

Nomogram for predicting the survival of gastric adenocarcinoma patients who receive surgery and chemotherapy

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Abstract

Background: Surgery is the only way to cure gastric adenocarcinoma (GAC), and chemotherapy is the basic adjuvant management for GAC. A prognostic model for predicting the individual disease-specific survival (DSS) rates of GAC patients who receive surgery and chemotherapy has not been established. **Objective:** We aimed to establish a survival nomogram for GAC patients who receive surgery and chemotherapy. **Methods:** We identified 5764 GAC patients who had received surgery and chemotherapy from the SEER (Surveillance, Epidemiology, and End Results) database. Approximately 80% (n=4034) of the included patients were randomly assigned to the training set, and the remaining patients (n=1729) were assigned to the external validation set. Nomogram was established by the training set and validated by the validation set. **Results:** Based on the results of a multivariate analysis, a nomogram was developed that encompassed age at diagnosis, number of regional lymph nodes examined, number of positive regional lymph nodes, sex, race, grade, derived AJCC stage, summary stage, and radiotherapy status. The C-index (Harrell's concordance index) of the model was higher than that of the traditional seventh AJCC staging system (0.707 vs 0.661). Calibration plots of the nomogram showed that the probability of DSS optimally corresponded to the survival rate. Integrated discrimination improvement (IDI) and categorical net reclassification improvement (NRI) showed visible improvement. IDI for 3-, 5- and 10- year DSS were 0.058, 0.059 and 0.058, respectively ($P>0.05$), and NRI for 3-, 5- and 10- year DSS were 0.380 (95% CI=0.316–0.470), 0.407 (95% CI=0.350–0.505), and 0.413 (95% CI=0.336–0.519), respectively. Decision curve analysis supported that the constructed nomogram was superior to the AJCC staging system. **Conclusion:** The proposed nomogram provides more-reliable DSS predictions for GAC patients who receive surgery and chemotherapy in the general population. According to validation, the new nomogram will be beneficial in facilitating individualized survival predictions and useful when performing clinical decision-making for GAC patients who receive surgery and chemotherapy.

Background

Gastric cancer (GC) remains an important type of cancer worldwide, with more than 1,000,000 new cases in 2018 and resulting in an estimated 783,000 deaths (equating to 1 in every 12 deaths globally), making it the fifth most commonly diagnosed cancer and the third leading cause of cancer deaths (1). GC has a routine appearance of adenocarcinoma in 90% of cases, with gastric adenocarcinoma (GAC) being the most-common subtype of GC (2). The incidence of GC varies between regions, with more than 70% of cases occurring in developing countries (3). The incidence rate is twofold higher in men than in women. Among men, it is the most commonly diagnosed type of cancer and the leading cause of cancer deaths in several western Asian countries, including Iran, Turkmenistan, and Kyrgyzstan. The incidence rates are markedly elevated in eastern Asia countries such as Mongolia, Japan, and the Republic of Korea (1).

Surgical resection is the main treatment modality for locally advanced GC, and complete resection is essential for curing it. However, while complete resection can remove the tumor that is visible in the surgical field (4), tumor recurrence remains possible since complete resection cannot eradicate any micrometastatic tumor cells that exist outside of the surgical field. Such invisible tumor cells gradually

multiply to become a mass that can be detected on imaging studies or physical examinations, corresponding to recurrence (5). The aim of adjuvant therapy is to eradicate micrometastatic tumor cells before and/or after surgery in order to improve the probability of a good survival outcome for the patient. Preoperative chemotherapy is favored in the European Union and the USA, whereas postoperative adjuvant chemotherapy is preferred in Asia (6).

Nomograms are widely used for cancer prognoses, primarily because of their ability to reduce complex statistical predictive models to a single numerical estimate of the probability of an event—such as death or recurrence—that is tailored to the profile of an individual patient (7, 8). User-friendly graphical interfaces for generating these estimates facilitate the use of nomograms during clinical encounters to inform clinical decision-making. Nomograms have in general been widely used as graphical representations of complex mathematical formulas, by combining several independent factors to construct a statistical prognostic model for estimating the prognosis in multiple malignancies (9).

Some nomograms for the survival prognosis of GC or GAC have been reported (10-15). However, no nomograms are available for the 10-year survival prognosis of GAC patients who have received surgery and chemotherapy. In the current study we aimed to establish a survival nomogram for GAC patients who receive surgery and chemotherapy.

Methods

Patients

The Surveillance, Epidemiology, and End Results (SEER) database covers approximately 30% of the total US population. It is composed of 18 registries containing clinical information on patients in the US with tumors. We obtained clinical information on GAC patients from the SEER database that allowed detailed analyses of survival in GAC. This study performed a retrospective review of all GAC patients in the SEER database who had received surgery and chemotherapy between 2004 and 2015. In order to evaluate the effect of lymph node status, patients with information on the number of regional lymph nodes examined (RNE) were included in the current study. Finally, a total of 5764 GAC patients who met all of the inclusion criteria were selected as the primary cohort. Approximately 80% ($n=4034$) of these patients were randomly assigned to the training set, and the remaining 1729 patients were defined as the external validation set.

