



## Research paper

# Development and validation of a prognostic nomogram to predict recurrence in high-risk gastrointestinal stromal tumour: A retrospective analysis of two independent cohorts



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## ABSTRACT

**Background:** The risk of recurrence in localised, primary gastrointestinal stromal tumour (GIST) classified as high-risk after complete resection varies significantly. Thus, we aimed to develop a nomogram to predict the recurrence of high-risk GIST after surgery to aid patient selection.

**Methods:** We retrospectively evaluated patients ( $n = 424$ ) with high-risk GIST who underwent curative resection as the initial treatment at two high-volume medical centres, between January 2005 and September 2019. The least absolute shrinkage and selection operator (LASSO) regression model was utilised to select potentially relevant features. Multivariate Cox proportional hazards analysis was used to develop a novel nomogram.

**Findings:** The nomogram comprised age, fibrinogen levels, prognostic nutritional index (PNI), platelet-lymphocyte ratio (PLR), mitotic counts and tumour size, which provided favourable calibration and discrimination in the training dataset with an AUC of 0.749 and a C-index of 0.742 (95%CI: 0.689–0.804). Further, it showed acceptable discrimination in the validation cohort, with an AUC of 0.778 and C-index of 0.735 (95%CI: 0.634–0.846). The time-dependant receiver operating characteristic (ROC) curves performed well throughout the observation period. Additionally, the nomogram could classify high-risk GISTs into 'very high-risk' and 'general high-risk' groups with a hazard ratio (HR) of 5.190 (95%CI: 3.202–8.414) and 5.438 (95%CI: 2.236–13.229) for the training and validation datasets, respectively.

**Interpretation:** The nomogram independently predicted post-operative recurrence-free survival (RFS) in high-risk GIST and showed favourable discrimination and calibration values. It may be a useful clinical tool for identifying 'very high-risk' GIST, by allowing treatment strategy optimisation in these patients.

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## 1. Introduction

Gastrointestinal stromal tumour (GIST) is a relatively rare mesenchymal tumour, with an annual global incidence rate of 1–2 cases per 100,000 individuals.<sup>1</sup> GIST can develop anywhere in the digestive tract, and shows resistance to radiotherapy and chemotherapy.<sup>2</sup> Curative surgical resection remains the main therapy for localised primary GIST, and the modified NIH classification has been widely applied to predict tumour recurrence after surgery.<sup>3</sup> However, GISTs

treated with surgical resection show recurrence in 50–90% cases within 5-years post-surgery, especially in the high-risk cases.<sup>4</sup> Furthermore, clinical risk classification for recurrence in high-risk GIST is not well-defined. Therefore, it is necessary to develop an efficient predictive model for accurate evaluation of recurrence in high-risk GIST.

Several recent studies have shown pathological indices, such as the tumour size, mitotic index, tumour site, and Ki-67 labelling index (LI) as independent prognostic factors to be useful for identifying patients at high-risk and ensuring tailored treatment.<sup>5–8</sup> Some pre-operative blood indices, especially inflammatory marks, have also proved to be valuable prognostic indicators.<sup>9–12</sup> Further, the nomogram serves as a disease-specific and clinically relevant prognostic model for predicting disease outcomes, and the first prognostic

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## Research in context

### Evidence before this study

We searched PubMed, Medline, and Google Scholar on Aug. 28, 2020, for articles describing nomograms and other models to predict recurrence level of patients diagnosed with high-risk GISTs, using the search terms 'gastrointestinal stromal tumour' or 'GIST' and 'high-risk' and 'nomogram' or 'predictive model' or 'prediction model' or 'clinical model' or 'clinical category', with no time restrictions. We also searched CNKI and Wanfang Data using the same terms in Chinese, with no time restrictions. We found a few previously published researches discussing the nomogram to predict recurrence level in patients with GISTs. We found no published work regarding nomograms or clinical models to predict recurrence in patients with high-risk GISTs.

### Added value of this study

We retrospectively evaluated patients ( $n = 424$ ) with high-risk GIST who underwent curative resection as the initial treatment at two high-volume medical centres between January 2005 and June 2019. The least absolute shrinkage and selection operator (LASSO) regression model was utilised to select potentially relevant features. Multivariate Cox proportional hazards analysis was used to develop a novel nomogram. To our knowledge, this study has the largest to use two independent cohorts to develop and validate a prediction nomogram in patients with high-risk GISTs. Additionally, our study classified high-risk GISTs into 'very high-risk' and 'general high-risk' groups, indicating the significant difference in the recurrence level of some patients with high-risk GISTs and provided a valuable and efficient nomogram model to predict the recurrence possibility, which requires further study for validation and improvement.

### Implications of all the available evidence

Curative surgical resection remains the main therapy for localised primary GIST, and the modified NIH classification has been widely applied to predict tumour recurrence after surgery. However, GIST treated with surgical resection shows recurrence in 50–90% cases within 5-years post-surgery, especially in the high-risk GISTs. Furthermore, clinical risk classification for recurrence in high-risk GIST is not well-defined. Therefore, it is necessary to develop an efficient predictive model for accurate evaluation of recurrence in high-risk GIST. The nomogram constructed in this study could help clinicians to recognize patients who have a potential for recurrence.

## 2. Methods

### 2.1. Patients selection

This retrospective study was approved by the Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology and Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, the need for informed consent was waived. A total of 1072 consecutive patients were diagnosed with GIST and treated at the Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (UHTMC—HUST) between January 2005 and June 2018. Patients classified under the high-risk category ( $n = 371$ ), based on the modified NIH classification, and treated with complete resection were included in the study. The inclusion criteria were: (1) pathologically confirmed localised single primary GIST; (2) complete R0 resection; and (3) complete follow-up data. The exclusion criteria were: (1) history of pre-operative adjuvant therapy or chemoradiotherapy, and (2) history of transfusion of blood components or colony-stimulating factor within 3 months before surgery. Therefore, based on these inclusion and exclusion criteria, 318 patients were included in the training dataset. Furthermore, the validation cohort of 106 patients (3:1), who satisfied the inclusion and exclusion criteria, was selected by a random extraction of GIST patients treated at the Department of Gastrointestinal Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University (RJHMSJ TU) between January 2008 and September 2019. The institutional review board at both the institutions approved this study and informed consent was obtained from all patients according to local requirements. All methods were performed in accordance with the approved guidelines.

