Original Article

Prognostic nomogram in patients with gastrointestinal stromal tumors: a SEER-based study

Pan Xu[1#], Wei Ding[2#], Feifei Zheng[3], Tingyan Ruan[1], Jing Liu[1], Junli Ding[1], Junying Xu[1]

[1]Oncology Department, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi People's Hospital, Wuxi Medical Center, Nanjing Medical University, Wuxi, China; [2]Gastroenterology, Naval Medical Center of PLA, Shanghai, China; [3]Department of Laboratory Medicine, Affiliated Hospital of Jiangnan University, Wuxi, China

Contributions: (I) Conception and design: P Xu; (II) Administrative support: W Ding, F Zheng; (III) Provision of study materials or patients: T Ruan, J Liu; (IV) Collection and assembly of data: P Xu; (V) Data analysis and interpretation: J Ding, J Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Junying Xu, MD; Junli Ding, MD. Oncology Department, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi People's Hospital, Wuxi Medical Center, Nanjing Medical University, No. 299 Qingyang Road, Wuxi 214000, China. Email: xujunying0629@163.com; dingjunli0629@163.com.

Background: Gastrointestinal stromal tumor (GIST) is a common mesenchymal tumor of the gastrointestinal system. They originate from the interstitial cells of Cajal located within the muscle layer and are characterized by over-expression of the tyrosine kinase receptor KIT.

Methods: Data from the Surveillance Epidemiology, and End Results (SEER) database of 1,213 patients diagnosed with GIST between 2010 and 2019 were dichotomized into a modeling set and a validation set at a 2:1 ratio. For the modeling set, both univariate and multivariate Cox regression analyses were used to identify independent prognostic factors. A nomogram was then constructed based on these determinants. Model efficacy was tested using receiver operating characteristic (ROC) curves, calibration curves, clinical decision curves, and risk stratification analysis in both subsets.

Results: Identified prognostic determinants included age, sex, pathological differentiation level, tumor-node-metastasis (TNM) stage, surgical intervention, radiotherapy, and marital status. The constructed nomogram showed area under the ROC curve (AUC) values of 0.822, 0.793, and 0.779 for 1-, 3-, and 5-year overall survival (OS) in the modeling set, respectively, while in the validation set, the values were 0.796, 0.823, and 0.806, respectively. Calibration plots from both sets confirmed the concordance between predicted and observed survival. Decision curve analysis (DCA) indicated significant clinical utility for the nomogram. Risk stratification of the patient data revealed distinct survival differences between high-risk and low-risk cohorts in both sets ($P<0.001$).

Conclusions: A novel and potent nomogram for the prognosis of GIST has been introduced. This model's precision offers crucial insights for clinical decisions, yet further external validation remains essential.

Keywords: Gastrointestinal stromal tumor (GIST); nomogram; prognostic; Surveillance Epidemiology, and End Results database (SEER database)

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Introduction

Gastrointestinal stromal tumors (GISTs) are rare tumors of the digestive system and include gastrointestinal stromal sarcoma (GISS) (1). Stemming from pluripotent mesenchymal cells, GISTs can evolve into the interstitial cells of Cajal (ICCs), pivotal pacemaker entities nestled between the circular and longitudinal muscular layers of the gastrointestinal tract's muscular propria (2). For patients with non-metastatic GISTs, laparoscopic surgical removal remains the primary therapeutic approach (3). In advanced GIST cases, clinicians typically resort to tyrosine kinase inhibitors (TKIs), such as imatinib, sunitinib, and regorafenib. These pharmaceutical agents demonstrate efficacy against certain GIST subtypes, yet their challenges persist, necessitating innovative therapeutic strategies (4). The recurrence rate remains high for GIST due to its rarity, even after intensive treatment (5). The literature regarding this malignancy primarily encompasses case studies and limited-scope retrospective analyses. Typically, prognostic assessments for GIST rely heavily on clinical expertise. Hence, the creation of a visual nomogram for survival prediction can offer clinicians an enhanced tool for individual prognosis assessments. We present this article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-27/rc).

Highlight box

Key findings

- The nomogram for the prognosis of gastrointestinal stromal tumor (GIST) has been introduced.

What is known and what is new?

- GISTs are rare tumors of the digestive system, which have poor prognosis. At present, there is no standard to evaluate the prognosis of patients with GIST. tumor-node-metastasis stage is a well-known prognostic factor.
- We found new prognostic factors, such as age, sex, pathological differentiation level, surgical intervention, radiotherapy, and marital status.

What is the implication, and what should change now?

- Leveraging this nomogram offers clinicians a reliable tool, enhancing the precision of their judgments. Nevertheless, performing broader external validations remains a crucial next step.