The inclusion criteria for GAC patients in the present study were as follows:

1. Site and morphology according to International Classification of Diseases for Oncology (ICD-O-3) histology/behavior code 8140/3, 8141/3, 8142/3, 8143/3, 8144/3, 8146/3, 8147/3, 8149/3, 8213/3, 8262/3, 8263/3, 8290/3, 8310/3, 8322/3, 8323/3, 8325/3, 8330/3, 8331/3, 8332/3, or 8333/3.
2. Site and morphology, according to ICD-O-3 primary site code C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.7, C16.8, or C16.9.
3. Known cause of death and known survival period after the diagnosis.

4. Received either local or major primary tumor resection.
5. Received chemotherapy.

The exclusion criteria for GAC patients in this study were as follows:

1. GAC was not the only primary cancer diagnosed.
2. Unknown AJCC stage.
3. Unknown TNM stage.
4. Unknown lymph node status.

Ethical approval

SEER data are de-identified before being released and so do not contain any personally identifying information. Since the data are publicly available, no ethical approval was required for this study.

Data collection

The factors associated with the survival of GAC patients who receive surgery and chemotherapy were identified by obtaining information on the clinicopathological characteristics of these patients such as the age at diagnosis, RNE, number of positive regional lymph nodes (RNP), sex, race, grade, derived AJCC stage, summary stage, and radiotherapy status. The end point was the disease-specific survival (DSS) rate, which was defined as the time from surgery to cancer-related death or the last follow-up. DSS was estimated and survival curves were produced using the Kaplan-Meier method and validated by the log-rank test.

Statistical analysis

Age, RNE, and RNP were continuous variables in this study. Age and RNE conformed to a normal distribution and so are expressed as mean \pm SD values, while RNP is expressed as median and interquartile-range values since it did not conform to a normal distribution. The other variables were categorical and are expressed as percentages. Independent factors predicting the survival time were determined using the Kaplan-Meier and Cox proportional-hazards models (16). Variables that were significant were further identified by a multivariate Cox proportional-hazards model via backward stepwise analysis.

A nomogram for predicting the 3-, 5-, and 10-year DSS rates was constructed using the results of the multivariate analyses. The predictive accuracy of the nomogram was estimated using Harrell's

concordance index (C-index) and the area under the time-dependent receiver operating characteristic curve (AUC). Calibration was assessed graphically by plotting the relationship between the predicted probability and the actual outcome using the Hosmer goodness-of-fit test (17). The improvement in the predictive accuracy of the new prediction model was evaluated by calculating the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) (18). Finally, decision-curve analysis (DCA) was employed to estimate the clinical applicability of the nomogram by quantifying the net benefits at different threshold probabilities (19).

All statistical analyses were performed using SPSS software (version 24.0, SPSS, Chicago, IL, USA) and R software. A two-sided *P* value of ≤ 0.05 was considered to be indicative of statistical significance.

Results

Patient baseline characteristics

After selection in SEER database according to the inclusion and exclusion criteria, 5764 patients who received surgery and chemotherapy were identified. Approximately 80% of them were randomly grouped into Training set, while the rest were selected into the validation set. In the training set, the age at diagnosis was 62.8 ± 11.6 years (range 22–92 years). There were 2905 (72%) male patients and 1129 (28%) female ones. These patients were predominantly white ($n=2805$, 69.5%), while 516 of them were black (12.8%) and 713 were of other races (17.7%). Their marital status comprised 2811 married patients (69.5%), 475 patients (11.8%) who were single or living with a domestic partner, and 748 patients (18.5%) were divorced or separated or widowed (DSW). The primary sites of GAC in 1698 patients (42.1%) were located in cardia, 1392 patients (34.5%) were located in pylorus, and 944 patients (23.4%) were located in other part of the stomach or the location were unknown. Poor differentiation (61.3%) was the most-common tumor grade, followed by moderate differentiation (33.5%), well-differentiated (3.2%), and undifferentiated (2.0%). Most patients (56.2%) were categorized as primary T category T2, 27.1% were T3, 8.8% were T1, and 8.0% were T4. About half of the patients (53.2%) were categorized as primary N category N1, 22.9% were N0, 18.0% were N2, and 5.9% were N3, while 89.6% were categorized as primary M category M0 and 11.4% were M1. Regional cancer (72.3%) was the most-common tumor summary stage, followed by localized cancer (14.0%) and distant cancer (13.7%). Almost half of the patients (44.6%) had the radiation record. The RNE was 18.2 ± 11.9 (range 1–87), and the median RNP was 2 (range 0–79). There were 1333 (33.0%), 1078 (26.7%), 846 (21%), and 777 (19.3%) patients categorized as AJCC stages II, III, I, and IV, respectively.

