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Development and validation of a nomogram for predicting survival in gastric signet ring cell carcinoma patients treated with radiotherapy

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There is no effective clinical prediction model to predict the prognosis of gastric signet ring cell carcinoma (GSRC) patients treated with radiotherapy. This study retrospectively analyzed the clinical data of 20–80-year-old patients diagnosed with GSRC between 2004 and 2019 from the Surveillance, Epidemiology, and End Results (SEER) database. Using Cox regression analyses revealed independent prognostic factors, and a nomogram was constructed. The C-index, net reclassification index (NRI) and integrated discrimination improvement (IDI) of the nomogram were greater than those of the TNM staging system for predicting OS, indicating that the nomogram predicted prognosis with greater accuracy. The area under the curve (AUC) values were 0.725, 0.753 and 0.745 for the training group; 0.725, 0.763 and 0.752 for the internal validation group; and 0.795, 0.764 and 0.765 for the external validation group, respectively. Calibration plots demonstrated high agreement between the nomogram's prediction and the actual observations. The risk stratification system was able to accurately stratify patients who underwent radiotherapy for GSRC into high- and low-risk subgroups, with significant differences in prognosis. The Kaplan–Meier survival analysis according to different treatments indicated that surgery combined with chemoradiotherapy is a more effective treatment strategy for improving OS in for GSRC patients. The nomogram is sufficiently accurate to predict the prognostic factors of GSRC receiving radiotherapy, allowing for clinicians to predict the 1-, 3-, and 5-year OS.

Keywords Gastric signet ring cell carcinoma, Radiotherapy, Nomogram, Overall survival, K-M

According to the most recent predictions provided by GLOBOCAN, there were 1,089,000 gastric cancer (GC) cases worldwide in 2020, ranking it fourth among all cancer types after lung, colorectal, and liver cancers[1]. Gastric signet ring cell carcinoma(GSRC), with at least 90% of poorly cohesive cells having signet ring cell morphology, accounts for 8 to 30% of cases at present, and the prevalence of GSRC has been increased in recent years[2,3]. At present, the critical treatment strategies strategy for GSRC is surgery, including endoscopic mucosal resection and traditional surgical resection. Studies have shown that GSRC has a better prognosis than other gastric cancer subtypes do in the early stage[4]. Unfortunately, GSRC is often detected at an advanced stage and has a greater tendency for peritoneal spread and lymph node invasion. Compared with those of other subtypes, R0 resection rates are lower, and a greater extent of lymph node dissection is needed for advanced GSRC[5]. Adjuvant localized or systemic treatment is regularly recommended before or after surgery[6,7]. According to the National Comprehensive Cancer Network (NCCN), radiotherapy is the standard adjuvant treatment for gastric cancer with R1 or R2 resection. For pT2N0M0 gastric cancer with R0 resection, the risk factors include (1) poorly differentiated or (2) high-grade cancer, (3) vascular infiltration, (4) neural infiltration, (5) age < 50 years, and (6) patients who have not undergone D2 lymph node dissection. Postoperative radiotherapy is recommended as long as any one of the conditions is met. For other stages of gastric cancer with R0 resection, if D2 lymph node dissection is not performed, radiotherapy is also recommended[8].

To date, several prognostic models exist for GSRC patients receiving surgery[9];however, radiotherapy is lacking. Although the disease progression in cancer patients is currently described by the American Joint Committee on Cancer (AJCC) staging system, other clinicopathological factors, such as age, sex, marital status, and the use of chemotherapy and surgery, as well as infiltration depth, affected lymph nodes, and histologic metastases, also significantly affect the survival of GSRC patients. Increasing evidence indicates that the TNM system is

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inappropriate for evaluating GSRC patient outcomes[10,11]. Nonetheless, nomograms—statistical graphs used to estimate the prognosis of cancer patients and comprising multiple independent parameters—are generally acknowledged as reliable tools for forecasting individual clinical outcomes[12,13]. Using the SEER database, we identified the prognostic factors and established a nomogram to guide the rational clinical selection of treatment modalities and improve survival for GSRC patients treated with radiotherapy.

Patients and methods

Data source and data extraction

Data on GSRC patients receiving radiotherapy were collected from the SEER database (2000–2021), which was submitted in November 2023. SEve*Stat software (version 8.4.3) produced by the Surveillance Research Program and National Cancer Institute was used to identify GSRC patients who underwent beam radiation. The inclusion criteria for patients were as follows: (1) patients were 20–80 years old; (2) had a pathological diagnosis of GSRC; and (3) were treated with external irradiation (beam radiation). The exclusion criteria were as follows: (1) had nonfirst primary cancer; (2) the survival time was not recorded or the survival time was no more than 1 month after diagnosis; (3) critical clinicopathological information, including T, N, and M stage, tumor size and grade, was not clear; and (4) the radioisotopes, radioactive implants, or radiotherapy status was unknown. The patient selection process is presented in Fig. 1. Since the SEER study data are publicly available, there was no need for the approval of the Ethics Committee.

Data classification

We collected data on the following baseline characteristics of GSRC patients treated with beam radiation, included: age, sex, race, marital status, primary tumor site, histological grade, surgery, chemotherapy, T stage, N stage, M stage, tumor size, etc. (1) Age was divided into three groups via the X-tile program, in order to obtain the best cutoff points (Yale University, New Haven, CT, USA): <57 years, 57–64 years, >64 years; (2) sex was divided into male and female; (3) race included white, black, and other (including yellow, Indian etc.); (4) marriage status was divided into married or unmarried (including widowed and divorced); (5) tumor size was divided into <39 mm, 39–69 mm, and >69 mm by the X-tile program; (6) the primary site was divided into the upper 1/3 (the cardia and fundus of the stomach), the middle 1/3 (the body of the stomach), the lower 1/3 (the gastric antrum and pylorus of the stomach), the curvature (lesser curvature and greater curvature of the stomach), and overlapping lesion of the stomach; (7) the histological grade was divided into grades I ~ II and III ~ IV; (8) the group was divided into surgical and nonsurgical groups; (9) the group was divided into chemotherapy and nonchemotherapy groups according to the chemotherapy status; (10) the T-stage was divided into T1, T2, T3 and T4; (11) the N-stage was divided into N0, N1, N2 and N3; and (12) the M-stage was divided into M0 and M1. The criteria for T stage, N stage, and M stage were referred to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system.

