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Development and validation of a prognostic nomogram for gastric GIST patients under 65 years of age

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Abstract

Background Gastric gastrointestinal stromal tumor (GIST) is the most common sarcoma of the digestive tract. Due to the fact that younger patients often present with more aggressive disease and exhibit different treatment responses compared to older patients, this study aimed to develop models to predict overall survival (OS) and cancer-specific survival (CSS) in postoperative gastric GIST patients under the age of 65, thereby aiding in the creation of optimal, individualized treatment strategies.

Methods We first reviewed demographic and clinicopathological characteristics data from 1990 to 2021 of patients diagnosed with GIST in the Surveillance, Epidemiology, and End Results (SEER) database. Subsequently, we examined the data of the external validation cohort from Northern Jiangsu People's Hospital. Utilizing Lasso analysis and multivariate Cox regression analyses, we confirmed the independent risk factors and created nomograms for the prediction of OS and CSS of postoperative gastric GIST patients under age 65, followed by validation with the external validation cohort. To assess the predictive ability of these nomograms, we employed the concordance index (C-index), calibration curves, time-dependent receiver operating characteristic (ROC), and decision curve analysis (DCA).

Results A total of 735 eligible gastric GIST patients from SEER were enrolled in the training cohort and 113 patients from Northern Jiangsu People's Hospital were enrolled in the validation cohort. 3 factors (grade, M stage, mitotic index) associated with OS and 4 factors (grade, T stage, M stage, mitotic index) associated with CSS were included in the model respectively. In the training cohort, the C-index was 0.706 (95% CI = 0.645–0.767) for OS and 0.880 (95% CI = 0.845–0.915) for CSS, while in the validation cohort, the C-index was 0.718 (95% CI = 0.618–0.818) for OS and 0.805 (95% CI = 0.715–0.895) for CSS. Calibration curves and ROCs for 3-, 5-, and 8-year OS and CSS showed high discrimination and calibration. DCA results showed that the nomograms had clinical value in predicting OS and CSS in gastric GIST patients.

Conclusion Our nomograms satisfactorily predicted OS and CSS in postoperative gastric GIST patients under age 65, which could assist clinicians in evaluating postoperative status, guiding subsequent treatments, and improving patient prognosis.

Keywords Gastrointestinal stromal tumor, Nomogram, Overall survival, Cancer-specific survival

1 Background

Gastrointestinal stromal tumors (GISTs) are the prevalent mesenchymal tumors in the gastrointestinal tract. They typically occur at a rate of approximately 1.2 per 100,000 individuals annually in the world [1]. GIST was first introduced by Mazur in 1983 [2], they were believed to arise from Cajal cells. Mutations in the kit [3] and platelet-derived growth factor receptor-alpha (PDGFR-α) [4] genes are regarded as the main cause of GIST. GIST is frequently found in the stomach, accounting for over half of all GIST cases [5, 6]. Clinically, GIST is known to cause symptoms such as bleeding, anemia, obstruction and pain [7].

Although GIST is rare, its incidence has been on the rise in recent years [8]. Furthermore, a significant proportion of GIST patients present with other malignancies concurrently [9]. Surgical resection remains the standard treatment for non-metastatic GIST patients, while imatinib-targeted therapy is commonly used for those with liver or peritoneal metastases [6, 10]. GIST exhibits a broad spectrum of prognoses, with gastric GIST typically having a relatively favorable prognosis [11]. However, an observational study from China reported that the 5-year survival rate for gastric GIST was approximately 66.5%, with younger patients being associated with worse clinical stages and higher risk, indicating a relatively poor prognosis [12]. Further studies have shown that younger patients are more likely to experience recurrence of GIST after surgery, with some research confirming that younger patients present with more advanced tumor stages at diagnosis, which are often associated with a higher likelihood of recurrence [13, 14]. This underscores the importance of considering age-specific factors in both prognostic forecasting and treatment planning for younger patients. Therefore, prognostic forecasting of young gastric GIST patients based on clinicopathological factors is critical and plays a significant role in the development of tailored treatment plans.

