Original Article

A novel nomogram for predicting survival of patients with poorly differentiated gastric adenocarcinoma

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Background: Poorly differentiated gastric adenocarcinoma (PDGA) is a common adenocarcinoma with less glandular structure in gastric cancer. To date, the factors affecting its prognosis remain unclear. In this study, we establish a novel prognostic nomogram for PDGA.

Methods: We screened the Surveillance, Epidemiology, and End Results (SEER) database and downloaded data from PDGA patients who underwent surgery between 2010 and 2015. We explored their clinicopathological characteristics and important prognostic factors such as overall survival (OS), using univariate and multivariate Cox proportional hazards regression analyses, then constructed a prognostic nomogram using the resulting significant variables to predict the OS. We verified performance of the nomogram externally using a separate Chinese set, and further compared its ability as well as the 8th edition of the American Joint Committee on Cancer (AJCC) staging system to predict prognosis.

Results: A total of 3,887 patients in the SEER database met our inclusion criteria and were therefore included in the analysis. Multivariate analysis showed that age, sex, tumor size, prime site of tumor, T stage, N stage, and M stage were all independent prognostic factors for PDGA. These factors allowed successful establishment of a nomogram model with high predictive power, based on external verification using a Chinese set comprising 632 PDGA patients. The nomogram showed a better discrimination advantage than the 8th edition of the AJCC staging system in predicting OS (C-index of nomogram *vs.* AJCC staging for SEER set: 0.707 *vs.* 0.663; Chinese set: 0.788 *vs.* 0.713).

Conclusions: The nomogram, established herein, was more accurate in predicting the 1-, 3-, and 5-year OS of PDGA patients than the traditional AJCC TNA staging system. Successful establishment of a PDGA prognostic nomogram is a further step towards individualized and precise treatment of gastric cancer.

Keywords: Poorly differentiated gastric adenocarcinoma (PDGA); prognostic model; nomogram

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Introduction

Gastric cancer (GC) is the third cause of cancer-related deaths, and a significant threat to human health worldwide (1). GC is a heterogeneous disease with various histological and molecular subtypes (2). In fact, recent research progress has revealed four molecular GC subtypes, including Epstein-Barr virus (EBV)-positive, the microsatellite instability (MSI), chromosome instability (CIN), and genomically stable (GS) subtype (3). Accurate diagnosis and development of effective treatment therapies require an effective way to simplify disease's heterogeneity based on its subtypes to study (4). Poorly differentiated gastric adenocarcinoma (PDGA), a common pathological type of gastric cancer, is an adenocarcinoma with less glandular structure (5). According to classifications by the World Health Organization (WHO) (6) and the Japanese classification of gastric carcinoma (7), poorly differentiated adenocarcinoma (PDA) comprises tumors that exhibit various morphologies, such as adenocarcinoma with poor cohesion, signet ring cell carcinoma, among others (5). There was a previous study showing that the PDGA showed weaker expression of CPP32, EMMPRIN, MUC-2, MUC-5AC, and MUC-6 (8). Yang *et al.* also reported that Epstein-Barr virus associated gastric cancer (EBVaGC) was positively associated with PDGA (9). In the present study, we focused on four common histological types of PDA in gastric cancer, including poorly differentiated adenocarcinoma, undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma.

Currently, the therapies for treating PDGA include surgical resection, radiotherapy, chemotherapy and molecular targeted therapy (10). Although significant progress has been made on this front, prognosis of PDGA remains challenging due to recurrence and metastasis (11,12). Furthermore, several studies have reported inconsistent results with regards to differentiation status, possibly due to varying sample sizes and inclusion criteria (13-16). Numerous studies have reported occurrence of MSI in solid-type PDA of the stomach. Particularly, MSI-positive solid PDA is more common in older, female gastric cancer patients, with pathological characteristics of these patients revealing consistent glandular composition and a significant correlation between MLH1 and PMS2 expression loss (5). One study has also demonstrated that solid-type PDA frequently lose MMR protein and the SWI/SNF complex (17). However, most patients with differentiated gastric adenocarcinoma tend to be male, with the tumors generally appearing hematogenous (18). Based on these, we hypothesized that the underlying prognostic factors for PDGA may be different from other histological types of gastric cancer. Therefore, developing a more specific therapy that directly targets PDGA may have clinical value in guiding development of treatment therapies. Consequently, we sought to explore the clinicopathological features of PDGA and formulate more detailed and effective treatment plans.