### 2.2. Collection of demographic, clinicopathological, and follow-up data

All the research data for patients were extracted from the electronic medical record system of the UHTMC—HUST and RJHMSJ TU databases. The demographic data included sex, age, and Charlson Comorbidity Index, which is a scoring system to measure comorbidity.<sup>14</sup> The pathological indicators included tumour site, tumour size, Ki-67 labelling index (LI), and mitosis index, the Ki-67 LI was evaluated by immunohistochemistry and the mitotic index was evaluated based on 50 consecutive high power fields (HPFs) in each sample. The pre-operative laboratory indicators included the white blood cell count (WBC), red blood cell count (RBC), and levels of blood platelet (PLT), haemoglobin (Hb), glutamic oxaloacetic transaminase (AST), and alanine transaminase (ALT). Besides the conventional pathological indicators, haematological inflammation biomarkers were assessed as potential independent prognostic factors in a few studies. Thus, we included the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), De Ritis Ratio (AST/ALT), prognostic nutritional index (PNI), and fibrinogen levels. All the pre-operative laboratory examinations were performed within 7 days before surgery. The SII was defined as  $SII = P \times N/L$ , where P, N, and L were the pre-operative peripheral blood platelet, neutrophil, and lymphocyte counts per litre, respectively. The PNI was calculated as  $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{lymphocyte count (per mm}^3\text{)}$ . Furthermore, the acknowledgement of imatinib adjuvant therapy after R0 resection in the study required uninterrupted treatment of patients with the drug for over 12 months.

Regular medical follow-up data were obtained using telephone calls, clinic visits, internet, and other interaction tools. The recurrence-free survival (RFS) was defined as the duration from surgery to the earliest evidence of recurrence or end of follow-up. Patients were followed up until 01 February 2019 for training dataset and 01 December 2019 for validation dataset.

nomogram developed by Gold et al. showed a good calibration of predictive recurrence in all GISTs.<sup>13</sup> However, the nomogram has a deficiency, in that it focuses on pathological results, and neglects pre-operative inflammatory or other blood indicators due to lack of consensus on the criterion of variant recurrence level in high-risk GIST.

Therefore, this study aimed to develop a novel prognostic nomogram, combining significant pre-operative blood and pathological indices based on high-risk GIST patient population, and included a large bi-institutional dataset gathered from two high-volume institutions. The predictive value of the nomogram was evaluated based on discrimination, calibration, and clinical utility in separate internal and external validation cohorts.

2.3. Selection of features

We applied the least absolute shrinkage and selection operator (LASSO) logistic regression algorithm in selecting the most significant predictive factors. The LASSO logistic regression algorithm can efficiently analyse the high-dimensional data. The minimum tuning parameter ( $\lambda$ ) for the LASSO logistic regression was determined using cross-validation.<sup>15</sup>

2.4. Statistical analysis

The continuous variables of patients were expressed as the mean  $\pm$  standard deviation ( $\sigma$ ) and interquartile range (IQR), while categorical variables were reported using absolute frequencies and percentages. The descriptive comparisons were made using Pearson's  $\chi^2$  test for categorical variables and the Mann-Whitney U rank sum test for continuous variables. First, we used LASSO logistic regression for 1000 bootstrap iterations to get significant predictors. Next, we then applied multivariate Cox proportional hazards analysis by forward step: LR. Further, the prognostic nomogram was calculated using significant predictors. For validating the nomogram, we calculated the area under the ROC curve (AUC) in both, the training and validation datasets and compared then with the Gold's nomogram. Furthermore, the Harrell's C index was generated for discrimination of multivariable prognostic nomogram using 1000 bootstrap iterations. Moreover, we evaluated the predictive power of the nomogram for recurrence in patients with high-risk GIST by plotting the calibration curves. The study applied the decision curve analysis (DCA) for evaluating the clinical utility of the nomogram based on net benefits at different threshold probabilities in the training and validation datasets.<sup>16</sup> Additionally, we analysed the potency of the nomogram to stratify patients with high-risk GIST.

Here, the SPSS software version 24.0 was used for statistical analysis, the X-tile software was used to obtain cut-off values,<sup>17</sup> and the R 3.6.1 software was used for analysis and mapping results. A bilateral  $p < 0.05$  was considered statistically significant.

2.5. Role of the funding source

This study has received funding from the National Natural Science Foundation of China (No. 81702386 and 81874184), The funders (PZ and KXT) had role in study design, data interpretation and review.

3. Results

3.1. Baseline characteristics of patients and outcomes

A total of 424 patients with high-risk GIST were included in this study, and the training dataset comprised of 318 patients with 106 patients in the validation dataset (Fig 1). The baseline characteristics of patients in the training and validation datasets have been summarised in Table 1. The median follow-up time was 42.0 (2, 168) months. During the follow-up period, 73 cases showed recurrence and 245 cases survived without recurrence in the training dataset. Further, the RFS rate in the training dataset after 3, 5, and 7 years was 86.1%, 74.3%, and 69.9%, respectively. Whereas, in the validation dataset, 20 cases showed tumour recurrence and 86 cases survived without recurrence. Additionally, the RFS rate in the validation dataset after 3, 5, and 7 years was 84.1%, 67.3%, and 59.8%, respectively.

3.2. Selection and design of prognostic predictors

The LASSO logistic regression algorithm was used to select the most significant predictors in the training dataset, which were used to construct the prognostic nomogram. A total of 19 clinical features were used in the LASSO logistic regression for 1000 bootstrap iterations, and 6 features with non-zero coefficients were subsequently selected with a minimum lambda value of 0.028 (Supplementary Figure 1). This algorithm ultimately included 6 predictors: patient age, tumour size, mitotic counts  $> 10/50\text{HPF}$ , pre-operative FIB, PLR, and PNI, and adjuvant treatment as a modified index. The cut-off values of tumour size, PNI and PLR were found to be 18.0 cm, 48.0, and 275, respectively, using X-tile analysis. Moreover, our study sub-divided the age and FIB predictors into several groups for better analysis.