The Surveillance, Epidemiology, and End Results (SEER) database is a population-based cancer registry in the United States, covering approximately 28% of the American population. This comprehensive and authoritative resource plays a crucial role in analyzing cancer incidence, survival trends, and treatment outcomes. With its extensive collection of cancer-related data, SEER serves as an indispensable tool for in-depth research into specific malignancies. Nomograms have become an essential prognostic tool in clinical practice, enabling physicians to individualize survival predictions and guide treatment decisions [15]. While several studies have developed predictive models for postoperative survival in GIST patients, these models often suffer from limitations, such as including patients of all ages without specific consideration for younger individuals, insufficient sample sizes, and a lack of external validation, which undermine their clinical reliability and applicability. Given that younger GIST patients often present with more aggressive disease and poorer prognoses, they require tailored predictive tools to optimize risk assessment and management strategies. To address this gap, our study specifically focuses on patients under 65 years of age and utilizes the SEER database to develop a more precise and reliable nomogram for predicting the prognosis of gastric GIST patients in this age group.

2 Methods

2.1 Data source and patient selection

This retrospective study was performed by using data from the SEER*Stat Software (version 8.4.2) and the Norther Jiangsu People's Hospital from January 2010 to December 2015. Patients with the criteria below were included: (1) patients who were 20–65 years old; (2) patients were identified by codes "8936" for ICD-O-3 histology types; (3) the primary site recode was "stomach". Patients who met the criteria below were excluded: (1) patients with multiple primary tumors; (2) patients without surgery or miss the information of surgery; (3) missing data on race, tumor size, regional nodes examined (RNE) or other clinical variables; (4) patients discovered by autopsy and death certificate and (5) survival time < 3 months. Figure 1 illustrates the patient selection procedure.

2.2 Statistics analysis

First, continuous variables in the clinical dataset were categorized based on predefined cutoff values. For example, age was categorized using 45 years as the threshold, regional lymph node dissection was categorized based on 4 nodes, and the time from diagnosis

