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Comparison of proximal and distal gastric neuroendocrine carcinoma based on SEER database

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The occurrence of gastric neuroendocrine carcinoma (GNEC) is on the rise, and its prognosis is extremely poor. We compared survival outcomes between distal and proximal GNEC and developed a nomogram incorporating tumor site to enhance personalized management for patients with GNEC. 1807 patients were divided into DGNEC and PGNEC groups. We performed analyses by using propensity score matching (PSM) and Fine-Gray competing risk methods. A predictive nomogram for the prognosis of GNEC was constructed and validated. The cumulative incidence of cancer-specific death (CSD) in the DGNEC group was lower than that in the PGNEC group. Subgroup analysis showed lower CSD of DGNEC in males, females, tumor sizes (≤ 2 cm, 2 < tumor size ≤ 5 cm, > 5 cm, and unknown), grade stage I-II, and AJCC stage I-III, chemotherapy or no chemotherapy, surgery or no surgery groups ($P < 0.05$). Multivariate analysis revealed a significant association between PGNEC and CSD (HR, 1.4; 95% CI 1.13–1.73; $P = 0.02$). The independent predictors of CSD in patients with GNEC were primary site, gender, age, tumor size, AJCC stage, T stage, N stage, grade stage, and surgery. A predictive model based on multivariate analysis was constructed to estimate the probability of CSD at 1-, 3-, and 5-year. The calibration curves demonstrated excellent consistency between the predicted and observed probabilities of CSD. Patients with DGNEC have a better prognosis than those with PGNEC. The model exhibits strong predictive capability for these patients.

Keywords Gastric neuroendocrine carcinoma, Location, Prognosis, Competing risk analysis, Nomogram

The number of gastric cancer (GC) cases worldwide reached 1,089,000 in 2020, with an age-standardized incidence rate of 11.1 per 100,000, resulting in 769,000 deaths and an age-standardized mortality rate of 7.7 per 100,000[1]. Gastric neuroendocrine carcinoma (GNEC) is a rare disease that accounts for only 0.1–0.6% of GC cases. Although GC incidence has been decreasing in recent years, GNEC incidence has been increasing annually because of the advancements in disease diagnosis and the popularization of gastroscopy[2,3]. The prognosis of GNEC is poorer compared to poorly differentiated gastric adenocarcinoma because of rapid tumor expansion, frequent invasion of lymphatic and vascular systems, elevated metastasis frequency, and assertive biological characteristics[4]. The majority of GNEC patients are typically diagnosed at advanced stages, often characterized by lymph node involvement or distant metastasis.

Although the stomach is often considered a distinct entity, it is classified according to two anatomical sublocations: proximal (emerging within the upper third of the stomach, encompassing the cardia or the gastroesophageal junction) and distal (originating from the remainder of the stomach region)[5]. Therefore, GC is usually divided into distal gastric cancer (DGC) and proximal gastric cancer (PGC). In a systematic review conducted from January 1990 to August 2016, Hirabayashi et al. found that EBV is more prevalent in tumors originating in the upper region of the stomach[6]. Male sex, alcohol or tobacco misuse, hiatal hernia, gastric reflux disease, columnar-lined esophagus, advanced age, cancer history, and high BMI (> 24 kg/m^2) were identified as independent risk factors for PGC. Conversely, *Helicobacter pylori* infection and a familial cancer predisposition independently increase the risk for DGC[7]. Lastly, there is a growing incidence of DGC among individuals under the age of 50, particularly in regions with historically low prevalence rates. These malignancies, categorized as early-onset gastric cancers, exhibit a correlation with the escalating occurrence of autoimmune gastritis and disruptions in stomach microbiota composition, potentially attributable to heightened utilization of antibiotics

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and acid-suppressive medications[8,9]. Surgery remains the most effective treatment for GNEC[10]. Distal D2-gastrectomy is the treatment of choice for DGC, while total D2-gastrectomy is often necessary for PGC. Although distal and total gastrectomies are both safe procedures, previous research has revealed some distinctions and raised concerns regarding the surgical and oncological outcomes of these procedures. A study by Cas de Jongh showed that compared with total D2-gastrectomy patients, distal D2-gastrectomy patients had shorter median hospital stays, fewer overall complications, lower anastomotic leakage, et al. Compared with total D2-gastrectomy patients, distal D2-gastrectomy has fewer complications, a quicker recovery after surgery, and a higher quality of life while maintaining comparable oncological effectiveness[11]. A systematic review and meta-analysis by Jiang et al. showed that anastomosis leakage, intra-abdominal infection, and overall post-operative sequelae were less common in patients who underwent distal D2-gastrectomy[12]. These biological characteristics, surgical approaches, and complications seem to result in very different prognoses for PGC and DGC[13]. Unfortunately, previous studies have focused on gastric adenocarcinoma, and no studies have been conducted to specifically target GNEC on DGC and PGC[14–17]. We still lack experience and validated measures for evaluating whether PGNEC and DGNEC show a different prognosis. Meanwhile, the relevant factors affecting the prognosis of GNEC remain a mystery.

Currently, the TNM staging system is a commonly used prognostic index. However, this evaluation method only includes some of the tumor characteristics and cannot accurately predict patient prognosis. For the treatment of GNEC, the identification of patients at high risk with a poor prognosis is paramount. Therefore, we developed a comprehensive prognosis prediction model based on the Fine-Gray competing risk model, which provides a convenient and quick individualized prediction tool for patients with GNEC and clinicians and a reliable reference for the treatment plan formulation.

Methods

Consistent with our prior research utilizing the surveillance, epidemiology, and end results (SEER) *Stat software (Version 8.3.5), patient data were sourced from the SEER 18 regions database [Incidence-SEER Research Plus data, 18 Registries (2010–2015)][18]. For external validation, 32 patients with GNEC were collected from Hangzhou TCM Hospital spanning from January 2013 to December 2018.

Patients who were eligible for inclusion were identified as follows: (1) aged over 18 years; (2) diagnosed with neuroendocrine carcinoma (8012, 8013, 8041, 8044, 8144, 8240, 8244, 8246, 8249); (3) survival time greater than one month; (4) located in the proximal or distal stomach.

The following patients were excluded: (1) those who survived for less than a month; (2) those with more than one cancer; and (3) those for whom clinicopathological, therapeutic, and follow-up data were lacking. Ultimately, 1807 instances were covered in this study. Initially, the patients were categorized into DGNEC and PGNEC groups to conduct alternative risk assessments. To create a predictive nomogram, the cases were divided into the training and validation groups. Figure 1 shows the process for choosing instances.

Clinicopathological variables

The SEER data repository was used to obtain demographic data (year of diagnosis, age, gender, race, marital status, grade stage, T stage, N stage, pathology, primary site, tumor size, radiation, chemotherapy, and surgery data). Patients were reassigned according to the 8th edition TNM classification, which was derived from the 7th edition TNM classification retained in the SEER database.

Statistical analysis

Categorical data were summarized using frequency counts and percentages, while continuous variables were presented as means and standard deviations. Differences in baseline clinicopathological characteristics were assessed using the *t*-test and chi-square test. The competing risk studies divided all patients into two groups: DGNEC and PGNEC group. The three endpoints of interest were cancer-specific death (CSD), other causes of death (OCD), and living. The cumulative incidence function (CIF) was employed for univariate analysis. Gray's test was used to identify intergroup differences in the CIF. Using the R package "cmprsk", the proportional subdistribution hazard model proposed by Fine and Gray was further utilized for the multivariate analysis to identify prognostic factors[19].