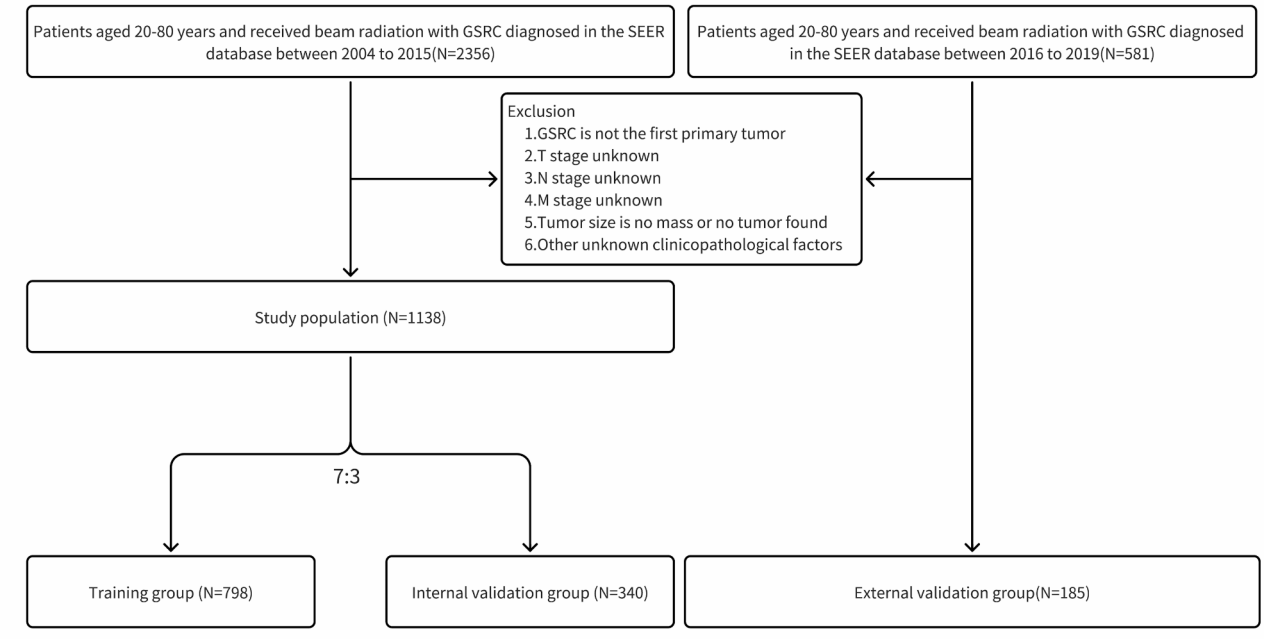

Fig. 1. The flowchart of including and dividing patients.

Statistical methods

Patients diagnosed from 2004 to 2015 were randomly divided into the training and internal validation groups. Patients from 2016 to 2019 comprised the external validation group. The information of 1323 patients was analyzed and plotted via R software (version 4.3.1). The variables in this study are all unordered categorical variables. Intergroup comparisons were conducted via the chi-square test or Fisher's exact test was used to analyze categorical variables with expected values < 5. The count data are expressed as the number of cases and rate (%). In R software, all variables were transformed into factor type variables, assigned values, and then fitted. The optimal cutoff values for age and tumor size were determined via X-tiles software[14]. The SEER database data were divided into a training cohort and a validation cohort at a ratio of 7:3 via the "caret" package. The variables in the modeling group included age, sex, race, marital status, primary tumor site, histological grade, T stage, N stage, M stage, tumor size, surgery and chemotherapy recode. The Kaplan–Meier method was used to plot survival curves for different treatments and risk stratifications according to the cutoff value (118.3576) of the nomogram score, after which log-rank tests were applied to compare survival curves. The "autoReg" package was used to perform univariate and multivariate Cox regression to screen for independent prognostic factors, and these factors were subsequently used to construct a nomogram via the "rms" and "survival" packages. The "survivalROC" package was used to plot the receiver operating characteristic (ROC) curves of the training and validation cohorts of the line graph model to verify the model differentiation. The greater the higher area under the curve (AUC) was the greater the predictive accuracy of the model. Calibration curves were plotted by bootstrapping with 1000 repetitions of playback sampling. Decision curve analysis, a method used to evaluate prediction models[15], was performed via the "dcurves" and "ggplot2" packages to evaluate the clinical effectiveness of the line graph model. In addition, the "survIDINRI" and "nricens" packages were used to calculate the NRI and IDI. The primary endpoint of our research for survival analysis was OS, which was defined as the time elapsed from diagnosis to death (regardless of cause) or the final follow-up date. A two-sided P value of less than 0.05 was regarded as statistically significant.

Results

Clinical features

In total, 1323 patients who were diagnosed with gastric signet ring cell carcinoma and treated with radiotherapy from the SEER database met the inclusion and exclusion criteria; 1138 patients were eligible from 2004 to 2015, and the essential clinicopathological characteristics of these patients are presented in Supplementary Table S1. There were no significant differences between the two groups ($P > 0.05$). Additionally, 185 patients were included from 2016 to 2019. The detailed baseline demographics and clinical characteristics are summarized in Table 1. Table 1 reported that, compared with patients in the training group and internal validation group, patients in the external validation group had a higher N stage, no surgeries performed and metastasis.

Univariate and multivariate Cox regression analyses

To identify predictors of OS among the 1138 patients in the training cohort, univariate and multivariate analyses were performed. As shown in Table 2, age, race, marital status, T stage, N stage, M stage and surgery were independent risk factors affecting patient prognosis. The Cox proportional hazards regression model was used to investigate in depth the effects of various parameters. OS multivariate analysis revealed increased hazard ratios for the following characteristics: older age, white race, being unmarried, having a higher T stage, having a higher N stage, being metastatic and not having undergone surgery for the primary tumor ($p < 0.05$).

Construction and interpretation of the nomogram

With the independent prognostic factors ($P < 0.05$) identified in the multivariate Cox regression analysis, we constructed a nomogram to predict 1-, 3- and 5-year OS in the training cohort (Fig. 2). Notably, chemotherapy records were also included. The nomogram revealed that surgical recoding had the greatest influence on prognosis, followed by M stage, T stage, N stage, age and other factors. The scores of each covariate were obtained by projecting each variable vertically onto the point scales. These scores were added together to obtain the total score of the patient. The scores for each subgroup variable are shown in Table 3. For example, a white man who was more than 64 years old and married was diagnosed with GSRC with T2N2M0 disease, and she underwent surgery, chemotherapy and radiotherapy. In the above example, the overall survival rate at 1 year was 82%. The overall survival rate at 3 years was 52%. The overall survival rate at 5 years was 40%. Consequently, our model can be used to predict the outcomes of individual patients according to their clinicopathological information.

