ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Prognostic Factors for Primary Localized Gastrointestinal Stromal Tumors After Radical Resection: Shandong Gastrointestinal Surgery Study Group, Study 1201

Xiaoqian Zhang, MD[1,2], Liang Ning, MD[2], Yulong Hu, MD[2], Shanfeng Zhao, MD[2], Zequn Li, MD[2], Leping Li, MD[3], Yong Dai, MD[4], Lixin Jiang, MD[5], Ailiang Wang, MD[6], Xianqun Chu, MD[7], Yuming Li, MD[8], Daogui Yang, MD[9], Chunlei Lu, MD[10], Linguo Yao, MD[11], Gang Cui, MD[12], Huizhong Lin, MD[13], Gang Chen, MD[14], Qing Cui, MD[15], Hongliang Guo, MD[16], Huanhu Zhang, MD[17], Zengjun Lun, MD[18], Lijian Xia, MD[19], Yingfeng Su, MD[20], Guoxin Han, MD[21], Xizeng Hui, MD[22], Zhixin Wei, MD[23], Zuocheng Sun, MD[24], Shuai Shen, MD[2], and Yanbing Zhou, MD[2]

[1]Division of General Surgery, Peking University First Hospital, Peking University, Beijing, China; [2]Department of General Surgery, Affiliated Hospital of Qingdao University, Qingdao, Shandong, China; [3]Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China; [4]Department of General Surgery, Qilu Hospital of Shandong University, Jinan, China; [5]Department of Gastrointestinal Thyroid Surgery, Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, Shandong, China; [6]Department of Gastrointestinal Surgery, Affiliated Hospital of Jining Medical University, Jining, Shandong, China; [7]Department of Gastroenterology Surgery, Jining No.1 People's Hospital, Jining, Shandong, China; [8]Department of Gastrointestinal Surgery, Binzhou Medical University Hospital, Binzhou, Shandong, China; [9]Department of Gastrointestinal Surgery, Liaocheng People's Hospital, Liaocheng, Shandong, China; [10]Department of Laparoscopic Surgery Center, Linyi People's Hospital, Linyi, Shandong, China; [11]Department of Gastrointestinal Surgery, Shengli Oilfield Central Hospital, Yantai, Shandong, China; [12]Department of General Surgery, Taian City Central Hospital, Taian, Shandong, China; [13]Department of Gastric Surgery, Qingdao Municipal Hospital, Qingdao, Shandong, China; [14]Department of Gastrointestinal Surgery, Tengzhou Central People's Hospital, Tengzhou, Shandong, China; [15]Department of General Surgery, Zibo Central Hospital, Zibo, Shandong, China; [16]The Fourth Department of General Surgery, Shandong Cancer Hospital, Jinan, Shandong, China; [17]Department of General Surgery, Weihai Municipal Hospital, Weihai, Shandong, China; [18]Department of General Surgery, Zaozhuang Municipal Hospital, Zaozhuang, Shandong, China; [19]Department of Gastrointestinal Surgery, Shandong Province Qianfoshan Hospital, Jinan, Shandong, China; [20]Department of General Surgery, Dezhou People's Hospital, Dezhou, Shandong, China; [21]Department of General Surgery, Affiliated Hospital of Taishan Medical University, Taian, Shandong, China; [22]Department of Surgery, People's Hospital of Rizhao, Rizhao, Shandong, China; [23]Department of General Surgery, Heze Municipal Hospital, Heze, Shandong, China; [24]Department of Surgery, Weifang People's Hospital, Weifang, Shandong, China

ABSTRACT

Background. Most previous risk-prediction models for gastrointestinal stromal tumors (GISTs) were based on Western populations. In the current study, we collected data from 23 hospitals in Shandong Province, China, and used the data to examine prognostic factors in Chinese patients and establish a new recurrence-free survival (RFS) prediction model.

Methods. Records were analyzed for 5285 GIST patients. Independent prognostic factors were identified using Cox models. Receiver operating characteristic curve analysis was used to compare a novel RFS prediction model with current risk-prediction models.

