Original Article

Development and validation of a nomogram to individually predict survival of young patients with nonmetastatic gastric cancer: A retrospective cohort study

Chaorui Wu, Nianchang Wang, Hong Zhou, Tongbo Wang, Dongbing Zhao

Department of Pancreatic and Gastric Surgery, National Cancer Centre/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract

Background/Aims: Evidence regarding gastric cancer (GC) patients <40 years old is limited. The aim of the study was to identify risk factors affecting overall survival (OS) of young patients with nonmetastatic GC and to establish a nomogram for prognostic prediction using data from the Surveillance, Epidemiology and End Results (SEER) database. Furthermore, this study sought to externally validate this nomogram in an independent patient cohort.

Patients and Methods: In this retrospective cohort study, the records of patients aged <40 years with nonmetastatic GC (n = 559), from the SEER database, between 2006 and 2015, were examined. The nomogram was established based on the Cox proportional hazards regression model using the SEER dataset. Patients with nonmetastatic GC (n = 201) in our department between 2009 and 2015 were selected as an external validation set. Discrimination and calibration were performed in both cohorts.

Results: The multivariate Cox model identified race, tumor subsites, tumor size, depth of invasion, lymph node metastasis, number of examined lymph nodes, and surgery as independent covariates associated with OS. The nomogram exhibited superior discriminative power than the eighth tumor, node, metastasis (TNM) staging system in both the training set [Harrell's concordance index (C index): 0.762 vs. 0.635, $P < 0.001$] and validation set (C index: 0.805 vs. 0.712, $P = 0.176$). Calibration of the nomogram was good in both cohorts.

Conclusions: We developed a nomogram predicting 3- and 5-year OS rates in young patients with nonmetastatic GC. Both the training set and validation set showed good discrimination and calibration, suggesting good clinical applicability.

Keywords: Gastric cancer, nomogram, risk factors, young patients

Address for correspondence: Dr. Dongbing Zhao, National Cancer Centre/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Pan-jia-yuan South Lane, Chaoyang District, Beijing - 100021, China.
E-mail: dbzhao@cicams.ac.cn

INTRODUCTION

Despite a decline in the incidence of gastric cancer (GC) in the last decades, concerns have been raised about the stable or even slightly increasing trend in young patients.[1] GC occurs primarily in elderly patients with an average onset age of 60 years, and conventionally those who receive a diagnosis before the age of 40 years are distinctively defined as "young."[2,3] GC in young patients

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shares more aggressive disease characteristics including delay of diagnosis, more diffuse lesions, advanced tumor stage, poorly differentiated histology, higher noncurability rate, and has a greater likelihood of underlying hereditary genetic abnormalities.[4-7] These factors have contributed to unfavorable prognosis in young patients, although this issue remains controversial.[8-11] However, current evidence guiding the management of young patients with GC is based on data derived from all patients but may be inappropriate for some.

In addition, in many cancer types, survival is increasing at a slower rate within the young population compared with other age groups, highlighting the need for more investigation on this vulnerable group.[12-14] To optimize choice of treatment strategies and maximize efficacy, it is necessary to precisely and individually estimate survival and choose corresponding treatment strategies. Nomograms have been developed to visually predict prognosis and optimize risk stratification by integrating prognostic factors into a prognosis-prediction tool.[15,16] To date, however, a well-constructed and externally validated nomogram for young patients with nonmetastatic GC remains missing.

Against this background, we sought to describe the clinicopathologic characteristics and develop a nomogram to predict 3- and 5-year overall survival (OS) rates based on a cohort of young patients with nonmetastatic GC from the Surveillance, Epidemiology and End Results (SEER) database. Furthermore, the nomogram was externally validated in an external patient cohort from our department.