Patients in the validation set showed similar characteristics to those in the training set. The clinicopathological characteristics of the patients included in the training and validation sets are listed in Table 1.

Nomogram construction

The multivariable Cox analysis revealed that the age at diagnosis, RNE, RNP, sex, race, grade, summary stage, and radiotherapy status can independently predict the DSS of GAC patients who receive surgery and chemotherapy (Table 2). All of the independent risk factors that were statistically associated with DSS were incorporated in the prognostic nomogram developed in this study (Figure 1).

Validation of the nomogram for DSS of GAC patients who receive surgery and chemotherapy

The constructed nomogram was externally validated using the validation set. The predictive capacity of the constructed nomogram was directly compared with the seventh edition of AJCC staging system for GC. The C-indexes for the training and validation sets were larger for the nomogram (0.694 and 0.707, respectively) than for the seventh AJCC staging system (0.651 and 0.661). The 3-, 5-, and 10-year AUCs for the nomogram were 0.744, 0.746, and 0.743, respectively, for the training set, and 0.744, 0.747, and 0.75 for the validation set, indicating a good model discrimination ability that was better than that of the seventh AJCC staging system (Figure 2).

Calibration plots for the proposal nomogram showed that the predicted 3-, 5-, and 10-year DSS probabilities for the SEER training and validation sets were almost identical to the actual observations (Figure 3).

The NRI values for the 3-, 5-, and 10-year DSS were 0.380 (95% CI=0.316–0.470), 0.407 (95% CI=0.350–0.505), and 0.413 (95% CI=0.336–0.519), respectively, in the validation set. These results indicate that the proposed nomogram presented a large improvement in predictive performance. Similarly, the IDI values for the 3-, 5-, and 10-year DSS were 0.058, 0.059, and 0.058, respectively, in the validation set ($P<0.05$), further validating the improved predictive performance of the nomogram.

Decision curve analysis

DCA plots for the 3-, 5-, and 10-year DSS discrimination ability are depicted in Figure 4. The proposed nomogram was found to consistently perform better than the seventh AJCC staging system.

Discussion

This study developed a nomogram for predicting the 3-, 5-, and 10-year DSS of GAC patients who receive surgery and chemotherapy based on multi-institution and multipopulation data in the SEER database. The AJCC staging system has been the most commonly used and most-effective program for predicting the prognosis of GAC patients (20). However, receiving both surgery and chemotherapy will result in many more important risk factors influencing the DSS, such as age, race, sex, marital status, primary cancer site, grade, and summary stage. We therefore implemented a more-comprehensive prognosis model in the form of a nomogram. This nomogram not only includes the AJCC staging system, but also system

demographics and other important clinical parameters. The overall survival of GAC patients is prolonged after they receive surgery and chemotherapy (21-24). The increasing number of GAC survivors—especially long-term survivors—makes the use of a nomogram for predicting their long-term survival prognosis highly desirable.

To our knowledge, the present nomogram is the first for predicting the 10-year DSS for GAC patients who receive surgery and chemotherapy. Zhong and colleagues constructed a similar nomogram for the 10-year survival prognosis of GC patients after they receive curative surgery, but that nomogram did not include the chemotherapy status (25). In addition, an external cohort of GAC patients from the same database was used to validate the present nomogram. The obtained results suggest that we have successfully constructed a reliable nomogram for predicting the 3-, 5-, and 10-year DSS of GAC patients who receive surgery and chemotherapy, since the nomogram validation demonstrated favorable discrimination and calibration.

The constructed nomogram includes several independent prognostic factors. Many studies have indicated that the age of cancer patients is an important prognostic factor for DSS (13, 26-28). Multivariate analyses showed that the RNP and older age were independent risk factors for the DSS of GAC patients who receive surgery and chemotherapy, with survival being worse in older patients. The current study found that the DSS of GAC patients who receive surgery and chemotherapy was negatively correlated with age. Moreover, the race that not white or black appeared to be a protective factor compared with being white (HR=0.765, 95% CI=0.668–0.877, $P<0.001$), while cancer with a primary site of the pylorus seemed to be protective compared with the cardia (HR=0.729, 95% CI=0.649–0.818, $P<0.001$). Undifferentiated classification was a risk factor compared with well-differentiated (HR=1.581, 95% CI=1.026–2.437, $P<0.001$), a higher AJCC stage was associated with a worse DSS, and compared with a localized summary stage, a distant summary stage was a risk factor for DSS (HR=1.726, 95% CI=1.263–2.659, $P<0.001$).