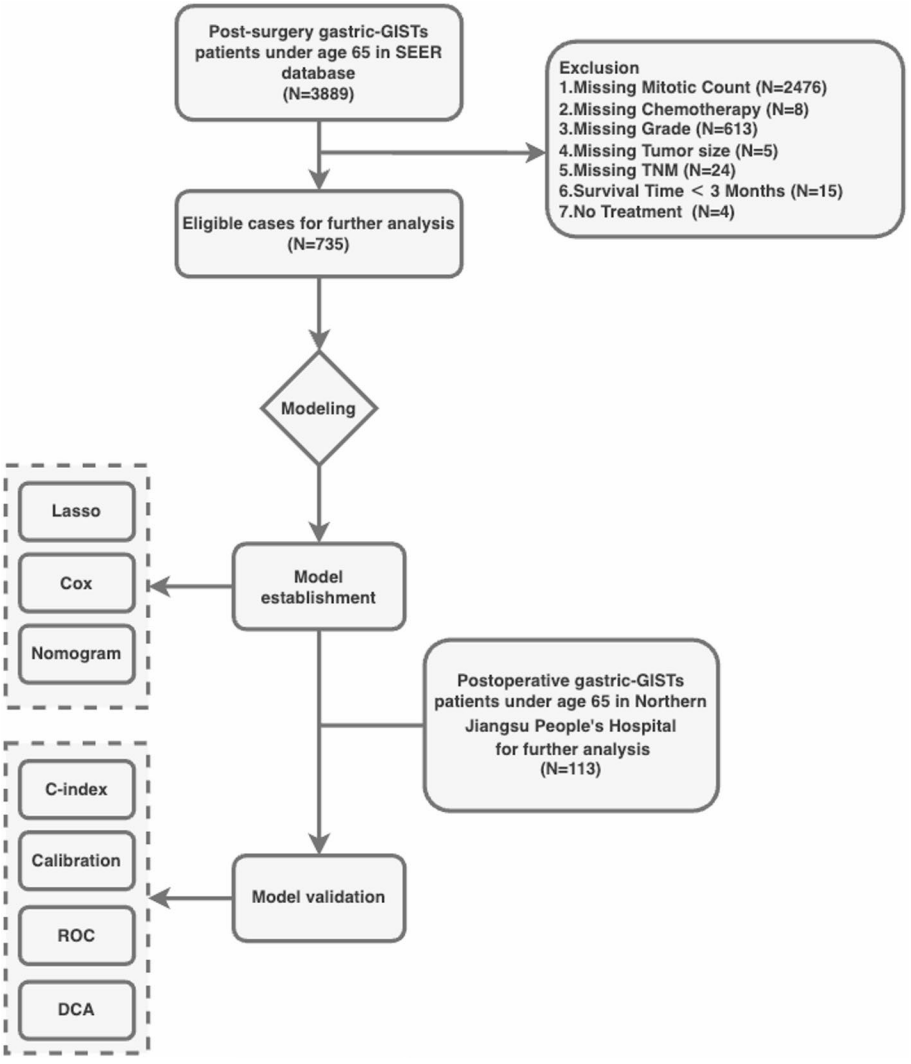

Fig. 1 Flowchart of the research

to surgery was categorized using 1 month and 3 months as cutoffs. The transformed variables were presented as counts and percentages. Additionally, the TNM staging data was reclassified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. To compare the categorical variables, chi-square tests and Fisher's exact tests were performed. Lasso regression was then applied to select relevant variables from the large set of clinical variables available [16]. Subsequently, Cox regression analysis was conducted to assess the independent prognostic factors. Based on the results of the regression analysis, a nomogram was constructed. The concordance index (C-index) was calculated to evaluate the discriminatory ability of the model, with a higher C-index indicating better discrimination. To assess the prognostic accuracy, time-dependent receiver operating characteristic (ROC) curves and the corresponding areas under the curves (AUCs) for 3-, 5-, and 8-year survival were generated. A calibration curve was created using 1000 bootstrap resamples to evaluate the consistency of the predicted survival probabilities. Finally, decision curve analysis (DCA) was performed on the development cohort to assess the clinical utility of the nomogram. The x-axis of the decision curve represents the threshold probability, while the y-axis shows the net benefit of clinical decisions based on this threshold. All statistical analyses were conducted using R software version 4.3.1, with the rms, tidyverse, timeROC, dcurves, pec, and glmnet packages. A significance level of $P < 0.05$ was considered statistically significant for all analyses.

3 Results

3.1 Patient characteristics

735 gastric GIST patients finally were included in this study from SEER as the training set and 113 gastric GIST patients from local database was the validation set. Table 1 summarizes the clinicopathological features of the training and validation cohorts. There were no substantial differences between the two cohorts except race.

3.2 Nomogram construction

Lasso regression was applied to analyze the correlation between variables and OS (Fig. 2A, B). All the 11 variables with non-zero coefficients were selected for multivariate analysis, included grade, M stage, mitotic index. After multivariate analysis of these 3 factors, all of them were found associated with OS ($P<0.05$) which is summarized in Table 2. Finally, we used these 3 factors to construct a 3-, 5-, and 8-year OS nomogram (Fig. 3A).

Lasso regression was also applied to analyze the correlation between variables and CSS (Fig. 2C and D). After multivariate analysis, 4 factors were associated with CSS ($P<0.05$, Table 2). The 4 independent prognostic factors were: grade (III, IV), T stage (T4), M stage (M1), mitotic index (> 10). Finally, we used these 4 factors to construct a 3-, 5-, and 8-year CSS nomogram (Fig. 3B).

3.3 Validation of nomogram

The training cohort demonstrated good accuracy in predicting OS with a C-index of 0.706 (95% CI = 0.645–0.767) and CSS with a C-index of 0.880 (95% CI = 0.845–0.915) (Table 3). The calibration plot revealed well-calibrated OS nomogram predictions both in training (Figure S1A–C) and validation cohort (Figure S2A-C), closely aligning with

Table 1 Characteristics of patients with gastric GIST in the training and validation cohorts

