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A Nomogram for Predicting Cancer-Specific Survival of Patients with Gastrointestinal Stromal Tumors

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Background: The aim of this study was to construct a nomogram to predict the prognosis of patients with gastrointestinal stromal tumor (GIST).

Material/Methods: We enrolled 4086 GIST patients listed in the SEER database from 1998 to 2015. They were separated to 2 groups: an experimental group (n=2862) and a verification group (n=1224). A nomogram was constructed by using statistically significant prognostic factors.

Result: A nomogram that included age, sex, marital status, tumor location, grade, SEER stage, tumor size, and surgical management was developed. It can be used to predict overall survival (OS), while adding AJCC 7th TNM stage can predict cancer-specific survival (CSS). The C-index used to forecast OS and CSS nomograms was 0.778 (95% CI, 0.76–0.79) and 0.818 (95% CI, 0.80–0.84), respectively.

Conclusions: The nomogram can effectively predict 3- and 5-year CSS in patients with GIST, and its use can improve clinical practice.

MeSH Keywords: Nomograms • SEER Program • Stomach Neoplasms

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Background

Gastrointestinal stromal tumors (GIST) are interlobar tumors that most often occur in the gastrointestinal tract [1]. They originate from the stromal cells of Cajal or their stem cell precursors. In histology, GIST consists of fusiform cells, epithelial cells, or mixed cells, that are arranged in bundles or are diffused [2]. GIST includes 3 types: benign, uncertain malignant potential, and malignant [1]. They occurs in every part of the digestive tract and are most common in the gastric stroma, accounting for about 60–70% of all cases. GIST has a broad prognostic spectrum; therefore, forecasting the prognosis of GIST patients based on clinicopathological factors is important and contributes to developing treatment plans.

The American Joint Committee on Cancer (AJCC) TNM staging system is now the most extensively used clinical tool in determining the treatment of tumor patients, but it fails to accurately reflect differences in the prognosis of various patients because the same TNM stage can have different clinical outcomes and is influenced by the assessment of clinicians [3–5]. The same treatment may then lead to inadequate or excessive treatment. A new type of line map has been established by Joensuu [6], in which the recurrence rate of patients with GIST was individually evaluated by mitotic count, tumor size, tumor location, and rupture, using magnetic resonance imaging (MRI). Compared with the TNM staging system, the model can provide a more accurate prognosis. However, age and sex can still affect the prognosis of patients, so we still need an improved system to analyze the clinical prognosis of patients with GIST.

A nomogram is considered a reliable tool for clinicians to use in predicting prognosis of patients with tumors. Compared with the AJCC system, TNM staging system can more accurately predict the survival time of patients with different tumors, and TNM staging system has been recognized in various studies [7,8]. Research using nomograms for GIST patients alone based on population-based data have not been reported. Thus, we used the database to develop a nomogram to more precisely predict the prognosis of GIST patients.

Material and Methods

Patients

We obtained patient data from the SEER database, and SEER*stat software (version 8.3.5; *http://seer.cancer.gov/seerstat/*) was used to screen the data. All patients were pathologically diagnosed as having GIST by morphological code (C22.0) between 1998 and 2015 from the SEER database. In accordance with the third edition of ICDO-3 for GIST (code 8936), 5381 patients with GIST were listed. Then, 4086 patients were selected from among the 5381 patients based on the following criteria: 1) no history of malignant tumor; 2) diagnosed with GIST; 3) followed up with known results; 4) detailed clinicopathological information.

Study variables

We calculated CSS and OS. For each patient, were obtained data on clinical variables, including age at diagnosis, race, sex, marital status, size, tumor grade, tumor site, SEER historical stage A, AJCC 7th edition TNM stage, mitotic count, surgical management, follow-up data, and cause of death. Tumor size and age were regarded as continuous variables.

Statistical analysis

We used the *t* test to construct nomogram baseline patient demographics. Differences between survival curves were analyzed using the log-rank test. We used univariate and multivariate Cox proportional hazards models to screen key prognostic factors. Univariate prognostic analysis was performed via log-rank and Kaplan-Meier analysis. The Cox proportional hazards model was used to obtain hazard ratios and 95% confidence intervals. A graphical nomogram was constructed from multivariate logistic regression models.