Validation of the nomogram and its clinical utility

The C-index of the OS predictive model was 0.684 (95% CI: 0.661–0.707) in the training group, 0.702 (95% CI: 0.667–0.737) in the internal validation group and 0.729 (95% CI: 0.685–0.773) in the external validation group; however, the C-index of the TNM staging system was 0.636 (95% CI: 0.612–0.661) in the training group, 0.646 (95% CI: 0.609–0.683) in the internal validation group and 0.669 (95% CI: 0.616–0.721) in the external validation group. Moreover, the NRI and IDI were used to compare the accuracy of the nomogram and the TNM staging system. The NRIs for the 1-, 3-, and 5- year OS rates were 0.268 (95% CI: 0.162–0.354, $P < 0.001$), 0.238 (95% CI: 0.152–0.317, $P < 0.001$), and 0.200 (95% CI: 0.114-0.300, $P < 0.001$), respectively, and the IDI values for the 1-, 3-, and 5-year OS rates were 0.081 (95% CI: 0.046–0.129, $P < 0.001$), 0.068 (95% CI: 0.042-0.100, $P < 0.001$), and 0.059 (95% CI: 0.037–0.090, $P < 0.001$), respectively, in the training cohort (Table 4). The values of the NRI and IDI for the internal and external validation cohorts were also obtained in Table 4, which indicated that the established nomogram performed significantly better than did the TNM staging system. A survival-related nomogram was constructed on the basis of the results of multivariate Cox regression analysis to plot ROC curves (Fig. 3), calibration curves (Fig. 4), and DCA curves (Fig. 5). The constructed nomogram

Variables	Training group ($N=798$) (%)	Internal validation group($N=340$) (%)	External validation group($N=185$) (%)	*P* value	χ^2
Age (years)				0.3869	4.1439
< 57	348 (43.61)	155 (45.59)	69 (37.29)		
57–64	183 (22.93)	70 (20.59)	49 (26.48)		
> 64	267 (33.46)	115 (33.82)	67 (36.22)		
Sex				0.74	0.60221
Male	472 (59.15)	202 (59.41)	104 (56.22)		
Female	326 (40.85)	138 (40.59)	81 (43.78)		
Race				0.2837	5.0355
White	529 (66.29)	236 (69.41)	137 (74.05)		
Black	96 (12.03)	33 (9.71)	16 (8.65)		
Others	173 (21.68)	71 (20.88)	32 (17.30)		
Marital status				0.8492	0.32695
Married	542 (67.92)	226 (66.47)	127 (68.65)		
Unmarried	256 (32.08)	114 (33.53)	58 (31.35)		
Primary site				0.141	12.236
1/3U	237 (29.7)	108 (31.76)	75 (40.54)		
1/3 M	73 (9.15)	32 (9.41)	16 (8.65)		
1/3L	259 (32.46)	113 (33.24)	51 (27.57)		
curvature	151 (18.92)	63 (18.53)	24 (13.00)		
overlapping lesion	78 (9.77)	24 (7.06)	19 (10.27)		
Size(mm)				0.2569	5.3104
< 39	265 (33.21)	129 (37.94)	66 (35.68)		
39–69	319 (39.97)	112 (32.94)	71 (38.38)		
> 69	214 (26.82)	99 (29.12)	48 (25.95)		
T stage				0.02699	14.248
T1	77 (9.65)	32 (9.41)	15 (8.11)		
T2	78 (9.77)	34 (10)	19 (10.27)		
T3	313 (39.22)	125 (36.76)	96 (51.89)		
T4	330 (41.35)	149 (43.82)	55 (29.73)		
N stage				< 0.0001	72.154
N0	156 (19.55)	79 (23.24)	48 (25.95)		
N1	360 (45.11)	152 (44.71)	40 (21.62)		
N2	208 (26.07)	76 (22.35)	45 (24.32)		
N3	74 (9.27)	33 (9.71)	52 (28.11)		
M stage				0.06665	5.4166
M0	736 (92.23)	313 (92.06)	161 (87.03)		
M1	62 (7.77)	27 (7.94)	24 (12.97)		
Grade				0.5387	1.2372
I ~ II	25 (3.13)	10 (2.94)	3 (1.62)		
III ~ IV	773 (96.87)	330 (97.06)	182 (98.38)		
Surgery				< 0.0001	20.303
Yes	714 (89.47)	299 (87.94)	143 (77.30)		
No	84 (10.53)	41 (12.06)	42 (22.70)		
Chemotherapy				0.4399	1.6426
Yes	762 (95.49)	319 (93.82)	174 (94.05)		
N0	36 (4.51)	21 (6.18)	11 (5.95)		

Table 1. Demographics and clinicopathological characteristics of the GSRC patients in 2004–2019. 1/3U Cardiac and fundus of the stomach; 1/3 M the body of the stomach; 1/3L gastric antrum and pylorus; curvature lesser or greater curvature of stomach; overlapping lesion overlapping lesion of the stomach.

was validated, and the AUCs were 0.725, 0.753 and 0.745 for the training cohort; 0.725, 0.763 and 0.752 for the internal validation cohort; and 0.795, 0.764 and 0.765 for the external validation cohort, respectively. The calibration curves were plotted close to the reference line, indicating that this line plot model predicted 1-, 3-, and 5 -year survival in good agreement with the actual situation. DCA can be used to evaluate the clinical utility of line plot models by measuring their clinical validity through the risk threshold (X-axis) and net benefit (Y-axis).