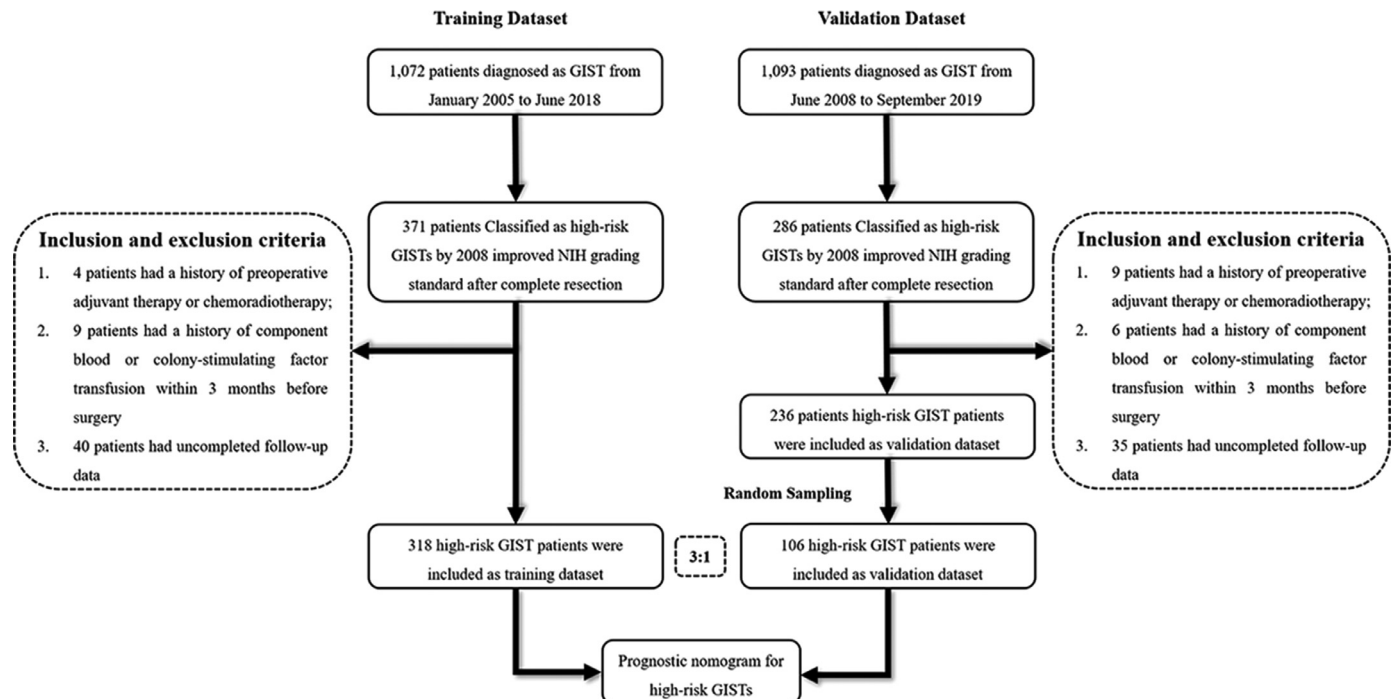


Fig 1. Study cohort.

**Table 1**  
Baseline demographic and clinical characteristics of patients.

Variable	Training Dataset (n = 318)	Validation Dataset (n = 106)	p-value
<b>Discrete Variables</b>			
Sex			0.428
Male	178 (56.0)	65 (61.3)	
Female	140 (44.0)	41 (38.7)	
Charlson comorbidity index			0.366
Value = 0	235 (73.9)	73 (68.9)	
Value = 1	61 (19.2)	23 (21.7)	
Value ≤ 2	22 (6.8)	10 (9.4)	
Tumour Site			0.061
stomach	103 (32.4)	46 (43.4)	
no stomach	215 (67.6)	60 (56.6)	
Tumour size (cm)			0.381
< 18	294 (92.5)	100 (94.3)	
≤ 18	24 (7.5)	6 (5.7)	
Mitotic counts (/50HPF)			<0.001
≤ 10	245 (77.0)	59 (55.7)	
> 10	73 (23.0)	47 (44.3)	
Adjuvant treatment			<0.001
No	183 (57.5)	27 (25.5)	
Yes	135 (42.5)	79 (74.5)	
<b>Continuous Variables <math>\bar{x} \pm \sigma</math> (IQR)</b>			
Age (years)	55.95 ± 11.32 (49–65)	59.32 ± 11.22 (53–68)	<0.001
WBC (10 <sup>9</sup> /L)	6.55 ± 2.92 (4.61–7.56)	6.40 ± 2.71 (4.70–7.44)	0.970
RBC (10 <sup>12</sup> /L)	3.65 ± 0.83 (3.08–4.26)	4.10 ± 0.71 (3.65–4.62)	<0.001
PLT (10 <sup>9</sup> /L)	236.62 ± 99.10 (168.00–301.00)	256.58 ± 101.80 (176.50–314.50)	0.163
Hb (g/L)	102.47 ± 40.90 (78.00–126.00)	116.27 ± 26.05 (94.50–135.00)	<0.001
PLR	255.88 ± 56.93 (121.10–259.62)	199.88 ± 109.25 (119.31–250.16)	<0.001
NLR	5.71 ± 1.99 (1.82–4.61)	3.40 ± 2.85 (1.95–3.72)	0.174
SII	1241.10 ± 3933.79 (387.88–1208.82)	880.73 ± 827.23 (399.39–989.95)	0.435
ALT (U/L)	20.69 ± 18.62 (10.00–25.00)	17.12 ± 9.29 (12.00–20.00)	0.299
AST (U/L)	21.24 ± 11.04 (15.00–23.30)	19.38 ± 10.00 (14.00–21.00)	0.038
De Ritis Ratio	1.31 ± 0.65 (0.86–1.59)	1.22 ± 0.41 (0.93–1.43)	0.737
PNI	44.03 ± 6.23 (40.95–48.86)	48.08 ± 7.22 (42.85–54.00)	0.004
FIB (g/L)	3.55 ± 1.43 (2.60–4.31)	3.22 ± 1.08 (2.46–3.79)	0.002
Ki-67 LI (%)	7.15 ± 9.01 (1.00–10.00)	10.83 ± 11.54 (2.50–20.00)	<0.001

P values were calculated by Mann-Whitney U test,  $\chi^2$  test or Fisher's exact test.

### 3.3. Development of multivariate prognostic nomogram

The multivariate Cox regression analysis indicated age, tumour size, mitotic counts, adjuvant treatment, and preoperative FIB, PLR and PNI as independent prognostic factors in the training dataset (Table 2), amongst these, age, tumour size, mitotic counts, and preoperative FIB, PLR and PNI (Supplementary Figure 2) were used to construct the nomogram. Each predictor corresponded to a specific point by drawing a straight line upward to the points axis such as FIB 2.0–2.5 g/L corresponded to 4.5 score in the points axis. The sum represented the RFS by drawing a straight line down to the total points axis (Fig 2). We have elaborated an instance, where a patient aged 50 years (2.7 points), pre-operative FIB 3.4 g/L (5.8 points), PNI ≤ 48.0 (3.6 points) and PLR > 275 (4.3 points), with pathological indicators indicating tumour size < 18.0 cm (0 points), and mitotic count > 10/

50HPF (5.3 points). Thus, the total points were 21.7, and the RFS after 3, 5, and 7 years was predicted to be approximately 75%, 55%, and 50%, respectively.

### 3.4. Internal and external data validation

To make an internal validation using the training dataset, the C-index was 0.742 (95%CI:0.689–0.804) for the prognostic nomogram, and with an AUC of 0.749, the prognostic nomogram showed an excellent discrimination capacity in predicting the 5-year RFS, which was superior to that of Gold's nomogram (0.749 vs. 0.558,  $Z = 4.415$ ,  $p < 0.001$ ). Conversely, to perform external validation using the validation dataset, the C-index was 0.735 (95%CI:0.634–0.846) for the prognostic nomogram, and with an AUC of 0.778, the nomogram performed consistent in this analysis as well. This was also superior to that of Gold's nomogram (0.778 vs. 0.570,  $Z = 2.193$ ,  $p = 0.028$ ). Additionally, the time-dependant ROC curve of the prognostic nomogram was found to be consistently more favourable in both training and validation datasets (Fig 3). Moreover, the prognostic nomogram had the smallest Akaike information criterion (AIC) value of 656.38. Further, the calibration curve indicated that the prognostic nomogram predicted the RFS of the patients with high-risk GIST in both the training and validation datasets (Fig 4).