Although there were several reports about nomogram for predicting survival of patients with gastric neuroendocrine neoplasms (19,20), up to date, no studies have separately reported the specific prognostic factors of PDGA. In view of the fact that histological type is essential to assess the tumor progression and prognosis (21), and PDGA is a common histopathological type in gastric cancer, we believe that it is necessary to establish a nomogram to predict overall survival (OS) for PDGA patients. Specifically, we targeted the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), which collects data on approximately 450,000 cases of malignant and *in situ* cancers each year in the United States. This database provides data on patient demographics, tumor morphology, stage at diagnosis, primary tumor sites, survival times, and vital status (22). In our study, we retrospectively analyzed clinicopathological features of PDGA patients based on the larger sample size in the SEER database, screened out independent prognostic risk factors, then used them to develop a nomogram for predicting prognosis of PDGA patients. In addition, we compared the prognostic power of our nomogram to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor TNM staging system, and finally validated it externally using data from an independent Chinese set.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2794).

Methods

Patient enrolment and data retrieval

We screened the SEER database (http://seer.cancer.gov/) and retrieved data from gastric cancer patients diagnosed with pathological PDA and who underwent surgery between 2010 and 2015 at Zhejiang Provincial People's Hospital. The last follow-up date of validation sets was January 2018. We extracted cases of gastric

cancer patients, with histological type PDA, based on the International Classification of Diseases for Oncology (ICD-O-3), 3rd edition. We further retrieved demographic and clinical information including age, gender, histological differentiation type, grade, primary tumor site, tumor size, tumor number, and the 7th AJCC TNM stage. We redefined the TNM staging according to the criterion described in the 8th AJCC guidelines. The inclusion criteria were as follows: (I) gastric cancer patients who underwent surgery; and (II) ICD-O-3 codes for histological type were adenocarcinomas [8140-8389]; (III) poorly differentiated or undifferentiated/anaplastic histological grade III or grade IV, respectively. Conversely, the exclusion criteria included: (I) without complete follow-up information; (II) without detail TNM stage information; (III) unknown histological differentiation type; (IV) unknown grade; (V)unknown primary tumor site; (VI) unknown tumor size; and (VII) unknown tumor number. In this study, the training set's data comes from a public database (SEER database) which does not require ethical approval. However, the validation set data from Zhejiang Provincial People's Hospital requires an ethics statement. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Zhejiang Provincial People's Hospital (Approval No. 2019KY017) and informed consent was taken from all the patients.

Construction of the nomogram

We used the retrieved SEER dataset as a training set to build an OS prognostic nomogram. First, we performed univariate analysis to screen for significant variables related to prognosis ($P<0.05$). Furthermore, we used multivariate Cox proportional hazard regression analysis to identify independent risk factors related to prognosis, then employed them to construct a prognostic nomogram using the rms package implemented in R software ("http://www.r-project.org/"). The resultant nomogram was subsequently used to predict 1-, 3- and 5-year OS for gastric cancer patients with PDA.

Nomogram validation

An independent set of Chinese patient data was used to externally validate prognostic performance of the nomogram. Briefly, we evaluated the discriminative power of our nomogram using the concordance index (C-index), by measuring the difference in predictive power between observed and the predicted results. In addition, we plotted receiver operating characteristic (ROC) curves and calculated the area under curve (AUC) to evaluate accuracy of the 1-, 3-and 5-year survival predictions.

Statistical analysis

We used the chi-square test to compare variables between training and validation sets, then performed survival analysis using Kaplan-Meier method and the log-rank test. Furthermore, we assessed the effectiveness of our nomogram to predict prognosis of patients by generating C index and AUC, then compared the results with those from the TNM staging (8th AJCC). All statistical analyses were performed using packages implemented in R software version 3.5.2 (R foundation for Statistical Computing, Vienna, Austria) at a 95% confidence interval (CI). Data followed by $P<0.05$ were considered statistically significant.

Results

Patient characteristics

Screening the SEER database revealed a total of 3,887 patients who met our inclusion criteria, and were therefore included in the training set. On the other hand, 632 Chinese patients met these criteria and were subsequently enrolled as a validation set (*Figure 1*). A summary of the patients' clinical characteristics across both study sets is outlined in (*Table 1*). In the SEER training set, 2,525 (64.96%) and 1,362 (35.04%) of the patients were males and females, respectively. Their median ages were 68 years (range, 19–97 years) and 34 months at diagnosis and follow-up, respectively. In the Chinese validation set, there were 423 (66.93%) and 209 (33.07%) males and females. Respectively, with median ages of 63 years (range, 21–89 years) and 31 months at diagnosis and follow-up, respectively. The proportions of tumor size ≤6.8 cm for the training and validation sets were 79.58 and 81.49%, respectively. In addition, patients in the SEER set exhibited even distribution of primary tumor sites in the stomach. Conversely, the gastric antrum or pylorus, accounted for the vast majority (71.99%) of the tumor site in the Chinese set. A higher proportion of single tumors was recorded in the Chinese, than the SEER set, at 98.26 and 78.67%, respectively. Moreover, a higher proportion of patients in the Chinese set (52.85%) who underwent surgery were