Results. Overall, 4216 patients met the inclusion criteria and 3363 completed follow-up. One-, 3-, and 5-year RFS was 94.6% (95% confidence interval [CI] 93.8–95.4),

85.9% (95% CI 84.7–87.1), and 78.8% (95% CI 77.0–80.6), respectively. Sex, tumor location, size, mitotic count, and rupture were independent prognostic factors. A new prognostic index (PI) was developed: PI = 0.000 (if female) + 0.270 (if male) + 0.000 (if gastric GIST) + 0.350 (if non-gastric GIST) + 0.000 (if no tumor rupture) + 1.259 (if tumor rupture) + 0.000 (tumor mitotic count < 6 per 50 high-power fields [HPFs]) + 1.442 (tumor mitotic count between 6 and 10 per 50 HPFs) + 2.026 (tumor mitotic count > 10 per 50 HPFs) + 0.096 × tumor size (cm). Model-predicted 1-, 3-, and 5-year RFS was $S(12, X) = 0.9926^{\exp(PI)}$, $S(36, X) = 0.9739^{\exp(PI)}$ and $S(60, X) = 0.9471^{\exp(PI)}$, respectively.

Conclusions. Sex, tumor location, size, mitotic count, and rupture were independently prognostic for GIST recurrence. Our RFS prediction model is effective for Chinese GIST patients.

Gastrointestinal stromal tumors (GISTs) are the most frequently diagnosed gastrointestinal mesenchymal tumors. The prevalence of GIST is 130 per million,[1,2] and the annual incidence is 4.3–21.1 per million.[3] Owing to developments in pathology and diagnostic technology, as well as increased levels of physician knowledge regarding GISTs, a gradual upward trend in the diagnosis of GISTs has been reported.[4,5] In 1983, Mazur and Clark observed that some gastric wall tumors did not originate from smooth muscle, but instead originated from perineurial or mesenchymal nerve sheath cells.[6] In 1998, Hirota et al. indicated that GISTs are derived from the interstitial cells of Cajal (ICCs).[7] Approximately 75–80% of GISTs harbor a mutation in KIT,[7,8] and approximately 10% contain a mutation in platelet-derived growth factor receptor-α (PDGFR-α).[9,10]

GISTs can be benign or malignant. R0 resection is the gold standard in the treatment of localized primary GISTs; however, the risks of recurrence and metastasis persist in some patients after resection. Adjuvant imatinib administration can improve the prognosis of unresectable or metastatic GISTs[11] and those of high-risk patients.[12,13] Imatinib is generally well-tolerated, but almost all patients have at least one adverse event.[13] For these reasons, it is critical to predict the risk of recurrence and metastasis, as a means of assisting with treatment planning.

Several risk-prediction models for GIST have been published.[14–22] The first consensus approach—the National Institutes of Health (NIH) consensus[14]—defines the risk of aggressive GIST behavior based on tumor size and mitotic count. The Armed Forces Institute of Pathology (AFIP) criteria[15] subdivided GIST patients into eight subgroups (1–6b) based on tumor size and mitotic count, and stratified them into five risk groups based on tumor site. The modified NIH consensus criteria[17] stratified GIST patients into four risk groups through the addition of two other risk factors—tumor site and rupture. Notably, in those studies, only a small portion of patients were Asian.[16,19] In the current study, we collected data from 23 hospitals in Shandong Province, China, and used the data to examine prognostic factors in Chinese patients and establish a new recurrence-free survival (RFS) prediction model.

METHODS

Patients

We retrospectively analyzed data of patients with a confirmed diagnosis of GIST from 23 hospitals in Shandong Province from 2001 to 2014. All the experimental protocols were approved by the Ethics Committee of Qingdao University, China. Demographic and clinical data were obtained from case records. Data on tumor location, size, mitotic count, rupture, and surgical margin were acquired from the operative reports and pathology reports.

