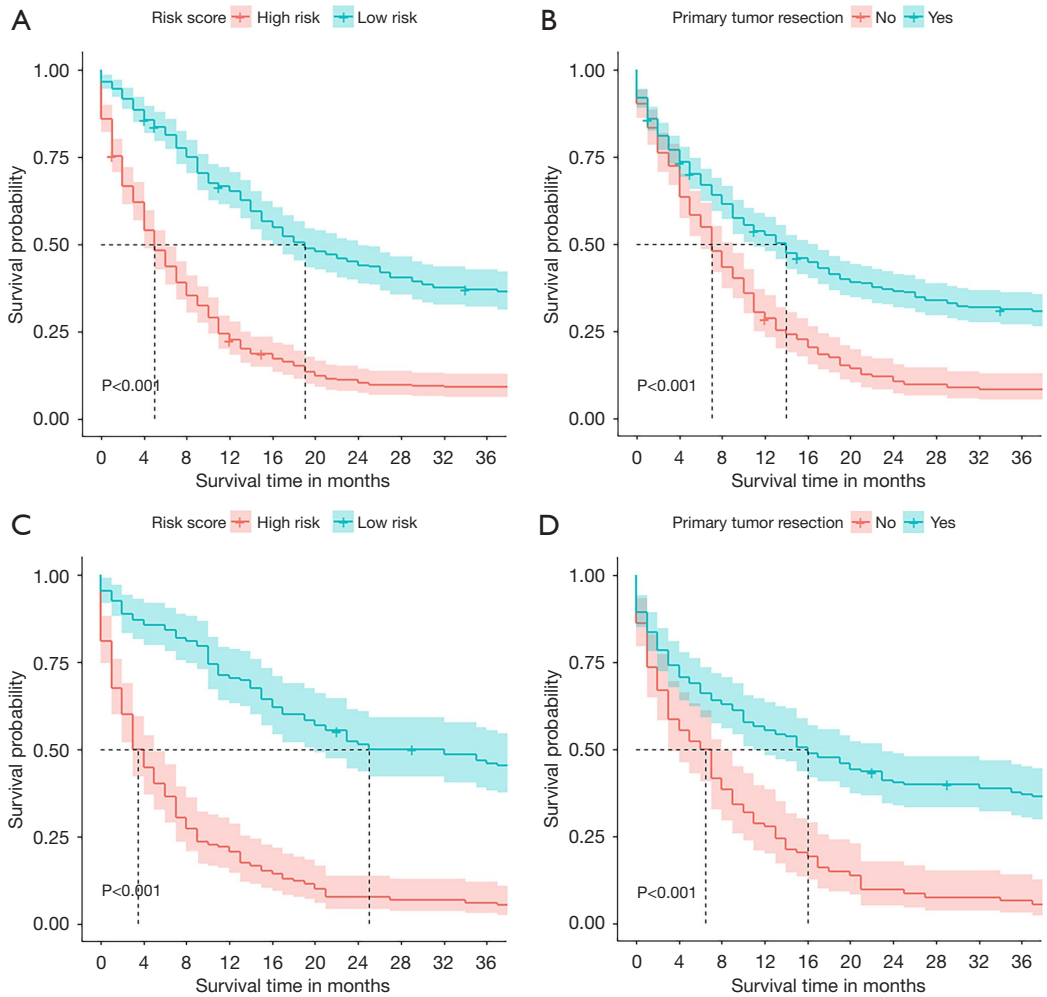

Figure 6 Kaplan-Meier survival curves based on risk stratification (A,C) and whether primary tumor surgery was performed (B,D) in the training cohort and validation cohort.

of death in rectal NEC (7). Taken together, some of these variables have been reported as predictive factors for gastric NEC patients in previous studies (8,9). Interestingly, the traditional T stage and M stage failed to show independent prognostic significance.