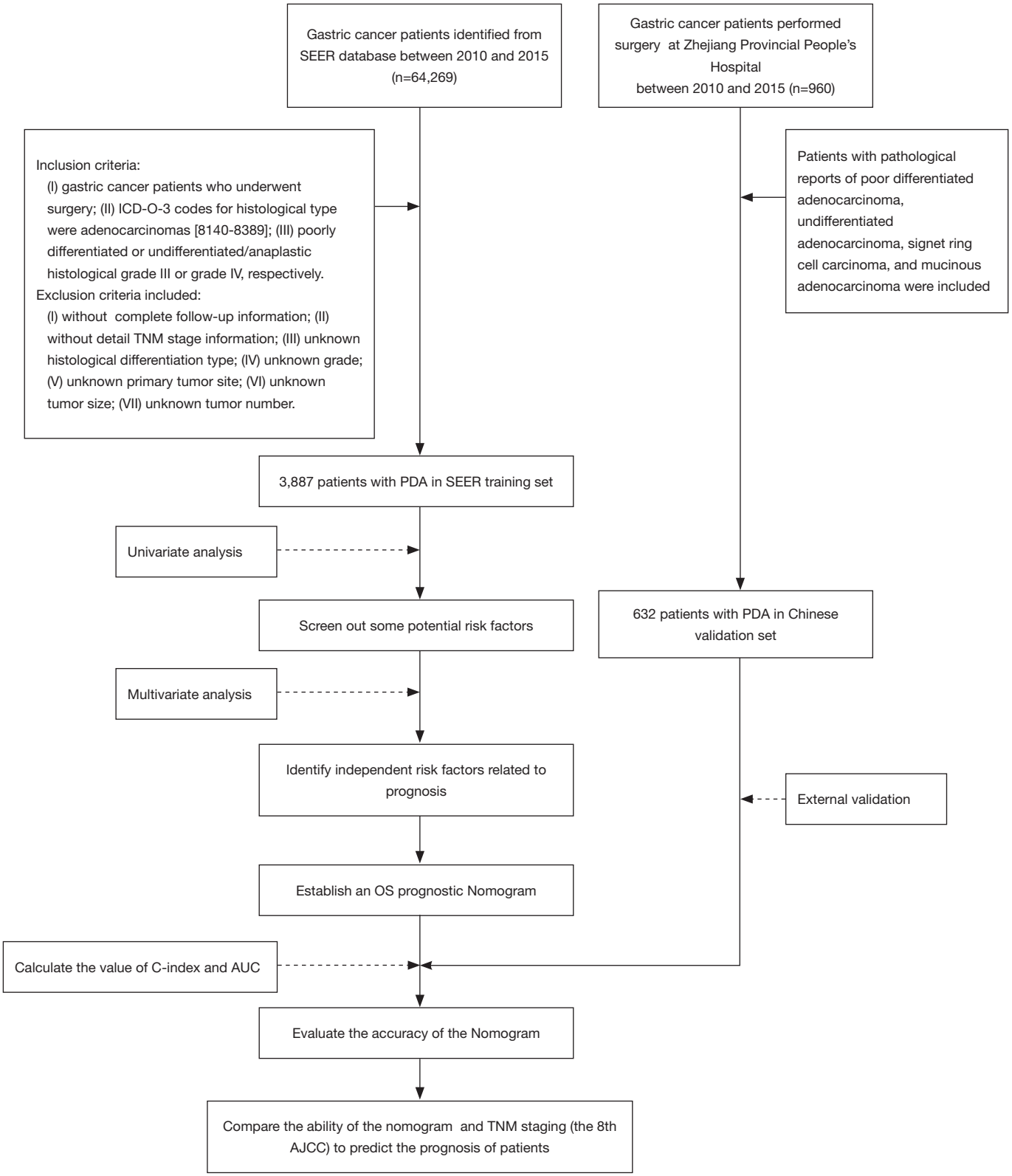

Figure 1 Graphical abstract. OS, overall survival; AUC, area under the curve; PDA, poorly differentiated adenocarcinoma; T, N, M stages come from AJCC; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

Table 1 The demographic and clinicopathological characteristics of the SEER training set and Chinese validation set