Characteristics	Training cohort	Validation cohort	*p*
Total patients	735	113	
Age at diagnosis (Year)			0.169
≥ 20, <45	177 (24)	20 (18)	
≥ 45, <65	558 (76)	93 (82)	
Sex			0.947
Male	332 (45)	52 (46)	
Female	403 (55)	61 (54)	
Race			**< 0.001**
White	432 (59)	0 (0)	
Black	195 (27)	0 (0)	
Other	108 (15)	113 (100)	
Location			0.934
Lesser curvature	74 (10)	10 (9)	
Great curvature	118 (16)	18 (16)	
Other	544 (74)	85 (75)	
Grade			0.202
Well differentiated (I)	382 (52)	52 (46)	
Moderately differentiated (II)	230 (31)	34 (30)	
Poorly differentiated (IIII)	52 (7)	14 (12)	
Undifferentiated (IV)	71 (10)	13 (12)	
T (AJCC 8th)			0.271
1	138 (19)	23 (20)	
2	261 (36)	33 (29)	
3	184 (25)	37 (33)	
4	152 (21)	20 (18)	
N (AJCC 8th)			0.353
0	716 (97)	108 (96)	
1	19 (3)	5 (4)	
M (AJCC 8th)			0.193
0	691 (94)	102 (90)	
1	44 (6)	11 (10)	
Regional nodes examined			0.311
0	561 (76)	93 (82)	
≥ 1, <4	65 (9)	9 (8)	
>4	109 (15)	11 (10)	
Chemotherapy			0.134
No	470 (64)	81 (72)	
Yes	265 (36)	32 (28)	
Diagnosis time (Month)			0.548
≤ 1	452 (61)	76 (67)	
>1, ≤3	253 (34)	33 (29)	
>3	30 (4)	4 (4)	
Summary stage			0.096
Regional	73 (10)	14 (14)	
Localized	613 (83)	88 (78)	
Distant	49 (7)	11 (10)	
Mitotic index (mitoses per 50 HPF)			0.241
<5	519 (71)	71 (63)	
≥ 5, <10	120 (16)	24 (21)	
≥ 10	96 (13)	18 (16)	

GISTs gastrointestinal stromal tumor, *AJCC* American Joint Committee on Cancer. Bold values indicate $p < 0.05$.

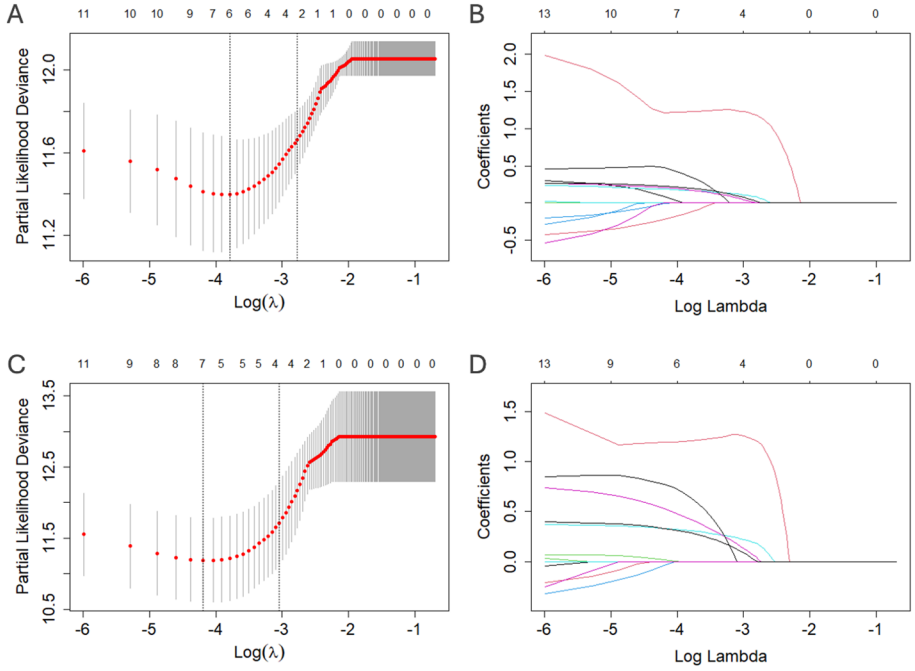

Fig. 2 Screening of variables based on Lasso regression. **A** Cross-validation plot for OS. **B** Distribution of Lasso regression coefficients for OS. **C** Cross-validation plot for CSS. **D** Distribution of Lasso regression coefficients for CSS. Each colored curve represents the Lasso coefficient of one variable at different lambda values