PATIENTS AND METHODS

Patient selection in the SEER database

The SEER database, released in 2018, was queried for this study. SEER, a US national population-based cancer registry, collects cancer incidence and survival data from 18 sites covering approximately 30% of the United States.[17] A total of 1627 patients aged <40 years with single primary pathologically confirmed GC between 2006 and 2015 were identified using specific site and histologic codes (site codes: C16.0–C16.6, C16.8–C16.9, histologic codes: 8010–8231, 8255–8576). Patients were excluded if they had incomplete tumor staging information (n = 105), distant metastasis (n = 525), unknown status of metastasis (n = 425), or unknown follow-up (n = 13). Finally, a total of 559 cases were designated as the training set for OS analyses.

Data retrieved from SEER database included patient demographics (sex, age at diagnosis, and race), clinicopathologic characteristics (tumor subsites, tumor size, differentiation, histology classification), surgery (surgery of primary site, number of lymph nodes (LN) examined and number of positive LN), survival time and vital status at last follow-up. Race was categorized as Asian or Pacific Islander (API) and non-API. Tumor location was classified as four subsites: cardia (C16.0); middle, including the fundus, body, or curvatures (C16.1, C16.2, C16.5, and C16.6); distal, comprising the antrum or pylorus (C16.3 and C16.4); and overlapping or not otherwise specified (C16.8 and C16.9). Histological types were classified according to Lauren's classification into diffuse type (histologic codes: 8020–8022, 8142, 8145 and 8490), intestinal type (8140, 8144, 8210–8211, 8260 and 8480–8481), or other.[18,19] Tumor size was transformed into a categorical variable based on optimal cutoff values obtained through the X-tile program. All cases were restaged according to the eighth American Joint Committee on Cancer (AJCC) TNM staging system. The end point of the study was OS which was calculated from the date of diagnosis to the date of death.

We also retrieved records of young patients with nonmetastatic GC between 2009 and 2015 from National Cancer Centre/Cancer Hospital in China. The inclusion criteria included complete demographic data, clinicopathological information, therapeutic procedure records and full follow-up results. In total, 201 patients met the inclusion criteria and were designated as the external validation set. The ethics committee of National Cancer Centre/Cancer Hospital approved this retrospective study.

Development of the nomogram

For nomogram construction, the SEER dataset was designated as the training set. In this cohort, survival for different variable values was compared using the log-rank test. Variables that achieved statistical significance at $P < 0.05$ were entered into the multivariate analyses via the Cox proportional hazards regression model. Included covariates were race, tumor subsites, tumor size, depth of invasion, lymph node metastasis, number of examined LN and surgery. Based on the predictive model with the identified prognostic factors, a nomogram was constructed for predicting 3- and 5-year OS rates.

Validation of the nomogram

The performance of the nomogram involved discrimination and calibration in both datasets. Both discrimination and calibration were evaluated using bootstrapping with 1000 resamples.[20,21] Discrimination was evaluated using the C index. The C index is measured on a scale of 0.5 (random chance) to 1 (perfect discrimination). Calibration was performed by comparing the predicted

survival probabilities with actual survival probabilities. External validation of the nomogram was performed using the validation set comprising the patient cohort in our department.

Statistical analysis

The cutoff points of tumor size were explored using the X-tile program (http://www.tissuearray.org/rimmlab/) which identified the cutoff values with the minimum *P* values from log-rank χ^2 statistics for the variable, in terms of OS. Univariate and multivariate analyses were performed with the Cox proportional hazards model using SPSS version 22.0 (IBM). Nomogram and calibration plots were computed with the rms package in R version 3.4.4 (http://www.r-project.org/). Statistical significance was set as $P < 0.05$ in a two-tailed test.

RESULTS

Clinical characteristics and survival

The demographic features and clinicopathological characteristics of the training and validation sets are presented in Table 1. Overall, the majority of patients were non-API (83.4%), with 54.2% of the cohort male and a median age of 35 years. The most frequent tumor subsites were the distal (27.9%) and middle (27.2%) regions of the stomach. In the training dataset, the median follow-up was 21 months, and 239 (42.8%) patients died prior to completion of the present study. The 1-, 3- and 5-year OS rates were 80.5%, 54.3% and 45.9%, respectively.