Demographic or characteristics	SEER training set (n=3,887)		Chinese validation set (n=632)		P value
	No.	Percentage, %	No.	Percentage, %	
Age at diagnosis (year)					<0.001
≤44	220	5.66	47	7.44	
45–59	863	22.20	193	30.54	
60–74	1,642	42.24	280	44.30	
≥75	1,162	29.89	112	17.72	
Sex					0.335
Female	1,362	35.04	209	33.07	
Male	2,525	64.96	423	66.93	
Tumor size (cm)					0.436
<3.7	1,555	40.01	251	39.72	
3.7–6.8	1,538	39.57	264	41.77	
>6.8	794	20.43	117	18.51	
Prime site of tumor					<0.001
Cardia/fundus	1,290	33.19	131	20.73	
Middle of gastric body*	1,222	31.44	46	7.28	
Antrum/pylorus	1,375	35.37	455	71.99	
Tumor number					<0.001
<2	3,058	78.67	621	98.26	
≥2	829	21.33	11	1.74	
AJCC T stage (8th)					<0.001
T1	612	15.74	66	10.44	
T2	500	12.86	110	17.41	
T3	1,733	44.58	234	37.03	
T4	1,042	26.81	222	35.13	
AJCC N stage (8th)					<0.001
N0	1,420	36.53	197	31.17	
N1	808	20.79	96	15.19	
N2	774	19.91	115	18.20	
N3a	631	16.23	147	23.26	
N3b	254	6.53	77	12.18	
AJCC M stage (8th)					<0.001
M0	3,536	90.97	606	95.89	
M1	351	9.03	26	4.11	

Table 1 (*continued*)

Table 1 (*continued*)

Demographic or characteristics	SEER training set (n=3,887)		Chinese validation set (n=632)		P value
	No.	Percentage, %	No.	Percentage, %	
AJCC TNM stage (8th)					<0.001
I	790	20.32	134	21.20	
II	1,255	32.29	138	21.84	
III	1,491	38.36	334	52.85	
IV	351	9.03	26	4.11	
Liver metastasis					0.354
No	3,761	96.76	607	96.04	
Yes	126	3.24	25	3.96	

*, middle of gastric body includes body of stomach, lesser curvature of stomach, and greater curvature of stomach. T, N, M stages come from the 8 edition AJCC Staging. AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

diagnosed with stage III cancer. On the other hand, we found no significant differences between the groups with regards to sex, tumor size, and liver metastasis, although age, prime site of tumor, tumor number, and TNM stage (8^{th} AJCC) were significantly different (P<0.05).

Nomogram establishment

Univariate analysis of the collected factors in the SEER training set revealed seven significant prognostic factors, including age, sex, tumor size, prime site of tumor, T stage (8^{th} AJCC), N stage (8^{th} AJCC), and M stage (8^{th} AJCC) (*Table 2*). Multivariate Cox analysis confirmed that these 7 factors were indeed independent prognostic risk factors for gastric cancer patients with PDA (*Table 3*). Since the TNM stage interacts with other factors, we excluded it from the Cox-regression model to prevent multicollinearity that renders model estimation thereby compromising accuracy. Subsequently, we used the selected independent predictive factors to establish a nomogram for 1-, 3- and 5-year OS (*Figure 2*). Summarily, the nomogram predicts the 1-, 3- and 5-year OS for each patient by summing up the scores displayed on the bottom scale. The calibration plots revealed an optimal agreement between nomogram-predicted OS and actual ones estimated by the Kaplan-Meier method (*Figure 3*). In addition, our nomogram's OS C-index was 0.707, whereas its AUCs for predicting the 1-, 3- and 5-year OS were 0.732, 0.776 and 0.787, respectively (*Figure 4A,B,C*).

External nomogram validation and assessment of its efficiency

External validation, using data from 632 Chinese patients from Zhejiang Provincial People's Hospital, confirmed the ability of our nomogram to predict OS. Specifically, the C-index for evaluating accuracy of the nomogram was 0.788, while AUC values for predicting 1-, 3-, and 5-year OS of the nomogram found to be 0.826, 0.871, and 0.836, respectively (*Figure 4D,E,F*). In SEER training set, the C-index of the 8^{th} AJCC TNM staging system was 0.663, whereas AUC values of the ROC for predicting 1-, 3-, and 5-year OS were 0.684, 0.738, and 0.745, respectively (*Figure 4A,B,C*). In the Chinese validation set, the C-index of the 8^{th} AJCC TNM staging system was 0.713, whereas AUC values of the ROC for predicting 1-, 3-, and 5-year OS were 0.738, 0.791, and 0.773, respectively (*Figure 4D,E,F*). Overall, our nomogram showed higher prognostic accuracy than the 8^{th} AJCC TNM staging system across the training and validation sets (*Table 4*).