Whether patients can benefit from surgery is still controversial and patients are needed to be carefully evaluated (10). The European Neuroendocrine Tumor Society (ENETS) consensus published in 2023 and National Comprehensive Cancer Network (NCCN) guidelines (version 2.2022) both assume that curative surgery is usually recommended in localized diseases and surgical resection of metastases is not recommended in advanced metastatic disease (11,12). On the contrary, the European Society for Medical Oncology (ESMO) and the North American Neuroendocrine Tumor Society (NANETS) consensus published in 2020 both suggest that patients with poorly differentiated NEC should not undergo resection because of the extremely poor prognosis that does not seem to be affected by surgical resection (13,14). A study that included poorly differentiated colorectal NEC found that primary tumor resection was not associated with survival in localized or metastatic disease (15). A study that included 49 pancreatic NEC patients observed that patients who underwent surgery had longer OS than those who did not (16 *vs.* 9.6 months), but the difference was not significant (16). In our study, the nomogram suggested primary tumor resection as a protective factor for patients with GEP-NEC. In subgroup analysis, median OS was observed for up to 22 months in patients with localized disease who underwent

surgery. In the entire GEP-NEC cohort, primary tumor resection significantly prolonged OS, although the median OS was short with only 14 months and 7 months for patients who received surgery and patients who did not (P<0.001). This is generally consistent with the results of a retrospective study that included 1,861 gastrointestinal NEC patients, which reported a median OS of 13.3 months for patients who underwent surgery (17). A study that included 4,171 stage IV GEP-NEC patients from the National Cancer Database (NCDB) found that the mortality rate of patients who underwent single-site surgery was 40% lower than that of patients who did not undergo surgery. The mortality rate of patients who underwent multisite surgery was 59% lower than that of patients who did not undergo surgery and 31% lower than that of patients who underwent single-site surgery (18). Another study that included 6,560 GEP-NEC patients from the NCDB observed that in comparison to open resection, laparoscopic and robotic resection were associated with reduced postoperative mortality within 30 and 90 days and extended OS (19). A recent study based on the SEER database also showed that primary tumor resection may prolong survival in patients with gastrointestinal NEC with bone metastases (20). As increased molecular pathology information becomes available, it is necessary to manage NEC patients as distinct patient groups and assess the benefits of surgery.

Chemotherapy is the mainstay of treatment for localized NEC and advanced disease. Clinically, platinum-based chemotherapy is the main treatment option. First-line chemotherapy regimens include platinum/etoposide or cisplatin/etoposide regimens (21,22). Our nomogram showed a significant impact of chemotherapy in the prediction of survival outcomes. For patients after radical surgery, adjuvant therapy is still recommended due to the high recurrence rate after radical surgery (3). Our subgroup analysis showed that in postoperative patients, median OS was prolonged by 8 months in patients who received adjuvant chemotherapy compared to patients who did not (16 *vs.* 8 months). In addition, for patients with advanced disease, previous studies found that palliative chemotherapy significantly prolongs survival in GEP-NEC patients with median OS of approximately 11–12 months (17,23-27); however, some of the studies do not distinguish between NEC and NET G3. As shown in our study, the median OS in GEP-NEC patients receiving and not receiving palliative chemotherapy was 9 and 2 months, respectively.

Collectively, our nomogram suggested that both surgery and chemotherapy were protective prognostic factors. As a recent database-based study of rectal NEC found, the combination of radical surgery and chemotherapy was associated with a higher survival rate compared to surgery or chemotherapy alone (7). Therefore, surgery plus chemotherapy may be the preferred approach for early-stage patients, and patients should be carefully selected.

ENETS consensus also indicated that course of radiation and chemotherapy is a reasonable treatment strategy for patients with specific comorbidities or specific tumor anatomical sites where surgery is not advisable (i.e., esophagus) (3). That suggestion is consistent in our study that our nomogram indicated that survival rate of GEP-NEC patients who received radiotherapy was higher than that of patients who did not. It is interesting to note that we did not find neoadjuvant chemotherapy was a significant independent prognostic variable in GEP-NEC cohort, although the small sample size was insufficiently powered. This is consistent with the results of a recent retrospective study of rectal NEC (7). While Ma *et al.* found that gastric NEC/mixed adeneuroendocrine carcinoma (MANEC) patients treated with neoadjuvant chemotherapy had better survival than patients who had surgery first (3-year OS rate 68.8% *vs.* 43.8%, 5-year OS rate 57.4% *vs.* 28.5%, respectively). Multivariate analyses also showed that neoadjuvant chemotherapy was an independent factor affecting OS (28). Another study found a better OS in patients who received neoadjuvant therapy and this gastrointestinal NEC cohort had a high proportion of margin-positive resection, thus suggesting that neoadjuvant therapy may have a stage-reducing effect (17). It would be worthwhile to increase the sample size to further explore the prognostic impact of neoadjuvant chemotherapy in GEP-NEC patients.