Identification of cutoff points for the tumor size in the validation set

X-tile plots were constructed and the maximum χ^2 log-rank value of 7.5478 (low vs. moderate), 5.8808 (moderate vs. high) and 24.3070 (low vs. high) ($P < 0.001$) was produced, applying 3.9 and 7.0 cm as the optimal cutoff values to divide the cohort into low, moderate and high-risk subsets in terms of OS [Figure 1].

Development of the nomogram

Results of the univariate and multivariate regression model are listed in Table 2. Univariate analysis suggested that race, tumor subsites, tumor size, differentiation, depth of invasion, lymph node metastasis, number of examined LN, and surgery are associated with OS ($P < 0.05$). Multivariable analyses continued to demonstrate that race, tumor subsites, tumor size, depth of invasion, lymph node metastasis, number of examined LN and surgery are independent risk factors for OS.

A nomogram predicting 3- and 5-year OS rates was established from selected covariates with hazard ratios from the Cox multivariate regression model in the training set [Figure 2]. Each subtype within these covariates was assigned a point on the point scale. By adding the total

Table 1: Demographic and clinicopathologic characteristics of the training and validation sets

Variables	Training set (*n*=559)		Validation set (*n*=201)	
	No. of patients	%	No. of patients	%
Age (years)				
Mean	35		35	
Sex				
Male	303	54.2	101	50.2
Female	256	45.8	100	49.8
Race				
Non-API	466	83.4		
API	93	16.6	201	100
Size (cm)				
Unknown	144	25.8	25	12.4
<4.0	194	35.3	101	50.3
4.0-7.0	144	49.7	62	30.8
>7.0	77	15.0	13	6.5
Examined LNs, No.				
<15	230	41.1	39	19.4
≥16	329	58.9	162	80.6
Differentiation				
Unknown	45	8.1	5	2.5
Well differentiated	16	2.9	1	0.5
Moderately differentiated	70	12.5	6	3.0
Poorly differentiated	411	73.5	187	93.0
Non-differentiated	17	8.1	2	1.0
Tumor subsites				
Cardia	138	24.7	10	5.0
Middle	152	27.2	61	30.3
Distal	156	27.9	107	53.3
Overlapping/NOS	113	20.2	23	11.4
Histological type				
Diffuse	293	52.4	104	51.7
Intestinal	243	43.5	70	34.9
Other	23	4.1	27	13.4
Depth of invasion				
T1	108	19.3	59	29.4
T2	63	11.3	21	10.4
T3	201	36.0	29	14.4
T4a	125	22.4	77	38.3
T4b	62	11.1	15	7.5
Lymph node metastasis				
N0	202	36.1	82	40.8
N1	143	25.6	30	14.9
N2	94	16.8	33	16.4
N3a	85	16.8	34	16.9
N3b	35	6.3	22	11
Cancer stage*				
IA	89	15.9	50	24.9
IB	42	7.5	17	8.4
IIA	63	11.3	12	6.0
IIB	80	11.3	20	10.0
IIIA	130	14.3	45	22.4
IIIB	102	23.3	46	22.9
IIIC	53	9.5	11	5.4
Surgery				
No surgery	95	17.0	20	10.0
Gastrectomy only	399	71.4	177	88.0
Combined organs resection	65	11.6	4	2.0

LN: Lymph nodes, API: Asian or Pacific Islander, NOS: Not otherwise specified. *Cancer was staged based on AJCC 8th TNM staging system

points together and locating it on the bottom scale, we were able to calculate the probability of 3- and 5-year OS.