Discussion

Individualized gastric cancer treatment, a multi-disciplinary collaboration and supplementation approach projected to improve efficacy of cancer treatment, is currently the

Table 2 Univariate analyses of OS in the SEER training set

Variables	Univariate analysis	
	HR (95% CI)	P value
Age at diagnosis (year)		
≤44	Reference	
45–59	1.072 (0.119–0.588)	0.557
60–74	1.315 (0.114–2.408)	0.016
≥75	2.178 (0.114–6.797)	<0.001
Sex		
Female	Reference	
Male	1.118 (0.052–2.143)	0.032
Tumor size (cm)		
<3.7	Reference	
3.7–6.8	1.136 (0.059–2.183)	0.029
>6.8	1.105 (0.069–1.442)	0.149
Prime site of tumor		
Cardia/fundus	Reference	
Middle of gastric body[a]	0.694 (0.063–5.814)	<0.001
Antrum/pylorus	0.768 (0.061–4.338)	<0.001
Tumor number		
<2	Reference	
≥2	1.039 (0.058–0.669)	0.504
AJCC T stage (8th)		
T1	Reference	
T2	1.153 (0.118–1.209)	0.227
T3	1.685 (0.098–5.335)	<0.001
T4	2.380 (0.105–8.239)	<0.001
AJCC N stage (8th)		
N0	Reference	
N1	1.704 (0.074–7.161)	<0.001
N2	2.091 (0.075–9.888)	<0.001
N3a	2.657 (0.078–12.546)	<0.001
N3b	3.209 (0.098–11.853)	<0.001
AJCC M stage (8th)		
M0	Reference	
M1	1.993 (0.086–8.039)	<0.001
AJCC TNM stage (8th)		
I	Reference	
II	–	<0.001
III	–	<0.001
IV	–	<0.001
Liver metastasis		
No	Reference	
Yes	1.221 (0.128–1.568)	0.117

[a], middle of gastric body includes body of stomach, lesser curvature of stomach, and greater curvature of stomach. T, N, M stages come from AJCC. AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

focus of numerous medical research. Since accurate tumor typing forms the basis of individualized tumor treatment, it is imperative to ensure proper classification of GC (23). Previous studies have described the importance of histological type in evaluating tumor progression and prognosis of gastric cancer patients (21). Furthermore, PDA, a common histopathological type of gastric cancer, has been implicated in poor prognosis of PDA than other types, although some studies have shown that PDA with good morphology has a good prognosis (5,17,18). In the present study, we believe that exploring prognostic risk factors in PDA patients is important, owing to its high incidence in gastric cancer. From our analyses, it was evident that some differences existed between PDGA patients in the SEER database and Chinese PDGA patients. Specifically, we found statistically significant differences between the groups with regards to clinicopathological characteristics, including age at diagnosis, prime site of tumor, tumor number, AJCC T stage (8^{th}), AJCC N stage (8^{th}), and AJCC M stage (8^{th}) in the two sets, which may result from a complex interaction between race, geographic location, culture, eating habits, and socioeconomic inequality. In addition, univariate a multivariate analysis of the clinicopathological characteristics and independent prognostic factors of 3,887 gastric cancer patients in the SEER database revealed 7 independent risk factors related to OS. These factors, including age, sex, tumor size, prime

Table 3 Multivariate analyses of OS in the SEER training set

Variables	Multivariate analysis	
	HR (95% CI)	P value
Age at diagnosis (years)		
≤44	Reference	
45–59	1.078 (0.118–0.635)	0.525
60–74	1.331 (0.113–2.531)	0.011
≥75	2.215 (0.113–7.021)	<0.001
Sex		
Female	Reference	
Male	1.119 (0.052–2.170)	0.030
Tumor size (cm)		
<3.7	Reference	
3.7–6.8	1.137 (0.059–2.193)	0.028
>6.8	1.110 (0.069–1.512)	0.131
Prime site of tumor		
Cardia/fundus	Reference	
Middle of gastric body[a]	0.689 (0.063–5.935)	<0.001
Antrum/pylorus	0.762 (0.061–4.451)	<0.001
AJCC T stage (8th)		
T1	Reference	
T2	1.152 (0.118–1.203)	0.229
T3	1.677 (0.098–5.288)	<0.001
T4	2.363 (0.105–8.172)	<0.001
AJCC N stage (8th)		
N0	Reference	
N1	1.709 (0.074–7.206)	<0.001
N2	2.090 (0.075–9.882)	<0.001
N3a	2.661 (0.078–12.575)	<0.001
N3b	3.210 (0.098–11.870)	<0.001
AJCC M stage (8th)		
M0	Reference	
M1	2.139 (0.071–10.784)	<0.001

[a], middle of gastric body includes body of stomach, lesser curvature of stomach, and greater curvature of stomach. T, N, M stages come from AJCC. AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

site of tumor, T stage (8th AJCC), T stage (8th AJCC), and T stage (8th AJCC) were used to build an OS nomogram model, which was externally validated using a Chinese patient population. The larger sample size of the two sets of data improves the accuracy and credibility of the research. And we used the ROC curve (1, 3, and 5 years of AUC value), the calibration plots, the C index (the value of the C index) to evaluate the accuracy of the model, and found that the prognostic model has high accuracy.