We excluded patients who did not undergo endoscopic or surgical resection, as well as those with positive surgical margins. Individuals with multiple neoplasms, primary metastatic disease, recurrent tumors, and other malignancies were excluded. We also excluded patients who received imatinib either before or after the surgery and died perioperatively, or whose age, sex, and date of surgery were unknown.

Statistical Analysis

The main endpoint of the study was RFS, while secondary endpoints included disease-specific survival (DSS) and overall survival (OS). RFS, DSS, and OS were estimated using the Kaplan–Meier method and compared using log-rank tests. To determine the hazard ratio (HR) for survival associated with each variable after radical resection, the univariate Cox proportional hazards model was employed. Multivariable Cox regression analysis was used to detect prognostic factors, and variables with a p value < 0.05 were entered into the final model to establish 1-, 3-, and 5-year RFS prediction models. The discrimination of the RFS prediction model was measured by concordance index (C-index), and the calibration of the RFS prediction model was assessed by comparing predicted RFS with actual RFS. We used the bootstrapping method for internal validation, and the data of 1000 bootstrap samples were analyzed, as in the study samples from our database.[23,24] A C-index of 0.5 means that the model does not have predictive power, whereas a C-index of 1 represents that the prediction result of the model is

completely consistent with the facts. All statistical analyses were performed using the SPSS 24.0 statistical software package (IBM Corporation, Armonk, NY, USA), Stata 15.1 software (StataCorp LLC, College Station, TX, USA) and R version 2.3 (The R Foundation for Statistical Computing, Vienna, Austria). *P*-values were two-sided and were considered as significant at a level of 0.05.

RESULTS

Demographic Data

We retrospectively analyzed the data of 5282 patients with GISTs from 23 hospitals in Shandong Province, China, from 2001 to 2014. A total of 50.3% (*n* = 2648) of patients were men and 49.1% (*n* = 2615) were women. The median age at diagnosis was 59 years (range 4–91) (Table 1).

Tumor Characteristics

Tumor location was known in all analyzed cases. More than half of the tumors were located in the stomach (56%, *n* = 2958), with the second most common location being the small intestine (24.1%, *n* = 1275). In addition, 11.6% (*n* = 661) of the tumors were located outside of the gastrointestinal tract, mainly in the omentum, mesentery, and retroperitoneum. The median tumor size was 5.0 cm (range 0.1–50 cm) in diameter. Regarding mitotic count, values lower than 5 per 50 high-power fields (HPFs) accounted for the largest proportion of cases (71.0%, 1916 of 2697). The tumor rupture group includes tumors that ruptured either preoperatively or intraoperatively. A total of 6.2% (291/700) tumors ruptured preoperatively or intraoperatively (Table 1).

Treatment

Based on tumor location and size, 7.7% (*n* = 408) of patients underwent endoscopic resection, while 83.1% (*n* = 4394) of patients underwent surgical resection, including open surgery, laparoscopy, and robotic surgery. A total of 0.9% (*n* = 46) of patients underwent laparoscopic-assisted endoscopic polypectomy. In 95.6% (*n* = 5050) of patients, the tumors were microscopically resected with negative resection margins (R0).

Survival Analysis

Of the 5285 enrolled GIST patients, 175 had missing data regarding age, sex, or date of surgery. Overall, 143 and 34 patients underwent R1 and R2 resection,

respectively. Fifty-eight patients underwent biopsy only, and one patient underwent transarterial chemoembolization (TACE). A total of 217 patients had other malignancies. One hundred and sixty-eight patients were diagnosed with multiple neoplasms or primary metastatic disease. Five patients died perioperatively owing to complications and 25 patients had recurrent/metastatic GIST. Three and 407 patients received imatinib before and after surgery, respectively. A total of 4216 patients met the inclusion criteria. The complete follow-up data of 3363 patients were obtained, which amounted to a follow-up rate of 79.8%. The median follow-up was 41 months (range 1–156 months). Of all patients, 2704 (80.4%) were alive without recurrence or metastasis; 236 patients (6.5%) were alive with disease. A total of 320 patients (9.5%) died of GIST, while 103 patients (3.1%) died of unrelated disease. In most cases, tumor recurrence or metastasis occurred within the first 5 years after resection, with a maximum interval of 9 years after resection. The liver and abdomen were the most common sites of metastasis.