Discrimination and calibration of the nomogram

We compared the discrimination of the nomogram with that of the eighth AJCC TNM classification system in the training set. The nomogram discrimination was 0.762 (95% CI = 0.733–0.791), which was superior to that of the traditional AJCC TNM classification (0.635, 95% CI = 0.597–0.673, $P < 0.001$). Discrimination was also enhanced compared with the eighth AJCC TNM staging with regard to the validation set (*C* index = 0.805, 95% CI = 0.705–0.855 vs. 0.712 and 0.667–0.756, $P = 0.176$), but the difference was insignificant. The prognostic model

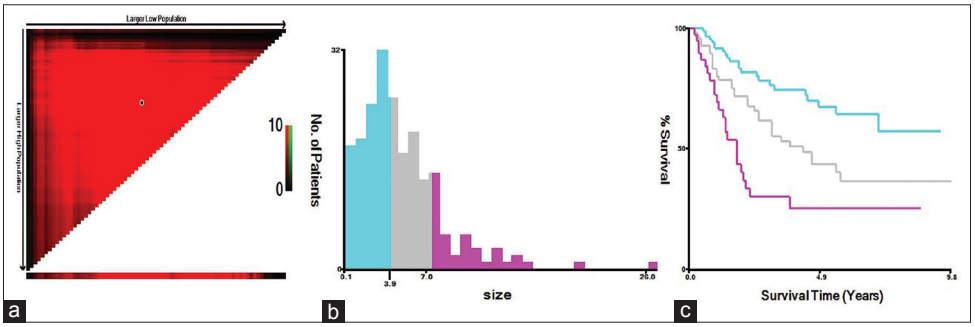

Figure 1: X-tile analysis of survival data from the SEER database. X-tile plot of the training set is displayed in the (a). The optimal cutoff value marked by the black circle in the Figure 1a is shown by a histogram of the entire cohort (b), and a Kaplan–Meier plot (c). *P* values were calculated using the cutoff point defined in the training set and validating it to the validation set. The figure shows the optimal cutoff points for young patients with gastric cancer (3.9 and 7.0 cm, $P < 0.001$)