To better acknowledge adjuvant treatment confusion factor in our model, we made internal and external data validations in patients with adjuvant treatment and without it respectively. The C-index for the nomogram 0.721 (95%CI:0.564–0.887) in patients with adjuvant treatment, and 0.752 (95%CI:0.687–0.817) in patients with no adjuvant treatment in the training dataset. Further, the C-index was 0.726 (95%CI:0.534–0.937) for the nomogram in patients with adjuvant treatment, and 0.752 (95%CI:0.613–0.894) in patients with no adjuvant treatment in validation dataset. These results showed a stable and favourable effectiveness of our nomogram.

### 3.5. Clinical utility and validity of the nomogram

The DCA curve indicated that the nomogram was feasible for making valuable and informed judgements of the prognosis (Fig 5). Our analysis indicated that if the threshold probability of recurrence in patients was approximately 0–50% predicted by this nomogram, use of this nomogram to guide treatment measures in patients with high-risk GISTs would provide more benefit than either the 'treat all patients' or the 'treat none patient' schemes. Moreover, martingale residuals of nomogram plots and cumulative martingale process plots showed a balanced hazards proportionality in the model (Supplementary Figure 3).

### 3.6. Performance of the prognostic nomogram in stratifying risk

To enhance the ability of the prognostic nomogram to stratify recurrence risk, we excluded adjuvant treatment index from further analysis. In the training dataset, the total prognostic scores calculated by the nomogram were categorised into two risk groups to predict the recurrence level: 'general high-risk' (score ≤ 20.6) and 'very high-risk' (score > 20.6) based on the cut-off value calculated using the X-tile software (Fig 6[a]). Other cut-offs including values based on the median score or tercile score are shown in Supplementary Figure 4. The HR for 'very high-risk' category was found to be 5.190 (95%CI:3.202–8.414) compared to the 'general high-risk' category. The comparisons of the cumulative probability of survival in each category in the validation dataset are shown in Fig 6(b), and the HR for 'very high-risk' was found to be 5.438 (95%CI:2.236–13.229) compared to the 'general high-risk' category. Additionally, the Kaplan–Meier curves in both, the training and validation datasets indicated the nomogram to be stable in predicting the probability of recurrence in patients with high-risk GIST (Fig 6[b]). Moreover, the



**Table 2**  
Multivariate COX regression analysis in training dataset.

Variable	n	HR (95%CI)	$\beta$ coefficient	p-value	Score
Age (years)					
≤ 40	30	Ref.			0.0
41–50	103	1.877 (0.726–4.854)	0.630	0.194	2.7
51–60	68	2.600 (0.914–7.403)	0.956	0.073	4.0
61–70	80	2.633 (0.968–7.163)	0.968	0.058	4.1
> 70	37	4.300 (1.551–11.921)	1.459	0.005	6.3
Tumour Size (cm)					
≤ 18	294	Ref.			0.0
> 18	24	2.552 (1.340–4.862)	0.937	0.004	4.0
Mitotic Counts (/50HPF)					
≤ 10	245	Ref.			0.0
> 10	73	3.008 (1.641–5.514)	1.101	<0.001	5.3
FIB (g/L)					
≤ 2.0	21	Ref.			0.0
2.0–2.5	62	2.777 (0.353–21.813)	1.021	0.332	4.5
2.5–3.0	67	2.891 (0.364–22.983)	1.062	0.316	4.7
3.0–3.5	40	3.634 (0.449–29.383)	1.290	0.226	5.8
3.5–4.0	91	8.733 (1.170–65.189)	2.167	0.035	9.8
> 4.0	37	9.396 (1.193–74.022)	2.240	0.033	10.0
PNI					
≤ 48.0	218	Ref.			3.5
> 48.0	100	0.450 (0.254–0.799)	-0.798	0.006	0.0
PLR					
≤ 275	247	Ref.			0.0
> 275	71	2.635 (1.360–5.107)	0.969	0.004	4.3

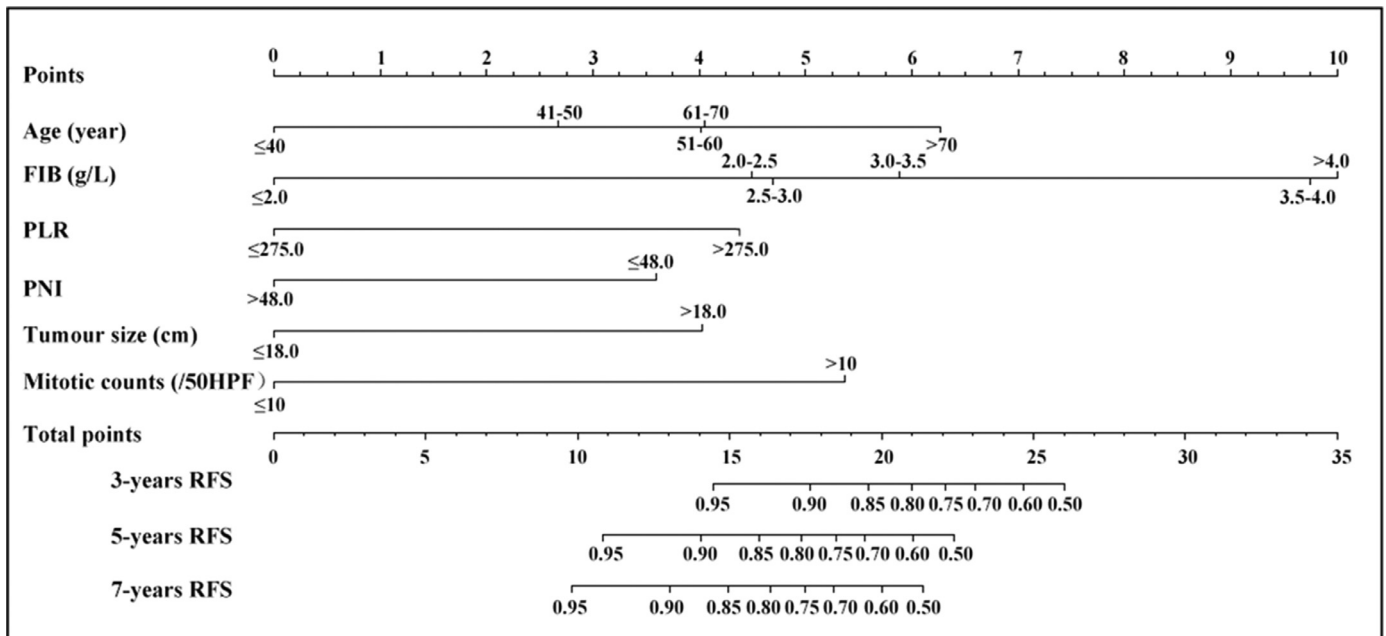
Kaplan–Meier curves for both patient groups treated with and without adjuvant therapy also showed stable discrimination (Fig 7).