Utilizing a one-to-one nearest-neighbor approach, PSM represents an advanced statistical methodology that emulates the conditions of randomized controlled trials, thereby mitigating variability. The standardized difference (SD) was utilized to assess the changes in variables pre- and post-PSM. An indication of ideal balance in baseline parameters was achieved when SD was ≤ 0.1.

Based on a comprehensive literature review and expert clinical recommendations, we identified key clinical variables closely linked to patient prognosis, including age, gender, race, marital status, grade stage, T stage, N stage, pathology, primary site, tumor size, radiation, chemotherapy, and surgery data. The training (70%, n = 1265) and the validation (30%, n = 542) groups were randomly selected from the total number of patients. Using the prognostic features found in the competing risk model, the 1-, 3-, and 5-year CSD nomogram was built using the training dataset. During the model construction process, each factor was assigned a score based on its contribution to the outcome variable (reflected by the size of the regression coefficient). The individual scores were then summed to obtain a total score. Finally, the total score was converted into a probability function to calculate the predicted outcome for each individual. The nomogram transforms complex regression equations into a visual graph, making the results of the predictive model more readable and facilitating patient evaluation. The methodical approach presented by Zhang et al. served as the foundation for this elaborate procedure[20]. The performance of the nomogram was assessed in both the training and validation groups using the area under the receiver operating characteristic curve (AUC) and calibration curves. To assess the expected and observed survival probabilities in the calibration curves, 1000 bootstrap resamples were used. Receiver

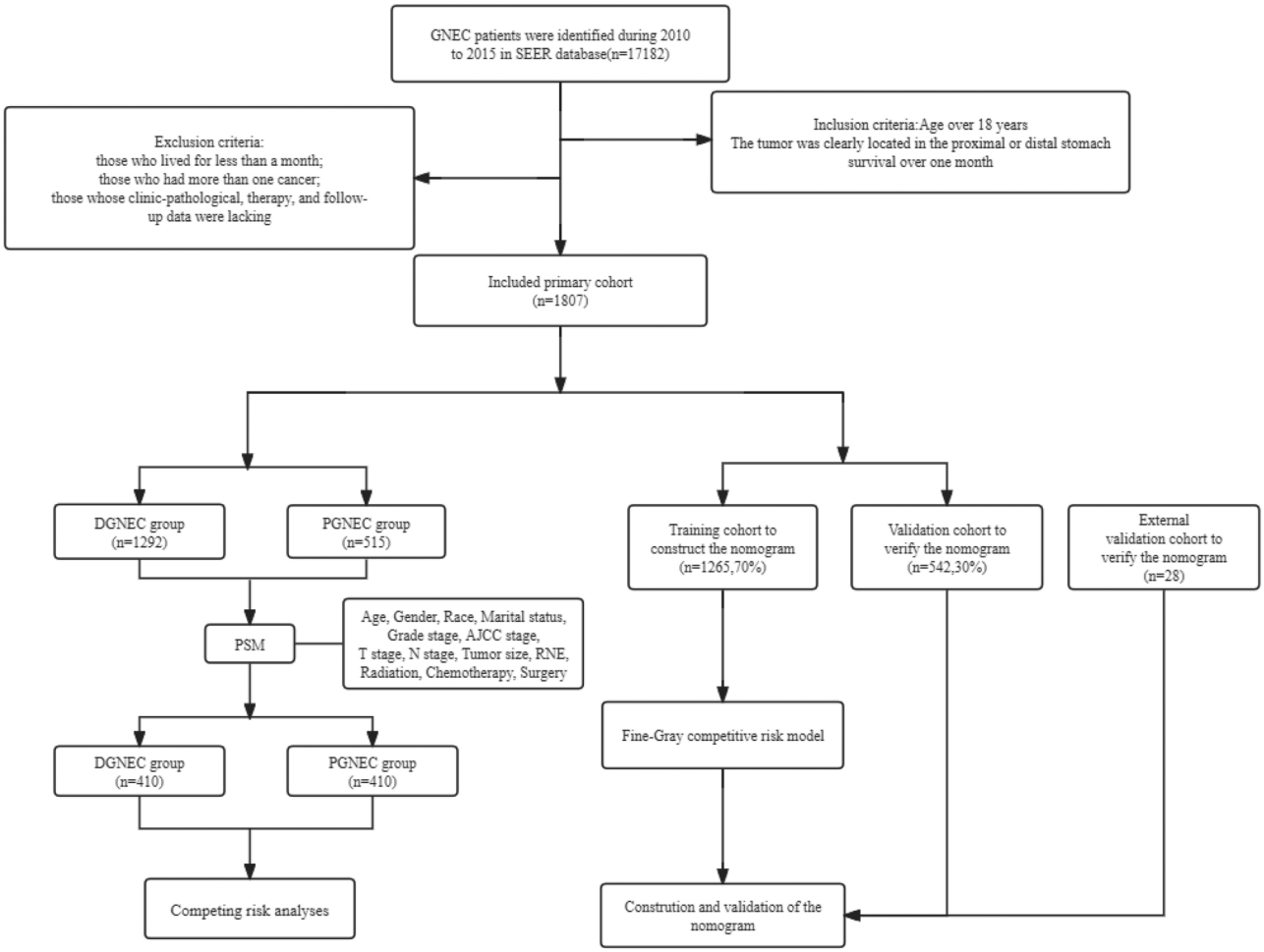

Fig. 1. The process for choosing patients.

operating characteristic (ROC) curves were utilized to calculate the AUC, thereby assessing and illustrating the predictive performance of the constructed model. The AUC of the ROC curve was calculated to assess and demonstrate the predictive performance of the model. A higher AUC indicates better discriminative ability of the model. Generally, an AUC < 0.60 is considered to indicate poor discrimination, 0.60–0.75 indicates acceptable discrimination, and > 0.75 indicates good discriminative ability. Calibration curves were drawn to assess the calibration of the predictive model, with the horizontal axis representing the predicted probability of an event according to the model, and the vertical axis representing the observed probability of an event. A fitted line with a slope close to 1 and an intercept close to 0 suggests good calibration of the model. The calibration for 1-year, 3-year, and 5-year outcomes was calculated for both the training and validation cohorts. R software introduced in our previous study served as the foundation for statistical analyses and visualizations[21]. Statistical significance was set at $P < 0.05$.