The proposed nomogram model contains risk factors that are easily available and collected through historical records. To further determine whether the prognostic model performed better than the traditional AJCC staging system, we evaluated its performance based on calibration, discrimination, IDI, NRI, and DCA. The proposed nomogram displayed a good discrimination ability by producing a C-index of 0.694 for the training set and 0.707 for the validation set. Moreover, the C-indexes of the AJCC staging system were lower than those of the proposed nomogram, as were the AUC values. The discriminative power of the nomogram is significantly better than that of the AJCC staging system. The plots for both the training and validation sets resembled a 45-degree line, showing that the proposed nomogram predictions were well calibrated (Figure 2). The NRI and IDI are more-sensitive indicators than the C-index, and the NRI indicated that the proposed nomogram reclassified the risk probabilities better than did the AJCC staging system, while the IDI demonstrated the superior ability of the constructed nomogram to distinguish cases compared with the AJCC staging system. Numerous previous studies have found benefits of applying DCA (29-33), and the results of the current study indicate that the 3-, 5-, and 10-year

DCA curves yielded net benefits greater than those of the AJCC staging system, both in the training and validation sets (Figure 4).

While the present nomogram model demonstrated high accuracy in predicting DSS, several limitations of this study must be considered. Firstly, data were collected from the SEER database, in which the chemotherapy status is only reported as either “yes” and “no/unknown.” Although all of the cases included in the current study were GAC patients who had received chemotherapy (by excluding the “no/unknown” ones in the SEER database), the lack of detailed chemotherapy information might have influenced the obtained results. Secondly, there are potentially other factors that could influence the prognosis of GAC cancer patients, and so further clinical research should be carried out to improve the nomogram. Thirdly, since our study had a retrospective design, it is inevitable that some important patient data might have been missing, decreasing the number of eligible cases. Fourthly, the results of this study would be more reliable if the nomogram model was externally validated using another independent, large-scale cohort, which would verify whether our findings are more-widely applicable. Despite these limitations, our prognostic nomogram is a significant and effective model for accurately predicting the individual survival outcomes of GAC patients who receive surgery and chemotherapy.

Conclusions

We have developed and validated a prognosis nomogram for GAC that has a high accuracy. The prognostic value of the nomogram was better than that of the traditional seventh AJCC staging system alone. The validation process indicated that the proposed nomogram provides more-reliable DSS predictions for GAC patients who receive surgery and chemotherapy in the general population. The nomogram will be beneficial for individualized survival prediction and useful in clinical decision-making for GAC patients who receive surgery and chemotherapy.

Abbreviations

GAC: gastric adenocarcinoma; DSS: disease-specific survival; PUC: Primary urethral carcinoma; AJCC: American Joint Committee on Cancer; SEER: Surveillance, Epidemiology, and End Results; OS: overall survival; CSS: cancer-specific survival; ICD-O-3: the third revision of International Classification of Disease for Oncology; TCC: transitional cell carcinoma; SCC: squamous cell carcinoma; AC: adenocarcinoma; HR: hazard ratio; CI: confidence interval; C-index: consistency index; AUC: area under the receiver operating characteristics curve; DCA: decision-curve analysis. RNE: number of regional nodes examined; DSW: divorced & separated & widowed; RNP: number of regional nodes positive; Sums: SEER Summary stage 2000

Declarations

Ethics approval and consent to participate

All of the authors signed the “SEER Research Data Agreement” in order to protect the patients’ privacy, which is consistent with ethical principles.

Consent for publication

All authors listed approved the publication of the manuscript

Availability of data and materials’

Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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Authors' contributions

CYW and JY was responsible for conception, design and quality control of this study. HZ, ZLZ, and BHL conducted data management, analysis and interpretation. CYW, YW, and ZG participated in statistical analyses. CYW, GXJ, JL, and XDL contributed to manuscript drafting and editing. XQR reviewed the manuscript.

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Tables

Table 1. Patient characteristics in the study

Characteristics	Training set (n=4034)		Validation set (n=1729)	
	n	%	n	%
age (years)				
Mean	62.8±11.6		62.5±11.4	
Range	22-92		17-94	
Sex				
Male	2905.0	72.0	1285.0	74.3
Female	1129.0	28.0	444.0	25.7
Race				
White	2805.0	69.5	1215.0	70.3
Black	516.0	12.8	207.0	12.0
Others	713.0	17.7	307.0	17.7
Marital				
Married	2811.0	69.7	1191.0	68.9
Single/Domestic Partner	475.0	11.8	239.0	13.8
DWS	748.0	18.5	299.0	17.3
Prime Site				
cardia	1698.0	42.1	756.0	43.7
pylorus	1392.0	34.5	571.0	33.0
others or primary site unknown	944.0	23.4	402.0	23.3
Grade				
Well	131.0	3.2	55.0	3.2
Moderately	1353.0	33.5	583.0	33.7
Poorly	2471.0	61.3	1053.0	60.9
Undifferentiated	79.0	2.0	38.0	2.2
Primary T category				
T1	353.0	8.8	141.0	8.2
T2	2267.0	56.2	984.0	56.9
T3	1093.0	27.1	477.0	27.6
T4	321.0	8.0	127.0	7.3
Primary N category				
N0	925.0	22.9	373.0	21.6
N1	2145.0	53.2	939.0	54.3
N2	728.0	18.0	317.0	18.3
N3	236.0	5.9	100.0	5.8
Primary M category				
M0	3614.0	89.6	1558.0	90.1
M1	420.0	10.4	171.0	9.9