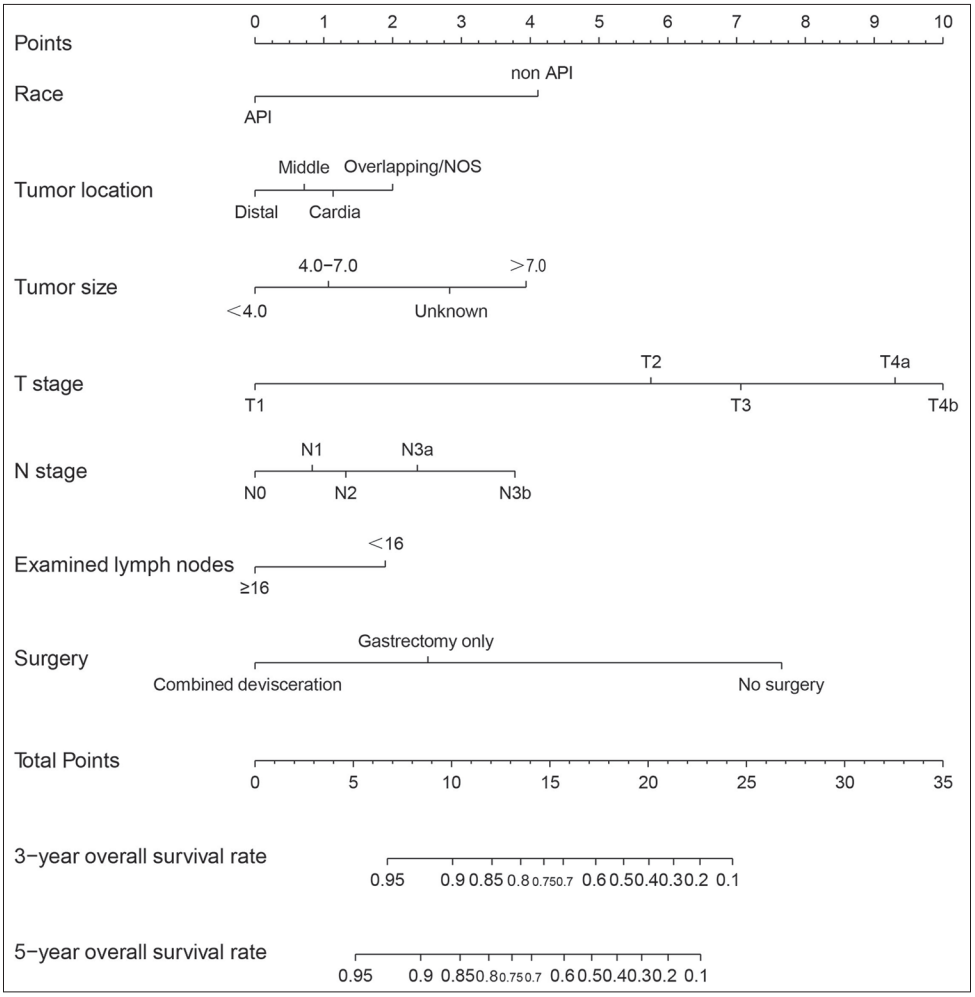

Figure 2: A nomogram to predict 3- and 5-year overall survival rates of young patients with nonmetastatic gastric cancer

Table 2: Univariate and multivariate Cox regression analysis of factors associated with OS in the training set

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.017 (0.990-1.044)	0.215		
Sex	1.050 (0.814-1.355)	0.706		
Race				
Non-API	1 [Ref.]		1 [Ref.]	
API	1.447 (1.060-1.974)	0.020	0.409 (0.269-0.624)	<0.001
Size (cm)				
Unknown			1 [Ref.]	
<4.0	1 [Ref.]		0.579 (0.377-0.889)	0.012
4.0-7.0	2.531 (1.884-3.400)	<0.001	0.738 (0.492-1.109)	0.738
>7.0	3.972 (2.779-5.677)	<0.001	1.294 (0.827-2.025)	0.258
Differentiation				
Unknown	1 [Ref.]		1 [Ref.]	
Well differentiated	0.404 (0.139-1.172)	0.095	0.589 (0.195-1.774)	0.347
Moderately differentiated	0.482 (0.267-0.871)	0.016	0.578 (0.309-1.081)	0.086
Poorly differentiated	0.844 (0.542-1.313)	0.451	0.895 (0.562-1.425)	0.639
Undifferentiated	0.655 (0.266-1.617)	0.359	0.511 (0.200-1.308)	0.162
Tumor subsites				
Overlapping/NOS	1 [Ref.]		1 [Ref.]	
Cardia	0.575 (0.406-0.816)	0.002	0.916 (0.621-1.352)	0.659
Middle	0.482 (0.335-0.693)	<0.001	0.751 (0.511-1.105)	0.144
Distal	0.484 (0.341-0.687)	<0.001	0.648 (0.443-0.950)	0.026
Histological type				
Other	1 [Ref.]			
Diffuse	1.340 (0.657-2.735)	0.421		
Intestinal	1.079 (0.524-2.220)	0.837		
Depth of invasion				
T1	1 [Ref.]		1 [Ref.]	
T2	2.421 (1.204-4.869)	0.013	3.365 (1.641-6.903)	0.001
T3	4.311 (2.456-7.568)	<0.001	4.407 (2.344-8.285)	<0.001
T4a	6.998 (3.949-12.402)	<0.001	6.984 (3.653-13.350)	<0.001
T4b	8.264 (4.466-15.292)	<0.001	8.142 (4.114-16.112)	<0.001
Lymph node metastasis				
N0	1 [Ref.]		1 [Ref.]	
N1	2.152 (1.514-3.060)	<0.001	1.205 (0.822-1.767)	0.339
N2	1.862 (1.249-2.776)	<0.001	1.270 (0.808-1.998)	0.300
N3a	2.123 (1.434-3.143)	<0.001	1.653 (1.052-2.597)	0.029
N3b	3.589 (2.202-5.851)	<0.001	2.384 (1.340-4.241)	0.003
Examined LNs, No				
<15	1 [Ref.]		1 [Ref.]	
≥16	0.622 (0.480-0.805)	<0.001	0.656 (0.475-0.907)	0.011
Surgery				
No surgery	1 [Ref.]		1 [Ref.]	
Gastrectomy only	0.296 (0.219-0.401)	<0.001	0.339 (0.222-0.518)	<0.001
Combined organs resection	0.311 (0.198-0.488)	<0.001	0.211 (0.119-0.375)	<0.001

OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, API: Asian or Pacific Islander, NOS: Not otherwise specified, LNs: Lymph nodes

for OS that was derived from the Western population also showed optimal discrimination in Asian population.