Although tumor site was not an independent predictor in our model, Kaplan-Meier survival curves illustrated that prognosis tended to differ by primary tumor site. Patients with colon, esophageal and rectal primaries had worse survival compared to other primaries. That is generally consistent with the results of some large European series (23). In addition, histology (large cell NEC *vs.* small cell NEC) appears to be a prognostic factor in some studies. Previous studies reported that the median survival and 5-year survival rate with large cell NEC were better than that of the patients with small cell NEC (16 *vs.* 6 months, 32% *vs.* 6%), but the statistical significance of the differences remains controversial (1,29). In our data,

specific histological classifications were mostly missing and therefore insufficient to explore their prognostic impact. The future development of genetic molecular markers with prognostic implications in the field of NEC would be promising (30-32).

We used C-index, ROC, calibration plots, DCA and IDI for internal validation and model comparison. For NEC, the TNM staging system of adenocarcinoma is now commonly applied (13). The model validation showed that the nomogram exhibited better survival predictive ability than that of the TNM staging system. The nomogram proved to have an excellent ability of discrimination with higher C-index and AUC of ROC curve in nomogram than TNM staging system. The calibration plots of the nomogram demonstrated a strong agreement between the predicted survival probability and the actual survival rate. Furthermore, the nomogram was demonstrated to be clinically useful compared with the TNM staging system through DCA. IDI indicated a significant overall improvement of the nomogram compared with the TNM staging system.

There are several limitations to this study. Firstly, gastroenteropancreatic neuroendocrine neoplasm (GEP-NEN) has undergone many changes in terminology and classification over the past decade, and high-quality data on GEP-NEC are often not available in registries. In this regard, we excluded the NET data and our nomogram was able to specifically predict the prognosis of the poorly-differentiated GEP-NEC population. Secondly, the study is lacking some important information to support the analysis of the impact of the variables, such as Ki-67, carcinoembryonic antigen (CEA), lactate dehydrogenase, thrombocyte level and neutrophil-to-lymphocyte ratio, which were considered to be predictive factors for NEC patients (33,34). Additional variables associated with the prognosis of GEP-NEC need to be included to further improve the predictive value of the model. Thirdly, detailed information about systemic therapy was not provided in the SEER database, for example, chemotherapy regimens were unknown. Results from the recent TOPIC-NEC phase 3 randomized clinical trial showed no statistically significant differences in OS between the etoposide plus cisplatin (EP) and irinotecan plus cisplatin (IP) groups in advanced high grade NEN of the digestive system. Notably, subgroup analysis showed that EP produced a more favorable OS in patients with pancreatic primary (26). A previous phase 2 clinical trial also confirmed similar efficacy for EP and IP regimens. In addition, the study found that IP was slightly more effective than EP in patients with non-small cell NEC (27). The prognostic impact of systemic treatment options including immunotherapy and whether to divide GEP-NEC into different entities are the next important clinical issues. Despite such limitations, our prognostic nomogram model proved to be an instructive and practical model to accurately predict individual outcomes in GEP-NEC patients.

Conclusions

In conclusion, this large population SEER database-based cohort analysis shows that GEP-NEC is a unique neuroendocrine neoplasm with special clinical and prognostic characteristics. Age, sex, N stage, tumor size, primary tumor resection, radiotherapy and chemotherapy were identified as independent prognostic factor of GEP-NEC. Based on those identified prognostic variables, we established a useful nomogram that can accurately predict individual OS of patients with GEP-NEC. In addition, the internal validation cohort shows that the predictive nomogram performs well through C-index, ROC, calibration plots, DCA and IDI. We believe that our nomogram and the important findings will assist clinicians in clinical decisions making and management, and will guide future prospective research for patients with GEP-NEC.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2215/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2215/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).

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