**4. Discussion**

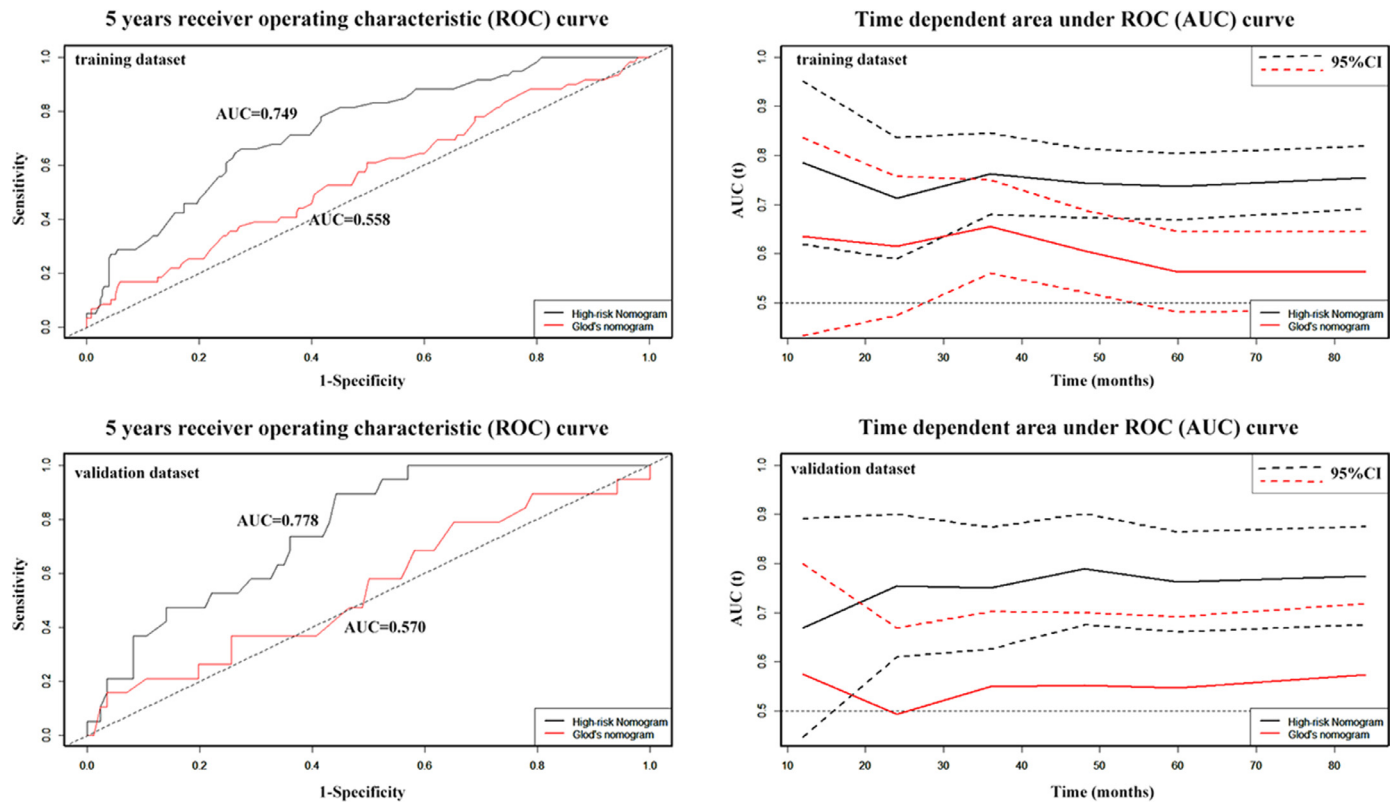
The clinical behaviour and outcomes vary in patients with high-risk GIST, and hence more accurate predictive models would be required to guide treatment. Thus, we developed a novel prognostic nomogram to allow accurate risk stratification, and promote understanding of recurrence for determining post-operative follow-up protocols and individual treatment strategies in patients with high-risk

GIST. We believe that this is the first time that a novel nomogram has been constructed to predict recurrence in patients with high-risk GIST.

Few studies had identified a few pathological indices, such as the mitotic index and Ki-67 LI as independent prognostic factors in high-risk GIST. Zhao et al. found that the mitotic count > 10/50 HPF could effectively sub-divide high-risk GIST<sup>5</sup>. Liu et al. suggested Ki-67 LI to be a promising indicator, and constructed a novel pathological prognostic score to identify “very high-risk” patients from high-risk GIST.<sup>6, 7</sup> Additionally, some pre-operative blood indices have been identified to predict the prognosis. Sun et al. hypothesised PNI to be a



**Fig 2.** The nomogram for preoperative prediction of recurrence in high-risk GISTs. Points are assigned for age, tumour size ≥ 18 cm, mitotic count > 10/HPF, preoperative FIB, PLR, PNI and adjuvant treatment. The score for each value is assigned by drawing a line upward to the points line, and the sum of the seven scores is plotted on the Total points line.



**Fig 3.** Receiver operating characteristic (ROC) curves and time-dependant ROC curves with 95% CI for high-risk nomogram vs. Glod's nomogram in training and validation datasets. AUC, area under the curve.

useful marker for predicting the prognosis in high-risk GIST.<sup>11</sup> Lu et al. suggested that elevated fibrinogen levels may serve as independent prognostic factor for poorer clinical outcomes in GIST<sup>9</sup>. A few other studies have suggested that elevated blood inflammatory indices, such as SII and PLR, serve as independent prognostic factors for poorer clinical outcome in GIST.<sup>10, 12</sup>

Therefore, to construct a novel clinical model for predicting prognosis at the pre-operative stage in high-risk GIST, 6 clinical indices were selected from the aforementioned 19 features using the LASSO logistic regression algorithm and multivariate Cox regression analysis. This LASSO algorithm has been widely used previously for the selection of key features and elimination of multicollinearity in multi-dimensional data analysis, as it is assumed to be a suitable selection method based on the strength of the univariate associations with outcome. Further, we observed that the mitotic count and pre-operative PNI were independent prognostic factors, consistent with previous studies. Tumour size > 18 cm may serve as a useful cut-off value based on a series of analysis, although size > 10 cm failed to be a suitable prognostic factor, consistent with the findings of the study by Zhao et al. Additionally, the pre-operative FIB and PLR were found to be valuable prognostic indicators in high-risk GIST, and FIB > 3.5 g/L may imply a high risk of recurrence. Moreover, this study indicated that patient age may serve as a hazard factor in high-risk GIST, especially for those aged > 70 years.

