Nomogram for individually predicting overall survival in rectal neuroendocrine tumors

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Abstract

Background This study was designed to develop a nomogram that predicts the overall survival (OS) of rectal neuroendocrine tumors (NETs).

Methods 310 patients with rectal neuroendocrine tumors in 5 hospitals in southern China were retrospectively analyzed. All the patients were assigned to the training set. A multivariable analysis using Cox proportional hazards regression was performed using the training set. And a nomogram was constructed. The validation set was performed using the data from Surveillance, Epidemiology, and End Result (SEER) databases of America (n=547).

Results In the training set, the nomogram exhibited improved discrimination power compared with the WHO grade guidelines (Herrell's C-index, 0.907 vs 0.809; p<0.001), and also improved compared with the seventh AJCC TNM classification (Herrell's C-index, 0.907 vs 0.829; p<0.001). In the SEER validation sets, discrimination was also excellent (C-index, 0.824 vs 0.734 and 0.824 vs 0.766 respectively compared with G grade and TNM classification; both p <0.001). Calibration of the nomogram predicted survival corresponding closely with the actual survival.

Conclusions We developed a nomogram predicting 1-, 3-year OS for rectal neuroendocrine tumors. Validation revealed excellent discrimination and calibration, suggested good clinical utility.

Background

Neuroendocrine tumors (NETs) are heterogeneous tumors originating from neuroendocrine cells and peptidergic neurons with neuroendocrine function which produce a variety of different hormones that can cause different symptoms. In recent years, the incidence of NETs, which are primarily derived from the gastro-entero-pancreatic system and lungs is increasing[1, 2]. The incidence of rectal neuroendocrine tumors is the highest within the gastrointestinal tract[3] and has increased 10 fold in the last 30 years[1]. However, outcomes for rectal NETs remain uncertain. So far, the most common predictive systems for NETs are AJCC and European Neuroendocrine Tumor Society (ENETS) TNM staging systems or the WHO grade guidelines, which is based on the mitotic count and Ki67 proliferative index. These systems lack other clinicopathological features that can influence outcomes such as age, gender, and tumor size. Thus, we are trying to create a system that takes clinicopathological features into consideration, and may provide more accurate prognosis and may direct clinical practice and decision making.

Nomogram is a pictorial representation of a complex mathematical formula[4]. Medical nomograms are currently among the most accurate and discriminatory method for predicting outcomes among patients with cancer[5]. Many take into clinical variables such as tumor grade, tumor size, patient age to build prognostic models which predict risk of cancer recurrence or mortality for individuals. A nomogram is a graphical calculation instrument based on any type of function such as logistic regression, Cox PHs regression models. When we build a nomogram, each variable is listed separately with a corresponding

number of points assigned to a particular magnitude of the variable, the cumulative point score for all the variables is

matched to a scale of outcome.

In the past few years, nomograms have been successfully established to quantify risk by combining prognostic factors in certain malignancies [6–10]. To date, however,

none have researched rectal NETs.

With this study, we have designed a nomogram that focuses on rectal NETs based on a relatively large cohort of patients who were treated in five hospitals in southern China. This nomogram was then used to predict the 1- and 3-year overall survival rates. The external validation used was the SEER database.

Materials And Methods

We retrospectively analyzed 442 patients with rectal NETs who were treated in 5 hospitals in southern China, but 102 patients lost to follow up to 3 years, and 30 patients had missing values, these 132 patients were excluded. So finally 310 patients were included in this study, including Sun Yat-sen University Cancer Center(SYSUCC, n = 143), the First Affiliated Hospital of Sun Yat-Sen University(SYSUFH, n = 56), Guangdong Genera Hospital(GGH, n = 54), Nanfang Hospital of Southern Medical University(SMUNH, n = 44), and Sun Yet-san Memorial Hospital of Sun Yat-sen University(SYSUMH, n = 13) from November 1993 to December 2013. The above five hospitals belong to Guangdong Neuroendocrine Neoplasms Cooperative Group and members of Chinese Study Group for Neuroendocrine Tumors (CSNET). The variables include age, gender, tumor sizes, surgery procedure, G grade, the depth of tumor invasion(T), the number of metastatic lymph nodes(N), distant metastases(M), TNM stage. All patients were followed for at least 3 years. An endoscopy with rectal Magnetic Resonance Imaging (MRI) or Endoscopic ultrasonography (EUS) at 6 and 12 months were required. One year later, patients were followed every 6 to 12 months. Abdominal and pelvic multiphasic Computed Tomography (CT) or MRI were required. And biochemical markers chromogranin A was considered if patients had clinical symptoms. All 310 patients were assigned to the training set. A multivariable analysis using Cox PHs regression was performed using the training set, and a nomogram was constructed.