Table 2 Multivariate analyses of OS and CSS in training cohort

	OS		CSS	
Characteristics	HR (95%CI)	p	HR (95%CI)	p
Grade				
Well differentiated (I)				
Moderately differentiated (II)	1.400 (0.813–2.411)	0.225	3.596 (1.293–9.994)	**0.014**
Poorly differentiated (III)	1.910 (0.939–3.886)	0.074	4.314 (1.387–13.420)	**0.012**
Undifferentiated (IV)	2.430 (1.255–4.704)	**0.008**	5.100 (1.682–15.466)	**0.004**
T (AJCC 8th)				
1				
2			1.295 (0.143–11.730)	0.818
3			4.426 (0.565–34.700)	0.157
4			8.104 (1.042–63.023)	**0.046**
M (AJCC 8th)				
0				
1	4.591 (2.777–7.590)	**< 0.001**	3.767 (2.045–6.941)	**< 0.001**
Mitotic index (mitoses per 50 HPF)				
<5				
≥ 5, <10	1.294 (0.791–2.291)	0.377	1.444 (0.665–3.134)	0.353
≥ 10	1.870 (1.083–3.227)	**0.025**	1.987 (1.025–3.849)	**0.042**

OS overall survival, *CSS* cancer-specific survival, *HR* hazard ratio, *CI* confidence interval. Bold values indicate p < 0.05.

observed probabilities across subgroups. In the validation cohort, OS and CSS exhibited C-indices of 0.718 (95% CI = 0.618–0.818) and 0.805 (95% CI = 0.715–0.895) respectively. The calibration plots in both sets affirmed optimal agreement between CSS predictions and actual observations (Figure S1D-F and Figure S2D-F). The accurate prediction model was further evaluated using time-dependent ROC curves. In the training cohort, the OS nomogram obtained AUC values of 0.745, 0.678, and 0.742 for 3-, 5-, and 8-year

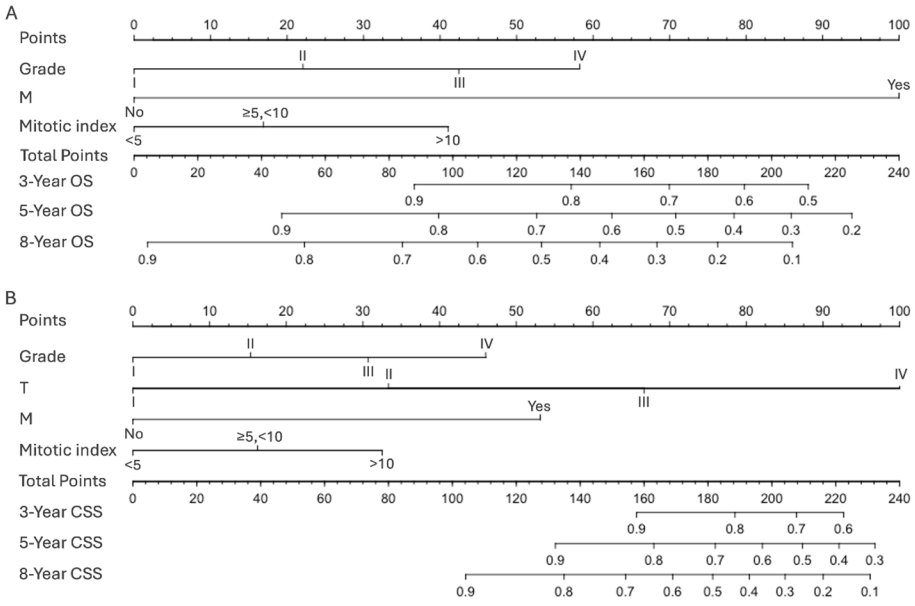

Fig. 3 Nomograms for predicting 3-, 5-, and 8-year **A** OS and **B** CSS of postoperative patients with gastric GIST under age 65

Table 3 C-indices for the models of OS and CSS

	OS		CSS	
	C-index	95%CI	C-index	95%CI
Training cohort	0.706	0.645–0.767	0.880	0.845–0.915
Validation cohort	0.718	0.618–0.818	0.805	0.715–0.895

C-index concordance index, *OS* overall survival, *CSS* cancer-specific survival, *CI* confidence interval