Verification of the nomogram

The nomogram was validated by measuring discrimination internally (training set) and externally (validation set). The discriminatory ability of every model was assessed using the concordance index (C-index). A high C-index indicates good capacity to distinguish patients with different survival conditions. SPSS 20.0 (IBM, Inc., Armonk, NY) and R software programs were used for analysis. $P<0.05$ indicated statistical significance.

Results

Demographic and pathological characteristics

We selected 4086 patients diagnosed with GIST. Patients were separated into a training group (n=2862) and a validation (n=1224) group.

The flowchart of data selection for the training group (n=2841) and validation group (n=2781) is presented in Figure 1, and patient characteristics are listed in Table 1. The average age was 62.67 years old, and 49.7% of patients were male. Most patients in the 2 sets were married (56.3%) and 61.6% were white. In addition to the unknown location, the most common tumor site was the fundus (15.4%), followed by the greater curvature (13.3%), lesser curvature (11.6%), body (9.2%),

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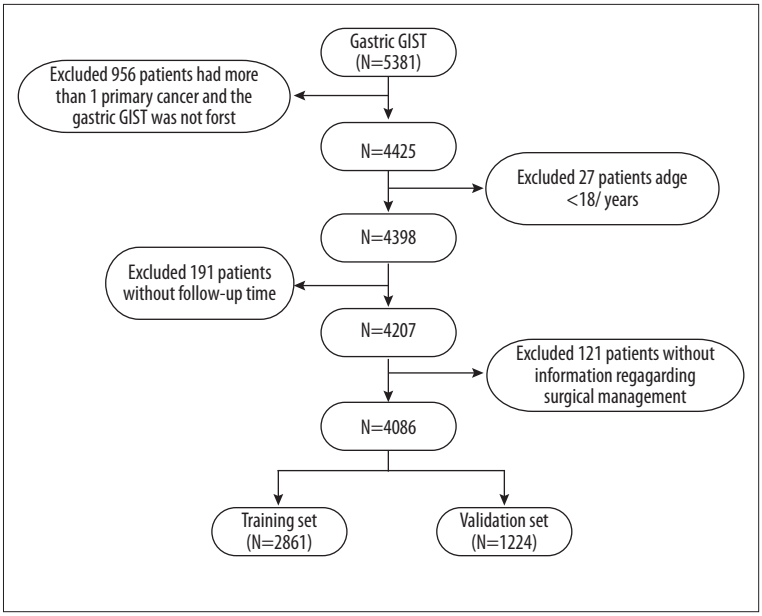

Figure 1. Flowchart of data selection.

Table 1. Patient demographics and pathological characteristics.

Variables	All patients (n=4086)		Training set (n=2862)		Validation set (n=1224)	
	No.	%	No.	%	No.	%
Age						
<50	718	17.6	497	17.4	221	18.1
50–64	1429	35	1007	35.2	422	34.5
65–79	1481	36.2	1031	36	450	36.8
≥80	458	11.2	327	11.4	131	10.7
Sex						
Female	2054	50.3	1436	50.2	618	50.5
Male	2032	49.7	1426	49.8	606	49.5
Race						
White	2517	61.6	1741	60.8	776	63.4
Black	976	23.9	693	24.2	283	23.1
Other/unknown	593	14.5	428	15	165	13.5
Marital status						
Married	2301	56.3	1618	56.5	683	55.8
Single	685	16.8	473	16.5	212	17.3
Unknown	1100	26.9	771	26.9	329	26.9
Tumor site						
Cardia	308	7.5	220	7.7	88	7.2
Fundus	630	15.4	418	14.6	212	17.3
Body	376	9.2	278	9.7	98	8

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Table 1 continued. Patient demographics and pathological characteristics.