Variables	Levels	Univariate Cox	Multivariate Cox
Age(years)	< 57		
	57–64	1.25 (1.02–1.54, $p = 0.035$)	1.18 (0.95–1.46, $p = 0.134$)
	> 64	1.44 (1.20–1.74, $p < 0.001$)	1.39 (1.15–1.69, $p = 0.001$)
Sex	Male		
	Female	0.94 (0.80–1.11, $p = 0.468$)	-
Race	White		
	Black	0.89 (0.69–1.14, $p = 0.358$)	0.97 (0.74–1.27, $p = 0.840$)
	Others	0.67 (0.54–0.83, $p < 0.001$)	0.74 (0.59–0.93, $p = 0.008$)
Marital status	Married		
	Unmarried	1.20 (1.02–1.43, $p = 0.032$)	1.25 (1.04–1.49, $p = 0.015$)
Primary site	1/3 U		
	1/3 M	0.77 (0.57–1.03, $p = 0.080$)	1.07 (0.78–1.46, $p = 0.677$)
	1/3 L	0.71 (0.58–0.87, $p = 0.001$)	0.94 (0.75–1.18, $p = 0.618$)
	curvature	0.61 (0.48–0.78, $p < 0.001$)	0.88 (0.68–1.15, $p = 0.352$)
	overlapping lesion	1.03 (0.77–1.36, $p = 0.862$)	1.02 (0.75–1.39, $p = 0.896$)
Size(mm)	< 39		
	39–69	1.31 (1.08–1.59, $p = 0.007$)	1.03 (0.84–1.27, $p = 0.748$)
	> 69	1.69 (1.38–2.08, $p < 0.001$)	1.26 (1.00–1.58, $p = 0.051$)
T stage	T1		
	T2	0.83 (0.55–1.24, $p = 0.361$)	1.02 (0.67–1.55, $p = 0.919$)
	T3	1.31 (0.96–1.79, $p = 0.090$)	1.36 (0.99–1.86, $p = 0.061$)
	T4	2.01 (1.47–2.73, $p < 0.001$)	1.90 (1.38–2.62, $p < 0.001$)
N stage	N0		
	N1	1.21 (0.96–1.52, $p = 0.107$)	1.08 (0.85–1.37, $p = 0.522$)
	N2	1.48 (1.16–1.90, $p = 0.002$)	1.34 (1.03–1.75, $p = 0.030$)
	N3	2.24 (1.65–3.06, $p < 0.001$)	1.79 (1.28–2.49, $p = 0.001$)
M stage	M0		
	M1	3.33 (2.54–4.37, $p < 0.001$)	2.14 (1.60–2.87, $p < 0.001$)
Grade	I ~ II		
	III ~ IV	1.02 (0.65–1.59, $p = 0.941$)	-
Surgery	Yes		
	No	3.58 (2.81–4.55, $p < 0.001$)	3.19 (2.40–4.25, $p < 0.001$)
Chemotherapy	Yes		
	No	1.26 (0.86–1.85, $p = 0.244$)	-

Table 2. Univariate and multivariate Cox regression analysis of GSRC in the training group. $N = 798$, events = 599, Likelihood ratio test = 214.69 on 19 df($p < 0.001$). 1/3U Cardiac and fundus of the stomach; 1/3 M the body of the stomach; 1/3L gastric antrum and pylorus; curvature lesser or greater curvature of stomach; overlapping lesion overlapping lesion of the stomach.

Figure 5 shows the DCA curves for the prognostic nomogram and TNM staging scheme. DCA revealed that the prognostic nomogram had greater net advantages than the TNM staging approach did, indicating greater clinical application value. The DCA curve in this study suggested a high net benefit and good clinical prediction.

Survival analysis

The prognostic nomogram provides an overall score, and on the basis of the cutoff value (118.3576) of the nomogram, we divided all patients into two subgroups, high- and low-risk groups, each suggesting a distinct prognosis. Figure 6A-C show the Kaplan–Meier survival curves, which indicate the prognosis for each group. There was a significant difference in survival among the three groups ($P < 0.05$). In the training set, the high-risk group had a 1-year OS of 66.6%, a 3-year OS of 40.1%, and a 5-year OS of 18.0%, and a median OS of 18 months (95% CI: 16–20). In the low-risk group, the 1-year OS was 88.6%, the 3-year OS was 66.9%, the 5-year OS was 54.7%, and the median OS was 81 months (95% CI: 60–105). In the internal validation set, the high-risk group had a 1-year OS of 71.2%, a 3-year OS of 29.9%, a 5-year OS of approximately 19.0%, and a median OS of 20 months (95% CI: 17–25). The low-risk group had a 1-year OS of 91.6%, a 3-year OS of 68.0%, a 5- year OS of 57.0%, and a median OS of 79 months (95% CI: 56-NA). In the external set, the high-risk group had a 12-month OS of 62.5%, an 18-month OS of 47.0%, a 24-month OS of 38.0%, and a median OS of 18 months (95% CI: 15–23). The low-risk group had a 12-month OS of 90.0%, an 18-month OS of 81.2%, and a 24-month OS of 74.0%. Given the short follow-up period, we did not observe a median survival time in the low-risk group of the external validation group. There were statistically significant differences in survival outcomes between the two