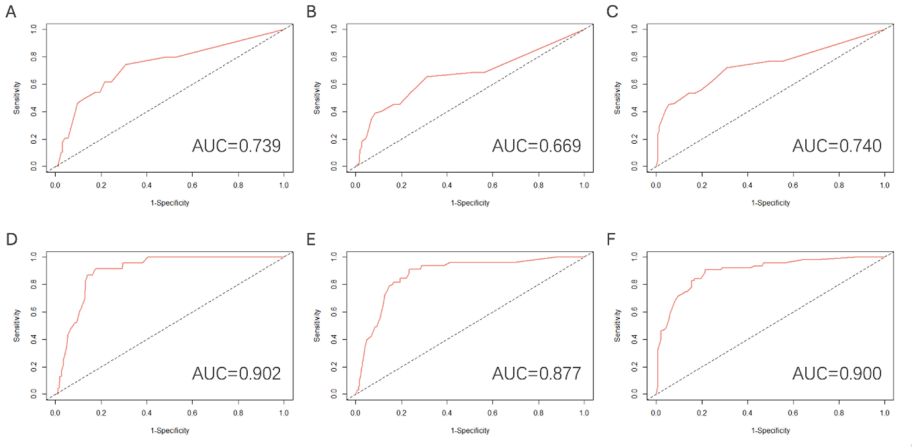

Fig. 4 The time-dependent ROC curves and AUC values of 3-, 5-, and 8-year OS (**A**–**C**) and CSS (**D**–**F**) in the training cohort

predictions (Fig. 4A–C), while in the validation cohort, the AUC values were 0.665, 0.770, and 0.851 (Fig. 5A–C). Similarly, the CSS nomogram yielded AUC values of 0.880, 0.865, and 0.901 for the 3-, 5-, and 8-year predictions in the training cohort (Fig. 4D–F) and 0.838, 0.871, and 0.856 in the validation cohort (Fig. 5D–F). In addition, the DCA

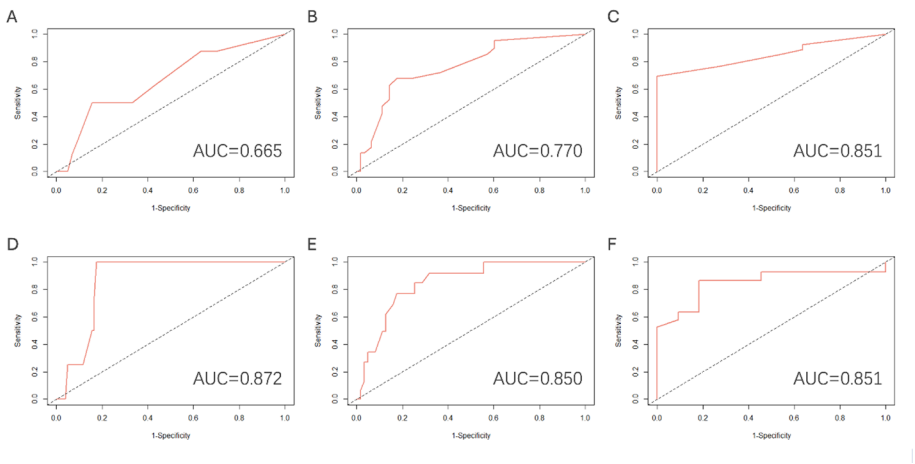

Fig. 5 The time-dependent ROC curves and AUC values of 3-, 5-, and 8-year OS (**A**–**C**) and CSS (**D**–**F**) in the external validation cohort

curves presented good positive net benefits at different time points both in training cohort and validation cohort (Figure S3 and S4).