The AJCC TNM staging system for malignant tumors has long been used as a basis for clinical treatment (24). However, response to treatment and prognosis are not usually consistent if the same treatment plan is adopted in patients with tumors with the same TNM stage (25-27). Although the TNM staging system is based on data collected globally, data from two countries, South Korea and Japan, account for 84.8% of data from Asian countries, which may have a significant impact on the analysis of Chinese patients (28). Fortunately, our OS nomogram model maybe solve this problem (29,30). Similarly, our nomogram was more accurate at predicting the OS of PDGA patients than the AJCC-TNM staging system, across both training and validation sets (C-index value in the SEER training set: 0.707 *vs.* 0.663; C-index value in the Chinese validation set: 0.788 *vs.* 0.713). In addition, the nomogram had a more prominent advantage than the 8th edition of the AJCC staging system, in that it integrated more potential independent prognostic risk factors to make personalized predictions of patient survival, thereby making better treatment strategies. Despite some differences between the Chinese and SEER sets, our nomogram still showed acceptable consistency in the external verification set, indicating that these differences will not reduce the effectiveness of the nomogram. Moreover, the calibration chart revealed excellent agreement between predicted probability and the actual observation, thereby affirming reliability and repeatability of the nomogram constructed herein.

Our study had several limitations. Firstly, we did not include racial factors, which may affect the accuracy of our results. Although there are differences in diet and treatment between American and Chinese patients, some basic information between patients is still comparable, such as the TNM staging of tumors. And there is currently no large public gastric cancer database available for analysis

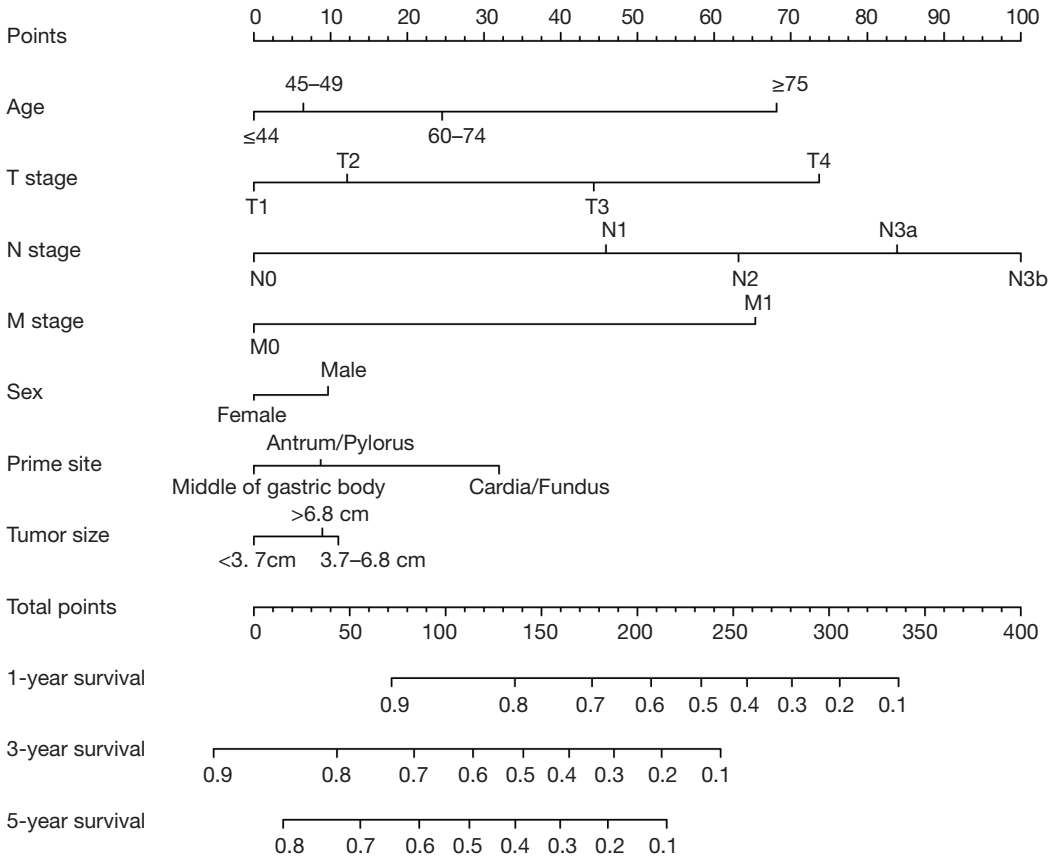

Figure 2 Nomogram for predicting 1-, 3-, 5-year OS of patients with PDGA.

in China. Therefore, we used the huge data of the SEER database to establish a nomogram and verified it with 632 samples collected from a single center in China. Therefore, this research still has certain reference value. Secondly, our external validation only used data collected from a single-center PDGA patient in China. Thirdly, treatment bias may have occurred. Since some patients in the SEER database had incomplete chemotherapy or radiotherapy data, or recorded data on chemotherapy or radiotherapy, but did not specify the specific chemotherapy or radiotherapy program. Considering that different chemotherapy or radiotherapy regimens may have different effects on the prognosis of patients with gastric cancer, and some chemotherapy or radiotherapy data are incomplete, this study did not include chemotherapy or radiotherapy data, which is also the focus of our future research.