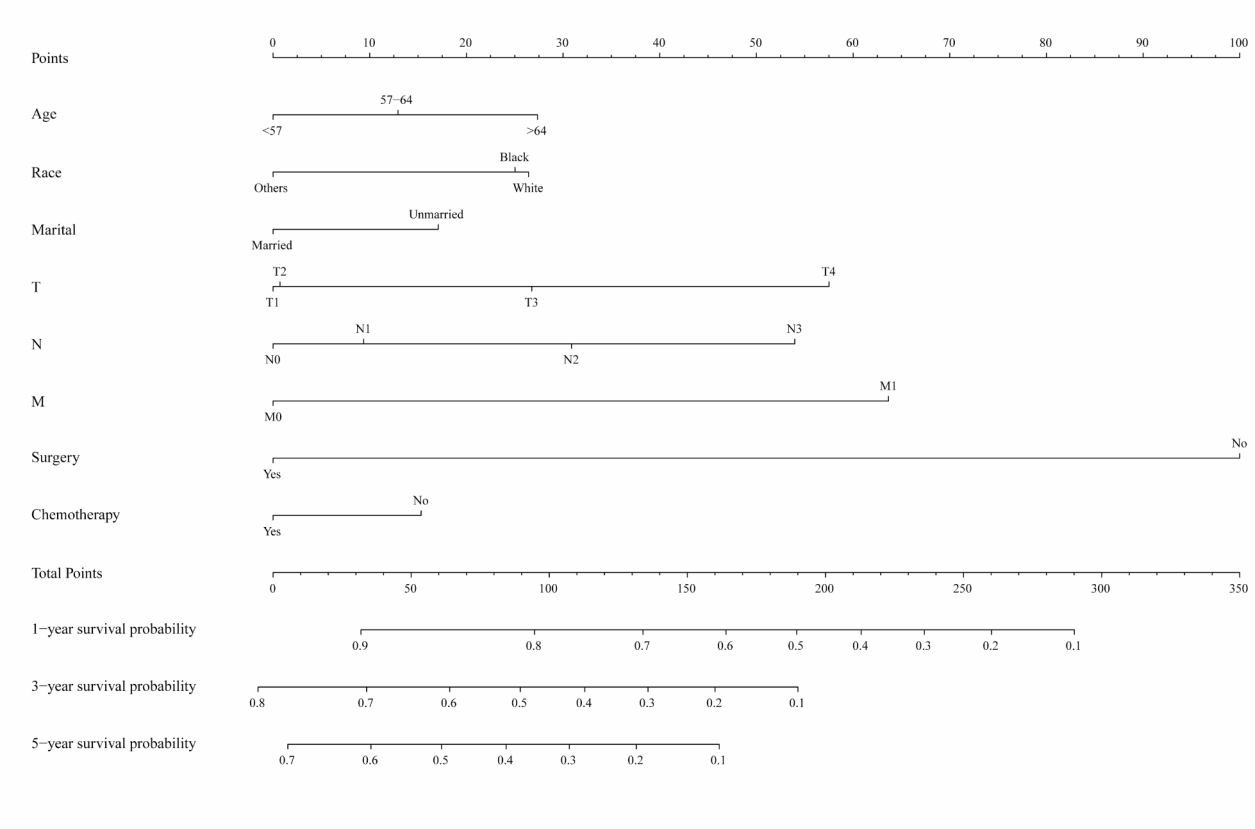

Fig. 2. Nomogram for predicting OS in GSRC patients by training group. Age(years); Marital, Marital status; N, N-stage; M, M-stage.

Variable	Levels	Points	Variable	Levels	Points
Age(years)	< 57	0	N stage	N0	0
	57–64	13		N1	9
	> 64	27		N2	31
Race	White	26		N3	54
	Black	25	M stage	M0	0
	Others	0		M1	64
Marital status	Married	0	Surgery	Yes	0
	Unmarried	17		No	100
T stage	T1	0	Chemotherapy	Yes	0
	T2	1		No	15
	T3	27			
	T4	58			

Table 3. The score of clinical variables in each subgroup.

groups. In addition, K-M survival curves were plotted by R studio (Fig. 6D-F) according to different treatment statuses and were divided into surgery combined with CRT groups ($n = 1109$), surgery combined with RT groups ($n = 47$), CRT groups ($n = 146$), and RT alone groups ($n = 21$), with median OS times of 34.0, 33.0, 10.0 and 4.0 months, respectively; surgery groups ($n = 1156$) and nonsurgery groups ($n = 167$), with median OS times of 34.0 and 9.0 months ($P < 0.001$); and median OS times of was 29.0 and 16.0 months ($P = 0.15$) in the chemotherapy group ($n = 1255$) and the nonchemotherapy group ($n = 68$), respectively.

Discussion

Currently, the use of radiotherapy in patients with gastric cancer is controversial. The Korean ARTIST and ARTIST II studies did not demonstrate a positive prognostic effect of radiotherapy[16,17]. We found that fewer than 50% of the samples included in these studies were diagnosed with GSRC. The reported results in terms of the

Index	Training group			Internal validation group			External validation group		
	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value	Estimate	95% CI	*P* value
NRI (vs. the TNM staging system)									
For 1-year OS	0.268	0.162–0.354	< 0.001	0.262	0.131–0.431	0.01	0.358	0.197–0.547	< 0.001
For 3(1.5)-year OS	0.238	0.152–0.317	< 0.001	0.239	0.121–0.354	< 0.001	0.362	0.196–0.518	0.002
For 5(2)-year OS	0.200	0.114–0.300	< 0.001	0.232	0.092–0.359	0.004	0.325	0.176–0.480	0.002
IDI (vs. the TNM staging system)									
For 1-year OS	0.081	0.046–0.129	< 0.001	0.097	0.033–0.184	0.004	0.088	0.035–0.175	0.004
For 3(1.5)-year OS	0.068	0.042–0.100	< 0.001	0.076	0.037–0.123	< 0.001	0.109	0.051–0.199	0.002
For 5(2)-year OS	0.059	0.037–0.090	< 0.001	0.063	0.028–0.107	0.002	0.097	0.044–0.178	< 0.001
C-index									
The nomogram	0.684	0.661–0.707	-	0.702	0.667–0.737	-	0.729	0.685–0.773	-
The TNM staging system	0.636	0.612–0.661	-	0.646	0.609–0.683	-	0.669	0.616–0.721	-

Table 4. The C-index, NRI and IDI of the nomogram and the TNM staging system alone in survival prediction for GSRC patients.

GSRC need to be interpreted with caution. The specialized type of adenocarcinoma of the GSRC is characterized by poor differentiation. Theoretically, GSRC is highly sensitive to radiotherapy. Luckily, many relevant studies have shown that radiotherapy is associated with a better prognosis for GSRC patients[18,19]. We found that age, race, marital status, TNM stage, and surgery recoding affected the prognosis of patients with GSRC receiving radiotherapy and constructed a nomogram to predict overall survival.

Previous investigations have demonstrated that age, race, and TNM stage are independent risk factors for both OS and CSS[18,19]. Older age and higher TNM stage are widely known to be associated with poor OS. The reason was that older people usually have more comorbidities, but younger patients have better physical and psychological conditions[20,21]. The T stage of gastric cancer refers to the depth of tumor infiltration. Chen et al. reported that T stage was the main factor affecting survival compared with other factors, with higher T stage being associated with poorer survival[18]. In the Zhang et al. reported that treatment strategies have a greater impact on prognosis[19], which is consistent with our results. Metastasis of regional lymph nodes is an essential indicator for predicting gastric cancer prognosis, and lymph node metastases and distant metastases indicate a worse prognosis[22,23]. Gastric cancer is significantly influenced by environmental factors, lifestyle factors, diet and genetics[7]. Interestingly, Zhang et al. reported that black patients have a worse prognosis than other patients[19]. In our study and a retrospective study by Chen et al.[18], white patients were worse than black patients and individuals of other races. White races have also been found to have a worse prognosis in patients with lung cancer and colorectal cancer[24,25]. The present study also identified marital status as a prognostic factor by using a nomogram and revealed that unmarried patients were more likely to die. This is probably because married patients receive more family support and financial support. One study reported that married patients tend to live longer than unmarried patients do[26]. To date, only a few studies have reported that marital status is associated with the survival of GSRC patients[27,28]. Unfortunately, we found no significant correlations between histological grade, sex, or tumor size and patient survival. In addition, Chon et al. and Zhang et al. reported that sex and histological grade did not seem to be risk factors for predicting the prognosis of GSRC[19,29]. With respect to histological grade, approximately 97% of the samples were Grade III/IV in our study.