One-, 3-, and 5-year RFS was 94.6% (95% confidence interval [CI] 93.8–95.4), 85.9% (95% CI 84.7–87.1), and 78.8% (95% CI 77.0–80.6), respectively; 1-, 3-, and 5-year DSS was 97.6% (95% CI 97.0–98.2), 90.7% (95% CI 89.7–91.7), and 88.9% (95% CI 87.7–90.1), respectively; and 1-, 3-, and 5-year OS was 97.1% (95% CI 96.5–97.7), 89.1% (95% CI 87.9–90.2), and 84.9% (95% CI 83.3–84.5), respectively (Fig. 1).

After being stratified by the modified NIH consensus criteria, no statistically significant differences were observed for the RFS (Chi square = 0.001, *p* = 0.982), DSS (Chi square = 0.03, *p* = 0.868), and OS (Chi square = 0.83, *p* = 0.361) rates of very low-risk and low-risk patients. Additionally, no statistically significant differences were observed between the OS rates of very low-risk patients and intermediate-risk patients (Chi square = 3.35, *p* = 0.067). There were significant differences among other groups (Chi square = 15.71–258.28, *p* = 0.000–0.003) (Fig. 2).

In univariate analyses, sex (HR 1.357, 95% CI 1.148–1.603, *p* < 0.001), age (HR 1.011, 95% CI 1.004–1.018, *p* = 0.002), tumor location, size (HR 1.094, 95% CI 1.085–1.103, *p* < 0.001), mitotic count (6–10 per 50 HPFs vs. < 5 per 50 HPFs: HR 5.940, 95% CI 4.618–7.640, *p* < 0.001; > 10 per 50 HPFs vs. < 5 per 50 HPFs: HR 12.196, 95% CI 9.328–15.947, *p* < 0.001), and rupture (HR 5.286, 95% CI 4.148–6.736, *p* < 0.001) were predictive of outcome. Compared with patients whose tumors originated in the stomach, RFS was worse for those with tumors that arose from the small bowel (HR 2.454, 95% CI 2.026–2.972, *p* < 0.001), the colorectum (HR 3.525, 95% CI 2.411–5.155, *p* < 0.001), or outside the gastrointestinal tract (HR 2.689, 95% CI 2.134–3.388,

TABLE 1 Demographic data and tumor characteristics

	All cases [n = 5285]	Cases included in the final analysis [n = 3363]
Age, years [median (range)]	59 (4–91)	59 (4–88)
≤ 20	15 (0.3)	10 (0.3)
21–40	376 (7.1)	263 (7.8)
> 40	4869 (92.6)	3090 (91.9)
NA	25	
Sex		
Female	2615 (49.7)	1716 (51.0)
Male	2648 (50.3)	1647 (49.0)
NA	22	
Tumor site		
Esophagus	221 (4.2)	84 (2.5)
Stomach	2958 (56.0)	2098 (62.4)
Duodenum	291 (5.5)	160 (4.8)
Jejunoileum	984 (18.6)	566 (16.8)
Colon	71 (1.3)	20 (0.6)
Rectum	149 (2.8)	62 (1.8)
E-GIST	611 (11.6)	373 (11.2)
Tumor size, cm [median (range)]	5 (0.1–50)	4.5 (0.1–50)
≤ 2	1074 (22.5)	725 (22.9)
> 2 to ≤ 5	1561 (32.7)	1115 (35.2)
> 5 to ≤ 10	1362 (28.5)	894 (28.2)
> 10	781 (16.3)	435 (13.7)
Multiple neoplasms	105	
NA	402	194
Mitotic count, per 50 HPFs		
≤ 5	1916 (71.0)	1418 (74.2)
6–10	522 (19.4)	327 (17.1)
> 10	259 (9.6)	165 (8.6)
NA	2588	1453
Tumor rupture		
Unruptured	4409 (93.8)	2944 (95.7)
Ruptured	291 (6.2)	132 (4.3)
NA	585	287