Calibration plots were generated to validate agreement between the actual survival rates and predicted survival rates by the nomogram [Figure 3]. The *x* axis is the survival rate predicted by the nomogram, whereas the *y* axis is the actual survival rate obtained using the Kaplan–Meier method. The dashed line represents the ideal reference line where predicted survival corresponded with the actual survival. The calibration curve presented a good agreement between the nomogram prediction and actual observation for 3- and 5-year OS rates in the training set and validation set.

DISCUSSION

In this study, we identified race, tumor subsites, tumor size, depth of invasion, lymph node metastasis, number of examined LN and surgery as independent prognostic factors for OS through univariate analysis and multivariate analysis. We further integrated these factors into a nomogram to predict 3- and 5-year OS rates and validated the model in an external patient cohort. The model is more predictive than the eighth AJCC TNM classification, with higher *C* indexes and good calibration in both cohorts.

Reports about the prognosis of young patients with GC have been controversial around the world. Young

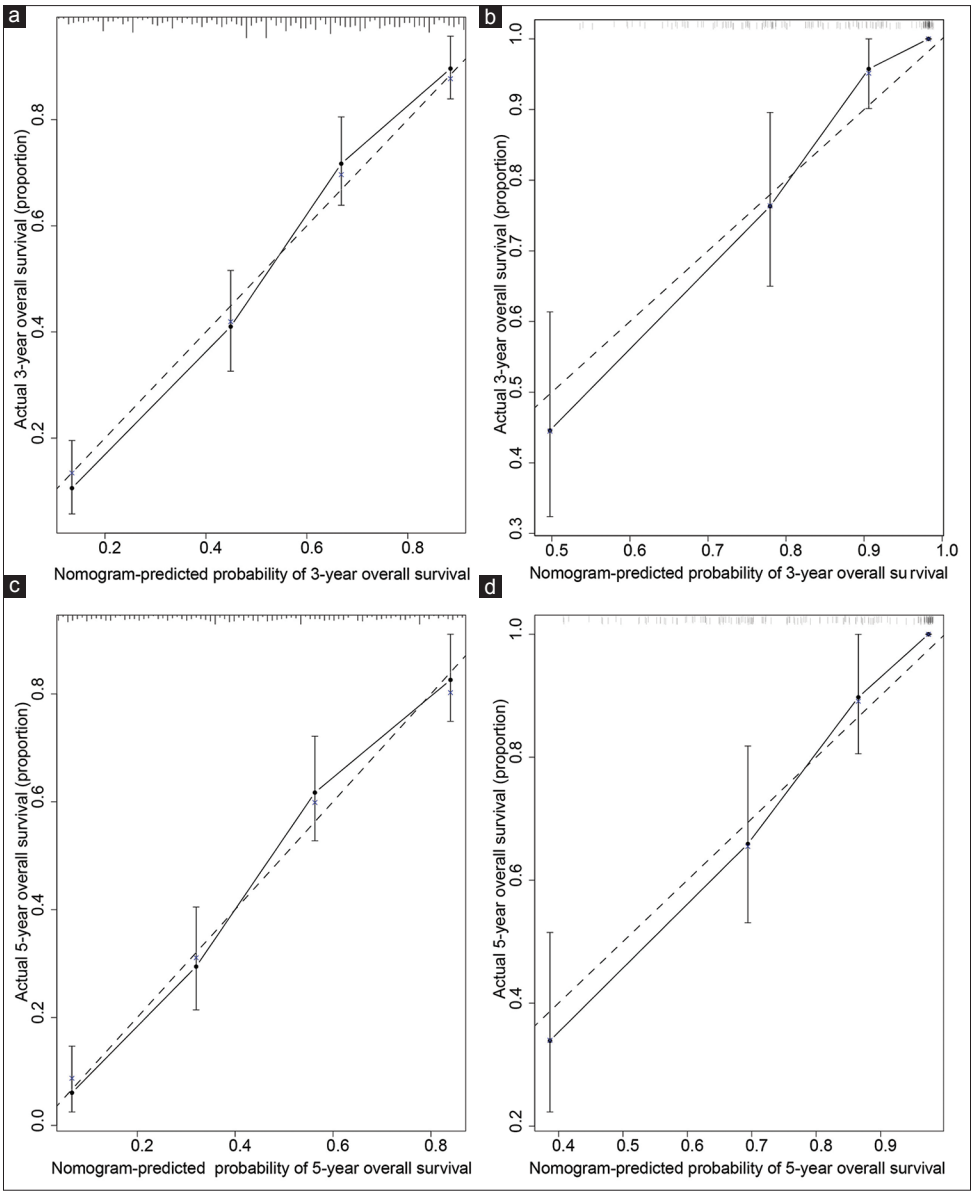

Figure 3: Calibration plots of the nomogram in the training set (a and c) and validation set (b and d). (a and b) Three-year overall survival and (c and d) 5-year overall survival. The *x*-axis represents the nomogram-predicted survival, and the *y*-axis represents actual survival and 95% CI measured by Kaplan–Meier analysis. The line represents the ideal reference line where predicted survival corresponds with the actual survival

patients have a greater likelihood of presenting without alarm symptoms, diffuse and signet-ring histology, more advanced tumor stage, and higher noncurability rate, suggesting that it should be treated as a separate entity.[2,22,23] However, such conclusions are limited by a retrospective design, small sample size, univariate analysis, significant confounding effects and limited data from the past 10 years in the existing studies. De *et al*. examined young adults with gastric adenocarcinoma from the National Cancer Database to describe demographics and to develop a nomogram to predict survival.[24] However, this nomogram was not externally validated in an independent center. To address these flaws, we developed our nomogram using records from a US-population database in the last 10 years and externally validated the nomogram in an independent cohort to ensure generality.