Methods

Data source

In this investigation, we utilized a retrospective approach with data sourced from the Surveillance Epidemiology, and End Results (SEER) database. Utilizing SEER*Stat software, information based on histological and pathological assessments from 2010–2019 was extracted. The dataset incorporated factors such as age, sex, primary location of the tumor, pathological grading, and staging (T, N, M, and overall), along with treatment methods, tumor dimensions, marital status, and ethnicity. Eligibility for inclusion encompassed (I) diagnoses between 2010 and 2019; (II) tumors primarily situated in the stomach; (III) confirmation of GIST via ICD-O-3 pathology; and (IV) availability of comprehensive follow-up details. On the other hand, exclusion criteria included (I) the presence of multiple primary tumors; (II) incomplete or unverified histological/pathological data; (III) ambiguous surgical details; (IV) lack of clarity regarding tumor categorization, differentiation level, and staging; (V) uncertain survival duration; and (VI) mortality linked to other malignancies or undetermined origins. After screening, we identified a cohort of 1,213 patients. These individuals were subsequently distributed into modeling and validation cohorts at a 2:1 ratio, resulting in 809 participants in the modeling subset, with the residual 404 assigned to the validation subset. Within the scope of inclusion criteria, we randomly selected a part of people as the validation cohort and the training. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Dataset fundamentals were articulated as percentages. Chi-square tests were used to compare rates, with significance acknowledged when $P<0.05$. Lasso regression was applied for formative steps on the modeling group's data. This allowed for the identification of substantial prognostic elements, which then entered the multifaceted analysis via the Cox proportional hazard regression model, presenting their respective hazard ratios (HRs) and 95% confidence intervals (95% CIs). Survival rates at distinct intervals—1, 3, and 5 years—were illustrated graphically. The discriminatory ability of the model was gauged through

the area under the receiver operating characteristic (ROC) curve (AUC). Calibration curves were used to further this analysis by juxtaposing predictions against tangible outcomes. Concurrently, a clinical decision curve analysis (DCA) illuminated the clinical utility of the nomogram. Based on inherent prognostic components, risk stratifications for GIST patients emerged. Employing R language, we generated survival state scatter plots. The Kaplan-Meier approach was applied to distinguish disparities between risk tiers, high and low. R language software, version 4.1.3, was used to craft all relevant visualizations and tables.

Results

Patient baseline characteristics

In our investigation, we sourced eligible patients diagnosed with GIST from 2010 to 2019 using the SEER database. The distribution between the modeling and validation groups was set at a 2:1 ratio as detailed in *Table 1*. A comparative analysis between these two groups revealed no significant variances in their clinical characteristics (P>0.05), ensuring the robustness and reliability of our model.

Table 1 Clinical characteristics of gastrointestinal stromal tumor patients

Characteristic	Training cohort (n=809)	Validation cohort (n=404)	P
Age (years)			0.531
<60	252 (20.8)	118 (9.7)	
≥60	557 (45.9)	286 (23.6)	
Sex			0.902
Female	387 (31.9)	191 (15.7)	
Male	422 (34.8)	213 (17.6)	
Primary site			0.033
Body	86 (7.1)	30 (2.5)	
Cardia	65 (5.4)	31 (2.6)	
Fundus	132 (10.9)	79 (6.5)	
Greater curvature	100 (8.2)	60 (4.9)	
Lesser curvature	84 (6.9)	59 (4.9)	
Overlapping lesion	34 (2.8)	22 (1.8)	
Pylorus	61 (5.0)	25 (2.1)	
Stomach	247 (20.4)	98 (8.1)	
Grade			0.171
I	174 (14.3)	69 (5.7)	
II	83 (6.8)	45 (3.7)	
III	20 (1.6)	18 (1.5)	
IV	38 (3.1)	18 (1.5)	
Unknown	494 (40.7)	254 (20.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Training cohort (n=809)	Validation cohort (n=404)	P
T			0.053
T1	134 (11.0)	54 (4.5)	
T2	244 (20.1)	136 (11.2)	
T3	204 (16.8)	85 (7.0)	
T4	143 (11.8)	93 (7.7)	
TX	84 (6.9)	36 (3.0)	
N			0.208
N0	776 (64.0)	394 (32.5)	
N1	33 (2.7)	10 (0.8)	
M			0.983
M0	695 (57.3)	348 (28.7)	
M1	114 (9.4)	56 (4.6)	
Stage			0.173
I	354 (29.2)	165 (13.6)	
II	79 (6.5)	57 (4.7)	
III	55 (4.5)	33 (2.7)	
IV	131 (10.8)	59 (4.9)	
Unknown	190 (15.7)	90 (7.4)	
Surgery			0.637
No	196 (16.2)	108 (8.9)	
Local surgery	80 (6.6)	39 (3.2)	
Gastrectomy	533 (43.9)	257 (21.2)	
Radiation			>0.99
None/unknown	806 (66.4)	402 (33.1)	
Yes	3 (0.2)	2 (0.2)	
Chemotherapy			0.899
No/unknown	464 (38.3)	234 (19.3)	
Yes	345 (28.4)	170 (14.0)	
Systemic treatment			0.673
No	578 (47.7)	291 (24.0)	
Before surgery	44 (3.6)	28 (2.3)	
After surgery	147 (12.1)	67 (5.5)	
Both before and after surgery	40 (3.3)	18 (1.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Training cohort (n=809)	Validation cohort (n=404)	P
Months from diagnosis to treatment			0.414
<1	382 (31.5)	179 (14.8)	
≥1	345 (28.4)	175 (14.4)	
Unknown	82 (6.8)	50 (4.1)	
Tumor size (cm)			0.275
<5	125 (10.3)	64 (5.3)	
≥5	150 (12.4)	60 (4.9)	
Unknown	534 (44.0)	280 (23.1)	
Marital status			0.644
Married	450 (37.1)	214 (17.6)	
Single	7 (0.6)	6 (0.5)	
Divorced/widowed/separated	310 (25.6)	163 (13.4)	
Unknown	42 (3.5)	21 (1.7)	
Race recode			0.699
White	484 (39.9)	229 (18.9)	
Black	166 (13.7)	93 (7.7)	
Other	154 (12.7)	80 (6.6)	
Unknown	5 (0.4)	2 (0.2)	