Conclusions

In conclusion, we successfully established a novel nomogram using patient data from the SEER database, and validated its efficiency in predicting prognosis of PDGA patients using a Chinese population. Our nomogram had more accurate and effective than the 8th AJCC TNM

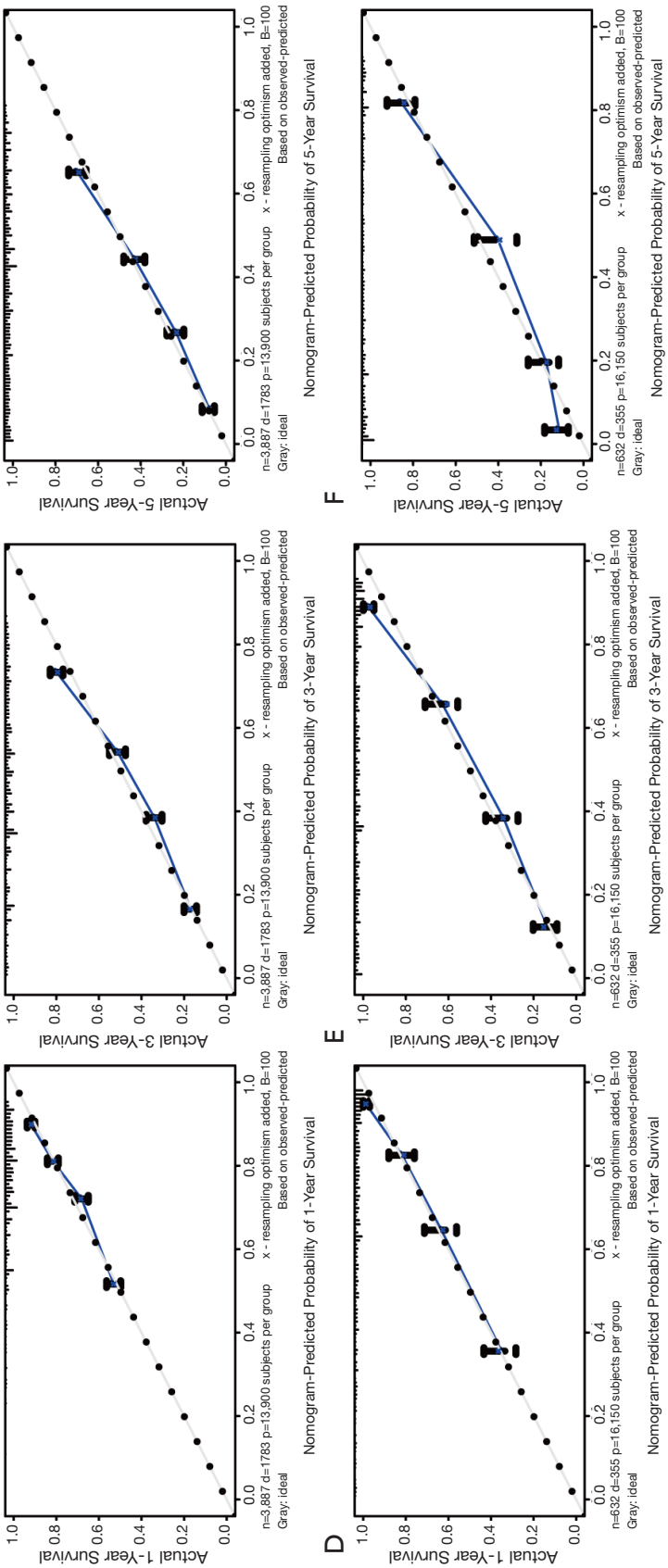

Figure 3 Calibration curve predicting (A) 1-year and (B) 3-year and (C) 5-year OS rates of patients with PDGA in the training set; (D) 1-year and (E) 3-year and (F) 5-year OS rates of patients with PDGA in the validation set.