Several clinicopathological characteristics and treatment information were identified as independent covariates associated with OS in young patients with nonmetastatic GC, including race, tumor subsites, tumor size, depth of invasion, lymph node metastasis, number of examined LN and surgery. In comparison to previous nomograms that targeted the entire population, tumor size was selected as an independent prognostic factor in our study. We categorized tumor size using optimal cutoff values for the sake of clinical convenience. Although continuous variables are more information-preserving than categorical

variables, adding the points from each variable together and obtaining the probability of survival on the total points row can be ambiguous and cumbersome. We also uncovered an interesting survival advantage of API over other race ethnicities in the Western population-derived training cohort, which has been confirmed by previous studies.[25-28] An investigation based on SEER database suggested that the GC survival gap could be partially attributed to a higher proportion of cardia tumors among the Western population, as also suggested in the present study.[29] Risk factor prevalence in different populations may account for this variation. A major risk factor for noncardia GC in Eastern countries is *Helicobacter pylori* infection, whereas obesity and gastroesophageal reflux in Western countries are associated with cardia cancer.[30-33] Regular screening and earlier diagnosis in Asian-Americans also partially accounted for this survival gap. In line with their stronger awareness of GC screening, their disease stage at diagnosis was earlier than that of non-Hispanic whites.[29] However, even after adjustment for tumor subsites, disease stage and other covariates, survival advantage in Asians remained significant. Further research is needed to investigate this phenomenon.

