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A new nomogram for recurrence-free survival prediction of gastrointestinal stromal tumors: Comparison with current risk classification methods

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ABSTRACT

Background: This study aimed to build a new risk stratification nomogram for gastrointestinal stromal tumors (GISTs) focused on a popular factor Ki-67 to enable individualized and precise predictions of the most suitable candidates for imatinib therapy.

Methods: We retrospectively collected clinicopathologic data of the patients diagnosed with GISTs from January 1998 to December 2015 at Southern Medical University Nanfang Hospital as the experiment group. And patients with GISTs at the Sun Yat-sen University Cancer Center from January 2007 to December 2012 were included as the validation group. The nomogram was built using Kaplan-Meier method and the Cox proportional hazards regression model. The receiver operating characteristic (ROC) curves were established to compare the discriminative ability of the new nomogram with other risk stratification systems, including the modified National Institute of Health (modified NIH) criteria, Armed Forces Institute of Pathology (AFIP) criteria, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic nomogram, and contour maps.

Results: In univariate analysis, the tumor size, site, mitotic count, tumor rupture and Ki-67 labeling index were significant factors (all $P < 0.05$) and included in the Cox model to build our nomogram. According to the ROC curve, our new nomogram showed the largest AUC value (0.778) compared with that of the other classification methods (contour maps, AUC = 0.743; AFIP, AUC = 0.719; MSKCC, AUC = 0.712; and modified NIH, AUC = 0.719).

Conclusion: Our new nomogram exhibits an excellent performance and might become a potential risk stratification to support therapeutic decision-making for GISTs.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumors in the gastrointestinal (GI) tract; these tumors arise most frequently (60–70%) in the stomach, although they may occur anywhere within the GI tract [1,2]. Mesenchymal tumors are thought to constitute less than 1% of primary GI neoplasms [2–4]; however, the potential for their occurrence should not be ignored. The annual incidence of GISTs in the United States is at least 4000 to 6000 new cases. In China, a survey of Shanxi Province from January 2000 to December 2005 identified 181 cases of GISTs [5]. However, in 2011, there were 153

Abbreviations: GISTs, gastrointestinal stromal tumor; AUC, area under the receiver operating characteristic curve; NIH, National Institute of Health; AFIP, Armed Forces Institute of Pathology; MSKCC, Memorial Sloan Kettering Cancer Center; RFS, recurrence-free survival; LI, labeling index; HPFs, high-power fields.

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cases of GISTs in Shanxi Province, and the incidence rate had increased to 4.3/million in China [6], and 7.8/million in the US [7].

It is widely known that GISTs are characterized by activating mutations in KIT or PDGFRA tyrosine kinase receptors [8–11]. Imatinib, a tyrosine kinase inhibitor (TKI), was first used for GISTs in 2000, and subsequent studies have confirmed that this drug can prolong the long-term prognosis of GIST patients in both moderate- and high-risk groups [12]. The ACOSOG Z9001 phase III double-blind multicenter trial of imatinib therapy showed an improved 1-year recurrence-free survival (RFS) compared with that of the placebo group (98% vs. 83%, respectively), favoring imatinib treatment over surgery alone in patients with completely removed primary GISTs at least 3 cm in maximal diameter and positive for KIT protein via immunohistochemistry [13]. In 2015, the National Comprehensive Cancer Network (NCCN) recommended TKI treatment for patients with a moderate or high risk of recurrence [14]. However, incorrect risk stratification might erroneously distinguish patients who require targeted treatment and those who do not, and opportunities for receiving targeted treatment might be missed when the recurrence risk is underestimated. Moreover, low-risk group patients are likely to be cured by surgery and may not receive further benefit from TKI treatment; adjuvant imatinib therapy may also have adverse effects on some patients [15]. Apart from assisting in the development of adjuvant therapy plans, correct risk stratification also facilitates decision making regarding the intensity of postoperative surveillance; thus, such stratification is critical for the personalized treatment of GISTs.