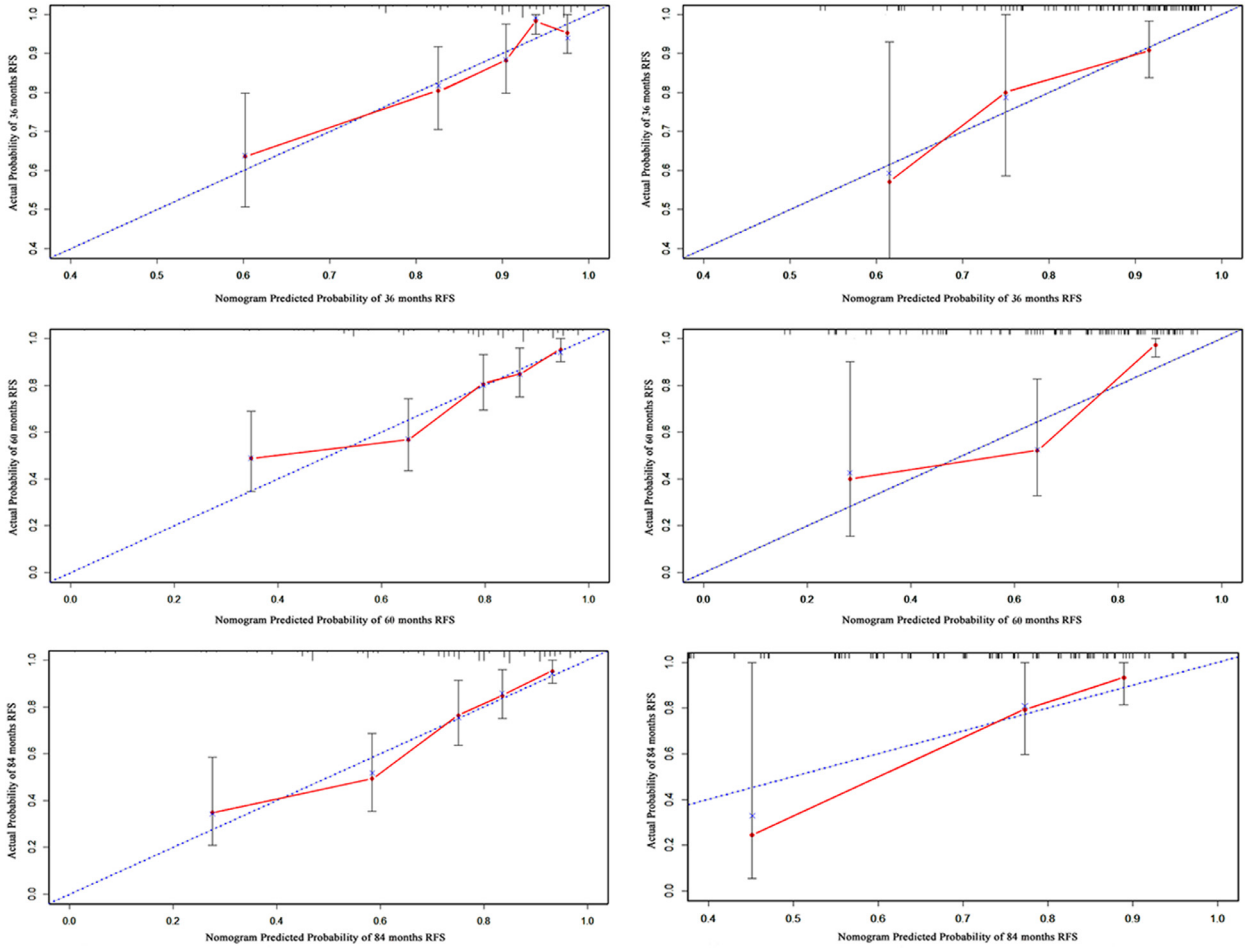
Nomograms have been applied as a disease-specific and clinically relevant prognostic model for predicting various outcomes. After the development of the first nomogram, which showed good applicability with a C-index of 0.78,<sup>13</sup> several studies have constructed nomograms to predict the prognosis in patients with GIST. Rossi et al. developed a survival nomogram using mitotic counts and tumour size as continuous variables, based on the analysis of 929 imatinib-naive GIST with long-term follow-up and a C-index of 0.72.<sup>18</sup>

Furthermore, Lee et al. constructed a prognostic nomogram for metastatic GIST treated with imatinib based on training set ( $n = 330$ ) and validation set ( $n = 236$ ), with a C-index of 0.75 (training) and 0.62 (validation) for OS, and 0.69 (training) and 0.62 (validation) for PFS.<sup>19</sup> Here, we focused on the prognosis of localised primary GIST classified as high-risk after complete resection, and constructed a nomogram based on the patients treated at two large medical institutions in China to predict the recurrence level. We developed this nomogram using 6 features with nonzero coefficients viz. age, tumour size, mitotic counts, and pre-operative FIB, PLR, and PNI. Moreover, we observed that combining traditional pathological indicators with a few pre-operative blood indices, such as FIB, PLR, and PNI could be more beneficial than traditional pathological indices alone in predicting the recurrence risk of patients with high-risk GIST. This may explain the deficiency in the modified NIH risk classification, which is based on pathological indices, in predicting the risk of recurrence in patients with high-risk GIST. Furthermore, adjuvant treatment with imatinib has helped prolong the RFS rates,<sup>20</sup> and primary high-risk GIST patients would be administered imatinib up to 3 years, as recommended by the National Comprehensive Cancer Network.<sup>21</sup> Thus, to increase the accuracy of our nomogram, we included imatinib adjuvant treatment in the analysis as a confounding factor caused by artificial selection bias. Moreover, we evaluated this model in patients treated with or without adjuvant treatment and results showed an effective discrimination.