Multiple GC survival nomograms have been built to predict survival for distinct populations. Kattan *et al*. constructed a nomogram in 2003 using Western patient data to predict GC survival after R0 resection.[34] We believe treatment modalities were largely different in a span of more than 10 years, so were practice patterns of physicians and surgeons who treated these patients. Wang *et al*. developed a nomogram for patients with insufficient LN retrieval.[35] However, radical surgery with extended lymphadenectomy is the standard surgical practice in most high-volume centers in China. Dikken *et al*. developed a nomogram to predict conditional probability of survival after curative gastrectomy with extended lymphadenectomy.[36] There were another three externally validated nomograms built from eastern patient dataset by Asian researchers.[37-40] It is imperative to note that younger patients were unrepresented in previous studies, suggested by their small percentage in the total study population (ranging from 7.3% to 9.5%). GC is less likely to affect younger people, with less than 5% of all new cases diagnosed in patients <40 years of age.[41] Due to various inherent biases we mentioned above, we decided not to validate previous nomograms in our cohort but rather to establish a new one and validate it in our exclusively Eastern younger patient cohort. Both the original and validation dataset were limited to subjects diagnosed between 2006 and 2015 in order to represent the contemporary practice patterns of GC management. It was a pity that the *C* index of our nomogram (0.762) was slightly inferior to that of previous ones (ranging from 0.742 to 0.87), which did not actually indicate inferior predictive value or clinical usefulness. The true measure of applicability is the successful validation of the nomogram in a cohort with similar characteristics, demographics and disease outcomes, which we have done in the current study. Although the *C* index of previous nomograms exceeded that of ours, this might just indicate features of the data from which they were derived.[42] The true comparison between different nomograms is applying them separately in the same population and comparing their *C* index.

It is uncommon to observe that the discrimination of the nomogram in training set is slightly inferior to the validation set. Usually, the discriminative performance of a nomogram in the original dataset is expected to be better than the validation dataset. More favorable prognosis and subsequent higher proportion of censored data in the validation dataset may account for its higher *C* index. First, lymphadenectomy in training set is less extensive than the validation set. The percentage of number of examined LN ≥16 (a threshold required by Japanese GC treatment guideline to ensure accurate staging[43]) is 58.9% and 80.6% in training set and validation set, respectively. More extensive lymphadenectomy improved the prognosis of the validation set and thus increased the percentage of censoring events. Moreover, a homogeneous racial break-up of Asian ethnicity in the training set is an independent factor for favorable survival, as confirmed by a previous and the present study.[29] With the most commonly applied methods of *C* index calculation, higher percentage of censored data will overestimate nomogram *C* index, whereas more death events will decrease the *C* index.[44]

We further compared the discrimination of this nomogram with that of the eighth AJCC TNM staging system. Discriminative superiority of the nomogram over the traditional TNM classification had been suggested in both cohorts, but statistical significance was not reached in the validation set ($P = 0.176$). We believe that small sample size of the validation set ($n = 201$) may contribute to this insignificance. The calibration plots of the training set and validation set illustrated good agreement between nomogram prediction and actual observation, suggesting that predictive performance of the nomogram was good.

There are several advantages of using this nomogram in this study. First, survival could be visually and individually estimated by both clinicians and patients through this scoring system. Second, identifying subsets of patients at high risk of unfavorable prognosis might have an impact on the choice of tailored treatment option. Third, because

our nomogram is a well-predicting tool for 3- and 5-year OS rates, a more reasonable follow-up schedule could be developed through this nomogram.

There are some limitations to this study. First, we excluded patients with incomplete information, which may cause a selection bias. Second, SEER database is population-based but not hospital-based, because information for all cancer cases are reported from local cancer registries. As such, parameters including *H. pylori* status, types of systemic therapy received, measurement of response to treatment and molecular data could not be analyzed. Third, discrimination of the nomogram was overestimated in the validation set due to a higher proportion of censored data. Finally, due to the retrospective design of our study, intrinsic biases of such a study format are hard to eliminate. Clearly, our results should be further validated in prospective multicenter studies before being applied in the clinical setting.

CONCLUSION

We established a nomogram for predicting 3- and 5-year OS rates for young patients with nonmetastatic GC using the US population-based database and validated in an independent patient cohort from our department. This nomogram could estimate survival precisely and individually and identify patients at high risk of unfavorable survival for whom individualized treatment strategy is required.

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Conflicts of interest
There are no conflicts of interest.

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