Various classification systems for patients with GISTs have been proposed. In 2002, Fletcher published a consensus approach [16]. The Armed Forces Institute of Pathology (AFIP) criteria were subsequently proposed by Miettinen in 2006 according to the long-term follow-up results of 1684 patients. In addition to the tumor size and mitotic rate, tumor site is considered as an important risk factor in AFIP criteria [17]. In 2008, the National Institute of Health (NIH) risk stratification system was modified to include both tumor location and rupture, and was renamed the modified NIH criteria; this new criterion has been widely accepted worldwide because it is easier to apply than the AFIP criteria. However, as a result of the larger sample size upon which the recommendations were based, some experts believe that the AFIP criteria are more accurate [18]. In 2009, the Memorial Sloan Kettering Cancer Center (MSKCC) developed a prognostic nomogram to predict the risk of recurrence [19], and three years later, Joensuu *et al* [20] developed a novel risk stratification method in which tumor size and mitosis count are treated as continuous nonlinear variables. Nevertheless, a lack of consensus remains with regard to which criteria have the best application value.

Ki-67, a nuclear marker, exists in actively proliferating cells. It is expressed in all phases of the cell cycle in stages G1, S, and G2. Ki-67 is considered a proliferation-related nuclear marker of tumor cells. To date, numerous studies have reported a correlation between Ki-67 expression and the malignant risk of GISTs [21–23]. Based on our previous study, the Ki-67 labeling index (LI) is a promising predictor of outcome in GISTs, particularly in high-risk patients, and it may have important clinical utility in identifying “very high risk” patients for rational targeted therapy [24]. However, the combined analysis of a panel of biomarkers or a risk index as a whole signature, rather than an individual analysis, might show the most promise to change clinical management [25,26].

The present study aimed to build and validate a new risk differentiation nomogram focusing on Ki-67, a reliable marker that is associated with the prognosis of many tumors. Moreover, we compared the predictive accuracy of our new nomogram with the modified NIH criteria, AFIP criteria, MSKCC nomogram and Joensuu's contour maps to assess its diagnostic value.

Materials and methods

Patients

Patients who were diagnosed with GISTs using standard pathologic criteria at the Southern Medical University Nanfang Hospital from January 1998 to December 2015 and patients at the Sun Yat-sen University Cancer Center from January 2007 to December 2012 were identified from the database.

Patients who met the following conditions were included: (1) undergoing complete resection with negative margins; (2) complete clinicopathological data were available; (3) not receiving imatinib therapy or other tyrosine kinase inhibitor therapy in a neoadjuvant or adjuvant setting; and (4) no evidence of metastatic disease at diagnosis. Patients with the following conditions were excluded: (1) pregnant or breastfeeding women or (2) patients with other serious diseases or a history of malignancy that might interfere with the results. This study was approved by the Institutional Review Board of Southern Medical University Nanfang Hospital and Institutional Review Board of Sun Yat-sen University Cancer Center.

Statistical analysis

The demographic and clinicopathologic data of the included patients were collected. The tumor size was measured and recorded by pathologists, with a breakpoint of $\leq$5 or >5 cm. The mitotic index was defined as the number of mitoses per 50 randomly selected microscopic high-power fields (HPFs) and was classified into two groups ($\leq$5/50 or > 5/50 HPFs). The expression level of Ki-67 was measured via immunohistochemistry with a cutoff point of $\leq$6% or >6% [24]. Tumor rupture was assessed during the operation by the surgeons. The RFS was defined as the time from histological diagnosis to the recurrence of the tumor. Patients who were alive without recurrence at the time of data collection and patients who died without recurrence were censored. We calculated the RFS probabilities with the Kaplan-Meier method. The log-rank test was performed for the univariate analysis of the clinicopathologic factors, and a final Cox proportional hazards regression model was used in the multivariate analysis to build a nomogram.

Receiver operating characteristic (ROC) curves were utilized to compare the accuracy of the different classification systems for risk stratification. The 5-year RFS probability was calculated in the MSKCC nomogram and the new nomogram. The areas under the curve (AUCs) of all risk stratification systems were calculated and compared. A two-tailed P-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 22.0 software (version 22.0; IBM, USA).

Results

Clinicopathological characteristics of patients

Between January 1998 and December 2015, 371 patients were diagnosed with localized GISTs and underwent complete resection without imatinib therapy or other TKI therapy in a neoadjuvant or adjuvant setting at Southern Medical University Nanfang Hospital. Among these patients, 130 patients without complete data were excluded from the analysis. Thirty patients whose tumors were not primary, 22 patients who had a history of malignant tumor and 6 patients who had positive margins were also excluded. Thus, 183 patients were included in the present study.