For the SEER database, we collected patients from 2005 to 2013 who were diagnosed with rectal NETs. There are 547 patients and they also had follow-up for at least for 3 years and this database was used as the validation set.

Methods

Construction of the Nomogram

We use the database from 5 hospital of China as the training set. To permit nonlinear relationships, continuous variable like tumor size was modeled with restricted cubic splines[11]. But for the continuous predictor age, a linear relationship with outcome was found to be a good approximation after assessment of nonlinearity using restricted cubic splines (Wald $P = 0.371$). Categorical variables were grouped for clinical reasons, and the decisions regarding grouping were made prior to modeling. A log-log survival plot of the categorical variables was used to determine whether the proportional hazards assumption was met, and all variables were fit to the proportional hazards assumption. Variables were selected using the forward stepwise selection method in the Cox PHs regression model. Based on the predictive model using the identified prognostic factors, a nomogram was constructed to predict 1- and

3-year OS rates.

Validation of the nomogram

The performance of the nomogram included discrimination and calibration using the SEER external validation set. Discrimination was evaluated using a concordance index (C-index), which quantifies the probability of two random patients, the patient who relapses first had a higher probability of the event of interest. Harrell's C-index, which is appropriate for censored data, was used to evaluate discrimination[12]. Calibration was performed by comparing the mean predicted survival rate with the mean actual survival rate determined using Kaplan-Meier analysis after grouping the nomogram-predicted survival by decile. Significance was set as $p < 0.05$ in a two-tailed test. All analyses were performed using SPSS version 20 (IBM, Armonk, NY, USA) and R version 2.13.2 (http://www.r-project.org) via the design and survival packages.

Results

Clinicopathologic characteristics of patients

310 patients in China and 547 patients from the SEER databases with rectal NETs were included in this study. All patients were followed for at least 3 years. The longest follow-up time was 224 months. The median survival time was 44 months. The clinicopathologic characteristics of the patients in the training set and validation

set were listed in Table 1.

Table 1
The clinicopathologic characteristics of the training and validation sets

Variable	Training Set (n = 310)		Validation Set (n = 547)	
	No. of patients	%	No. of patients	%
Median age (years)	49.1 ± 13.6		58.7 ± 13.1	
Gender				
Male	195	62.9	276	50.5
Female	115	37.1	271	49.5
Surgical treatment				
Endoscopic resection	139	44.8	-	-
Transanal excision	50	16.1	-	-
Radical resection	89	28.7	-	-
No surgical treatment	33	10.6	-	-
Tumor Size (cm)	250	80.6	286	52.3
< 2	28	9.0	98	17.9
2–4	32	10.3	163	29.8
> 4				
G classification				
G1	235	75.8	226	41.3
G2	45	14.5	59	10.8
G3	30	9.7	262	47.9
T Staging				
T1	231	74.5	303	55.2
T2	38	12.3	81	14.8
T3	31	10.0	100	18.3
T4	10	3.2	64	11.7
N Staging				
N0	264	85.2	353	64.7

TNM: Tumor Node Metastasis

Variable	Training Set (n = 310)		Validation Set (n = 547)	
N1	46	14.8	194	35.3
M Staging				
M0	277	89.4	423	77.3
M1	33	10.6	124	22.7
TNM Staging	220	71.0	267	48.8
	31	10.0	48	8.8
	26	8.4	108	19.7
	33	10.6	124	22.7
TNM: Tumor Node Metastasis				

Independent prognostic factors in the training set

The univariate analysis demonstrated that age, gender, surgical treatment, grade, tumor size, T staging, N staging, M staging and TNM stage were statistically significant (Table 2). When we put these variables into the Cox PHs regression model, we found that age, grade, tumor size and TNM stage were independently correlated with prognosis. Table 3 shows the results of the variable selection with hazard ratios and P-values.Prognostic nomogram for OS