Variables	All patients (n=4086)		Training set (n=2862)		Validation set (n=1224)	
	No.	%	No.	%	No.	%
Antrum	314	7.7	213	7.4	101	8.3
Pylorus	12	0.3	9	0.3	3	0.2
Lesser curvature	474	11.6	327	11.4	147	12
Greater curvature	545	13.3	383	13.4	162	13.2
Overlapping stomach lesion	257	6.3	193	6.7	64	5.2
Stomach NOS	1170	28.6	821	28.7	349	28.5
Tumour size						
≤5	1329	32.5	926	32.4	403	33
5.1–10	1016	24.9	703	24.6	313	25.6
>10	787	19.3	538	18.8	249	20.3
Unknown	954	23.3	695	24.3	259	21.2
Mitotic index, mitoses/50 HPF						
<5	1237	30.3	849	29.7	388	31.7
5–10	170	4.2	129	4.5	41	3.3
>10	174	4.3	123	4.3	51	4.2
Unknown	2505	61.3	1761	61.5	744	60.8
Grade						
I	514	12.6	357	12.5	157	12.8
II	401	9.8	280	9.8	121	9.9
III	163	4	118	4.1	45	3.7
IV	240	5.9	162	5.7	78	6.4
Unknown	2768	67.7	1945	68	823	67.2
Stage						
Localized	2739	67	1904	66.5	835	68.2
Regional	397	9.7	296	10.3	101	8.3
Distant	710	17.4	499	17.4	211	17.2
Unknown	240	5.9	163	5.7	77	6.3
Surgery						
Performed	3371	82.5	2361	82.5	1010	82.5
None	715	17.5	501	17.5	214	17.5

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Table 2. Univariate and multivariate analyses of overall survival in the training set.

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* vlue
Age	<0.001		
<50		Reference	
50–64		1.328 (1.050–1.680)	0.018
65–79		2.450 (1.954–3.070)	<0.001
≥80		4.859 (3.749–6.299)	<0.001
Sex	<0.001		
Female		Reference	
Male		1.408 (1.221–1.624)	<0.001
Race	<0.001		
White		Reference	
Black		1.107 (0.942–1.301)	0.218
Other/unknown		0.807 (0.652–0.999)	0.049
Marital status	<0.001		
Married		Reference	
Single		1.419 (1.167–1.724)	<0.001
Unknown		1.059 (0.896–1.253)	0.5
Tumor site	<0.001		
Cardia		Reference	
Fundus		0.682 (0.516–0.901)	0.007
Body		0.734 (0.540–0.997)	0.048
Antrum		0.537 (0.372–0.774)	<0.001
Pylorus		2.852 (1.037–7.843)	0.042
Lesser curvature		0.755 (0.551–1.034)	0.079
Greater curvature		0.735 (0.551–0.981)	0.036
Overlapping stomach lesion		0.874 (0.629–1.212)	0.418
Stomach NOS		0.789 (0.618–1.007)	0.057
Tumour size	<0.001		
≤5		Reference	
5.1–10		1.230 (0.964–1.568)	0.096
>10		1.462 (1.124–1.903)	0.005
Unknown		1.850 (1.472–2.326)	<0.001
Mitotic index,mitoses/50 HPF	<0.001		
<5		Reference	
5–10		0.902 (0.469–1.736)	0.758
>10		1.107 (0.586–2.088)	0.755
Unknown		1.109 (0.716–1.717)	0.643

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Table 2 continued. Univariate and multivariate analyses of overall survival in the training set.

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* vlue
Grade	<0.001		
I		Reference	
II		1.158 (0.760–1.766)	0.494
III		2.083 (1.322–3.283)	0.002
IV		1.823 (1.270–2.754)	0.004
Unknown		1.132 (0.802–1.596)	0.481
Stage	<0.001		
Localized		Reference	
Regional		1.464 (1.181–1.815)	<0.001
Distant		2.339 (1.931–2.832)	<0.001
Unknown		1.264 (0.969–1.649)	0.084
AJCC 7th stage	<0.001		
I		Reference	
II		0.603 (0.282–1.289)	0.192
III		1.504 (0.684–3.306)	0.31
IV		1.069 (0.612–1.845)	0.812
Unknown		1.270 (0.734–2.196)	0.392
Surgery	<0.001		
None		Reference	
Performed		0.435 (0.365–0.518)	<0.001

antrum (7.7%), cardia (7.5%), overlapping stomach lesion (6.3%), and pylorus (0.3%). The tumor size was mostly less than 5 cm (32.5%). Except for tumors in unknown locations, most tumor mitotic rates were under 5 mitoses/50 high-power field (HPF). About 67% of the patients had GIST in the localized stage, 17.4% (710) had distant stage, and 9.7% (397) had regional stage, in accordance with the SEER stage system. The median time for follow-up was 47 months in the training group and 46 months in the validation group. In the training group, 539 patients died from GIST and 327 patients died from other causes.