Fifty-six patients who were diagnosed with GISTs and met the previous criteria at Sun Yat-sen University Cancer Center were included as the validation group. Table 1 shows the basic

Table 1
Clinicalpathological characteristics of patients with GISTs in both experiment and validation groups (n [%]).

	Experiment group (n = 183)	Validation group (n = 56)
Gender		
Male	94 (51.4)	36 (64.3)
Female	89 (48.6)	20 (35.7)
Age (mean ± SD, years)	54.21 ± 13.75	57.45 ± 17.44
Tumor location		
Gastric	161 (88.0)	33 (58.9)
Non-gastric	22 (12.0)	23 (41.1)
Tumor size		
≤5 cm	122 (66.7)	27 (48.2)
>5 cm	61 (33.3)	29 (51.8)
Mitotic index		
≤5/50 HPFs	131 (71.6)	28 (50.0)
>5/50 HPFs	52 (28.4)	28 (50.0)
Tumor rupture		
Yes	5 (2.7)	0 (0.0)
No	178 (97.3)	56 (100.0)
Ki-67 LI		
≤6%	165 (90.2)	41 (73.2)
>6%	18 (9.8)	15 (26.8)
Recurrence		
Yes	22 (12.0)	11 (19.6)
No	161 (88.0)	45 (80.4)
Mean follow up time (mean ± SD, months)	57.73 ± 36.11	78.37 ± 33.17

GISTs: gastrointestinal stromal tumors, HPFs: high-power fields, LI: labeling index, SD: standard deviation.

characteristics of the patients in the validation and experiment groups. The mean follow-up times of the experiment and validation groups were 57.73 ± 36.11 months and 78.37 ± 33.17 months, respectively. Twenty-two patients recurred in the experiment group compared with 11 patients in the validation group. Rupture occurred in 5 patients in the experiment group and in no patient in the validation group.

Nomogram establishment to predict the prognosis for GIST patients

In the experiment group, the univariate analysis showed that 5 variables of the clinicopathological characteristics were significantly associated with the RFS, including the tumor size ($P < 0.001$), site ($P < 0.001$), mitotic count ($P < 0.001$), rupture ($P < 0.001$) and Ki-67 LI ($P = 0.011$) (Table 2). A new nomogram was built based on this population that included these factors using a Cox proportional hazards model (Fig. 1). The results of the Cox regression analysis showed that the tumor size, site, mitotic count and Ki-67 LI remain independent risk factors for RFS ($P = 0.002$, hazard ratio [HR] 7.355 [2.037–26.562] for tumor size; $P = 0.013$, HR 3.753 [1.329–10.598] for site; $P = 0.006$, HR 3.738 [1.461–9.560] for mitotic count; and $P = 0.026$, HR 3.416 [1.157–10.090] for Ki-67 LI) (Table 2). The concordance index of the nomogram is 0.859 ± 0.061. The calibration curve of our nomogram is shown in Fig. 2 and demonstrated good agreement between the nomogram predicted RFS and the observed RFS.

Table 2
Univariate and multivariate analyses of prognostic factors for RFS of GISTs.

	P value of univariate analysis	*P* value of multivariate analysis	HR (95% CI)
Age (>60 vs. ≤ 60 years)	0.111	–	–
Gender (male vs. female)	0.505	–	–
Tumor size (>5 vs. ≤ 5 cm)	<0.001	0.002	7.355 (2.037-26.562)
Tumor site (non-gastric vs. gastric)	<0.001	0.013	3.753 (1.329-10.598)
Tumor rupture (yes vs. no)	<0.001	0.189	–
Mitotic count (>5 vs. ≤ 5/50 HPFs)	<0.001	0.006	3.738 (1.461-9.560)
Ki-67 LI (>6% vs. ≤ 6%)	0.011	0.026	3.416 (1.157-10.090)

GISTs: gastrointestinal stromal tumors, RFS: recurrence-free survival, HR: hazard ratio, HPFs: high-power fields, LI: labeling index, CI: confidence interval.

ROC analysis was used to compare the prognostic accuracy of the previously described GIST risk classification systems in the validation group (Fig. 3). According to our data, the largest AUC value was identified for our new nomogram (AUC = 0.778, 95% CI 0.647–0.878), followed by the contour maps (AUC = 0.743, 95% CI 0.609–0.851), AFIP criteria (AUC = 0.719, 95% CI 0.583–0.831), modified NIH criteria (AUC = 0.719, 95% CI 0.583–0.831), and MSKCC nomogram (AUC = 0.712, 95% CI 0.576–0.825).