Table 2
Univariate analysis of the clinicopathological features of the training set

Variable	HR	*P-value*	95%CIs	
			Lower	Upper
Age (years old)	5.965	< 0.001	2.830	12.572
gender	0.551	0.033	0.271	1.120
Surgical treatment	41.171	< 0.001	8.762	193.470
Tumor size (cm)	15.086	< 0.001	5.983	38.036
G grade	23.911	< 0.001	6.085	93.959
T staging	0.186	< 0.001	0.123	0.283
N staging	0.055	< 0.001	0.026	0.116
M staging	0.067	< 0.001	0.030	0.151
TNM stage	18.699	< 0.001	7.301	47.885
HR: hazard ratios; CI: confidence interval; TNM: Tumor Node Metastasis				

Table 3
Selected variables according to the Cox Proportional Hazards Regression model

Variable	HR	*P-value*	95%CIs	
			Lower	Upper
Age (years old)	2.438	0.0046	1.316	4.516
Tumor size (cm)	2.834	0.0351	1.075	7.469
G grade	6.922	< 0.001	2.441	19.626
TNM stage	1.930	< 0.001	1.374	2.709
HR: hazard ratios; CI: confidence interval; TNM: Tumor Node Metastasis				

A nomogram was constructed based on the result of the Cox proportional hazards regression predicting 1- and 3- year overall survival (Fig. 1). Each point can be determined by drawing a line straight upward from each variable to the point axis. The total points are then calculated by summing each point to indicate the probability of 1- and 3-year survival.

Comparison of predictive accuracy for OS between nomogram and TNM staging system or G grade system

The concordance index of the nomogram was 0.907 (95%CI, 0.902–0.912) for predicting the OS of the rectal NETS, which was superior to both predictions based on the seventh AJCC TNM classification and WHO grade guidelines, with concordance indices of 0.829 (95%CI, 0.821–0.837; $p < 0.001$) and 0.809(95%CI,

0.800-0.818; $p < 0.001$) respectively.
Comparison the accuracy between the prediction by nomogram and actual observation for OS
A calibration plot was generated to validate the similarities between the survival rates predicted by the nomogram and the actual survival rate (Fig. 2).The x-axis represents the survival rate predicted by the nomogram, whereas the y-axis presents the actual survival rate obtained using the Kaplan-Meier method. The results demonstrate that the predicted 1-and 3-year overall survival rates closely correspond with the actual survival rates within a 10% margin of the error according to both

training and validation sets.

Discussion

Neuroendocrine tumor (NETs) is a relatively rare tumor, the incidence of neuroendocrine tumors in the United States was 5.25/100000[1] in 2004. According to the SEER database, the incidence of gastrointestinal NETs is increasing in recent years[13]. The incidence of rectal NETS rates is the highest in the gastrointestinal tract, accounting for about 29%[3]of gastrointestinal NETs. However, most NETs seem to be sporadic, and risk factors for sporadic NETs are poorly understood.

There are few studies that focus on rectal NETs and these studies contain limited patient cohorts[14–16]. Our study included 310 patients with rectal NETs and is the

largest Chinese cohort up to date.

With the application and popularization of endoscopic techniques, the rectal neuroendocrine tumors are diagnosed earlier nowadays, and most of them are treated with endoscopic surgery. Of course, if the tumor size is large or involves the metastatic lymph nodes, more extensive surgery is indicated. We can see that the tumor size or lymph node involvement will influence the surgery procedure and furthermore influence patient outcomes. However, there are several clinicopathological features that can influence patients' outcome. According to published data and our analysis, grade, the depth of tumor invasion (T), the number of metastatic lymph nodes(N), distant metastases(M) and age at diagnosis are the most common factors that influence outcomes. Chi[17] et al. found that tumor grade was an independent prognostic factor, while Weinstock[14] et al. found that tumor stage was a independent prognostic factor; Chagpar[18] et al. found that the depth of tumor invasion, tumor size, lymph node metastasis and distant metastasis were independent

prognostic factors.