Results

From 2010 to 2015, 1807 patients of GNEC were enrolled in the SEER database, while 32 patients from Hangzhou TCM Hospital were identified as the external validation cohort. Of all patients, 1292 (71.5%) and 515 (28.5%) patients had DGNEC and PGNEC, respectively. The two groups demonstrated significant differences across multiple parameters (all $P < 0.05$), including age, gender, race, marital status, tumor grade, AJCC stage, T stage, N stage, tumor size, regional nodal evaluation (RNE), and treatment modalities such as radiation, surgery, and chemotherapy. The DGNEC patients typically exhibited a greater proportion of Grade I (18.0% vs. 14.2%), Grade II (44.5% vs. 42.5%), AJCC I (35.9% vs. 27.2%), AJCC II (27% vs. 22.5%), tumor size ≤ 2 cm, those who received radiation (81.5% vs. 65.8%), those aged > 60 years (79.9% vs. 67.8%), and those who didn't receive chemotherapy (63.6% vs. 42.5%), and who received surgery (86.4% vs. 65.2%). The PGC group presented a high percentage of males (70.1% vs. 57.4%), married patients (61.6% vs. 57.8%), Grade IV (4.7% vs. 1.5%), AJCC III stage (31.3% vs. 23.7%), AJCC IV (19.0% vs. 13.4%), T2 stage (20.6% vs. 16.7%), T3 stage (35.7% vs. 28.1%), N1 (31.3% vs. 22.2%), those who received radiation (34.2% vs. 18.5%), who received chemotherapy (57.5% vs. 36.4%), and who didn't received surgery (34.8% vs. 13.6%). As the characteristics of the two groups didn't match, a 1:1 PSM was employed to minimize the impact of confounding variables. After PSM, there were no significant

differences in multiple indexes between the two groups ($P > 0.05$) (Table 1). The standard deviations (SDs) of the majority of the variables after PSM was < 0.1, demonstrating a good balance (Fig. S1). Ultimately, 820 individuals were divided into two groups: 410 patients in the DGNEC group and 410 patients in the PGNEC group. Table 1 illustrates the demographic characteristics of both groups before and after PSM.

Survival analysis

Before PSM, patients in the DGNEC group showed significantly better cancer-specific survival (CSS) and overall survival (OS) compared to those in the PGNEC group ($P < 0.001$). (Figs. 2A, B). After PSM, significant differences in OS and CSS were observed between the two groups likewise (Figs. 2C, D). When the competing risk variables were considered, cumulative incidence plots were created, and the DGNEC group showed a significantly reduced CSD ($P < 0.001$). Additionally, compared with patients in the PGNEC group, patients in the DGNEC group experienced reduced 1-, 3-, and 5-year CIF of the CSD (17.68% vs. 26.75%; 34.69% vs. 46.90%; 5-year: 39.45% vs. 54.18%, $P < 0.001$) (Table 2). Then, subgroup analyses of AJCC stage, chemotherapy, sex, grade stage, surgery, tumor size, T stage, and N stage were performed. It turned out that the DGNEC group had a reduced CSD in cohorts of male gender, female gender, tumor size (≤ 2 cm, $2 <$ tumor size ≤ 5 cm, > 5 cm and unknown), grade I-II stage, and AJCC I-III stage, chemotherapy yes or none, surgery yes or none groups. (Fig. S2).

Similar results can be observed after PSM that significant differences existed between DGNEC and PGNEC in the 1-, 3-, and 5-year CIF of CSD (1-year: 18.24% vs. 25.02%; 3-year: 33.52% vs. 44.05%; 5-year: 37.31% vs. 51.36%, $P < 0.01$) (Table 2). We conducted the subgroup analyses again, which showed that patients in the PGNEC group experienced more CSD in the following areas: male gender, female gender, tumor size (≤ 2 cm, $2 <$ tumor size ≤ 5 cm, > 5 cm and unknown), grade I-II stage, and AJCC I-III stage, chemotherapy yes or none, surgery yes or none groups (Fig. 3).

Univariate and multivariate analysis

Further independent analyses were conducted where all patients were randomly divided into two groups for model development: a training group comprising 70% of the patients ($n = 1265$), and a validation group comprising the remaining 30% of the patients ($n = 542$). There were no apparent distinctions in the clinical baseline characteristics between the two groups. In the multivariate competing risks regression analysis, the PGNEC on CSD had a significant connection (HR, 1.40; 95% CI 1.13–1.73; $P = 0.002$) (Table 3). Table S1 shows the results of the multivariate subdistribution hazards model on OCD before and after PSM. The CIF values at 1, 3, and 5 years for the CSD were calculated through univariate analysis. Important factors (with a statistical significance level of $P < 0.05$) were identified through multivariate analysis using the Fine-Gray proportional subdistribution hazards model. According to the results of the multivariate competing risk analysis, primary site, gender, age, tumor size, grade stage, AJCC stage, T stage, N stage, and surgery were all independent predictors of CSD in patients with GNEC (Table 4). Taking into account the information about the T and N stages included in the variable AJCC stage, we did not include it in our following analyses.

Constructing and verifying the nomogram

A nomogram for assessing the probabilities of experiencing CSD at 1, 3, and 5 years was developed based on variables determined in the multivariate analysis (Fig. 4). Primary site, gender, age, tumor size, grade, surgery, AJCC stage were independent risk factors affecting the prognosis of GNEC patients. Clinicians can calculate the cumulative score by adding up the points corresponding to each patient's prognostic characteristics. The cumulative total score means the probability of CSD in individual patients at various time intervals. The nomogram derived from the training cohort was tested by the validation cohort and external validation cohort. The 1-, 3-, and 5-year AUC of the training group were 0.788, 0.819, and 0.833, respectively, whereas those of the validation group were 0.804, 0.824, and 0.834, respectively, and those of external validation group were 0.809, 0.860, 0.879 respectively. These results demonstrated a high discriminating capacity of the model (Fig. 5A–C). In addition, we tested the prediction accuracy of the model by using calibration plots (Fig. 5D–F), which showed a strong concordance in all datasets. These findings proved the high reliability and extreme precision of our nomogram.

Discussion

Gastric cancer is one of the serious threats to human health. While the incidences of GC and DGC have decreased recently, the incidence of PGC has been rising rapidly in both] Western and Asian countries[22]. Although the prognosis of GC has recently improved, GNEC still has a poorer prognosis than gastric adenocarcinoma or even poorly differentiated gastric adenocarcinoma because of its rapid progression, chemotherapy resistance, and increased susceptibility to distant recurrence[23]. For gastric patients with GC and clinicians, it is more desirable to know the individual-specific survival rate, especially for patients with GNEC. Several studies have shown that the prognosis of DGC differs from that of PGC. However, these studies mainly focused on gastric adenocarcinoma and have never been conducted in GNEC. Recently, Song et al. developed and confirmed a nomogram to estimate 1-, 3-, and 5-year CSS for GNEC individuals following surgical resection and suggested that cardiac cancer is an independent prognostic risk factor for GNEC[24]. Therefore, we identified 1807 GNEC patients using the SEER database, carried out competing risk analysis and KM survival analysis of DGNEC and PGNEC, and created a nomogram to predict the 1-, 3-, and 5-year CSS of GNEC patients. To our best understanding, this is the first study to compare DGNEC and PGNEC.