Notably, owing to the lack of obvious symptoms in the early stages, the majority of GCs diagnosed in advanced stages are still amenable to surgical resection[30]. Most patients had locally advanced disease with high TNM stage in the present study. Among the currently published nomograms, surgery records are considered a prognostic factor included in the prediction models[18,19,27]. With respect to other factors, surgery records are the main factor influencing survival[27], which is similar to the findings of our study. The role of chemotherapy is controversial. A retrospective study by Li et al. revealed that the 5-year overall survival rates of patients in the neoadjuvant chemotherapy group and surgery-first group were 50.0% and 65.0%, respectively[31]. Fluorouracil plus leucovorin, oxaliplatin and docetaxel as a perioperative therapy has been found to be effective for treating GSRC[6]. Adjuvant chemotherapy has been shown in other studies to be effective in treating GSRC[32]. As shown in the Table 2, multivariate Cox regression analysis revealed that chemotherapy was not associated with patient survival. However, we found a prognostic difference between the chemotherapy and nonchemotherapy groups in the subsequent survival analysis (Fig. 6F).

Our results also revealed that the median OS rates were 34.0 and 33.0 for patients who underwent surgery combined with CRT and surgery combined with RT (Fig. 6D), respectively, which were significantly better than those of patients in the chemoradiotherapy and RT alone cohorts. Therefore, surgery is an effective treatment for improving OS in patients with GSRC. Although the specific dosing regimen and treatment sequence used in the surgery combined with CRT group were uncertain, a survival benefit for GSRC patients could be demonstrated. Follow-up studies are still needed to determine the optimal treatment modality. In addition, we found that in the radiotherapy alone group, there were more elderly people with distant metastases, as shown in Supplementary Table S2. Additionally, they may hold negative treatment intentions. The prognostic performance of these drugs

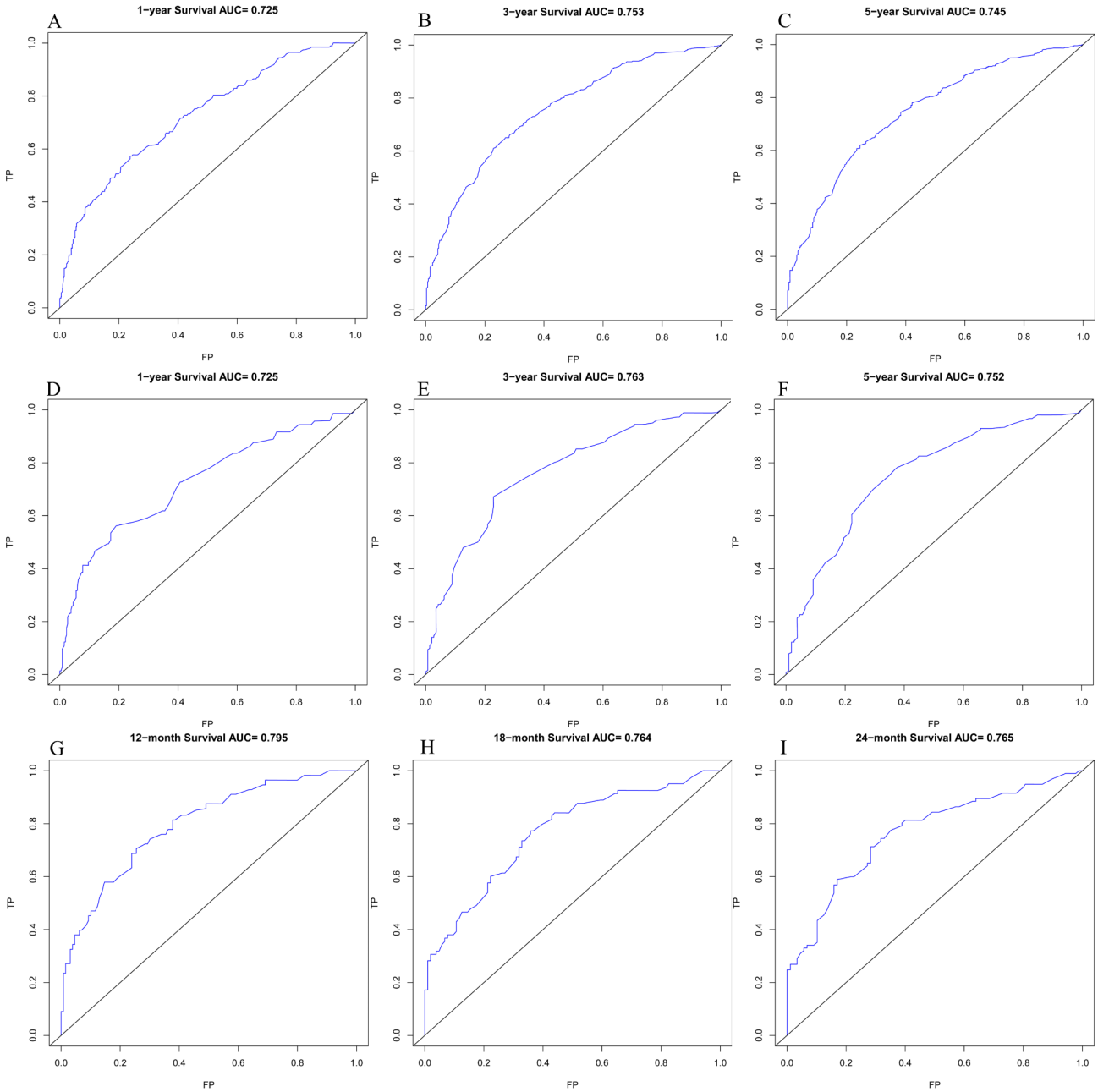

Fig. 3. ROC curves of OS in training group (**A**-**C**), internal validation group (**D**-**F**) and external validation group (**G**-**I**) for validating nomogram models. TP, True Positive; FP, False Positive; AUC, area under curve.

is poor, and we therefore suggest suggested that these patients could participate in clinical trials and apply some immunologic and targeted drugs to improve the survival rate.