4 Discussion

GIST accounts for 3-4% of gastrointestinal malignancies, with gastric stromal tumors being a particular focus of this study [17]. GIST incidence is typically concentrated in individuals aged 50 to 60 [7]. However, younger patients generally have a poorer prognosis [12], even in cases of gastric GIST, which typically demonstrate a better prognosis compared to GIST in other locations. Surgery is considered the gold standard treatment for gastric GIST, with a significant number of patients achieving a cure through surgery. However, surgical malpractice can lead to tumor rupture and an increased probability of recurrence. Once gastric GIST recurs, it results in a very poor prognosis and significantly reduces patient survival. According to a study involving 81 patients, most recurrences of GISTs in patients who have undergone complete resection occur within 3 years [18]. However, certain cases of recurrence may occur much later. Papalambros et al. reported the case of a 71-year-old man who experienced recurrence of GIST at the gastrojejunal anastomosis 8 years after undergoing partial gastrectomy for a very small primary gastric GIST [19]. Our study focuses on investigating and establishing OS and CSS in patients under age 65 with gastric GIST at 3-, 5-, and 8-year intervals postoperatively. We analyzed the clinicopathological features and prognostic factors of these patients' using data from the SEER database as well as independent data from our center. We developed and validated a nomogram for predicting OS and CSS in postoperative patients under age 65 with gastric GIST. In our study, we used the Lasso regression algorithm to identify independent factors associated with OS and CSS. The three variables identified as independent factors for OS were tumor grade, M-stage, and mitotic index. Similarly, for CSS, tumor grade, T-stage, M-stage, and mitotic index were identified as independent factors. Based on these variables, we constructed two parsimonious nomograms for OS and CSS, which greatly improved the clinical significance of our study and demonstrated high accuracy. Additionally, the nomograms, especially for CSS, performed well in external validation.

In the OS nomogram, the M-stage made the most significant contribution among the three parameters. Tumor grade and mitotic index worked together to better predict patient prognosis. The CSS nomogram included an additional factor, T-stage. Unlike the OS nomogram, in the CSS nomogram, T-stage made the second major contribution, while tumor grade became the most significant factor. Nonsignificant factors, such as race, were excluded from the nomogram. Although race was the only differing factor between the training and validation cohorts, the validation remained stable, indicating a strong model applicable to different countries. Adjuvant therapies, including targeted therapy and chemotherapy, were not considered independent factors in Lasso regression. This result seems to depart from the traditional view, likely because these therapies are generally associated with poor tumor features rather than treatment failure [20]. In a randomized, non-blind, multicenter study evaluating imatinib in 147 patients with advanced GIST, partial responses were achieved in 54% of patients overall [21]. Additionally, a 10-year follow-up RCT conducted by Heikki Joensuu et al. demonstrated that long-term treatment with imatinib can prevent approximately 50% of deaths caused by GIST after surgery [22]. Our study did not screen all GIST patients for imatinib therapy criteria, which needs further exploration in subsequent studies.

Metastasis significantly impacts patient survival, as evidenced by various studies. It also played a crucial role in both of our constructed nomogram prediction models. Risk factors affecting GIST metastasis include tumor size, high-risk tumor classification, and tumor rupture caused by surgery [23], Some studies have indicated that laparoscopic surgery for GISTs of 5 cm or smaller can be safely performed, but laparoscopic surgery for GISTs larger than 5 cm can increase the risk of tumor rupture [24]. However, this remains controversial. In a retrospective study of 903 GIST patients with a minimum 5-year follow-up period, it was observed that the short-term prognosis of patients who underwent laparoscopic surgery was comparable to open surgery, regardless of tumor size exceeding 5 cm [25]. Advances in laparoscopic technology may have contributed to this outcome. However, it is well-established that patients with metastases have a poor prognosis. Despite significant advancements in the clinical management of advanced GIST, challenges like imatinib resistance still require emphasis [26]. Lymph node metastasis is rare for gastric GIST, thus routine lymphadenectomy is not recommended in surgery [27]. In our study, lymph node metastasis did not influence patient prognosis, and lymphadenectomy did not improve patient survival.

The latest NCCN guidelines confirm that mitotic index and tumor size are crucial predictors of malignant potential and aid in risk stratification [6], which our study also supported. Mitotic index is significantly associated with the survival of many malignant tumors such as cutaneous melanoma [28], breast cancer [29] and lung cancer [30]. However, the reliability of mitotic counting is controversial due to various factors, including differing criteria for identifying mitosis among pathologists, variations in the size of the microscope field-of-view during counting, and the impact of tissue fixation on the count [31]. In numerous studies over the years, tumor size has been regarded as a significant factor impacting the prognosis of GIST [32, 33]. This is due to the higher likelihood of oversized tumors to spontaneously rupture, leading to abdominal metastases, and their increased tendency to cause obstruction, bleeding, and other gastrointestinal symptoms [1, 5]. In the 8th edition of AJCC, T is graded based on tumor size. Hence, in this study, T was utilized as a substitute for tumor size in the table, where it assumes a crucial role

in the CSS prediction model. Apte et al. found that imaging always underestimated gastric GIST size. Potentially, the exophytic nature of GIST may cause a reduction in echogenic resolution at the farthest extent of the tumor [34]. In recent years, many clinicians have focused on aligning the imaging size of gastric cancer GIST with the pathological size [35]. However, surgical resection remains the gold standard for determining tumor size.