In this study, age, gender, race, marital status, grade stage, AJCC stage, T stage, N stage, tumor size, RNE, radiation, chemotherapy, surgery, and survival time were significantly different between DGNEC and PGNEC. The survival times of DGNEC and PGNEC were 42 months and 33.4 months, respectively ($P < 0.001$). According

Characteristics	Before PSM				After PSM			
	[ALL]	DGNEC	PGNEC		[ALL]	DGNEC	PGNEC	
	N = 1807	N = 1292	N = 515	P value	N = 820	N = 410	N = 410	P value
Age								
≤ 60	427 (23.6%)	261 (20.2%)	166 (32.2%)	< 0.001	234 (28.5%)	120 (29.3%)	114 (27.8%)	0.699
> 60	1380 (76.4%)	1031 (79.8%)	349 (67.8%)		586 (71.5%)	290 (70.7%)	296 (72.2%)	
Gender								
Female	705 (39.0%)	551 (42.6%)	154 (29.9%)	< 0.001	270 (32.9%)	130 (31.7%)	140 (34.1%)	0.504
Male	1102 (61.0%)	741 (57.4%)	361 (70.1%)		550 (67.1%)	280 (68.3%)	270 (65.9%)	
Race								
White	1129 (62.5%)	712 (55.1%)	417 (81.0%)	< 0.001	625 (76.2%)	311 (75.9%)	314 (76.6%)	0.87
Non_White	678 (37.5%)	580 (44.9%)	98 (19.0%)		195 (23.8%)	99 (24.1%)	96 (23.4%)	
Marital status								
Married	1064 (58.9%)	747 (57.8%)	317 (61.6%)	0.16	500 (61.0%)	253 (61.7%)	247 (60.2%)	0.72
Unmarried	743 (41.1%)	545 (42.2%)	198 (38.4%)		320 (39.0%)	157 (38.3%)	163 (39.8%)	
Grade								
I	306 (16.9%)	233 (18.0%)	73 (14.2%)	< 0.001	144 (17.6%)	79 (19.3%)	65 (15.9%)	0.482
II	794 (43.9%)	575 (44.5%)	219 (42.5%)		346 (42.2%)	174 (42.4%)	172 (42.0%)	
III	664 (36.7%)	465 (36.0%)	199 (38.6%)		304 (37.1%)	146 (35.6%)	158 (38.5%)	
IV	43 (2.4%)	19 (1.5%)	24 (4.7%)		26 (3.2%)	11 (2.7%)	15 (3.7%)	
AJCC_stage								
I	604 (33.4%)	464 (35.9%)	140 (27.2%)	< 0.001	266 (32.4%)	139 (33.9%)	127 (31.0%)	0.766
II	465 (25.7%)	349 (27.0%)	116 (22.5%)		205 (25.0%)	103 (25.1%)	102 (24.9%)	
III	467 (25.8%)	306 (23.7%)	161 (31.3%)		217 (26.5%)	106 (25.9%)	111 (27.1%)	
IV	271 (15.0%)	173 (13.4%)	98 (19.0%)		132 (16.1%)	62 (15.1%)	70 (17.1%)	
T_stage								
T1	587 (32.5%)	437 (33.8%)	150 (29.1%)	< 0.001	270 (32.9%)	141 (34.4%)	129 (31.5%)	0.826
T2	322 (17.8%)	216 (16.7%)	106 (20.6%)		162 (19.8%)	80 (19.5%)	82 (20.0%)	
T3	547 (30.3%)	363 (28.1%)	184 (35.7%)		258 (31.5%)	127 (31.0%)	131 (32.0%)	
T4	351 (19.4%)	276 (21.4%)	75 (14.6%)		130 (15.9%)	62 (15.1%)	68 (16.6%)	
N_stage								
N0	952 (52.7%)	699 (54.1%)	253 (49.1%)	0.001	439 (53.5%)	226 (55.1%)	213 (52.0%)	0.709
N1	448 (24.8%)	287 (22.2%)	161 (31.3%)		217 (26.5%)	103 (25.1%)	114 (27.8%)	
N2	225 (12.5%)	166 (12.8%)	59 (11.5%)		91 (11.1%)	47 (11.5%)	44 (10.7%)	
N3	182 (10.1%)	140 (10.8%)	42 (8.2%)		73 (8.9%)	34 (8.3%)	39 (9.5%)	
Tumor_size								
≤ 2 cm	448 (24.8%)	354 (27.4%)	94 (18.3%)	< 0.001	182 (22.2%)	94 (22.9%)	88 (21.5%)	0.856
≤ 5 cm	686 (38.0%)	484 (37.5%)	202 (39.2%)		312 (38.0%)	159 (38.8%)	153 (37.3%)	
> 5 cm	444 (24.6%)	321 (24.8%)	123 (23.9%)		184 (22.4%)	88 (21.5%)	96 (23.4%)	
Unknown	229 (12.7%)	133 (10.3%)	96 (18.6%)		142 (17.3%)	69 (16.8%)	73 (17.8%)	
RNE								
0	494 (27.3%)	279 (21.6%)	215 (41.7%)	< 0.001	293 (35.7%)	148 (36.1%)	145 (35.4%)	0.975
1–15	668 (37.0%)	532 (41.2%)	136 (26.4%)		246 (30.0%)	122 (29.8%)	124 (30.2%)	
≥ 16	645 (35.7%)	481 (37.2%)	164 (31.8%)		281 (34.3%)	140 (34.1%)	141 (34.4%)	
Radiation								
None	1392 (77.0%)	1053 (81.5%)	339 (65.8%)	< 0.001	614 (74.9%)	309 (75.4%)	305 (74.4%)	0.809
Yes	415 (23.0%)	239 (18.5%)	176 (34.2%)		206 (25.1%)	101 (24.6%)	105 (25.6%)	
Chemotherapy								
None	1041 (57.6%)	822 (63.6%)	219 (42.5%)	< 0.001	428 (52.2%)	218 (53.2%)	210 (51.2%)	0.625
Yes	766 (42.4%)	470 (36.4%)	296 (57.5%)		392 (47.8%)	192 (46.8%)	200 (48.8%)	
Surgery								
None	355 (19.6%)	176 (13.6%)	179 (34.8%)	< 0.001	221 (27.0%)	110 (26.8%)	111 (27.1%)	1
Yes	1452 (80.4%)	1116 (86.4%)	336 (65.2%)		599 (73.0%)	300 (73.2%)	299 (72.9%)	
csd	0.4 (0.5)	0.4 (0.5)	0.5 (0.5)	< 0.001	0.4 (0.5)	0.4 (0.5)	0.5 (0.5)	< 0.001
total_d	0.6 (0.5)	0.5 (0.5)	0.7 (0.5)	< 0.001	0.6 (0.5)	0.5 (0.5)	0.7 (0.5)	< 0.001
ocd	0.3 (0.7)	0.3 (0.7)	0.3 (0.7)	0.876	0.3 (0.7)	0.3 (0.7)	0.3 (0.7)	0.849
time	39.6 (30.0)	42.0 (30.2)	33.4 (28.8)	< 0.001	38.1 (30.1)	41.6 (30.6)	34.7 (29.2)	0.001
status	0.7 (0.7)	0.7 (0.7)	0.8 (0.7)	< 0.001	0.8 (0.7)	0.7 (0.7)	0.8 (0.7)	0.012

Table 1. the demographic characteristics of both groups before and after PSM.