Summary stage				
Localized	565.0	14.0	225.0	13.0
Regional	2915.0	72.3	1281.0	74.1
Distal	554.0	13.7	223.0	12.9
Radiation recode				0.0
Yes	1800.0	44.6	772.0	44.7
No/Unknown	2234.0	55.4	957.0	55.3
RNE				
mean	18.2±11.9		18.2±11.7	
range	1-87		1-77	
RNP				
median	2		2	
range	0-79		0-51	
AJCC				
0	846.0	21.0	355.0	20.5
1	1333.0	33.0	574.0	33.2
2	1078.0	26.7	477.0	27.6
3	777.0	19.3	323.0	18.7

Abbreviations;RNE = Number of regional nodes examined, DSW= divorced & separated &widowed, RNP= Number of regional nodes positive, AJCC=American Joint Committee on Cancer.

Table 2 Selected variables by multivariate Cox regression analysis

Characteristics	HR	95% CI	p-value
Age	1.009	1.005-1.013	0.001
Race			
White	reference		
Black	1.020	0.884-1.175	0.790
Others	0.765	0.668-0.877	0.001
Prime Site			0.001
cardia	reference		
pylorus	0.729	0.649-0.818	
others or primary site unknown	0.749	0.660-0.849	
Grade			
Well	reference		
Moderately	1.026	0.743-1.417	0.877
Poorly	1.379	1.004-1.894	0.047
Undifferentiated	1.581	1.026-2.437	0.038
Summary stage			
Localized	reference		
Regional	1.208	0.919-1.587	0.175
Distal	1.726	1.263-2.359	0.001
Radiation recode			
Yes	reference		
No/Unknown	1.084	0.986-1.192	0.094
RNE	0.974	0.970-0.979	0.001
RNP	1.06	1.051-1.069	0.001
AJCC			
I	reference		
II	1.340	1.064-1.687	0.013
III	1.900	1.507-2.397	0.001
IV	2.285	1.750-2.981	0.001

Abbreviations; RNE = number of regional nodes examined, DSW= divorced & separated & widowed, RNP= number of regional nodes positive, AJCC=American Joint Committee on Cancer.