Univariate and multivariate Cox regression analyses

Single-factor analysis indicated that variables such as age, pathological differentiation, stages T, N, M, and tumor-node-metastasis (TNM) as well as surgical intervention radiation treatment, systemic treatments, post-diagnosis therapy duration, and marital status played a pivotal role in influencing the overall survival (OS) of patients. From an examination of both single-factor and multifactor analysis for the modeling group, it became evident that age, gender, pathological grading, TNM staging, surgical procedures, radiation exposure, and marital status stood out as autonomous determinants of an unfavorable prognosis for those diagnosed with GIST. This is elaborated upon in *Table 2*.

Construction and validation of the prognostic nomogram

Based on the significance of various parameters from the multifactorial assessment, we allocated distinct scores to each. By summing these scores, we generated a comprehensive prognosis evaluation for patients. In our modeling cohort, the multivariate investigation identified age, sex, pathological grade, TNM classification, surgical intervention, radiation therapy, and marital status as pivotal factors determining the outcome in GIST cases. Using the aforementioned seven criteria, we devised a nomogram to project survival outcomes, particularly focusing on the 1-, 3-, and 5-year OS probabilities; details can be observed in *Figure 1*. For the ROC analysis, the AUC metrics for the 1-, 3-, and 5-year survival probabilities in the modeling cohort were 0.822, 0.793, and 0.779, respectively, while those for the validation cohort were respectively 0.796, 0.823, and 0.806, suggesting robust model precision (refer to *Figure 2*). Furthermore, a calibration curve was formulated to reaffirm the predictive efficiency of our model. In this curve, the X-axis illustrates the survival probabilities as per the nomogram, while the Y-axis shows the actual patient outcomes. The congruence between the dotted and solid trajectories within the diagram denotes the nomogram's precision. Intriguingly, the calibration curve's observed

Table 2 Univariate and multivariate analyses for prognosis of gastrointestinal stromal tumor patients in the modeling group

Characteristics	Total	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (years)			<0.001		<0.001
<60	252	Reference			
≥60	557	2.111 (1.502–2.968)	<0.001	2.414 (1.678–3.472)	<0.001
Sex			0.046		0.029
Female	387	Reference			
Male	422	1.267 (1.059–1.673)	0.046	1.413 (1.039–1.921)	0.028
Primary site			0.097		0.475
Fundus	132	Reference			
Body	86	0.864 (0.513–1.453)	0.580	1.256 (0.731–2.158)	0.408
Lesser curvature	84	0.849 (0.513–1.404)	0.524	1.043 (0.610–1.784)	0.878
Stomach	247	1.372 (0.956–1.969)	0.086	1.239 (0.843–1.822)	0.276
Cardia	68	1.090 (0.628–1.892)	0.760	0.773 (0.430–1.387)	0.387
Overlapping lesion	34	1.260 (0.873–1.485)	0.760	0.837 (0.574–1.175)	0.387
Greater curvature	100	1.294 (0.673–2.488)	0.440	1.214 (0.614–2.400)	0.577
Pylorus	61	0.599 (0.294–1.221)	0.159	0.684 (0.329–1.420)	0.308
Grade			0.037		0.044
I	174	Reference			
II	83	1.277 (0.719–2.270)	0.404	1.437 (0.788–2.622)	0.237
III	20	1.880 (0.782–4.518)	0.158	2.167 (0.855–5.494)	0.103
IV	38	2.281 (1.227–4.242)	0.009	1.660 (0.787–3.504)	0.183
Unknown	494	1.673 (1.125–2.488)	0.011	0.832 (0.521–1.330)	0.443
T			<0.001		0.305
T1	134	Reference			
T2	244	0.941 (0.580–1.526)	0.806	0.925 (0.558–1.534)	0.764
T3	204	1.139 (0.763–1.699)	0.524	1.124 (0.727–1.738)	0.599
T4	143	1.558 (1.024–2.371)	0.038	1.700 (0.987–2.928)	0.056
TX	84	3.253 (2.143–4.936)	<0.001	1.339 (0.790–2.268)	0.278
N			0.013		0.232
N0	776	Reference			
N1	33	1.970 (1.144–3.392)	0.014	0.598 (0.260–1.375)	0.226
M			<0.001		0.370
M0	695	Reference			
M1	114	2.692 (1.967–3.686)	<0.001	0.599 (0.199–1.797)	0.360