Data are expressed as *n* (%) unless otherwise specified

NA not available, *E-GIST* extra-gastrointestinal stromal tumor, *HPFs* high-power fields

$p < 0.001$). On the other hand, RFS was better for those with tumors located in the esophagus than for those whose tumors originated in the stomach (HR 0.228, 95% CI 0.057–0.918, $p = 0.038$) (Fig. 3).

In multivariate analyses, esophageal GISTs were excluded because of the small number of patients. Log-rank tests did not reveal any significant RFS differences between small intestinal GISTs, colorectal GISTs, and E-GISTs (extra-gastrointestinal stromal tumors). For this reason, we combined these three groups into a single group for comparisons with gastric GISTs. The six variables that were significant in univariate analyses ($p < 0.05$)

were entered into the multivariate Cox regression model. Sex (HR 1.310, 95% CI 1.052–1.632, $p = 0.016$), tumor location (HR 1.419, 95% CI 1.144–1.760, $p = 0.001$), size (HR 1.100, 95% CI 1.081–1.120, $p < 0.001$), mitotic count (6–10 per 50 HPFs vs. ≤ 5 per 50HPFs: HR 4.231, 95% CI 3.261–5.489, $p < 0.001$; > 10 per 50 HPFs vs. ≤ 5 per 50 HPFs: HR 7.585, 95% CI 5.678–10.134, $p < 0.001$), and rupture (HR 3.522, 95% CI 2.573–4.822, $p < 0.001$) were the variables that showed significant and independent associations with prognosis (Table 2).