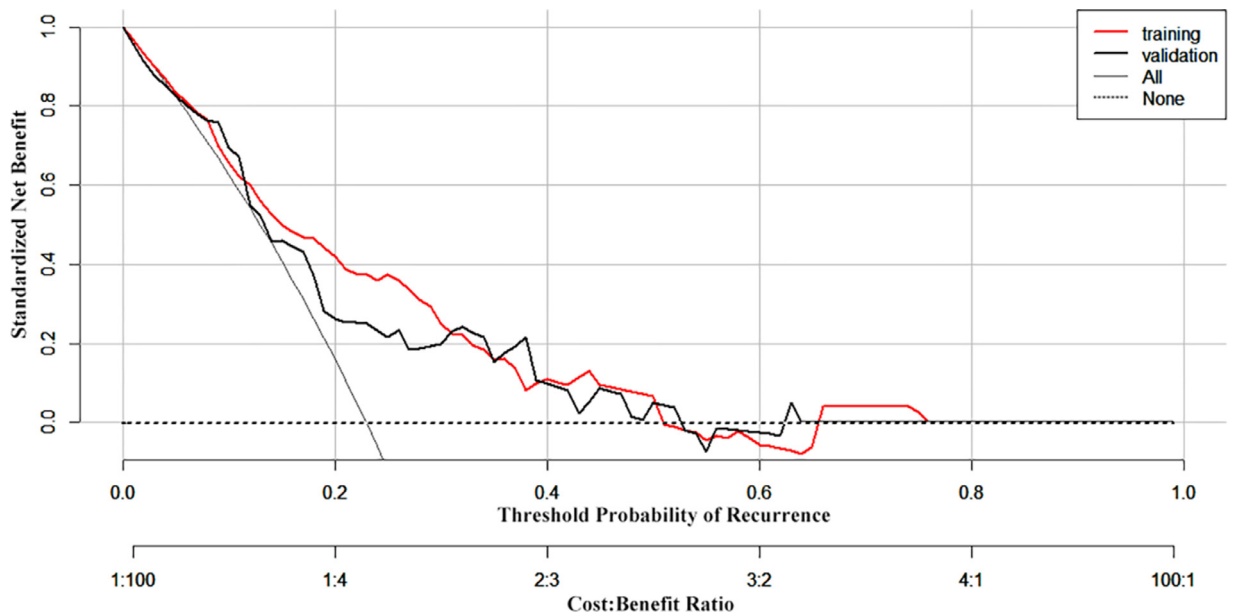
To ascertain the predictive ability of the nomogram, we first validated it in the training dataset by the cross-validation method. Our analysis suggested that the nomogram provided favourable discrimination and calibration values in the training dataset. Additionally, the nomogram was tested using the external validation dataset at a high-capacity medical centre, and the analysis confirmed the discrimination capability and indicated acceptable calibration. By excluding the

Training Dataset (n=318)

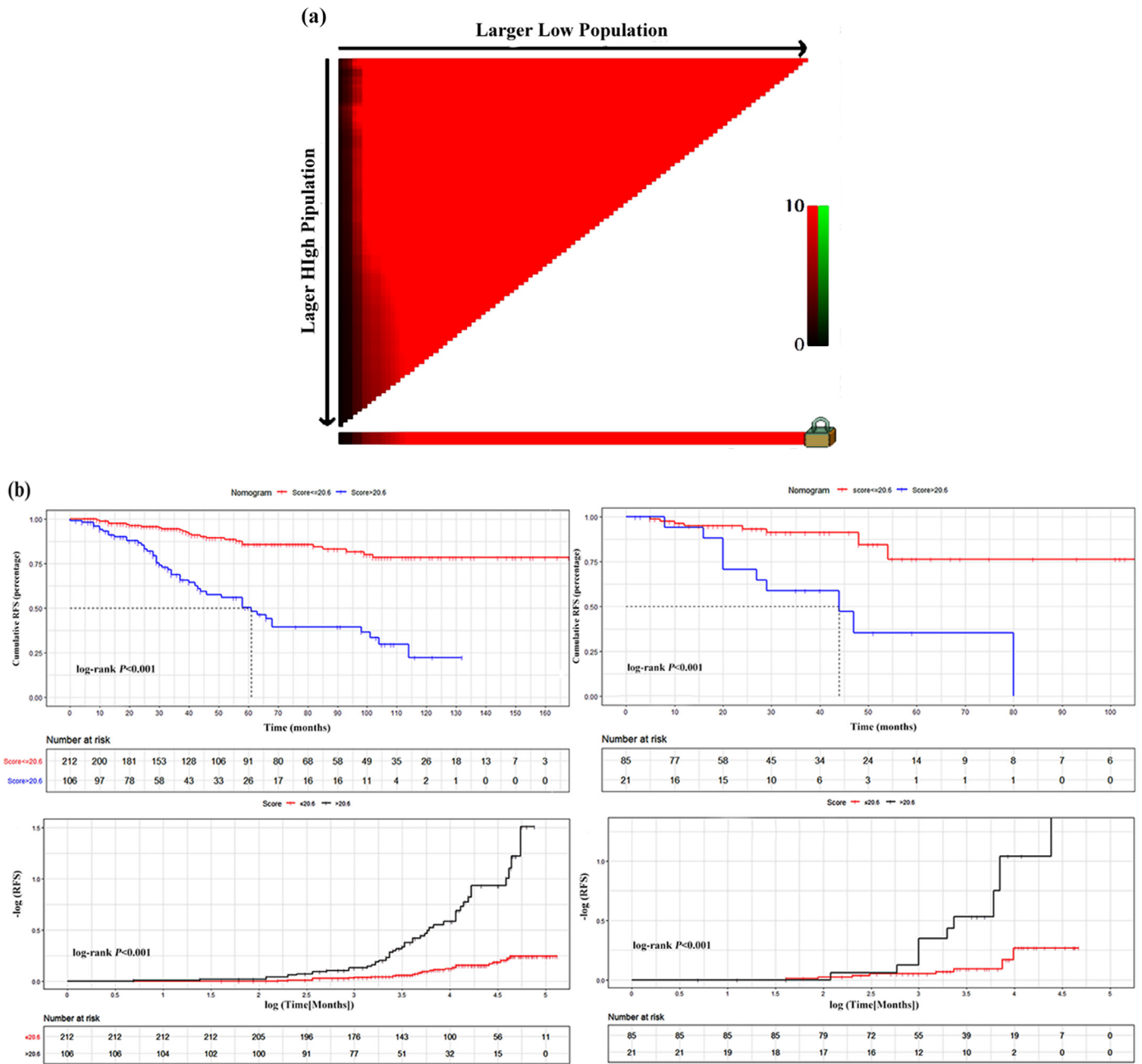
Validation Dataset (n=106)



**Fig 4.** Calibration plots for the training and validation cohort that show the predicted and observed (with 95% confidence intervals) recurrence-free survival (RFS) rates at 36, 60 and 84 months.



**Fig 5.** The decision curve analysis (DCA) for the nomogram in training and validation dataset. The grey line represents the treat-all-patients scheme. The dotted line represents the treat-none scheme. The black line represents prediction nomogram scheme in validation dataset. This graph gives expected net benefit of patients with high-risk GISTs using different clinical schemes.



**Fig 6.** (a) X-tile analysis of the total risk score in the train cohort and cut-off value calculated. (b) Survival curves stratified by the score calculated by the prognostic nomogram ('general high-risk' [score  $\leq 20.6$ ] and "very high-risk" [score  $> 20.6$ ]) in the training and validation cohort.