Discussion

As previously discussed, accuracy in evaluating the risk of recurrence after surgery in patients with GISTs is critical to determine the appropriateness of adjuvant treatment and the intensity of postoperative surveillance. To establish a more reliable prognostic prediction model, in addition to mostly studied predicting factors such as tumor size, location, mitotic count and rupture, we included Ki-67 LI to reflect the tumor cell proliferation activity. The univariate analyses in our study demonstrated a tumor size >5 cm, mitotic count >5/50 HPFs, Ki-67 LI > 6%, nongastric location, and tumor rupture were significantly associated with increased recurrence rates. The new nomogram was constructed based on the Cox regression model using significant risk factors in multivariate analyses including tumor size, site, mitotic count and Ki-67 LI. And our new nomogram exhibited satisfactory performance with higher AUC compared with the currently employed risk classification criteria.

In recent decades, tumor location is recognized as an important factor that affects recurrence. Our study also verified gastric GISTs showed a more favorable course than non-gastric GISTs, which is consistent with previous studies [17]. Moreover, in patients with high-risk GISTs who received imatinib treatment, a COX regression analysis showed that a tumor location of the small intestine was an independent risk factor for prognosis [27]. Dematteo *et al* [28] also determined that patients with colonic or rectal GISTs had a high rate of recurrence, with only 20% of patients free of recurrence after long-term follow-up. Miettinen *et al* [29] identified tumors located in the fundus or at the gastroesophageal junction to be unfavorable factors for recurrence, whereas tumors located in the antrum showed more favorable outcomes ($P < 0.001$).

Tumor rupture is another factor that should not be ignored. Rutkowski *et al* [30] documented rupture as an independent risk factor for recurrence, and tumor rupture was included as a variable in the modified NIH classification system in 2008. In Hølmebakk's [31] study, the 5-year recurrence rates were 64%, 29% and 31% in patients with major rupture, minor rupture and no rupture, respectively ($P = 0.001$), and the peritoneal recurrence rates for patients with major, minor and no defects were 52%, 25% and 19%, respectively ($P = 0.002$). Nevertheless, in our data, no statistical significance was identified in the tumor rupture by multivariate analysis, which may be a result of the low incidence rate of this signature.

Apart from these risk factors mentioned above, tumor size and mitoses have also been widely studied and identified as prognostic variables by several large series of completely resected GISTs. In Kim's study, multivariate analyses indicated a correlation between a poor RFS and a high mitotic count (≥5/50 HPFs; OR 3.0) as well as

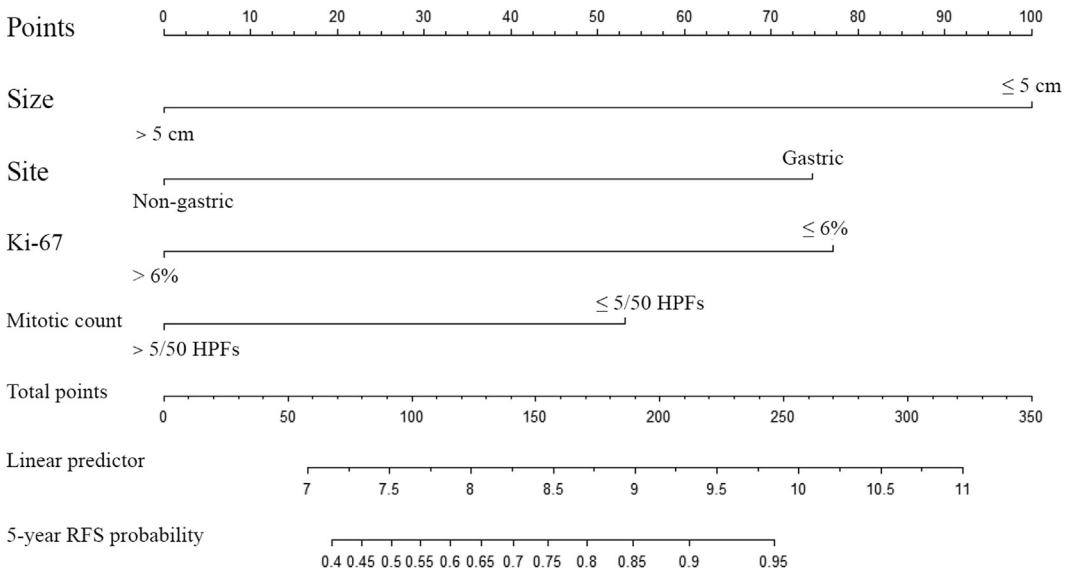

Fig. 1. Nomogram to predict the probabilities of 5-year recurrence-free survival with gastrointestinal stromal tumors.