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Total	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Stage			<0.001		0.040
I	354	Reference			
II	79	0.499 (0.239–1.039)	0.063	0.458 (0.201–1.041)	0.062
III	55	1.765 (1.021–3.051)	0.042	1.345 (0.660–2.738)	0.414
IV	131	3.328 (2.342–4.730)	<0.001	2.896 (0.892–9.396)	0.077
Unknown	190	2.081 (1.446–2.995)	<0.001	1.080 (0.673–1.734)	0.749
Surgery			<0.001		0.031
No	196	Reference			
Local surgery	80	0.343 (0.215–0.549)	<0.001	0.632 (0.221–1.803)	0.391
Gastrectomy	533	0.231 (0.172–0.310)	<0.001	0.407 (0.154–1.077)	0.070
Radiation			0.002		0.008
None/unknown	806	Reference			
Yes	3	6.988 (1.721–28.382)	0.007	8.783 (1.796–42.940)	0.007
Chemotherapy			0.069		0.487
No/unknown	464	Reference			
Yes	345	1.292 (0.980–1.704)	0.069	1.410 (0.542–3.666)	0.481
Systemic treatment			0.025		0.349
No	578	Reference			
Before surgery	44	0.986 (0.520–1.870)	0.966	1.014 (0.308–3.335)	0.982
After surgery	147	0.557 (0.373–0.833)	0.004	0.554 (0.209–1.467)	0.235
Both before and after surgery	40	0.614 (0.272–1.389)	0.242	0.693 (0.192–2.506)	0.576
Months from diagnosis to treatment			<0.001		0.248
<1	345	Reference			
≥1	82	2.949 (1.999–4.352)	<0.001	2.024 (0.795–5.152)	0.139
Unknown	382	0.877 (0.645–1.192)	0.402	1.197 (0.849–1.688)	0.306
Tumor size (cm)			0.540		0.637
<5	125	Reference			
≥5	150	1.388 (0.674–2.859)	0.374	0.889 (0.413–1.917)	0.764
Unknown	534	1.401 (0.768–2.556)	0.272	1.137 (0.607–2.129)	0.688
Marital status			0.004		0.007
Married	450	Reference			
Single	7	0.739 (0.103–5.301)	0.763	1.156 (0.156–8.544)	0.887
Divorced/widowed/separated	310	1.670 (1.257–2.219)	<0.001	1.765 (1.281–2.431)	<0.001
Unknown	42	1.399 (0.728–2.687)	0.313	1.166 (0.581–2.338)	0.666

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Total	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Race			0.081		0.508
White	484	Reference			
Black	166	1.405 (1.010–1.957)	0.044	1.313 (0.926–1.862)	0.127
Other	154	0.887 (0.605–1.298)	0.536	1.085 (0.728–1.617)	0.687
Unknown	5	0.000 (0.000–Inf)	0.993	0.000 (0.000–Inf)	0.993

CI, confidence interval.

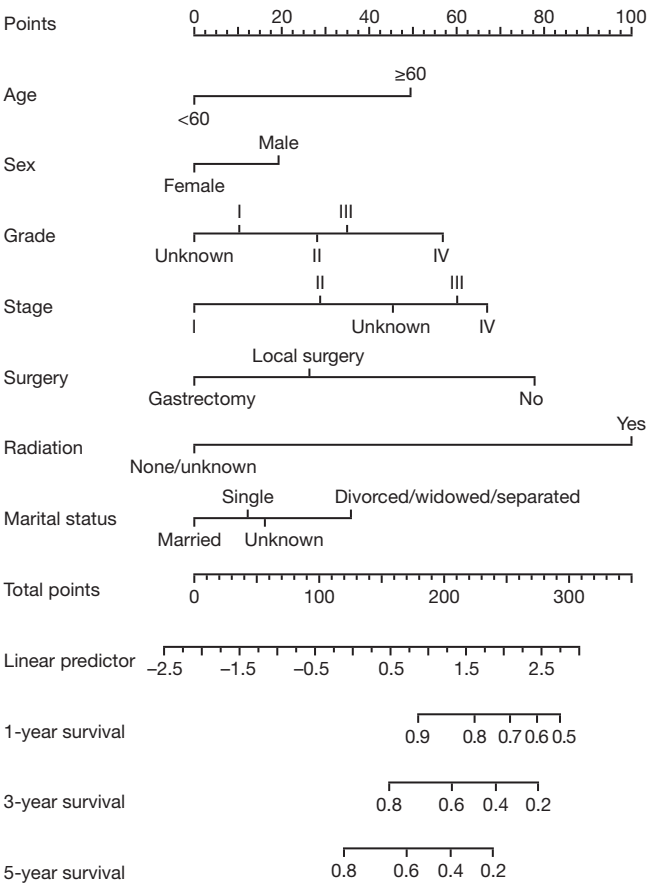

Figure 1 Nomogram chart forecasting 1-, 3-, and 5-year OS outcomes in gastrointestinal stromal tumor patients. OS, overall survival.

versus projected values for the 1-, 3-, and 5-year survival probabilities in both the modeling and validation cohorts were notably aligned (see *Figure 3*). Additionally, our clinical DCA reaffirmed the efficacy of our model in both groups, indicating its potential clinical utility and patient benefit (displayed in *Figure 4*).