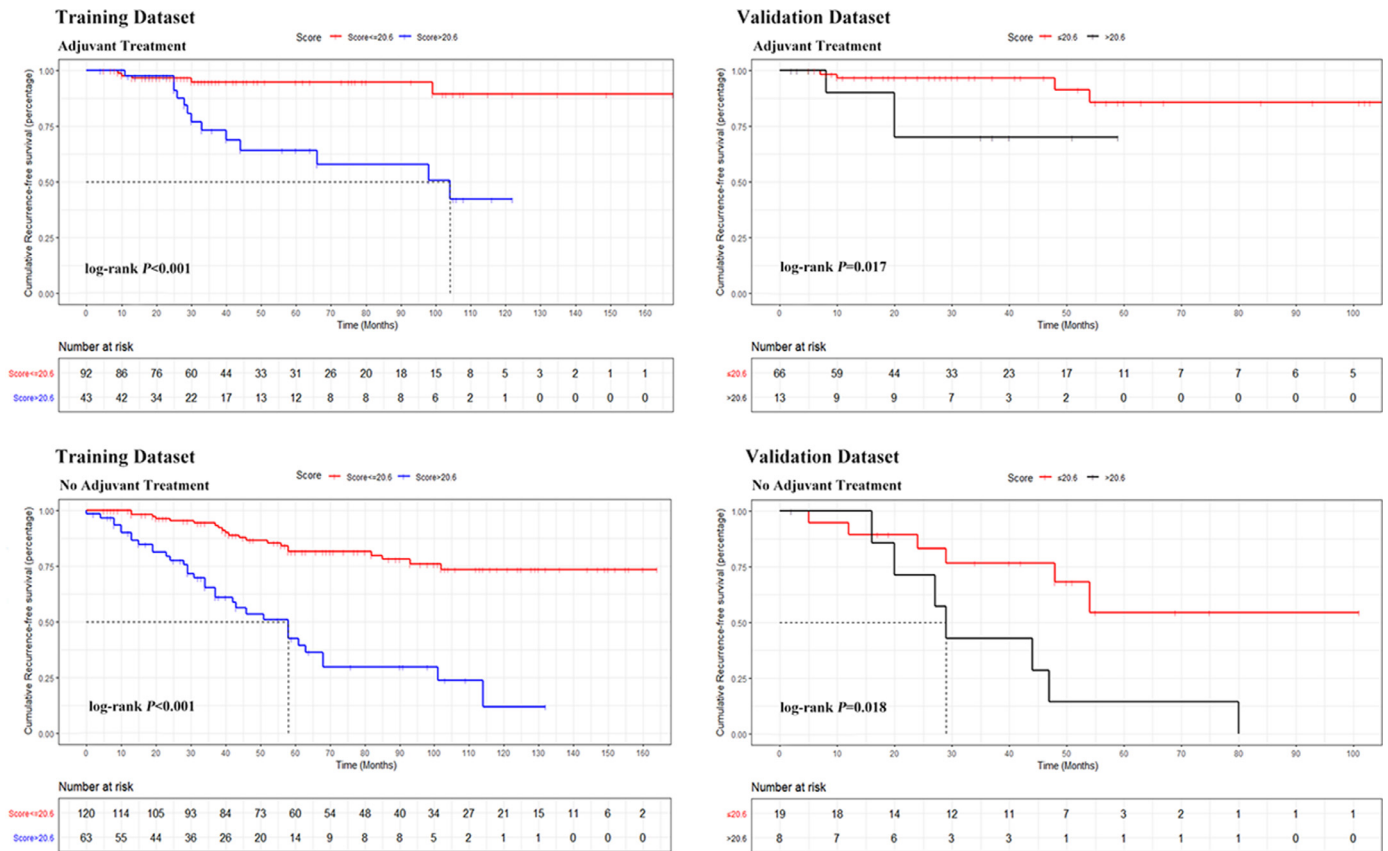
statistical magnitude, the nomogram showed a conclusive efficiency and availability in predicting the recurrence level in high-risk GIST. Furthermore, the calibration curve suggested consistency between the predictive outcomes for RFS after 3, 5, and 7 years, and the actual survival outcomes observed in both the datasets. When the threshold probability of recurrence was 0–50%, the DCA analysis indicated that use of the nomogram was beneficial than the mere treat-all-patients or treat-no-patients scheme. Moreover, to precisely identify recurrences or metastases in high-risk GIST, we applied the nomogram for stratifying risk of recurrence using the X-tile analysis. Our analysis indicated that the cut-off value of nomogram score could sub-divide the high-risk GIST into the 'very high-risk' (score  $> 20.6$ ) and 'general high-risk' (score  $\leq 20.6$ ) groups. The Kaplan–Meier analysis suggested a statistically significant difference in recurrence levels between the two groups. Thus, this observation highlights the need

for more careful monitoring of such 'very high-risk' GIST, using a predictive nomogram, which would aid the clinicians in administering an alternative post-operative adjuvant therapy suitable to patients with high-risk GIST.

However, the study has a few limitations. First, though the nomogram was developed and validated using patient dataset from two large medical centres, our study consisted of a retrospective cohort with inherent limitations. Second, the 3-year adjuvant imatinib treatment could not be completed by the end of follow-up period in few patients, this may have caused inaccuracies in the inference from the adjuvant therapy data-points.

In conclusion, the novel nomogram developed in our study may allow clinicians to better predict the risk of recurrence in patients with high-risk GIST, as validated in the internal and external datasets. Moreover, this tool may stratify the 'very high-risk' patients, and thus





**Fig 7.** Survival curves stratified by the score calculated by the prognostic nomogram (“general high-risk” [score ≤20.6] and “very high-risk” [score >20.6]) in the patients with adjuvant treatment and without adjuvant treatment.

increase its utility in current prognostic models for accurate risk evaluation. We anticipate that the prognostic nomogram may benefit in clinical care for interpretation of some clinical phenomena, and in optimising post-operative treatment decision-making in patients with high-risk GIST.

**Contributors**

Prof. Peng Zhang and Prof. Kaixiong Tao were responsible for the study conceptualisation and design. Yao Lin and Xin Chen searched relevant literatures. Yao Lin, Wang Ming, Yang Wenchang, Jie Jia, and Wenze Wan collected the clinical and follow-up data. Yao Lin, Chengguo Li, and Tao Wang preformed statistical analysis. Yao Lin and Peng Zhang interpreted the data. Yao Lin and Wang Ming drafted the manuscript and figures. Peng Zhang edited the manuscript. Prof. Kaixiong Tao and Prof. Hui Cao reviewed the manuscript. All the authors read approved the final manuscript.

**Declaration of Competing Interests**

The authors declare that they have no conflict of interests and personal relationships with other people or organizations.

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**Data Sharing Statement**

Data are available from the corresponding author upon reasonable request.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.ebiom.2020.103016](https://doi.org/10.1016/j.ebiom.2020.103016).

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