When we discuss prognosis, all elements above should be taken into consideration. However, the most common predictive systems, TNM classification and grade only focus on a portion of these variables and sometimes these two conflict. For example, if a patient has a grade 1 tumor with liver metastasis, according to the grade predictive system, this patient is low-grade and has a good prognosis. On the contrary ,when we put this patient into the TNM system, it is late-stage and has a poor prognosis. Conclusively, these two systems are limited in predicting outcomes.

But nomograms can take into account these variables in a Cox PHs regression. However, only a few nomogram studies focus on NETs. Modlin[19] et al. focused on small-intestinal neuroendocrine tumors and Ye L[20] et al. built a nomogram to predict outcomes for pancreatic neuroendocrine tumors. However, these studies have relatively small samples and do not include rectal NETs. This study presents the first

nomogram for predicting the prognosis of rectal NETs.

In our studies, four clinicopathological factors were independently correlated with prognosis in both the Chinese and SEER databases including age, tumor size, grade and TNM classification, according to the Cox PHs regression model. Thus, we

used these four factors when designing the nomogram.

This nomogram includes both grade and TNM stage were included, thereby addressing some of the limitations of the other predictive models. As expected, the predictive accuracy of the nomogram was superior to both predictions of TNM classification and WHO grade guidelines, with concordance indices of 0.907

compared with 0.829 and 0.809, $p < 0.001$ respectively.

As for the age and tumor size, we also found that they are both important elements that influence prognosis. Zhang X[21] et al. reported that young age was a favorable prognostic factor while Li P[22] et al. reported that lymph node metastasis was related to the tumor diameter and further more influence the prognosis of the rectal NETs. In our study, we found that patients likely have a decreased rate of

survival with increasing tumor size.

It seems that Ki-67 or mitotic rate per 10 high-power fields could be the better variable, because they are continuous variables which have a wider range prediction and be more individual compared with the categorical variables. However, we combine these two variables as grade, in order to simplify this model and make sure this nomogram can be used easily. Another reason is that Ki-67 (G classification) was categorized as “well differentiated”, “moderately differentiated”, or “poorly differentiated/undifferentiated” in the SEER database. Once an external validation is undertaken, it might be necessary to treat the parameters consistently between the training and validation sets. We

hypothesize that the nomogram will improve if the cutoff of the Ki-67 index is changed in the future. Thus, the use of a continuous Ki-67

index variable might be better for establishing the nomogram.

This study has some limitations. One is that we did not include the functional status and medical treatment as variables. According to the NCCN guidelines,

patients with metastatic neuroendocrine tumor and carcinoid syndrome should be treated with somatostatin analogues[23]. However, even though our 5 hospitals are the biggest centers in southern China, medical resources are limited. Some patients could not wait to receive the continuous therapy and went to the other hospitals. Others declined treatment secondary to cost or lack of understanding. Given these limitations, we opted to not include these variables so as to not compromise the nomogram.

Another limitation was that most of the patients were diagnosed within the last 3 years as this disease was better realized. With the routine use of endoscopy, the incidence of rectal NETs is increasing in recent years, but given the lack of numbers, we could not perform 5-year overall survival rate. With time, we can collect more

patients and variables and improve upon the nomogram.

Conclusion

We have developed an individualized nomogram for precisely predicting OS for patients with rectal NETs. Its advantages as a prognostic tool when compared to traditional TNM staging systems or WHO grade classifications should allow it to

make a significant clinical impact in the near future.

Abbreviations

NETs
neuroendocrine tumors
SEER
Surveillance, Epidemiology, and End Result
TNM
Tumor Node Metastasis
AJCC
American Joint Committee on Cancer
ENETS
European Neuroendocrine Tumor Society
NCCN

National Comprehensive Cancer Network
OS
overall survival

Declarations

Ethics approval and consent to participate

Approved by the Ethics Committee of Sun Yat-sen University Cancer Center, the First Affiliated Hospital of Sun Yat-Sen University, Guangdong General Hospital, Nanfang Hospital of Southern Medical University and Sun Yat-sen Memorial Hospital of Sun Yat-sen University and written informed consent was obtained from all patients prior to surgery. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or

comparable ethical standards.

Consent for publication Not applicable**Availability of data and material**

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

Conception and design: XF, GW, YC, JC, ZZ and YL.