Risk stratification analysis

Utilizing the predictive indicators present in the nomogram, we categorized the individuals from both the modeling and validation cohorts into high-risk and low-risk segments. With R language, we graphically represented the survival patterns of these subgroups (refer to *Figure 5*). Evidently, the scatterplot elucidated a higher mortality rate among high-risk participants than among their low-risk counterparts. A subsequent Kaplan-Meier survival evaluation revealed that the low-risk segment demonstrated a substantially elevated survival trajectory in both cohorts relative to the high-risk segment. The marked discrepancy in the OS trajectories between these risk divisions was underpinned by a significant difference (P<0.001), reinforcing the adept predictive caliber of our constructed nomogram (see *Figure 6*).

Discussion

Over the decade from 2010 to 2019, our investigation encompassed 1,213 cases diagnosed with GIST. This expansive datas*et all*owed for a robust assessment of the survival metrics, specifically at the 1-, 3-, and 5-year marks. From our evaluations, several variables emerged as key independent prognostic indicators: age, sex, pathological differentiation, TNM stage, surgical intervention, radiotherapy, and marital status.

The literature suggests that individuals around the age of 60 are predominantly diagnosed with this condition (6,7). Aligning with these findings, we utilized 60 years as a critical age threshold, deducing age's profound impact

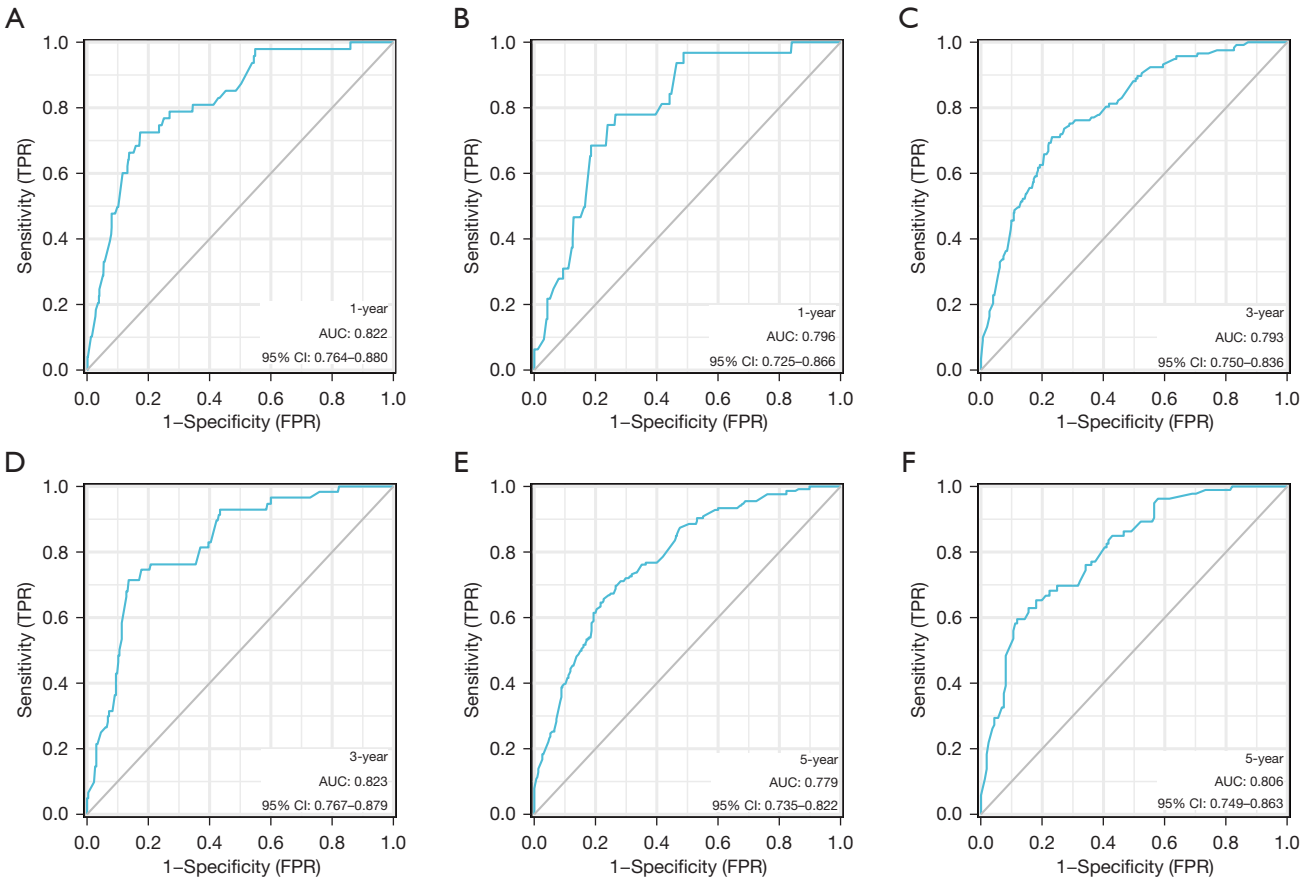

Figure 2 ROC curves evaluating the nomogram's precision for 1-, 3-, and 5-year projections. (A,C,E) The modeling cohort; (B,D,F) the validation cohort. TPR, true positive rate; FPR, false positive rate; AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic.