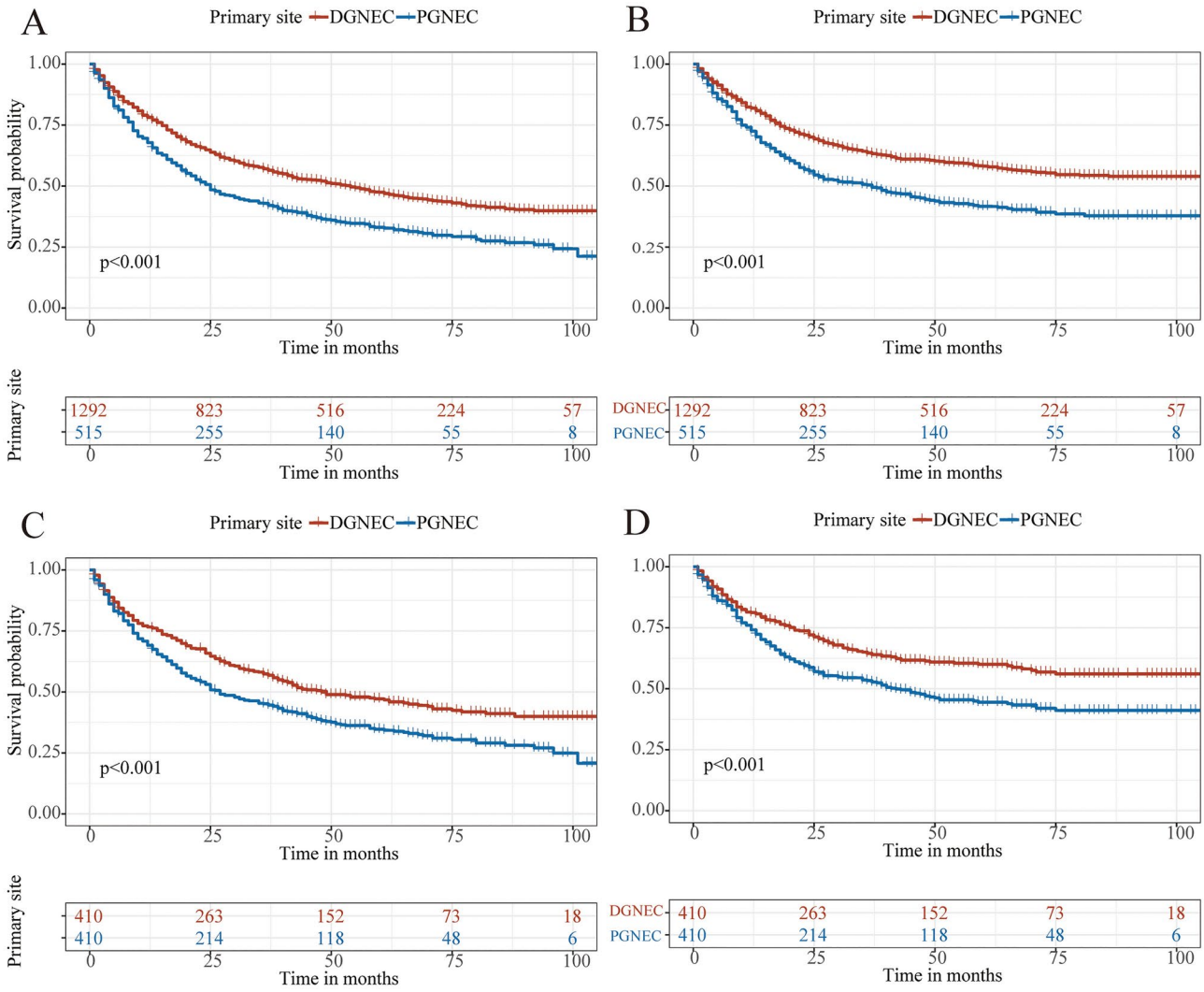

Fig. 2. KM analyses of patients with GNEC. (**A**) OS curves before PSM, (**B**) CSS curves before PSM. (**C**) OS curves after PSM and (**D**) CSS curves after PSM.

to our PSM analysis, DGNEC may have a superior prognosis than PGNEC. A review of 3689 patients found that GNEC had a worse prognosis than gastric adenocarcinoma and was more likely to develop distant lesions than matched patients with GNEC. In a multifactorial analysis, for GNEC, stage T3 to T4, and lymphatic metastasis were separate risk variables associated with distant recurrence[25]. It is generally believed that the prognosis of GNEC is poorer than that of Gastric adenocarcinoma; however, Li et al. found that the prognosis of GNEC was better than that of Gastric adenocarcinoma in Caucasians, indicating significant differences in ethnicity[25,26].

Our multivariate subdistribution proportional hazards analysis identified several independent risk factors for CSD in patients with GNEC. These factors include PGNEC, male, advanced age, larger tumor size, higher AJCC stage, and higher tumor grade. Therefore, patients with these risk factors warrant great attention. Xu et al. found that advanced TNM stage, large tumor size, and older age were independent risk factors for OS in GNEC[27]. Additionally, Hu et al. found independent prognostic variables for GNEC including surgical intervention, age, distant metastasis, T stage, N stage, and grade stage[2]. Song et al. created a nomogram for patients with GNEC who underwent surgery using age, gender, grade, T stage, N stage, metastasis, primary site, tumor size, RNE, and chemotherapy, demonstrating a well-performing model[24]. Higher AJCC stage, higher grade stage, and larger tumor size typically denoted more aggressive tumor behavior and poorer prognosis. Age is another risk factor, potentially associated with increased chronic illnesses and poorer general health in older patients. Recent research has shown that as tumor staging progresses, the risk of GNEC recurrence and mortality increases[28]. Many studies suggest that female gender is a protective factor against GNEC, which could be related to lower rates of smoking, alcohol consumption, and intake of grilled foods among women. Additionally, sex hormones in

	Cancer-specifc death (%)				Other causes death (%)			
	1-year CIF	3-year CIF	5-year CIF	P value	1-year CIF	3-year CIF	5-year CIF	P value
Before PSM								
DGNEC	0.1768	0.3469	0.3945	0	0.0413	0.083	0.1312	0.8239
PGNEC	0.2675	0.469	0.5418		0.0546	0.1023	0.1274	
After PSM								
DGNEC	0.1824	0.3352	0.3731	1.00E-04	0.0516	0.0917	0.1559	0.8314
PGNEC	0.2502	0.4405	0.5136		0.0589	0.1085	0.1399	

Table 2. The cumulative incidence of CSD and OCD in two groups before and after PSM.