Nomogram construction

In the training group, all variables in the nomogram were related to OS. Table 2 shows the independent prognostic variables, such as age, race, sex, marital status, size, grade, tumor site, SEER historical stage A, AJCC 7th TNM stage, mitotic count, and surgical management. Results of multivariate analysis identified 8 independent predictive factors: age, sex, marital status, tumor location, grade, SEER stage, tumor size, and surgical management. On the basis of these 8 variables, we built the overall survival (OS) nomogram in the training set (Figure 2A). For cancer-specific survival (CSS), 9 independent predictive factors were identified: age, sex, marital status, tumor location, grade, SEER stage, tumor size, AJCC 7th TNM stage, and surgical management (Table 3). The CSS nomogram is shown in Figure 2B.

Verification of the nomogram

Internal and external validation was performed for the nomogram. Internal validation showed that the C-index used to predict OS and CSS nomograms was 0.778 (95% CI, 0.76–0.79) and 0.818 (95% CI, 0.80–0.84), respectively (Table 4), and it was consistent with the actual OS and CSS. When the validation cohort for external validation was used, the C-index was 0.794 for OS (95% CI, 0.77–0.82) and 0.843 (95% CI, 0.82–0.87) for CSS, respectively. Moreover, the nomogram in the training

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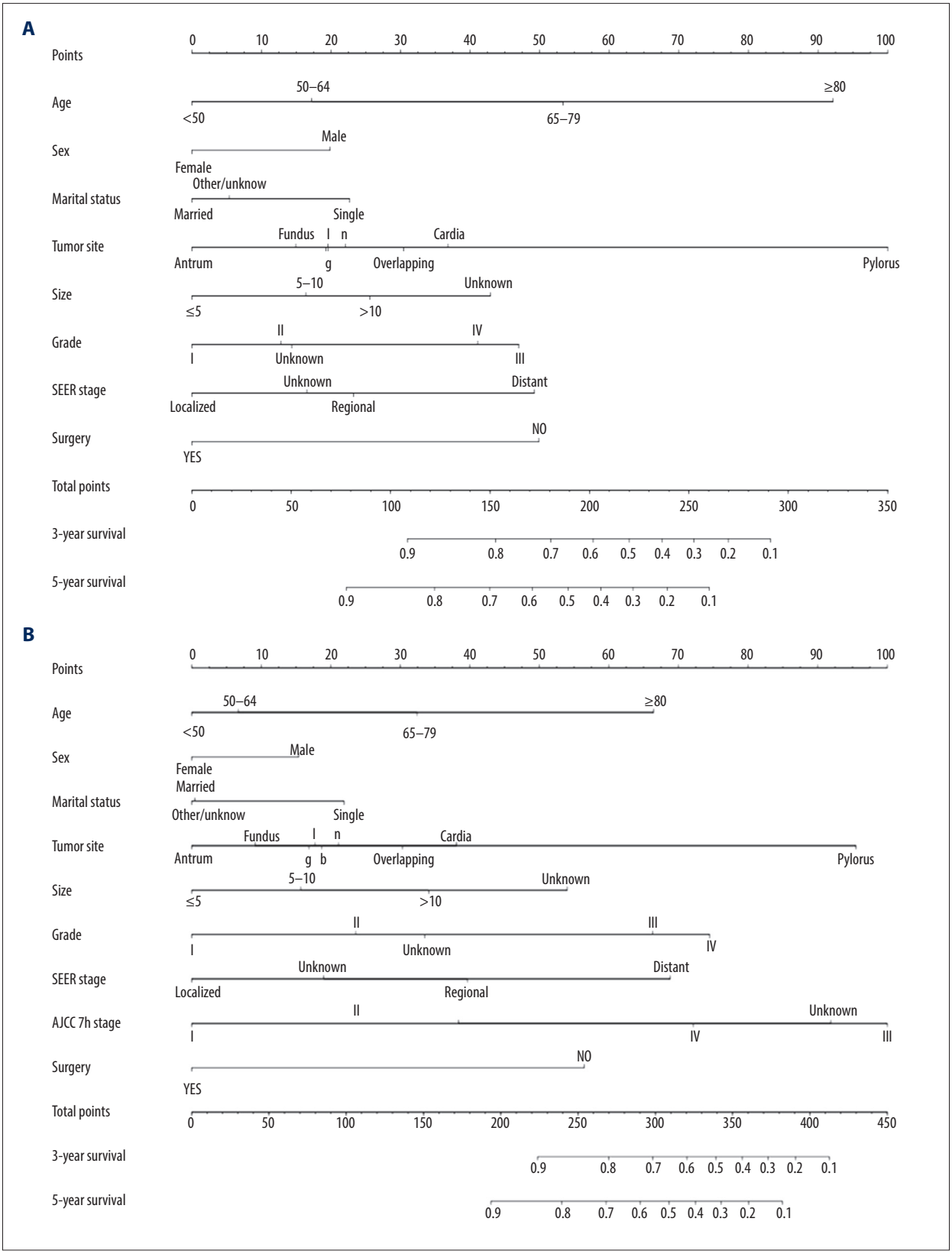