on prognosis. In a unique revelation of this study, gender was identified as an influential prognostic factor, with females in China exhibiting a heightened predisposition toward soft tissue sarcomas (8). Furthermore, marital status's role in cancer prognosis has been underscored in various retrospective evaluations (9,10). Our multivariate analysis echoes these sentiments, reinforcing marital status as a pivotal prognostic element, likely attributed to the emotional and psychological support offered through marital bonds. Beyrouti and colleagues elucidated the rarity of stomach sarcoma and the dependence of its prognosis on varied parameters (11). Consistent with prior research, this study accentuates the inverse relationship between the AJCC staging post-GIST resection and the 5-year disease-free survival (DFS) rate (12). The prognosis of GIST is significantly influenced by TNM stage. Surgical interventions remain paramount in managing GIST. Shannon *et al.* pinpointed augmented OS in older patients undergoing resection, albeit with notable mortality risks (13). Peiper *et al.* highlighted the favorable outcomes following an extensive initial resection (14). Meanwhile, a study by Gronchi *et al.* underscored the disparities in OS among patients with varied resection extents (15). Our data included some ambiguities regarding surgical methodologies. However, we broadly categorized surgical intervention as a binary factor, underscoring its profound positive influence on prognosis. Traditionally, GIST treatments seldom involve radiotherapy. However, scholars in certain studies propose its potential benefits (16,17). Zhang *et al.* conducted a comprehensive review, suggesting radiotherapy's efficacy in selecting advanced GIST cases, albeit without discernible survival enhancements (18). Our research posits radiotherapy as an influential prognostic factor, albeit indicative of an adverse prognosis. Further