Our nomograms highlighted the significance of tumor grade. In the context of the multivariate analyses, grade I was linked with OS, while grades II, III, and IV were associated directly with CSS. Research using public databases identified an adverse correlation between poor tumor grade and liver metastasis [36]. Inferior tumor grades often indicate an unfavorable prognosis [37]. Age also impacts the prognosis of GIST, with older patients usually displaying an unfavorable prognosis compared to younger counterparts due to generally poor health conditions [38]. An intriguing observation was that nearly all gastric GISTs in patients under 20 years, along with a significant proportion in patients under 40 years, were Succinate Dehydrogenase (SDH) deficient. Notably, SDH-deficient GISTs tend to be multiple and often relate to an adverse outcome [39]. In a single-center study, approximately 14% of GIST patients were found to have other non-GIST tumors, the majority being gastric cancers [40], A study by Shen et al. suggested that the risk of death due to GIST was notably heightened in patients with GIST as their sole disease, compared to those diagnosed with GIST as a secondary malignancy [37]. Considering the slow incremental trend of gastric mesenchymal stromal tumor incidence and the observed shift towards younger demographics, it becomes a priority for clinicians to maintain high vigilance for prompt detection and treatment, potentially affording these patients a better prognosis.

Our nomograms provide a practical and reliable tool for clinicians to make individualized prognostic assessments for gastric GIST patients under 65 years old. By incorporating key prognostic factors such as tumor grade, mitotic index, and TNM staging parameters, these models enable effective risk stratification, allowing clinicians to classify patients into different prognostic groups. This facilitates personalized follow-up strategies, where low-risk patients may require routine monitoring, while high-risk individuals may benefit from more frequent imaging and clinical evaluations. Such an approach enhances individualized treatment planning, potentially improving long-term patient outcomes.

However, our study has several limitations. Firstly, as a retrospective study based on the SEER database, selection bias is inevitable. Moreover, due to missing data, a large number of patients were excluded, with the final analysis including less than 20% of the available cases, potentially impacting the representativeness of the study cohort. Secondly, the SEER database lacks crucial clinical variables, such as tumor recurrence, surgical approach, and adjuvant therapy, which may limit the predictive power of the nomograms. Thirdly, the relatively small sample size prevented us from performing internal validation, leading us to rely on external validation to assess the model's generalizability. Finally, further validation in large-scale, prospective studies is essential to confirm the clinical utility of our nomogram and ensure its widespread applicability in real-world settings.

5 Conclusion

We aimed to construct a robust survival prediction model that would accurately assess the 3-, 5-, and 8-year OS and CSS of postoperative gastric GIST patients under the age 65. The nomogram demonstrated excellent performance in both our training and external validation cohorts, making it a reliable tool for predicting patient outcomes. However, despite its reliability, there is a clear need for additional clinical data to integrate more risk factors and enhance the model's accuracy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-03092-z.

Supplementary Material 1

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Not applicable.

Author contributions
Yifan Cheng and Shuyang Gao collated the study data, assisted with data analysis, and wrote the initial draft of the paper. Zhen Tian, Shuai Zhao, Ruiqi Li, Jiajie Zhou and Yayan Fu conceived and designed the study. Qiannan Sun and Daorong Wang revised the article.

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Data availability
The data presented in this study are available on reasonable request.

Declarations

Ethics approval and consent to participate
This study conformed with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Northern Jiangsu People's Hospital (2019KY-022). Informed Consent was obtained from all the participants involved in the study.

Consent for publication
All authors have reviewed and agreed to the published version of the manuscript.

Competing interests
The authors declare no competing interests.

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