Based on the estimated regression coefficients, PI = 0.000 (if female) + 0.270 (if male) + 0.000 (if gastric
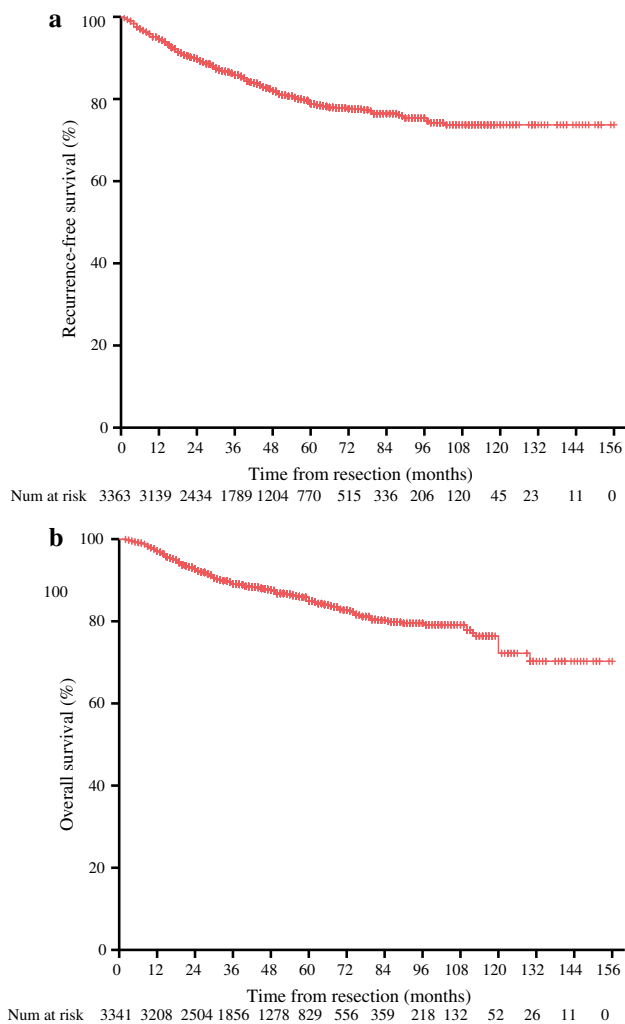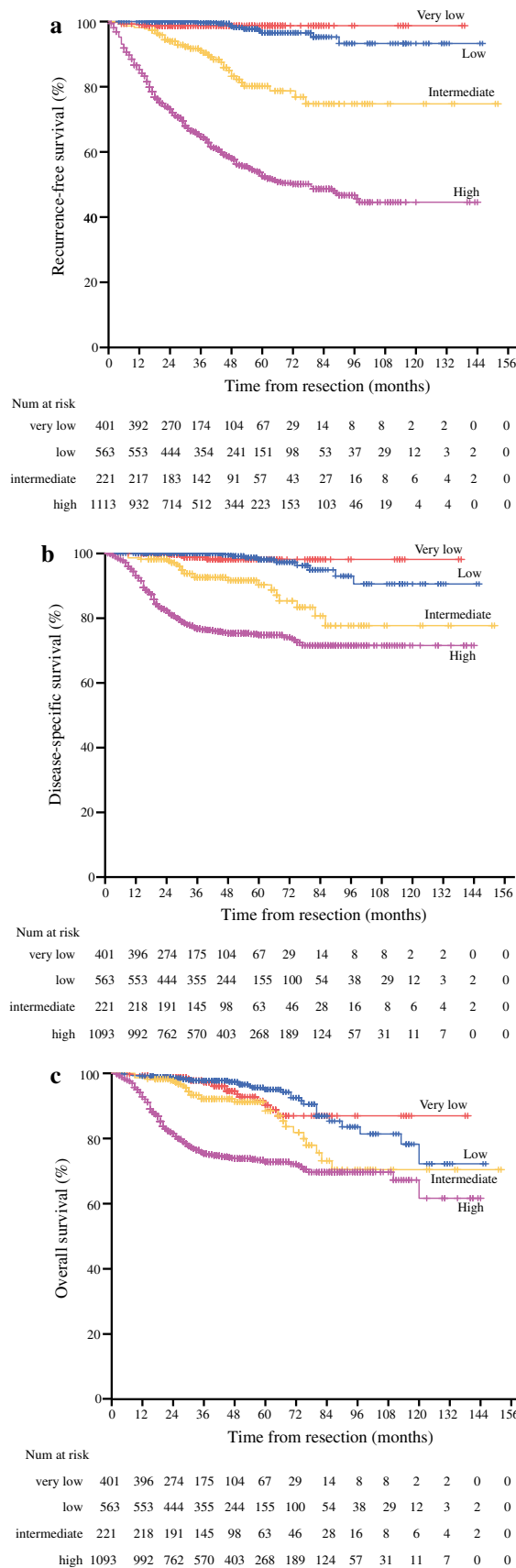
FIG. 1 (**a**) Recurrence-free survival and (**b**) overall survival. *Num* number

GIST) + 0.350 (if non-gastric GIST) + 0.000 (if no tumor rupture) + 1.259 (if tumor rupture) + 0.000 (tumor mitotic count < 6 per 50 HPFs) + 1.442 (tumor mitotic count between 6 and 10 per 50 HPFs) + 2.026 (tumor mitotic count > 10 per 50 HPFs) + 0.096 × tumor size (cm). Predictions of 1-, 3-, and 5-year RFS were obtained from the model as follows: $S(12, X) = 0.9926^{\exp(PI)}$, $S(36, X) = 0.9739^{\exp(PI)}$, and $S(60, X) = 0.9471^{\exp(PI)}$, respectively. For instance, for a male patient with a ruptured small intestinal GIST 10 cm in diameter and with > 10 mitoses per 50 HPFs, the PI is 0.98 and the 1-, 3-, and 5-year RFSs are 38.2%, 3.2%, and 0.1%, respectively. As another example, for a female patient with an unruptured