Figure 2. Construction of nomograms. (**A**) Nomogram for predicting the OS of GIST. (**B**) Nomogram for predicting CSS. CSS– cancer-specific survival; OS – overall survival; GIST – gastrointestinal stromal tumor.

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Table 3. Univariate and multivariate analyses of CSS in the training set.

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* value
Age	<0.001		
<50		Reference	
50–64		1.101 (0.853–1.421)	0.461
65–79		1.682 (1.300–2.175)	<0.001
≥80		3.001 (2.193–4.106)	<0.001
Sex	<0.001		
Female		Reference	
Male		1.286 (1.073–1.543)	0.007
Race	0.003		
White		Reference	
Black		1.105 (0.903–1.353)	0.332
Other/unknown		0.866 (0.665–1.128)	0.286
Marital status	0.001		
Married		Reference	
Single		1.382 (1.093–1.749)	0.007
Unknown		0.969 (0.778–1.208)	0.781
Tumor site	<0.001		
Cardia		Reference	
Fundus		0.621 (0.432–0.895)	0.01
Body		0.724 (0.488–1.074)	0.108
Antrum		0.542 (0.334–0.879)	0.013
Pylorus		2.589 (0.619–10.827)	0.193
Lesser curvature		0.729 (0.481–1.104)	0.136
Greater curvature		0.720 (0.495–1.046)	0.085
Overlapping stomach lesion		0.873 (0.578–1.318)	0.519
Stomach NOS		0.770 (0.563–1.052)	0.101
Tumour size	<0.001		
≤5		Reference	
5.1–10		1.285 (0.899–1.836)	0.169
>10		1.712 (1.200–2.445)	0.003
Unknown		2.380 (1.715–3.304)	<0.001
Mitotic index, mitoses/50 HPF	<0.001		
<5		Reference	
5–10		0.877 (0.397–1.940)	0.747
>10		0.968 (0.446–2.096)	0.933
Unknown		1.108 (0.656–1.872)	0.702

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Table 3. Univariate and multivariate analyses of CSS in the training set.

Variable	Univariate analysis	Multivariate analysis	
	P value	HR (95% CI)	*P* value
Grade	<0.001		
I		Reference	
II		1.467 (0.719–2.990)	0.292
III		2.961 (1.478–5.931)	<0.001
IV		3.399 (1.797–6.429)	<0.001
Unknown		1.712 (0.946–3.099)	0.076
Stage	<0.001		
Localized		Reference	
Regional		1.917 (1.469–2.504)	<0.001
Distant		3.103 (2.438–3.949)	<0.001
Unknown		1.360 (0.959–1.928)	0.085
AJCC 7th stage	<0.001		
I		Reference	
II		1.929 (0.602–6.179)	0.269
III		5.485 (1.663–18.094)	0.005
IV		3.101 (1.182–8.133)	0.021
Unknown		4.062 (1.538–10.730)	0.005
Surgery	<0.001		
None		Reference	
Performed		0.402 (0.324–0.499)	<0.001

Table 4. Discrimination efficiency.