Figures

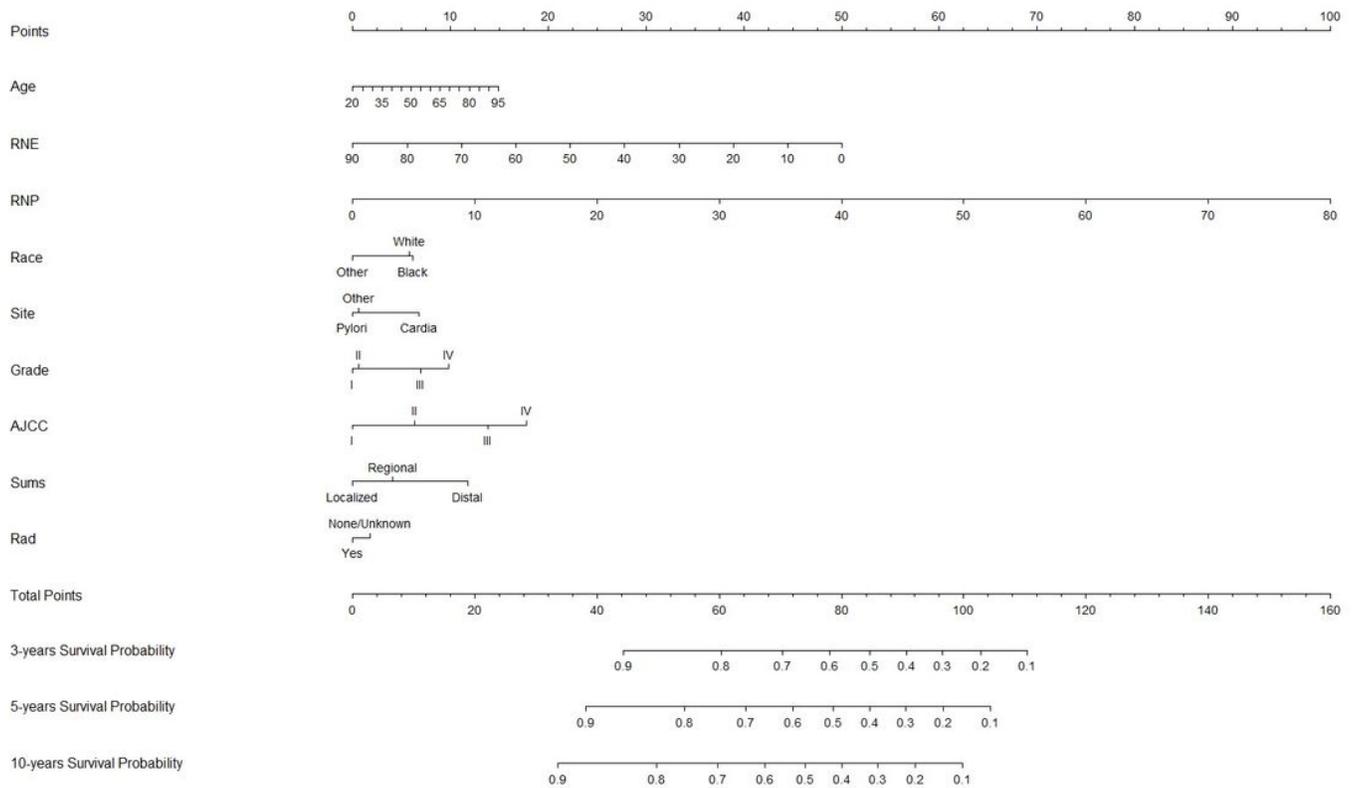


Figure 1

Nomogram predicting 3-,5- and 10-year survival. RNE = Number of regional lymph nodes examined, RNP = number of regional nodes positive, Site = Prime Site, Grade = Differentiation classification, I:Well differentiated, II: Moderately differentiated, III: Poorly differentiated, IV: Undifferentiated, AJCC=Derived AJCC Stage Group, 7thed, Sums = SEER Summary stage 2000, Rad = Radiation recode, Yes: Beam Radiation/ Combination of beam with implants or isotopes/ Other radiation (1973-1987 cases only) /Radiation, NOS method or source not specified/ Radioactive implants/ Radioisotopes, NO:None/Unknown/refused/recommended, unknow if administered.