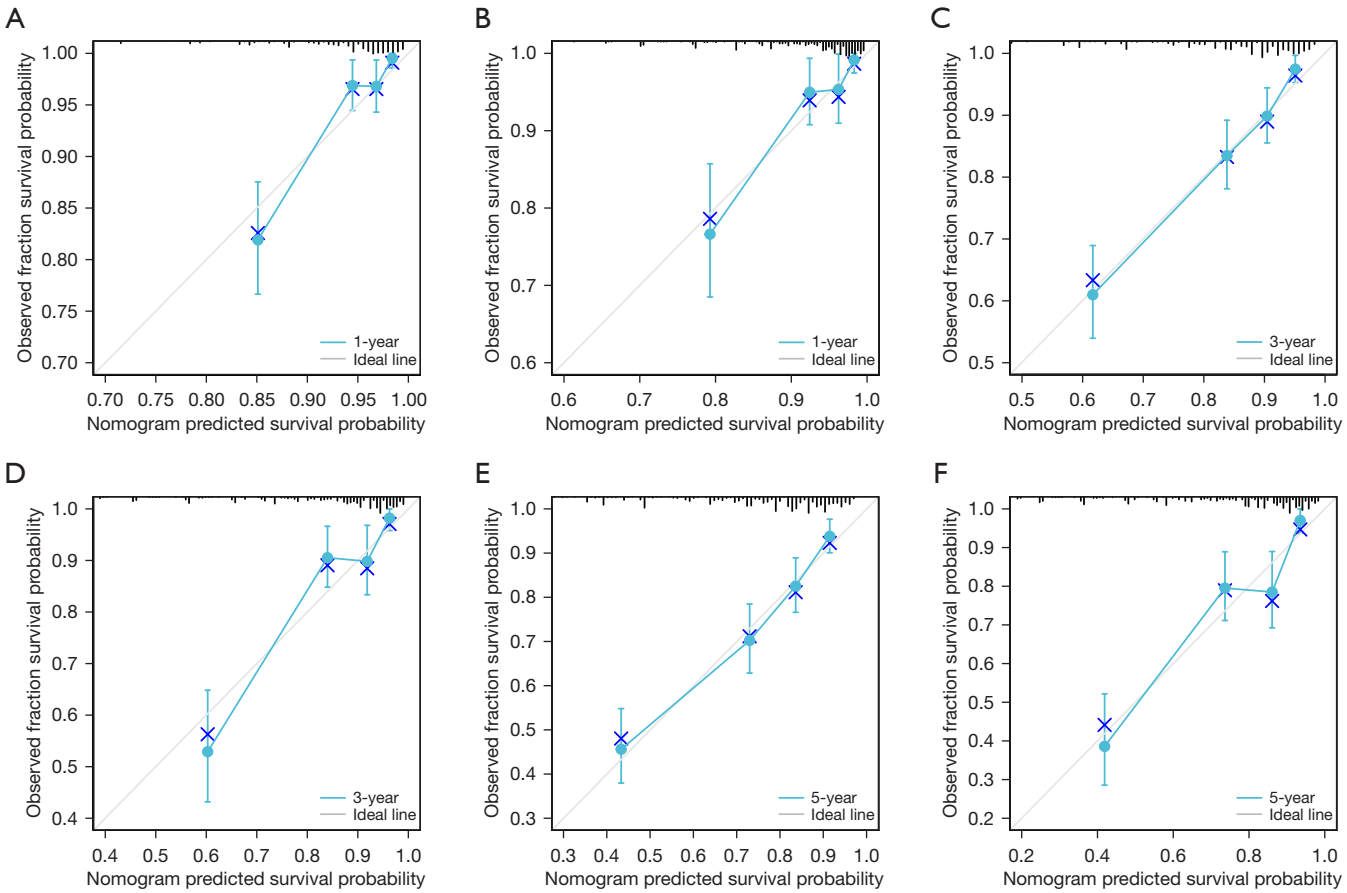

Figure 3 Calibration plots for the nomogram's 1-, 3-, and 5-year OS predictions. The x-axis represents the predicted OS, while the y-axis indicates the observed OS. (A,C,E) The modeling cohort; (B,D,F) the validation cohort. OS, overall survival.

prospective evaluations are warranted to delve deeper into this association.

Our investigations demonstrate that the nomogram model holds promise in accurately forecasting the survival outcomes of individuals with GIST, thereby enhancing the precision of clinical judgments. Nevertheless, the limitations of this study also need to be noted. First, the SEER database, a prominent clinical cancer repository in the U.S., predominantly represents Black and White populations, leaving the Asian demographic underrepresented. Second, inherent to its retrospective nature, this work may encompass unforeseen selection biases. Last, our validation was internally confined; expanded validation through alternate databases or prospective evaluations remains paramount. For those diagnosed with GIST, early surgical intervention combined with reinforced psychological support is pivotal. However, large-sample, multicenter retrospective and prospective studies are still needed to provide better guidance on whether postoperative adjuvant radiotherapy should be performed and what kind of surgery should be followed by adjuvant radiotherapy. The original data in SEER database did not contain these clinical characteristics (e.g., mitotic rate, depth of invasion), so statistics could not be made. The study does not show any effect of tumor size, which may be related to the insufficient number of cases and the lack of external validation, and further research is needed. Factors such as type of driver mutations, germline *vs.* sporadic, and variant mutations within specific exons, allow selecting the type of targeted therapy that would benefit the most patients with advanced disease or patients at increased risk for recurrence. The proposed nomogram ignores the most important advances in the prognostication and therapy of GISTs. This is a limitation of this study, and further research is needed.