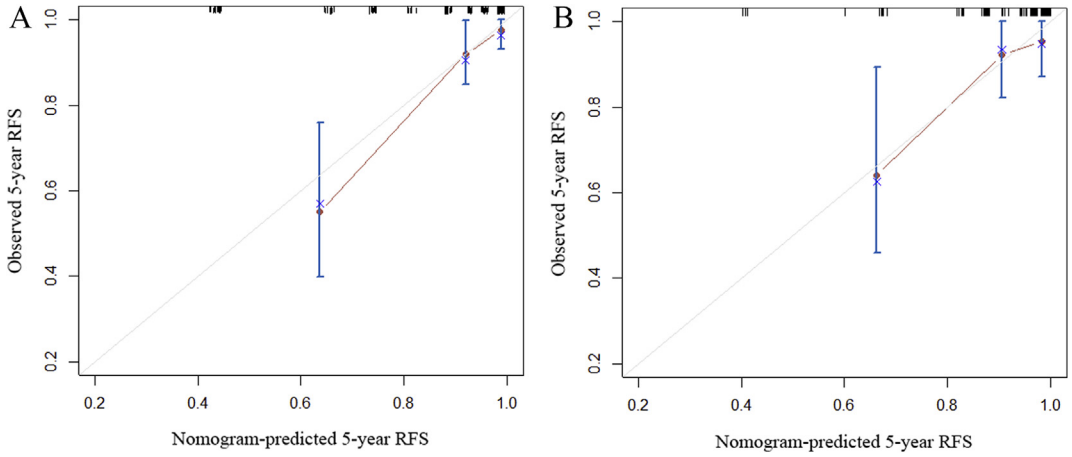

Fig. 2. Calibration curves for the new nomogram of estimating 5-year RFS in patients with GISTs. A. Calibration curve in the experiment group. B. Calibration curve in the validation group. RFS: recurrence-free survival, GISTs: gastrointestinal stromal tumors.

a large tumor size (≥5 cm; OR 4.2) [32]. Martín *et al* [33] found that the 5-year RFS for different tumor size categories was 82% ± 12% (0–5 cm), 79% ± 11% (5–10 cm), and 42% ± 17% (10 cm) respectively; these authors also reported a significantly higher RFS rate in patients with tumor mitoses fewer than 5/50 HPFs than those with mitoses more than 10/50 HPFs ($P < 0.001$). Though the significance of tumor size and mitoses as prognosis determining parameters have been demonstrated in several studies [21,33], these two factors, especially mitotic counts, can be influenced by many factors, such as the fixed time interval, quality of pathological specimens, microscope type, pathology doctors' diagnostic experience and different selected areas to count. Take microscope type—the potential strongest influencing factor for example. Depending on the field-of-view number (FOV) and the applied eyepiece, the field area per HPF differs from microscope to microscope, and therefore mitotic rate might be consequently different. To reduce the impact, the microscope type should be consistent, and counting mitotic counts per total area of 5 mm^2 is an alternative method [19,34]. Appleman *et al* [35] found that in GIST patients with tumor recurrence, 13% of them exhibited a mitotic count of 1–5/50 HPFs, and 2% showed no mitotic count. Therefore, a poor, incorrect prognostic result may be obtained if only relying on the mitotic count.

To reduce the inaccuracy of tumor behavior prediction by merely relying on mitotic counts, we integrated another proliferation-related parameter—Ki-67 into our nomogram. Ki-67, also referred to as MKI67, appears in actively proliferating cells in the G1, S, and G2 phases and is one of the most studied proliferation-related nuclear markers of tumor cells. In immunohistochemical staining, the nucleus in the proliferative phase is stained brown, and the nucleus that is not in the proliferative phase is not stained, which could eliminate the morphological observation bias and enable the cell proliferation activity to be easily identified. Several studies have demonstrated that Ki-67 is useful in predicting the malignant potential of GISTs [21,24]. Liu *et al* [24] reported that Ki-67 is a significant predictor of overall survival (OS) alongside the tumor size and mitotic index, its prognostic significance was still maintained in subgroup analysis when stratified by modified NIH criteria, tumor size, mitosis, tumor site, and histological subtype. Notably, in high-risk GIST patients, Ki-67 LI had a significantly higher AUC value than any modified NIH criteria