Data collection and assembly: XF, GW, WW, YZ and Y.JZ

Data analysis and interpretation: XF and GW

Manuscript writing: XF and GW

First and co-first author: XF and GW

Final approval of manuscript: All authors

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Figures

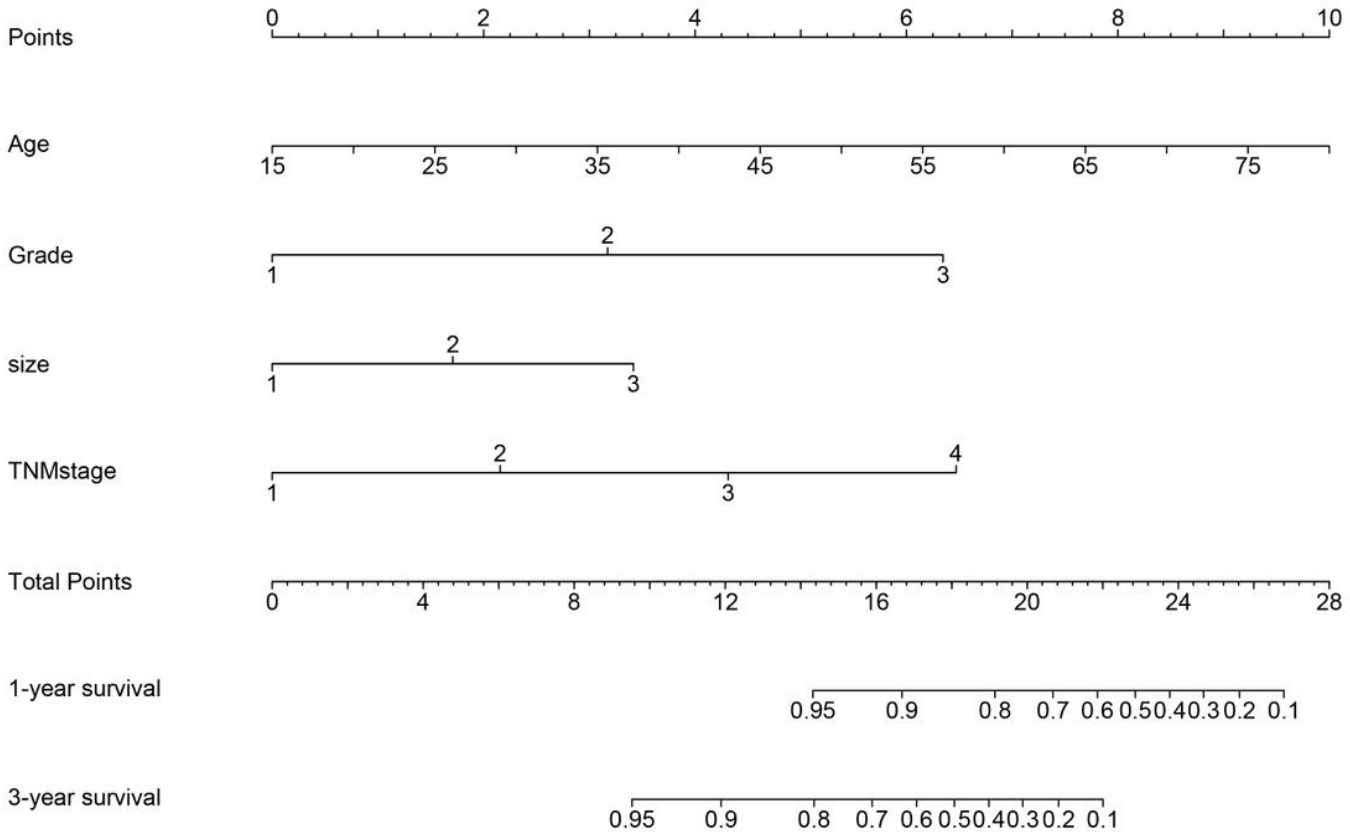

Figure 1

nomogram predicting 1- and 3-year OS with rectal NETS The nomogram summed the points identified on the scale for each variable.The total points projected on the bottom scales indicate the probability for 1- and 3- year overall survival