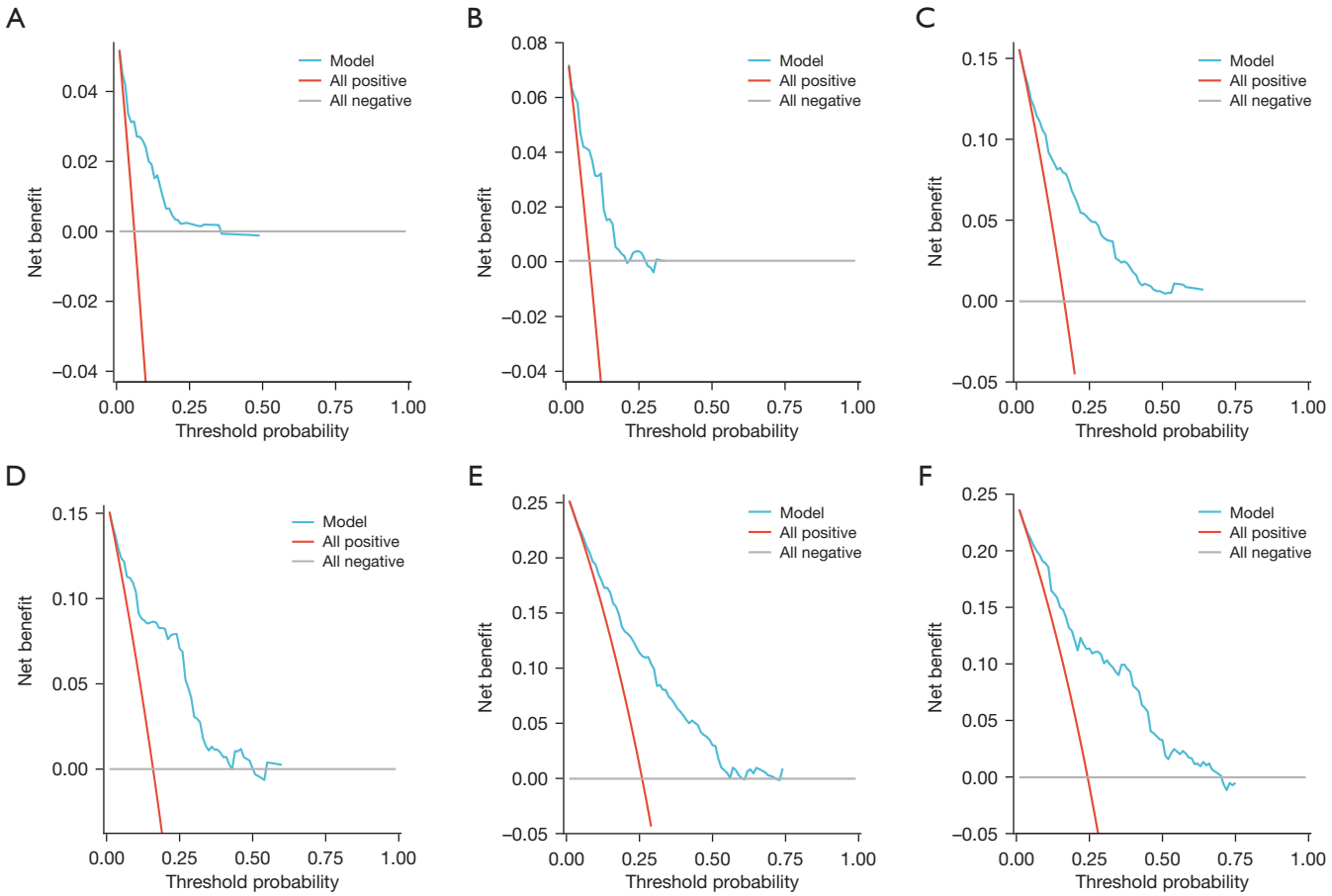

Figure 4 Decision curve analyses illustrating the net benefits of the nomogram's 1-, 3-, and 5-year OS predictions. (A,C,E) The modeling group; (B,D,F) the validation set. OS, overall survival.

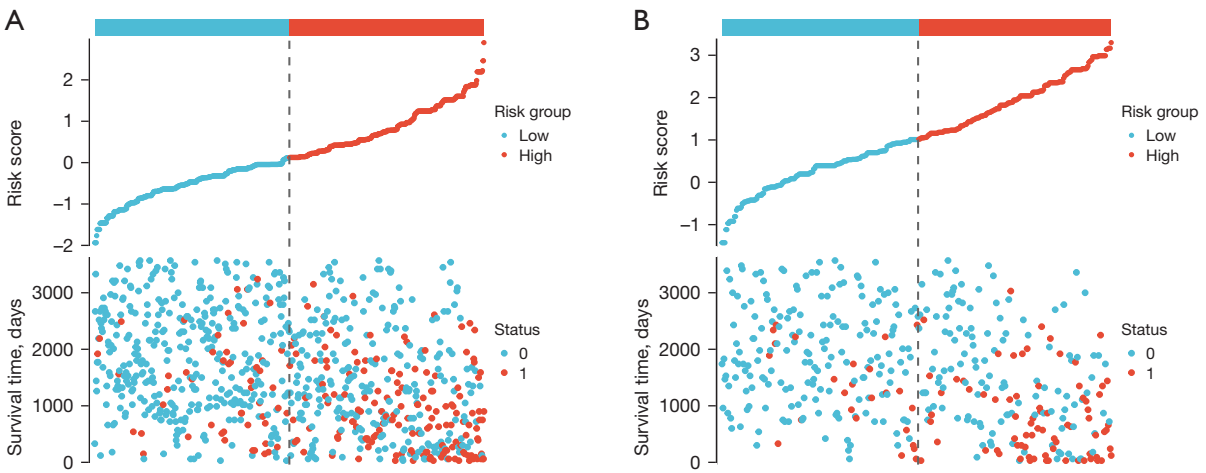

Figure 5 Diagrams presenting risk factors for both cohorts. (A) The modeling group; (B) the validation group. 0 means alive, 1 means dead.

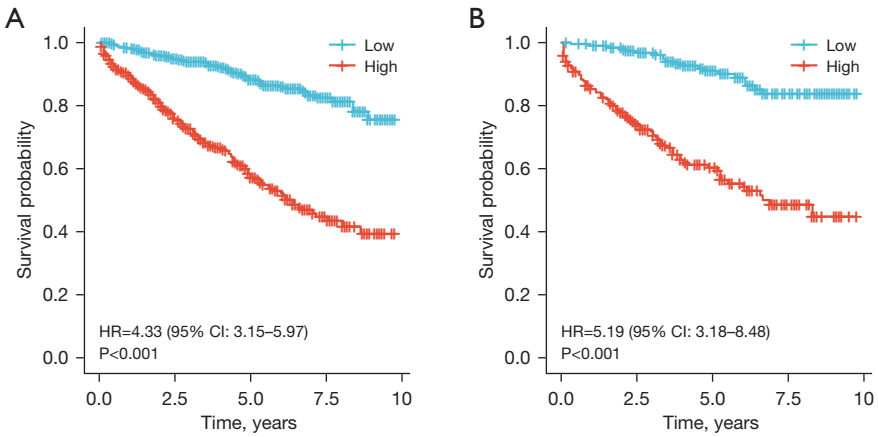

Figure 6 Depiction of survival curves for both groups. (A) The modeling cohort; (B) the validation group. HR, hazard ratio.

Conclusions

Our research is pioneering in devising a survival prognosis tool for individuals diagnosed with GIST. Leveraging this nomogram offers clinicians a reliable tool, enhancing the precision of their judgments. Nevertheless, performing broader external validations remains a crucial next step.

Acknowledgments

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Footnote

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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).

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