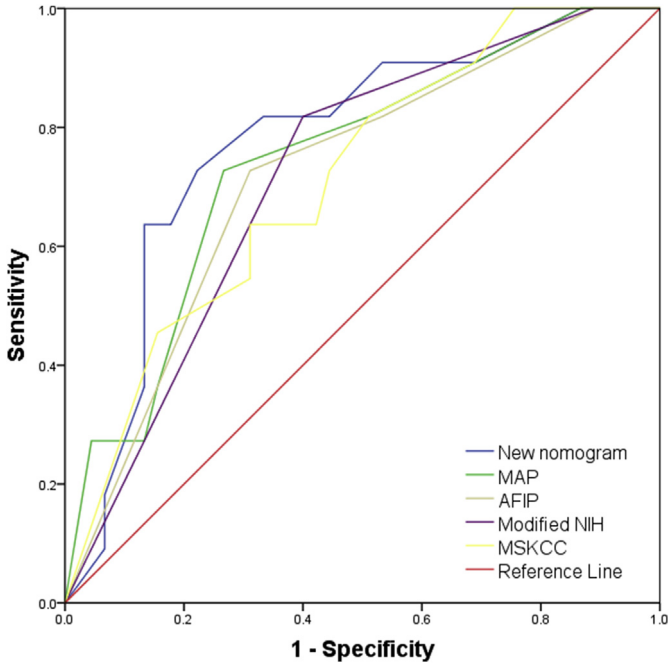

Fig. 3. Receiver operating characteristic curves for each risk model in predicting RFS of GISTs in the validation group. The AUC values were 0.778 for the new nomogram, 0.743 for the counter maps, 0.719 for the AFIP criteria, 0.712 for the MSKCC nomogram, and 0.719 for the modified NIH criteria. RFS: recurrence-free survival; GISTs: gastrointestinal stromal tumors, AUC: area under the curve, AFIP: Armed Forces Institute of Pathology, MSKCC: Memorial Sloan Kettering Cancer Center, NIH: National Institute of Health.

component, which suggested that this parameter may act as an effective complement to the modified NIH criteria. Our findings validated the value of Ki-67 LI in prognosis prediction of GISTs. Current publications also suggest that a high Ki-67 index may indicate metastasis and recurrence [36].

By combining Ki-67 and above mostly studied risk factors, the predictive ability of our nomogram was better than that of the MSKCC nomogram and other risk classification schemes. There are two advantages in our new nomogram compared with the MSKCC nomogram. First, adding Ki-67 to the new nomogram might make it more accurate and comprehensive for tumor biological behavior reflection and patient prognosis prediction. Second, all factors in our nomogram are categorical variables, which would make the nomogram more convenient to use in clinical practice. In addition, our nomogram outperformed the contour maps. Apart from taking the new factor Ki-67 into account, we think the reason is that contour maps emphasize tumor rupture and nongastric tumor sites, which rarely occur in both clinical practice and our data.

There are many other factors associated with tumor prognosis, including macroscopic findings, gene expression, transcription factors and protein levels. Martin-Broto J stated that deletions involving codons 557 and/or 558 (critical deletions) of exon 11 of KIT are relevant to the prognosis of RFS in GIST patients [37]. Further studies on these factors may facilitate the development of a more well-rounded prognostic system for GISTs.

There are several limitations in the present study. First, this investigation was a retrospective study, which might result in bias during the analysis, and prospective studies are required to verify our conclusions. Second, the validation group was relatively small, further studies including more patients to validate our nomogram is needed. We aim to continue following the outcomes of this patient cohort while adding more patients and continuing the analysis. However, the current study is the first study to include tumor size, site, mitotic count, and Ki-67 together in the nomogram. Furthermore, a large patient number may result in more effective evidence for prognostic comparison research.

Conclusion

In summary, our study suggests a new nomogram based on tumor size, site, mitotic count and Ki-67, which may be able to be used in clinical practice to predict the risk of GIST recurrence.

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The sponsor of the study had no role in the design of the study; collection, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

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