We statistically analyzed the clinicopathological information of 1323 samples from the SEER database. We used multivariate Cox regression analysis to identify factors affecting the prognosis of GSRC patients receiving radiotherapy and constructed a prognostic nomogram. Our risk prediction model demonstrated good discriminatory power in the validation sets, with C-indices of 0.684 (95% CI: 0.661–0.707), 0.702 (95% CI: 0.667–0.737) and 0.729 (95% CI: 0.685–0.773) in the training cohort, internal validation cohort and internal validation cohort, respectively. The positive NRI and IDI of the nomogram compared with those of the TNM staging system further indicated that the nomogram had better predictive capability. We also applied ROC curves, calibration curves, and DCA to demonstrate the model's validity. The AUC values for these nomograms are relatively high, which indicates that our prediction model has high accuracy. The calibration plots indicated good consistency between the predicted and observed proportions, confirming that there were no significant differences between the predicted and actual outcomes. Compared with the TNM staging system, our nomogram had better accuracy at predicting 1-, 3-, and 5-year OS. The DCA revealed that the clinical effectiveness of the line graph prediction model was better. These findings demonstrate the accuracy, clinical utility and generalizability

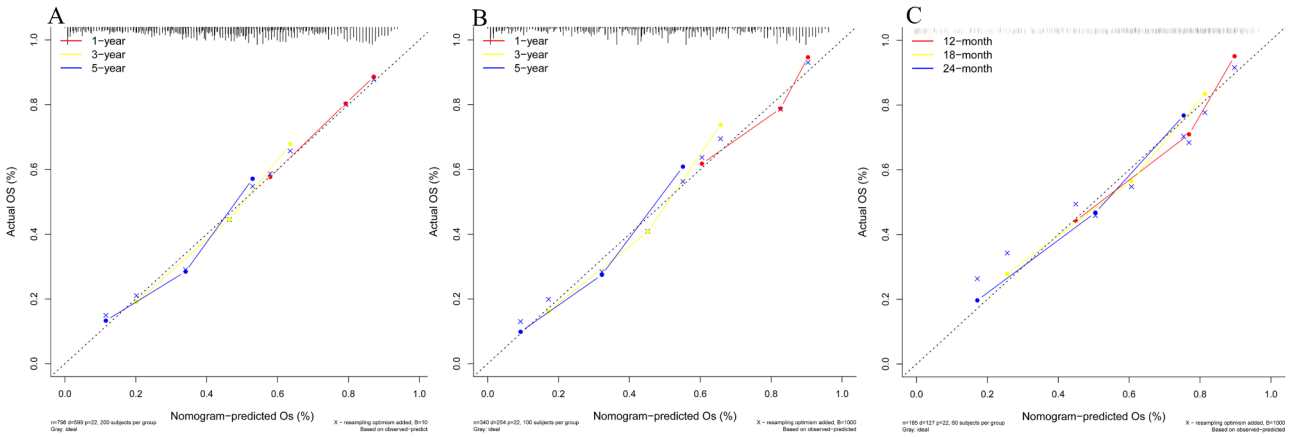

Fig. 4. The calibration plots for predicting 1-, 3-, 5-year overall survival in the training group (**A**) and internal validation group (**B**), for predicting 12-, 18-, 24-month overall survival in external validating cohort (**C**).

of this nomogram. In addition, when the patients were stratified by nomogram score, the low-risk group had a better overall survival rate than the high-risk group did ($p < 0.001$). More intensive treatment and humanistic and psychological support should be implemented in high-risk subgroups. The immunotherapy of GSRC has gradually become a hot topic in recent years. Programmed death 1(PD-1) was expressed in 23% of GSRC[33]. The elevated level of MSI expression in most GSRC patients also further validates that GSRC patients with high MSI expression may benefit from immunotherapy[34]. As more immune hyporesponsive mechanisms are revealed[35], high-risk GSRC patients may have more available treatment strategies.

Despite these noteworthy results, this investigation has certain constraints. First, this was a retrospective study based on the SEER database, and potential selection bias may have occurred. Second, the SEER database does not specify information that would have been crucial, including specific biochemical parameters, such as CEA and CA19-9 levels, specific chemotherapy schedules and doses, patients' lifestyles, nutritional status, etc., which would also have some impact on the nomogram's predictive ability. Finally, the SEER database does not mention the regimen or dose of radiotherapy, and it does not specify the specific radiotherapy technique, which has limited research on the survival benefits of patients treated with radiation therapy to some extent. Our future work and efforts will be directed toward addressing the aforementioned restrictions to improve the practical value of the nomogram.

Conclusion

On the basis of clinicopathological factors identified via univariate and multivariate Cox analyses, we created a nomogram. The nomogram can effectively assist physicians in forecasting the 1-, 3-, and 5-year overall survival of GSRC patients receiving radiation therapy. The results showed that our prediction model significantly outperformed the AJCC staging systems and successfully predicted individual survival. Furthermore, this nomogram might help stratify the risk and aid in the clinical decision-making of GSRC patients.