	Training cohort		Validation cohort	
	HR	95% CI	HR	95% CI
Nomogram	0.778	0.76–0.79	0.794	0.77–0.82
SEER stage	0.665	0.65–0.68	0.668	0.64–0.70
AJCC TNM 7th stage	0.588	0.57–0.60	0.6	0.57–0.63
Nomogram	0.818	0.80–0.84	0.843	0.82–0.87
SEER stage	0.722	0.70–0.74	0.737	0.70–0.77
AJCC TNM 7th stage	0.625	0.61–0.64	0.634	0.61–0.66

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group, the SEER stage, and the AJCC 7th TNM staging system were compared. The results showed that a nomogram for discriminating patients with GIST performed better than the SEER and TNM 7th edition staging systems (Table 4).

Discussion

Nomograms were introduced into the medical field by scholars in 1928 [9]. They are currently used in various cancers to evaluate the individualized prognosis [10–12]. Nomograms are simple and easy to use and exhibit high clinical precision. Moreover, they can elevate staging systems from the group level to the individual level and can be used to predict approximate survival under any circumstances [13]. In the present study, a nomogram was built to predict patient prognosis. We compared the performances of our nomogram, SEER staging, and the AJCC 7th TNM stage system in the training group. Our results showed the nomogram performed better than the SEER and TNM 7th staging systems.

We identified 9 factors that could predict the CSS of patients with GIST – age, sex, marital status, tumor location, grade, SEER stage, tumor size, AJCC 7th TNM stage, and surgical management – which were consistent with previous studies [14–16]. Age has been regarded as a key prognostic factor in some reports and old age as an independent risk factor in other studies, indicating a reduced survival rate [17–19]. The older and more anxious the patients were, the less their desire to know the prognostic outcome [20]. Moreover, most women prefer to talk with others, whereas men usually choose deal with their cancer on their own. Some studies suggest patients communicate without reservation with family members [21]. Women with lower education levels were much more interested in knowing their survival rate [22]. Moreover, the partner can improve the prognosis [23–25]. Notably, the prognosis in the cardia and pylorus is better than that in the antral and other parts, which may be related to the obvious obstruction of the gastric cardia and the pylorus than that of the gastric antrum, and the earlier clinical findings.

The method used in this study has several advantages. Our nomogram is more accurate than the AJCC TNM staging system [26]. It effectively uses a rigorous design to provide a solid foundation for the individualized treatment of different gastric stromal tumors for clinicians. The prognoses of stage-III patients with the same TMN stage vary according to sex, age, marital status, and location of the tumor in the stomach. Prognostic differences are visually observed in the nomogram, which may result in different treatments. We calculated the scores of each individual. Discrimination and calibration indicated that the models were valid. Different nomogram-integrating anticancer treatments might further improve survival prediction. From the nomogram, 9 variables were obtained, which provided information on GIST and could also determine the correlation of developed tools. Although the model was built on the basis of a large population-based cohort and could increase the accuracy of the nomogram, the SEER database contained no data on chemotherapy and other targeted therapy, which could lead to bias. In addition, many possible predictive variables were excluded, such as pain, C-reactive protein, albumin, and molecular markers. Therefore, the use of this model, combined with tumor markers and other indicators, may more accurately predict patient prognosis.

Conclusions

The nomogram in our study was constructed by using statistically significant prognostic factors, including age, sex, marital status, tumor location, grade, SEER stage, tumor size, and surgical management. It performs better than the SEER and TNM 7th edition staging systems in discriminating patients with GIST. Our nomogram can more precisely predict the prognosis of GIST patients, and has clinical significance as it can guide individualized treatment.

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