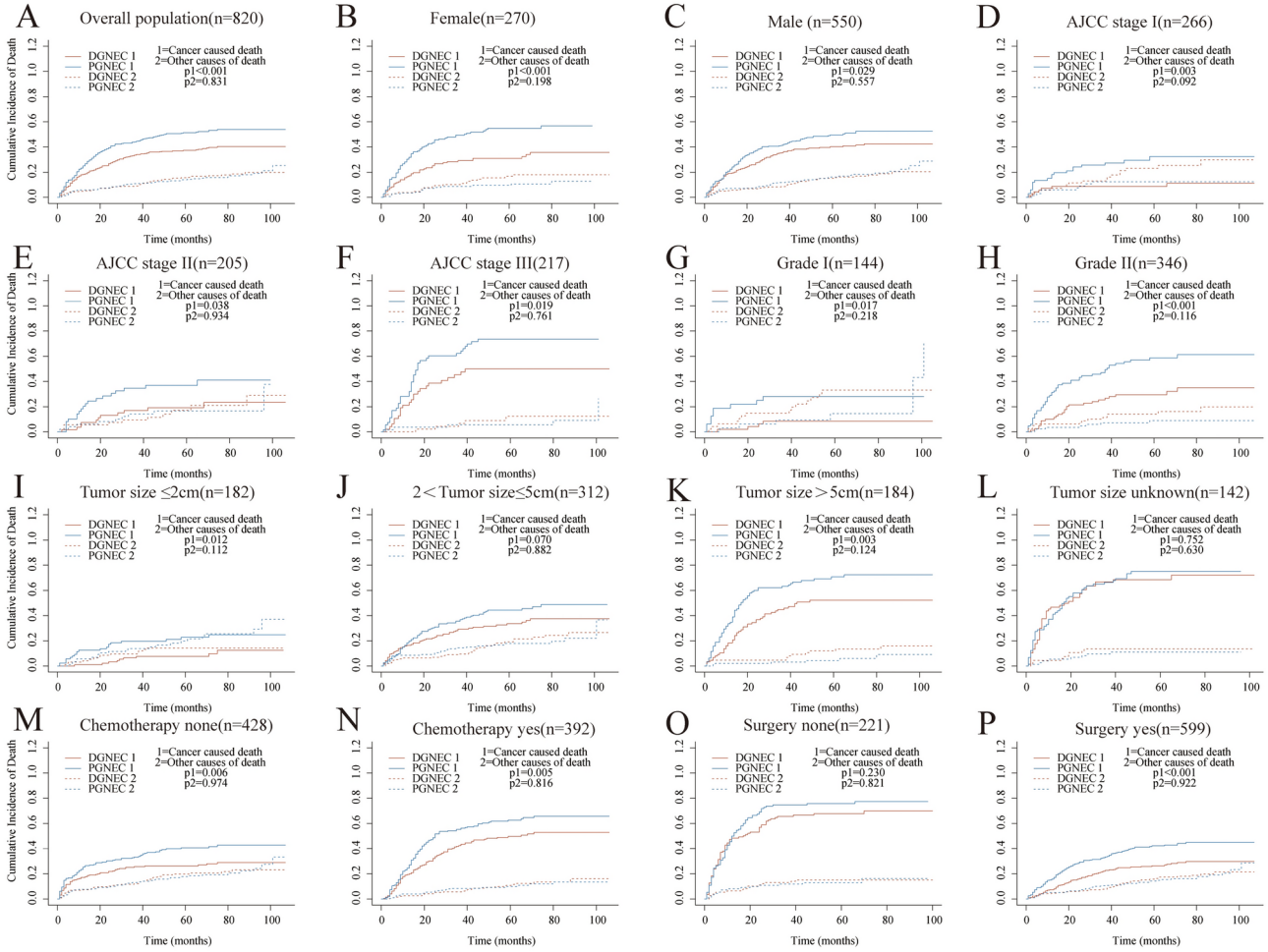

Fig. 3. Cumulative incidence curves for patients of GNEC in overall patients and various subgroups and after PSM. All patients combined (**A**) overall population, (**B**) female, (**C**) male, (**D**) AJCC stage I, (**E**) AJCC stage II, (**F**) AJCC stage III, (**G**) grade I, (**H**) grade II, (**I**) tumor size ≤ 2 cm, (**J**) 2 < tumor size ≤ 5 cm, (**K**) tumor size > 5 cm, (**L**) tumor size unknown, (**M**) chemotherapy none, (**N**) chemotherapy yes, (**O**) surgery none, (**P**) surgery yes.

females, particularly estrogen, may delay cancer progression by regulating mechanisms such as cell proliferation, apoptosis, and immune responses, potentially playing a protective role in the occurrence and development of GNEC.

For GNEC, Numerous studies have demonstrated that surgical resection serves as an independent protective factor, suggesting the advantages of surgical treatment[27,29,30]. Our research has also shown that surgery is an independent protective factor for GNEC, which is consistent with our findings. Therefore, our study supports the suggestion that these patients should undergo surgery. Liu et al. developed a nomogram based on data from a single center, demonstrating that both N-stage and Ki67 are independent predictors of survival in GNEC

Characteristics	Before PSM			After PSM		
	HR	95% CI	P-value	HR	95% CI	P-value
Primary site						
DGNEC	Reference			Reference		
PGNEC	1.28	1.08–1.51	0.005	1.4	1.13–1.73	0.002
Age						
≤60	Reference			Reference		
>60	1.27	1.08–1.5	0.004	1.37	1.08–1.75	0.009
Gender						
Female	Reference			Reference		
Male	1.13	0.97–1.33	0.12	0.98	0.77–1.25	0.88
Race						
White	Reference			Reference		
Non_White	1.02	0.87–1.18	0.83	0.93	0.73–1.17	0.52
Marital_status						
Married	Reference			Reference		
Unmarried	1.3	1.12–1.51	0.001	1.13	0.9–1.41	0.31
Grade						
I	Reference			Reference		
II	2.36	1.66–3.36	<0.001	1.92	1.18–3.15	0.009
III	2.53	1.76–3.64	<0.001	1.94	1.18–3.2	0.009
IV	3.74	2.17–6.44	<0.001	5.2	2.81–9.61	<0.001
AJCC_stage						
I	Reference			Reference		
II	1.12	0.8–1.57	0.51	1.06	0.65–1.72	0.81
III	1.27	0.84–1.93	0.26	1.06	0.6–1.87	0.84
IV	2.53	1.72–3.72	<0.001	2.12	1.27–3.56	0.004
T_stage						
T1	Reference			Reference		
T2	0.93	0.69–1.26	0.64	0.9	0.58–1.39	0.63
T3	1.2	0.88–1.65	0.25	1.18	0.75–1.86	0.47
T4	1.48	1.06–2.08	0.022	1.14	0.7–1.84	0.6
Tumor_size						
≤2 cm	Reference			Reference		
≤5 cm	1.95	1.44–2.65	<0.001	1.89	1.17–3.03	0.009
>5 cm	2.36	1.7–3.27	<0.001	3.49	2.13–5.71	<0.001
Unknown	1.94	1.36–2.78	<0.001	2.68	1.63–4.42	<0.001
RNE						
0	Reference			Reference		
1–15	0.79	0.55–1.12	0.18	0.69	0.44–1.09	0.11
≧16	0.58	0.4–0.83	0.003	0.54	0.33–0.87	0.012
Radiation						
None	Reference			Reference		
Yes	0.94	0.78–1.14	0.54	0.94	0.73–1.23	0.67
Chemotherapy						
None	Reference			Reference		
Yes	0.77	0.64–0.93	0.006	0.73	0.54–0.97	0.03
Surgery						
None	Reference			Reference		
Yes	0.51	0.35–0.74	<0.001	0.45	0.28–0.71	0.001

Table 3. The outcomes of the multivariate subdistribution hazards model regarding CSD before and after PSM.

patients, with N-stage having a more significant impact[31]. Lymph node (LN) metastasis tends to occur early in GNEC, and many patients are no longer candidates for surgery by the time of diagnosis, underscoring the critical importance of early detection and intervention. Hanrui Chen's study revealed that GNEC has higher