FIG. 2 (**a**) Recurrence-free survival, (**b**) disease-specific survival, and (**c**) overall survival, stratified by the modified National Institutes of Health consensus criteria. *Num* number
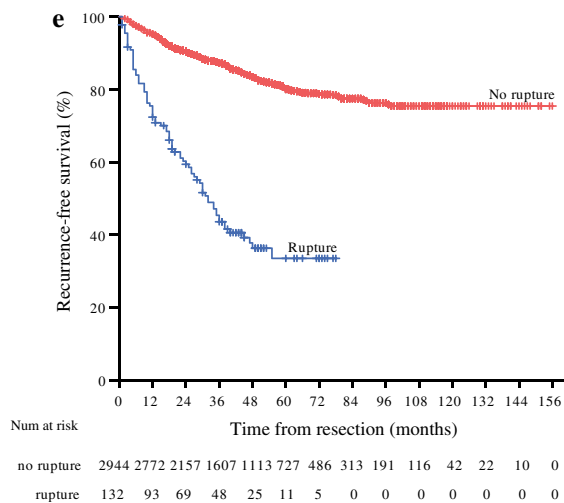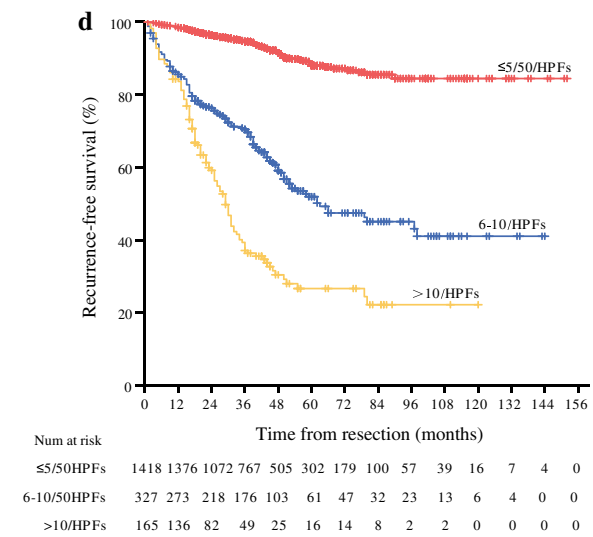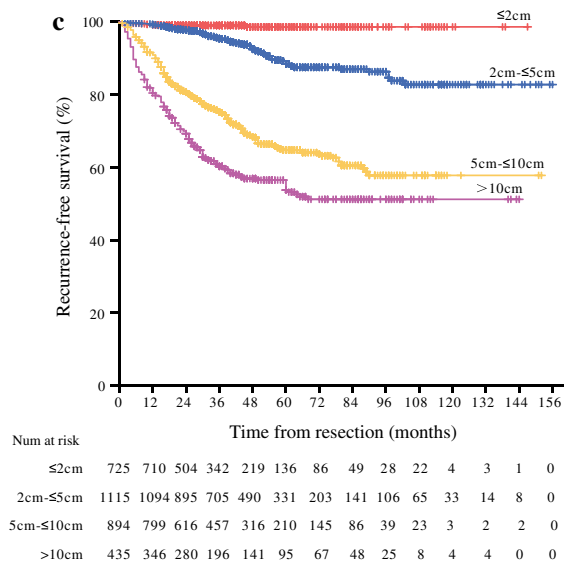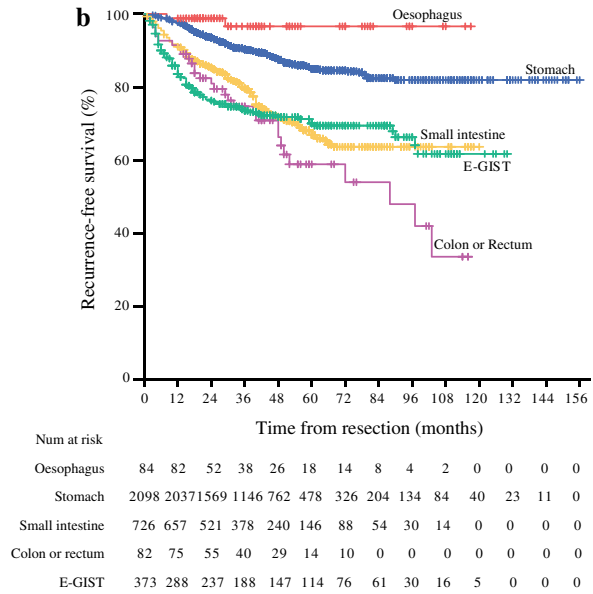
a