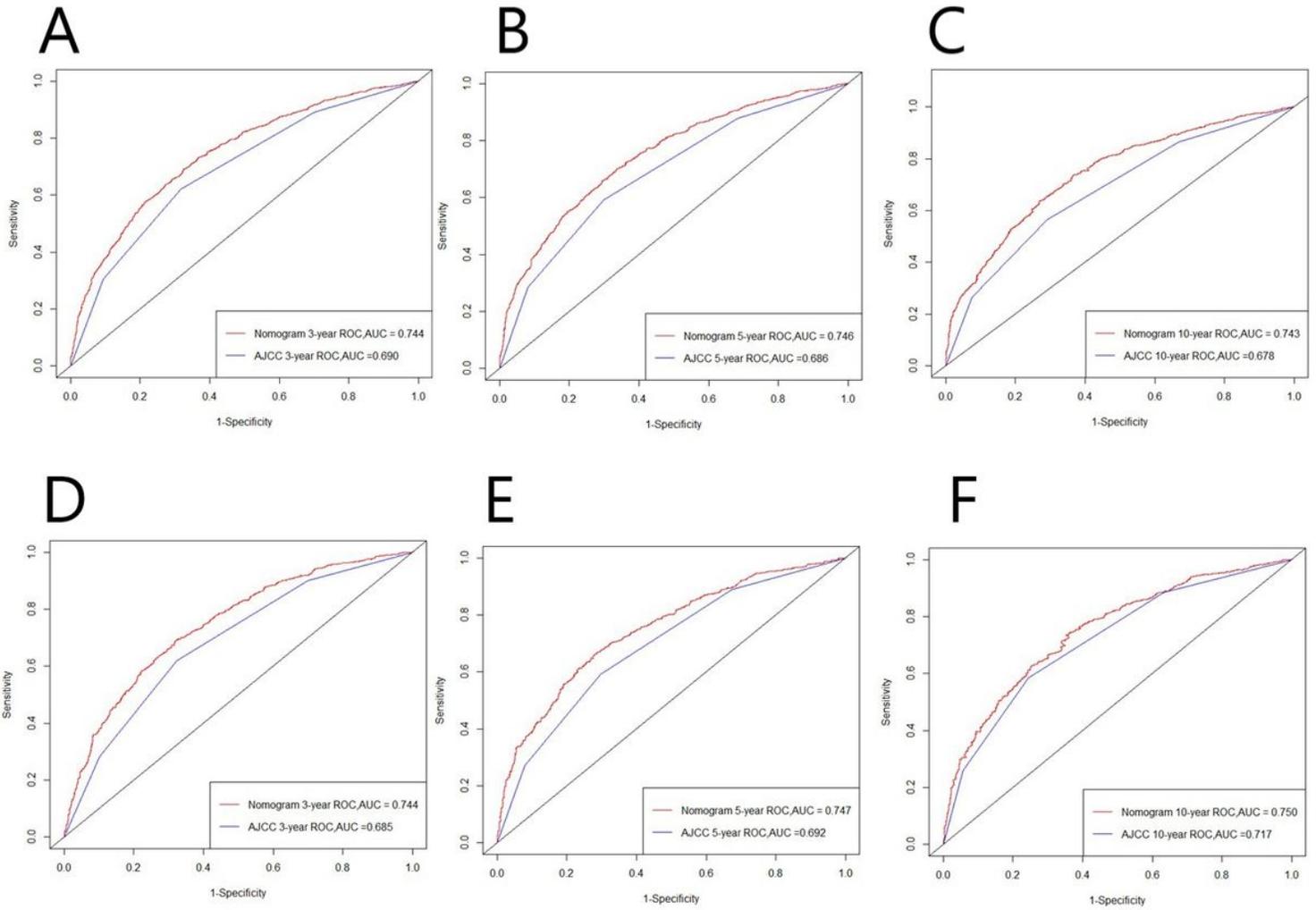


Figure 2

ROC curves. The ability of the model to be measured by the C index. A, B, C 3-,5-, 10-year CSS came from the training set, and D, E, F 3-,5-, 10-year CSS came from the validation set.

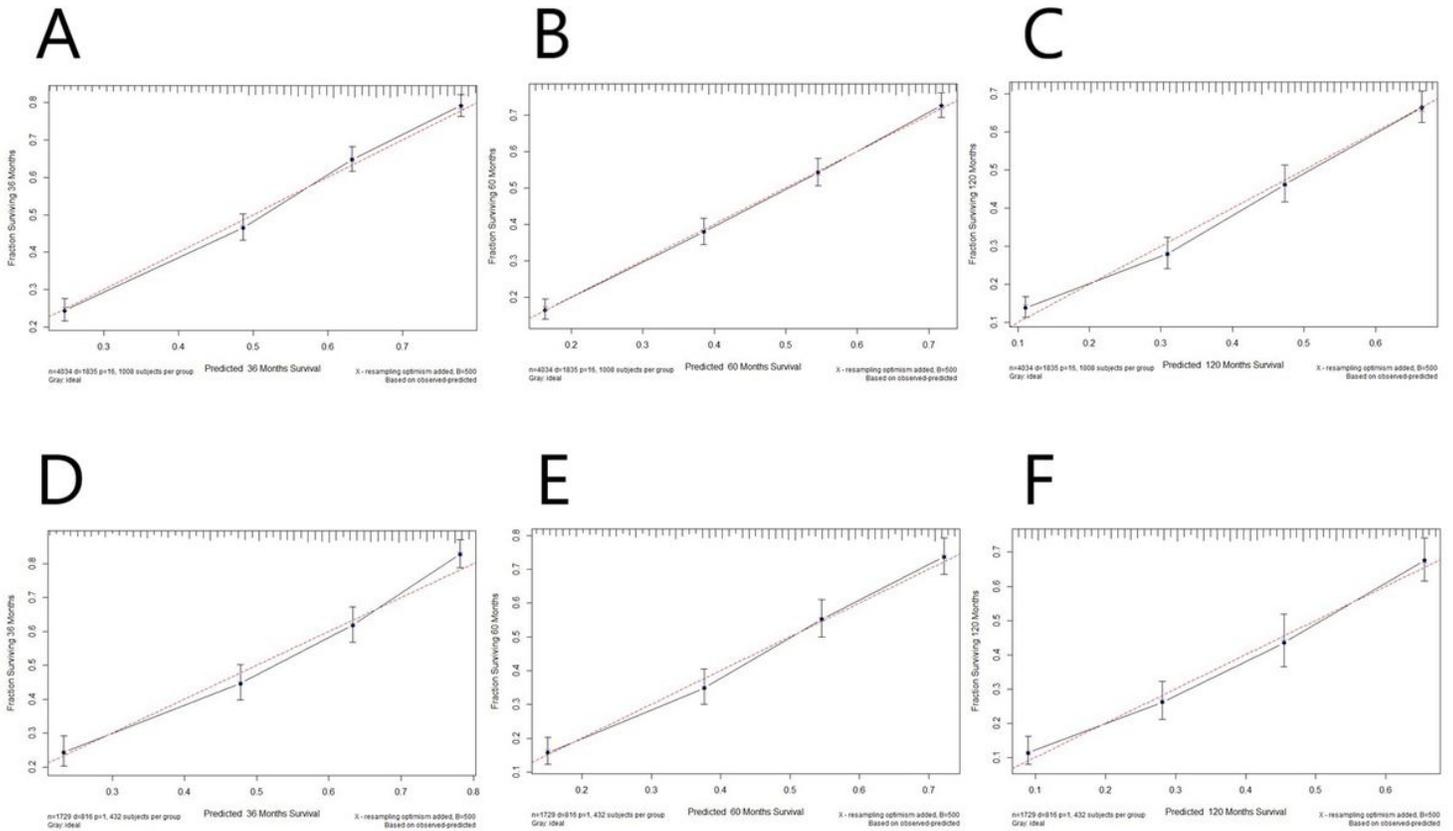


Figure 3

Calibration plots. Show the relationship between the predicted probabilities base on the nomogram and actual values of the train set (A, B, C) and validation set (D, E, F).