	CSD(%)				Subdistribution proportional hazards model		
Characteristics	1-year CIF	3-year CIF	5-year CIF	P value	HR	95% CI	P value
Primary site							
DGNEC	0.1725	0.3373	0.3873	0.0000			0.03795
PGNEC	0.2726	0.4762	0.5475		1.1995	1.0567–1.4581	0.0380
Age							
≤60	0.1385	0.3174	0.375	0.0116	Reference		
>60	0.2204	0.3949	0.4499		1.3372	1.0918–1.6377	0.0050
Gender							
Female	0.1807	0.332	0.3646	0.0009	Reference		
Male	0.2129	0.4038	0.4737		1.2447	1.0299–1.5044	0.0235
Race							
White	0.2096	0.3829	0.4406	0.3662			
Non_White	0.1849	0.365	0.4177				
Marital status							
Married	0.1721	0.3642	0.4263	0.2829			
Unmarried	0.2443	0.3949	0.4414				
Grade							
I	0.0848	0.1327	0.1381	0.0000	Reference		
II	0.2009	0.356	0.4274		2.5222	1.6476–3.8611	0.0000
III	0.2395	0.4873	0.5482		2.7938	1.806–4.3219	0.0000
IV	0.4286	0.7857	0.8214		5.5513	3.1059–9.9221	0.0000
AJCC stage							
I	0.1066	0.1713	0.1971	0.0000	Reference		
II	0.1143	0.2586	0.3035		1.3425	0.9838–1.8319	0.0633
III	0.2317	0.5348	0.6284		2.9435	2.1583–4.0143	0.0000
IV	0.5016	0.7641	0.8363		5.0456	3.5703–7.1305	<
T stage							
T1	0.1421	0.2242	0.2502	0.0000			
T2	0.1473	0.2604	0.3115				
T3	0.1951	0.4591	0.5437				
T4	0.3583	0.61	0.6801				
N stage							
N0	0.1303	0.2175	0.2504	0.0000			
N1	0.2817	0.5085	0.5756				
N2	0.2244	0.4991	0.6209				
N3	0.3333	0.727	0.7991				
Tumor size							
≤2 cm	0.0712	0.1405	0.1636	0.0000	Reference		
≤5 cm	0.1982	0.3834	0.4526		2.0105	1.4378–2.8112	0.0000
>5 cm	0.2589	0.5226	0.5915		2.5875	1.8165–3.6858	0.0000
Unknown	0.3567	0.5507	0.6081		1.8363	1.254–2.689	0.0018
RNE							
0	0.3478	0.5167	0.5346	0.0000	Reference		
1–15	0.1715	0.3327	0.3945		1.1886	0.7491–1.8858	0.4632
≥16	0.1177	0.3141	0.3918		0.9411	0.5891–1.5035	0.7995
Radiation							
None	0.2133	0.3536	0.4067	0.0051	Reference		
Yes	0.1563	0.4548	0.5213		0.9545	0.747–1.2197	0.7097
Chemotherapy							
None	0.1941	0.2832	0.3188	0.0000	Reference		
Yes	0.2094	0.5045	0.5881		0.7965	0.6313–1.0049	0.0550
Surgery							
None	0.4709	0.689	0.6984	0.0000	Reference		
Yes	0.1368	0.3029	0.369		0.3385	0.2067–0.5545	0.0000

Table 4. The CSD of cumulative incidences and multivariate subdistribution proportional hazards analysis.

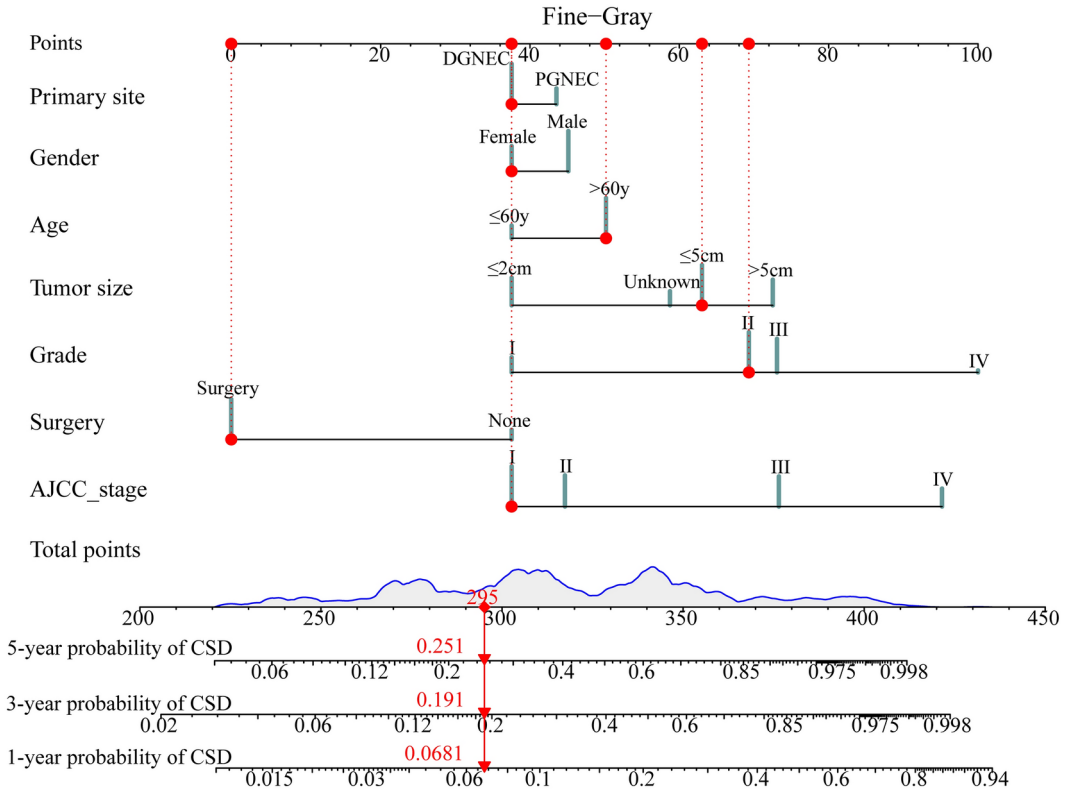

Fig. 4. Nomogram based on the competing risk analysis to predict CSD probabilities at 1-, 3-,and 5-year.

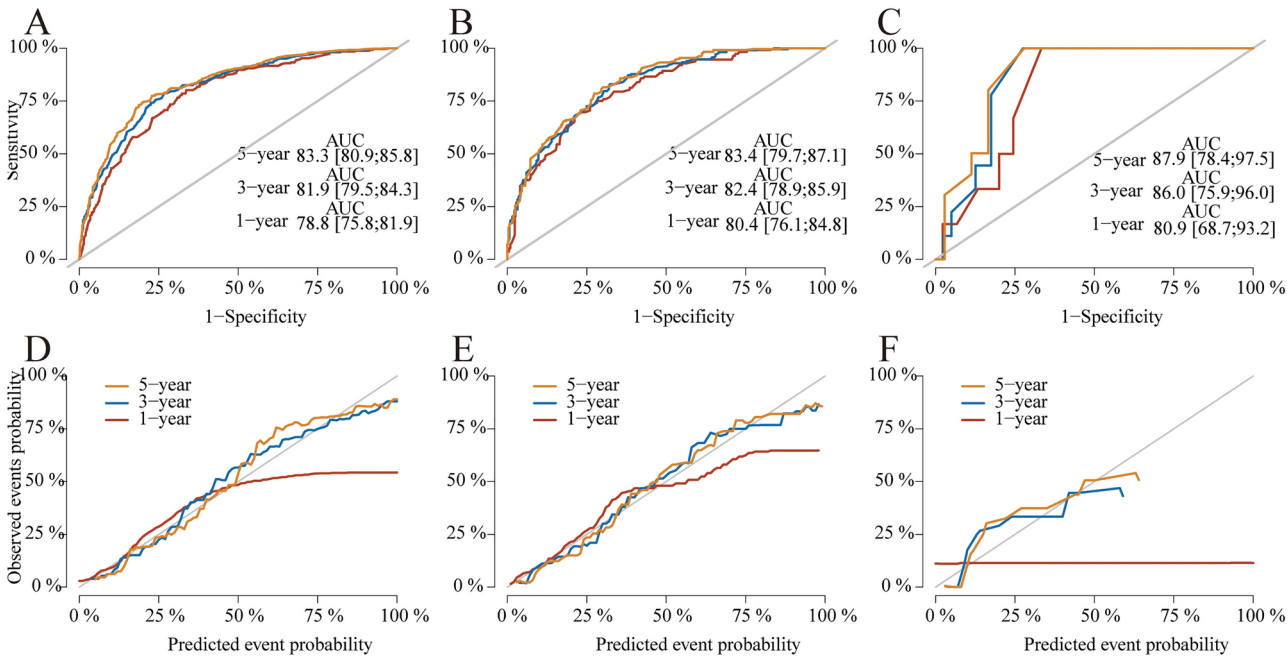

Fig. 5. ROC curves at the 1-, 3-, and 5-year points (**A**) the training, (**B**) internal validation, (**C**) external validation; calibration curves at the 1-, 3-, and 5-year points (**D**) the training, (**E**) internal validation, (**F**) external validation.

rates of lymphatic and liver metastasis compared to gastric adenocarcinoma, with survival times decreasing as the rate of lymph node metastasis increases[32].