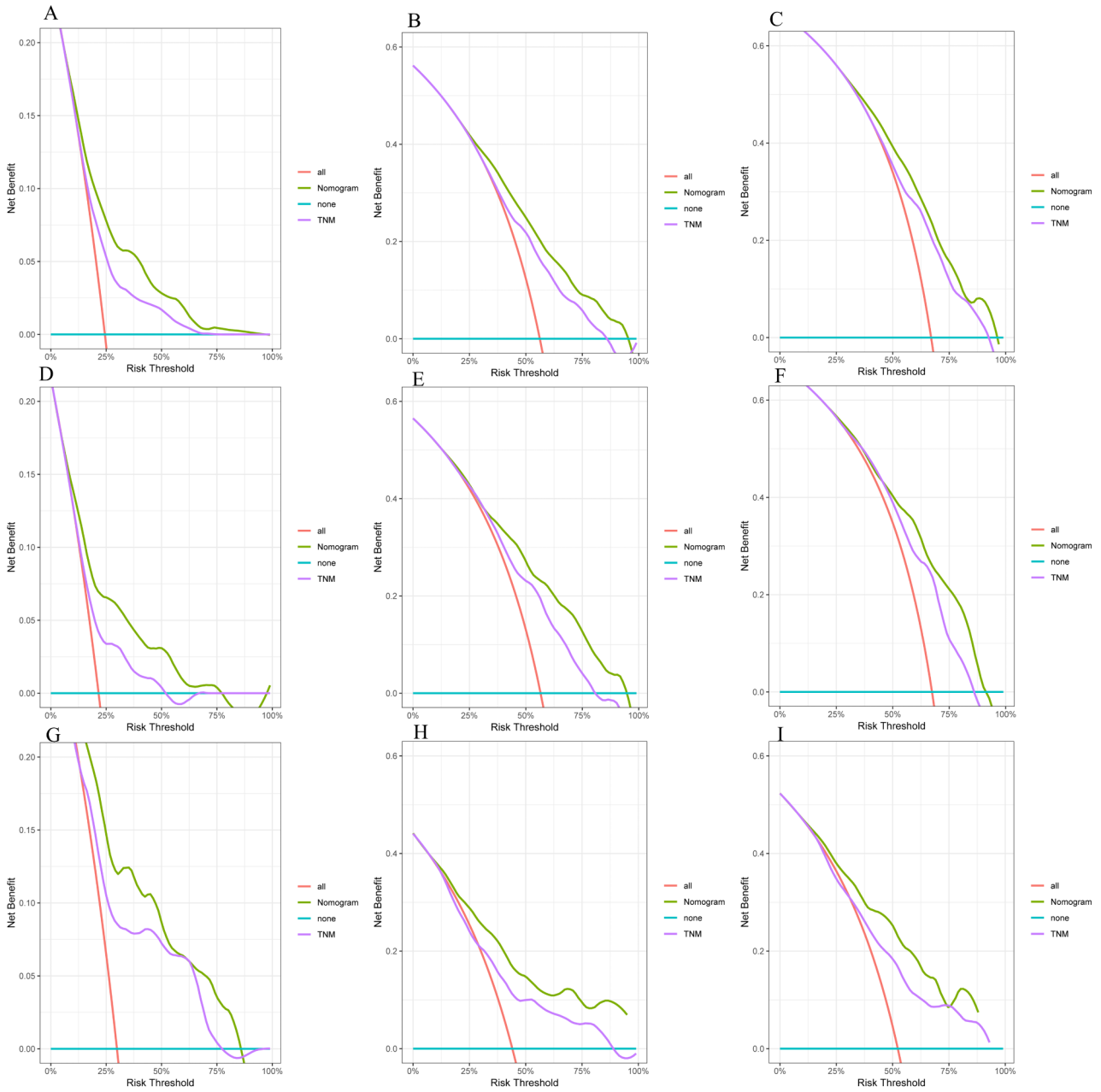

Fig. 5. The 1-, 3-, and 5-year DCA curves of nomogram in training group (**A**-**C**) and internal validation group (**D**-**F**). The 12-, 18-, 24-month DCA curves of nomogram in external validation group (G-I). DCA, decision curve analysis.

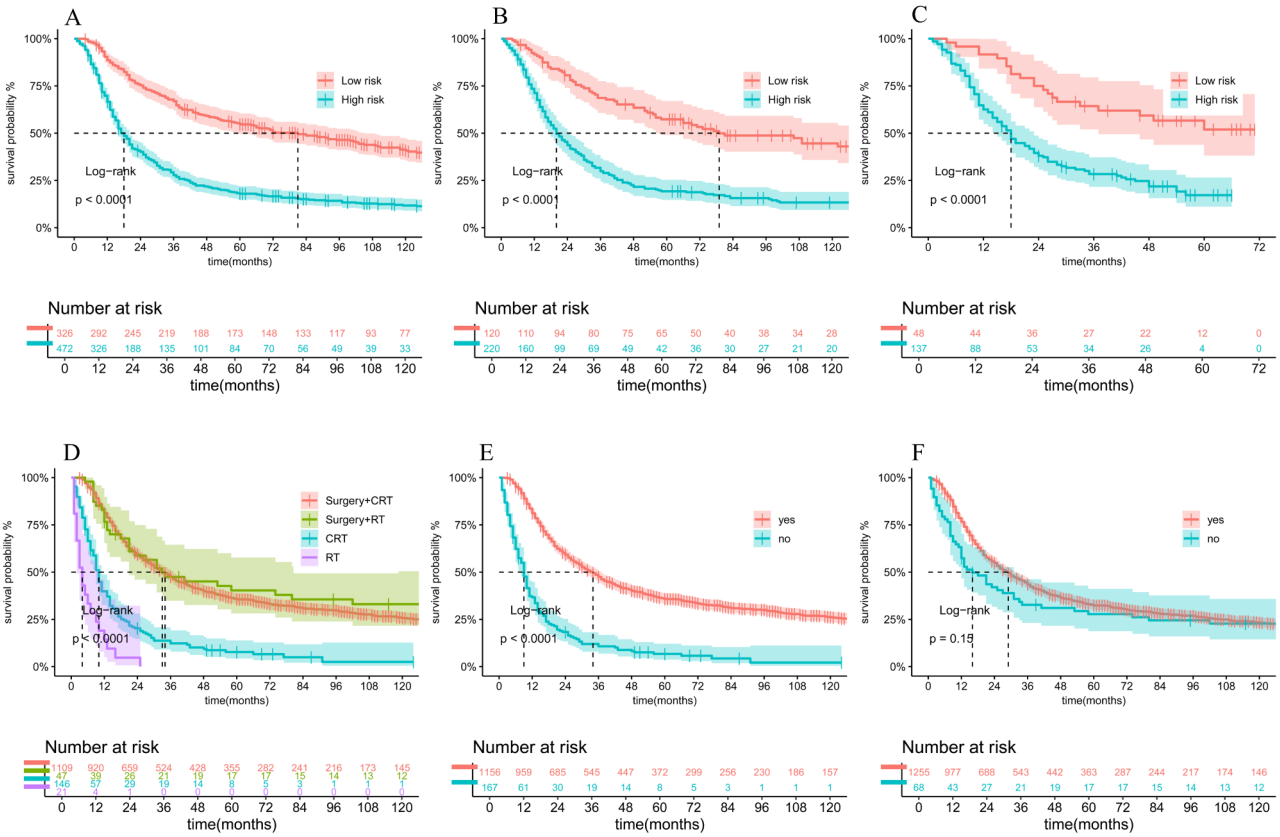

Fig. 6. Kaplan–Meier curves of OS for patients in the low-, and high-risk groups in the training group (**A**), internal validation group (**B**) and external validation group (**C**). The Kaplan-Meier survival analysis curves for OS according to different treatments (**D**), surgery recode (**E**), chemotherapy recode (**F**). RT, radiotherapy; CRT, chemotherapy combine with radiotherapy.

Data availability

These data can be found in the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 17 Registries, Nov 2023 Sub (2000-2021).

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Author contributions

GM W and Q W contributed to data collection and analysis, GM W and YM L wrote the manuscript, G X and GM W contributed to the conception and designed the study, G X supervised the completion and provided the assistance. All the authors approved the final version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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