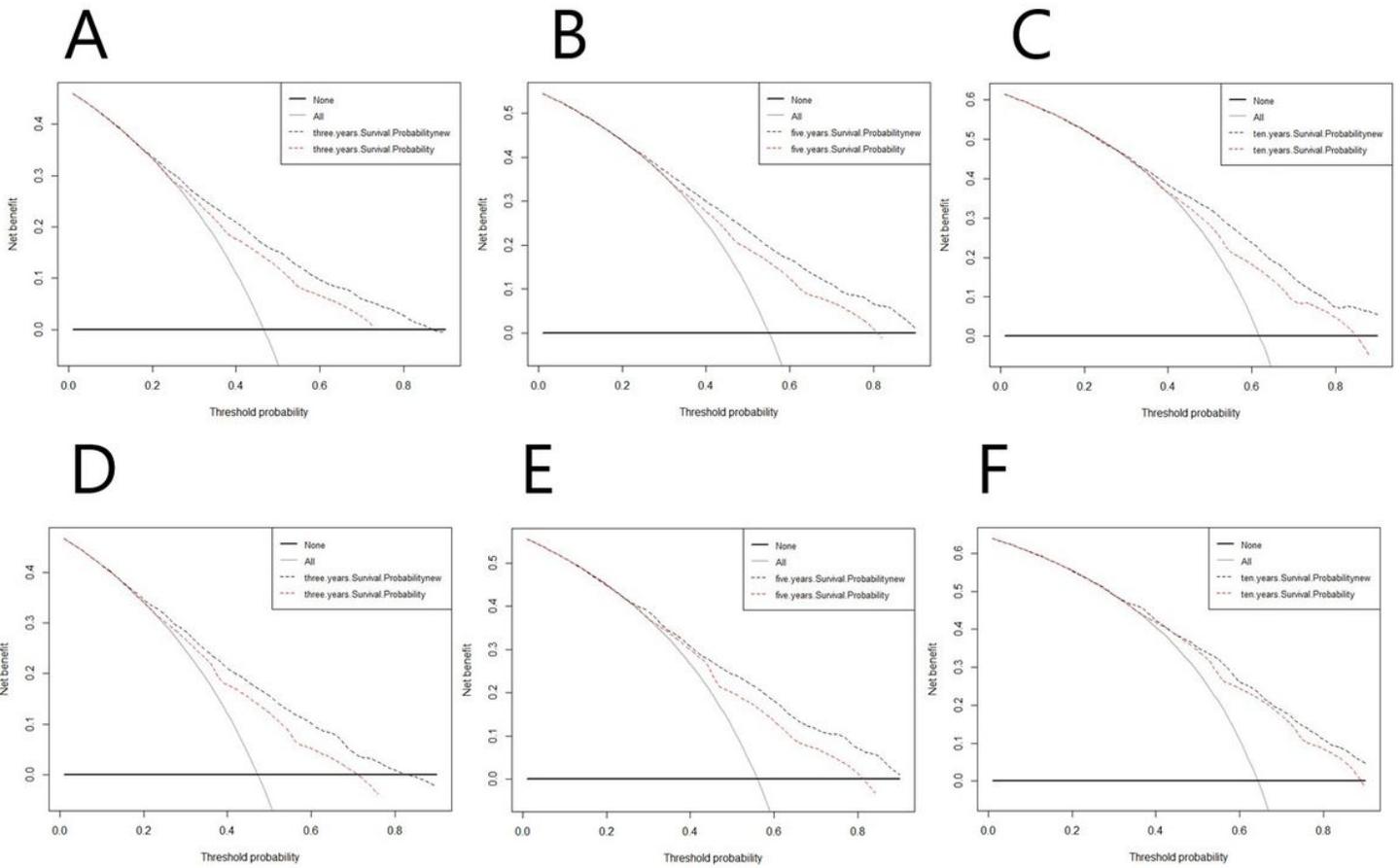


Figure 4

Decision curve analysis. In the figure, the abscissa is the threshold probability, the ordinate is the net benefit rate. The horizontal one indicates that all samples are negative and all are not treated, with a net benefit of zero. The oblique one indicates that all samples are positive. The net benefit is a backslash with a negative slope. A, B, and C came from the training set; and D, E and F came from the validation set.