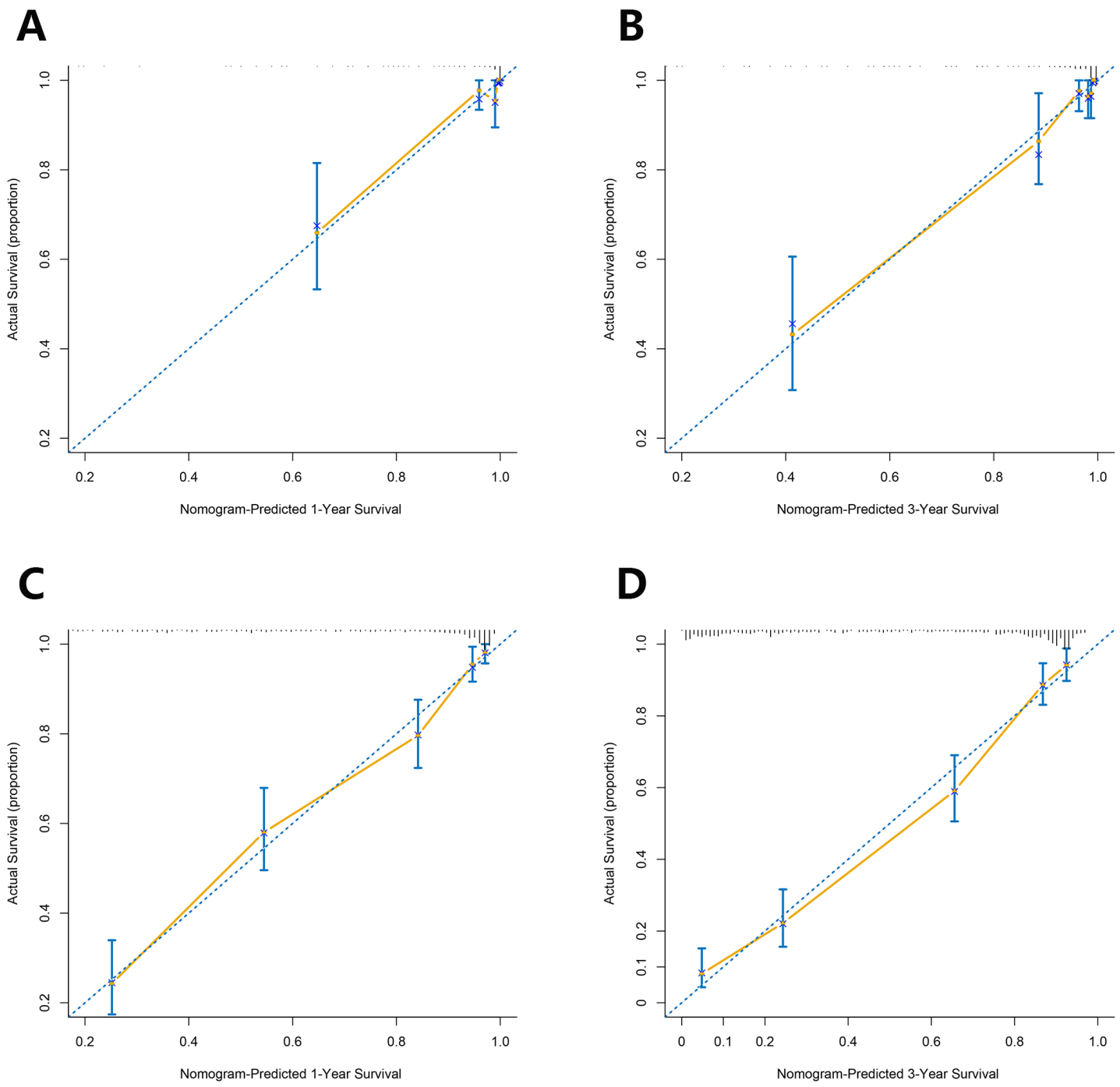

Figure 2

The calibration of the nomogram in the training and validation sets The x-axis represents the survival rate predicted by the nomogram, whereas the y-axis presents the actual survival rate. The 95% CIs were measured via a Kaplan-Meier analysis. All predictions lie within a 10% margin of error. (A)1-year OS in the training set. (B) 3-year OS in the training set. (C)1-year OS in the validation set. (D)3-year OS in the validation set.