However, the use of chemotherapy in patients with GNEC remains controversial. In our study chemotherapy was found to be a predictive factor for patients with GNEC survival by multivariate analysis. A previous study showed that the OS of surgical patients with GC containing NEC was lower than that of patients with gastric adenocarcinoma. However, there was no significant difference in OS among patients receiving neoadjuvant therapy, suggesting that neoadjuvant therapy may be ineffective for these malignant tumors[33]. A retrospective study of 69 G-NEC patients by Ma et al. showed that the OS of those patients receiving neoadjuvant chemotherapy was significantly higher than that of patients undergoing preoperative surgical resection, suggesting that it may be beneficial to consider adjuvant therapy after local surgical resection of NEC[34]. A single-center study confirmed that distal GNEC has a higher proportion of lymphovascular invasion and perineural invasion than distal gastric adenocarcinoma, and mDCF chemotherapy may be effective for distal GNEC[35]. Du et al. analyzed patients of GNEC in AJCC stage I-II in the SEER database and concluded that patients with stage I-II GNEC can't benefit from postoperative adjuvant chemotherapy[18]. Lin et al. found no survival benefit in 804 patients with resectable GNEC who received adjuvant chemotherapy[36]. Neoadjuvant chemoradiotherapy is widely used for locally advanced gastrointestinal tumors, and previous studies have reported that patients receiving preoperative chemoradiotherapy had fewer harvested lymph nodes[37–39]. However, there is limited literature on the effectiveness of perioperative treatments, such as neoadjuvant chemotherapy or chemoradiotherapy, in adequately downstaging GNEC and improving the rate of radical resection. A single-center study showed that neoadjuvant chemotherapy or chemoradiotherapy followed by surgery could result in long-term survival for some patients with locally advanced GNEC[40]. Fuhai Ma's retrospective analysis demonstrated that neoadjuvant chemotherapy could enhance the survival outcomes of GNEC patients. Multivariate analysis identified both neoadjuvant chemotherapy and N-stage as independent prognostic factors, with the number of LNs retrieved being similar between the neoadjuvant chemotherapy group and the direct surgery group. However, the study did not compare the rates of positive LN detection between the two groups[34]. A nationwide retrospective study conducted in the Netherlands found no statistically significant difference in OS between patients with esophageal and gastric neuroendocrine carcinoma who underwent neoadjuvant chemotherapy and those who did not[41]. Jiahui Chen found that the prognosis of GNEC patients who did not receive neoadjuvant chemotherapy was worse than that of gastric adenocarcinoma patients. However, after neoadjuvant chemotherapy, there was no significant difference in survival rates between the two groups, suggesting that neoadjuvant chemotherapy may be effective for neuroendocrine carcinoma[25]. The role of radiotherapy in GNEC remains unclear. Most studies do not believe that radiotherapy can improve OS in GNEC. A study on large-cell neuroendocrine carcinoma of the gastrointestinal tract suggested that surgery and radiotherapy could improve OS, but regrettably, it only included 20 GNEC patients[42]. A single-center multivariate analysis identified gastrectomy and chemoradiotherapy as risk factors influencing overall survival in gastric cancer patients[43]. In our study, radiotherapy was significant in univariate analysis but not in multivariate analysis, possibly due to the higher proportion of distal gastric cancer and the low proportion of patients receiving radiotherapy.

While several studies have investigated the impact of tumor location on the prognosis of gastric cancer, these analyses have not been extended to GNEC[5,14]. In our study, we developed and validated a prognostic nomogram for patients of GNEC, focusing on tumor sites, which demonstrated outstanding predictive ability in estimating the personalized risk of CSD at 1, 3, and 5-year intervals. Risk indicators that were easily obtained from patient hospitalization records were included in the nomogram model. Clinicians and patients of GNEC were able to assess the benefits of the treatment and make accurate prognostic predictions using variable scores. In clinical practice, the nomogram can help assess the risks and benefits of treatment, thus optimizing therapeutic options. For example, for a patient with GNEC, doctors can use the nomogram to estimate survival rates at 1, 3, and 5 years. Based on these estimates, they can decide whether to pursue more aggressive treatment options (such as surgery or chemotherapy) or to adopt a more conservative observational approach. This tool provides patients and clinicians with a means to communicate visually. Patients could make more sensible treatment decisions if they knew their likelihood of survival through the nomogram chart. In addition, a few factors with higher scores, such as PGNEC, may raise concerns about a poor prognosis.

This study has a few limitations. First, the SEER database lacks several key prognostic variables, such as comorbidities, smoking history, diabetes, and cardiovascular diseases, which may have led to the omission of important factors influencing CSD. Second, the absence of genetic data, Ki-67 levels, and chemoradiotherapy regimens in the SEER database prevented us from assessing the impact of genetic mutations, predispositions, or therapeutic regimens on the CSD of patients with GNEC. These absences may introduce inaccuracies in individualized risk assessments, potentially affecting the nomogram's applicability to certain populations. For example, specific genetic mutations linked to poorer prognoses might be missed, leading to the misclassification of high-risk patients as low-risk. Additionally, selection bias was unavoidable in the retrospective analysis, even when PSM was used to reduce heterogeneity between the groups. Because of the relatively limited size of the external validation group, additional multicenter prospective validations are necessary. Despite these drawbacks, the extensive dataset could provide a valuable survival experience for patients with GNEC and clinicians.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author and the SEER database (https://seer.cancer.gov/). For further inquiries, the corresponding author can be reached for additional information.

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Author contributions

LJ-K: proposed the research questions; was responsible for drafting and revising the manuscript; reviewed and approved the final version of the paper. CB-Y: was responsible for collecting and analyzing data; reviewed and approved the final version of the paper. SJ-N: was responsible for collecting and analyzing data; reviewed and approved the final version of the paper. HJ-J: was responsible for collecting and analyzing data; reviewed and approved the final version of the paper. XW-L: was responsible for drafting and revising the manuscript; reviewed and approved the final version of the paper.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The SEER database can be accessed publicly and provides patient data without specific identification, so ethics approval and informed consent were not required. The human data used in this study were in accordance with the Declaration of Helsinki in the manuscript. The study was approved by the Ethics Committee of Hangzhou TCM Hospital. In compliance with national legislation and institutional guidelines, the procurement of written informed consent was deemed unnecessary for participation in this study.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-76689-z.

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