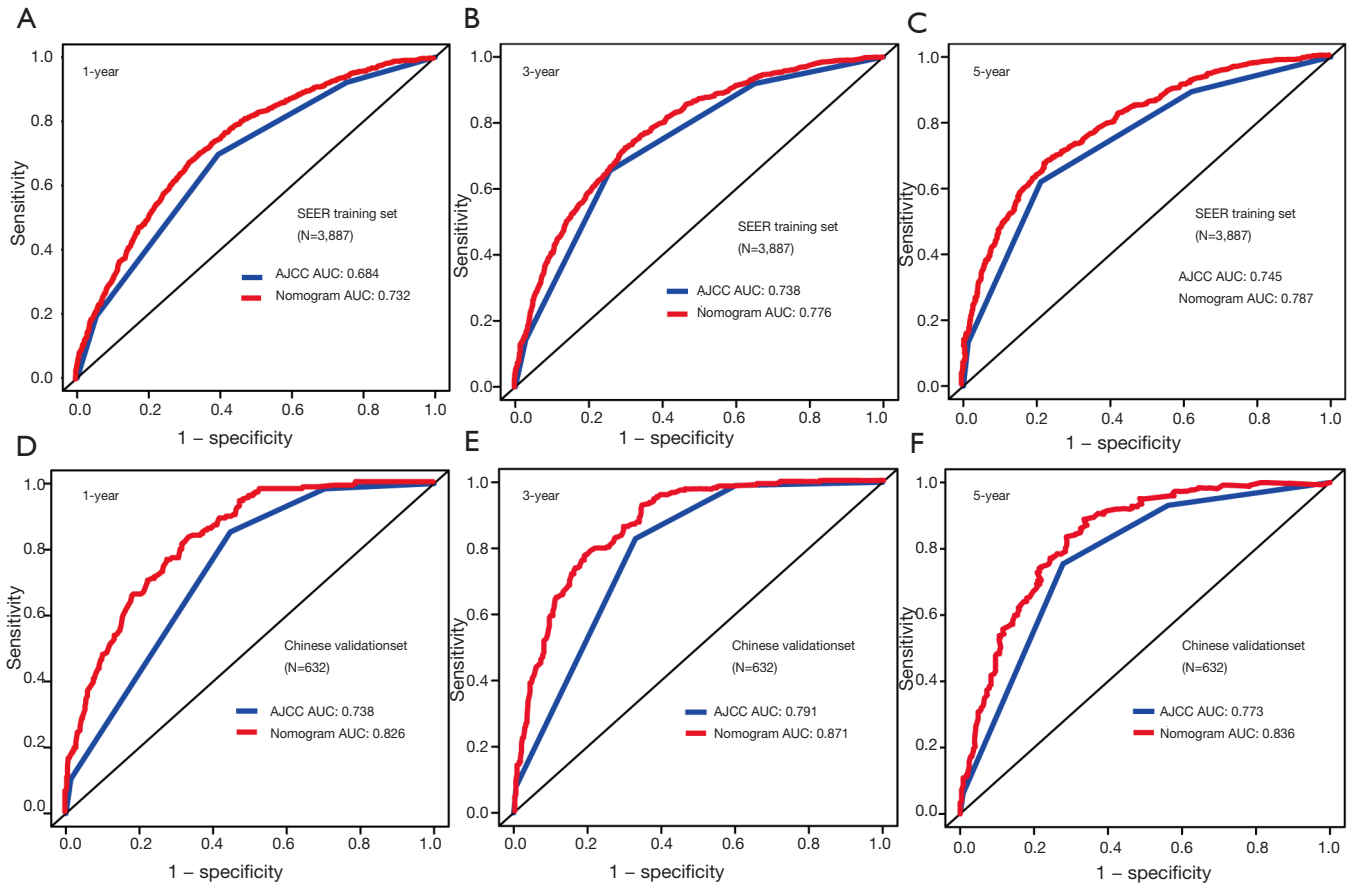

Figure 4 Comparison between AUCs from our nomograms and the 8th AJCC TNM staging system for predicting OS at 1-year (A), 3-year (B), and 5-year (C). SEER training set and 1-year (D), 3-year (E), and 5-year (F). The Chinese validation set. OS, overall survival; AUC, area under the curve; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

Table 4 Comparison of the C-index and AUC for nomogram and the 8th edition of AJCC TNM staging system

System	C-index	AUC		
		1-year survival	3-year survival	5-year survival
SEER training set				
The 8th AJCC TNM Staging System	0.663	0.684	0.738	0.745
Nomogram	0.707	0.732	0.776	0.787
P value	<0.001	<0.001	<0.001	<0.001
Chinese validation set				
The 8th AJCC TNM Staging System	0.713	0.738	0.791	0.773
Nomogram	0.788	0.826	0.871	0.836
P value	<0.001	<0.001	<0.001	<0.001

AUC, area under the curve; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

staging system, hence more suitable for future development of personalized treatment for patients.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Zhejiang Provincial People's Hospital (Approval No.: 2019KY017) and informed consent was taken from all the patients.

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