Num at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
female	1716	1613	1278	941	640	424	287	183	101	69	27	14	3	0
male	1647	1526	1156	848	564	346	228	153	105	52	18	9	8	0

b

Num at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
Oesophagus	84	82	52	38	26	18	14	8	4	2	0	0	0	0
Stomach	2098	2037	1569	1146	762	478	326	204	134	84	40	23	11	0
Small intestine	726	657	521	378	240	146	88	54	30	14	0	0	0	0
Colon or rectum	82	75	55	40	29	14	10	0	0	0	0	0	0	0
E-GIST	373	288	237	188	147	114	76	61	30	16	5	0	0	0

c

Num at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
≤2cm	725	710	504	342	219	136	86	49	28	22	4	3	1	0
2cm-≤5cm	1115	1094	895	705	490	331	203	141	106	65	33	14	8	0
5cm-≤10cm	894	799	616	457	316	210	145	86	39	23	3	2	2	0
>10cm	435	346	280	196	141	95	67	48	25	8	4	4	0	0

d

Num at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
≤5/50HPFs	1418	1376	1072	767	505	302	179	100	57	39	16	7	4	0
6-10/50HPFs	327	273	218	176	103	61	47	32	23	13	6	4	0	0
>10/HPFs	165	136	82	49	25	16	14	8	2	2	0	0	0	0

e

Num at risk

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
no rupture	2944	2772	2157	1607	1113	727	486	313	191	116	42	22	10	0
rupture	132	93	69	48	25	11	5	0	0	0	0	0	0	0

gastric GIST 10 cm in diameter and with ≤ 5 mitoses per 50 HPFs, the PI is 0.96 and the 1-, 3-, and 5-year RFSs are 98.1%, 93.3%, and 86.8%, respectively.

The overall apparent C-index of the RFS prediction model was 0.850. In internal validation, the RFS prediction model's performance was assessed using the bootstrapping method. The bootstrapping corrected C-index was 0.850 (95% CI 0.830–0.870). Figure 4 shows the calibration of the RFS prediction model was assessed by comparing the predicted RFS with the actual RFS.

In the assessment of accuracy, we used receiver operating characteristic (ROC) curve analyses to compare the proposed RFS prediction model and the modified NIH consensus criteria, the AFIP criteria, and Gold's nomogram. The area under the ROC curve (AUC) of the RFS prediction model was 0.879 (95% CI 0.859–0.899, $p < 0.001$), whereas the AUC of the modified NIH consensus criteria was 0.833 (95% CI 0.812–0.855, $p < 0.001$), the AUC of the AFIP criteria was 0.853 (95% CI 0.831–0.876, $p < 0.001$), the AUC of the 2-year nomogram was 0.857 (95% CI 0.836–0.879, $p < 0.001$), and the AUC of the 5-year nomogram was 0.857 (95% CI 0.835–0.878, $p < 0.001$) (Fig. 5).

DISCUSSION

In this study, we retrospectively analyzed the records of patients with a confirmed diagnosis of GIST in Shandong Province, China, as a means of evaluating the risk factors for recurrence of GIST after radical resection, and of developing an RFS prediction model that would be applicable to the Chinese population. We then assessed the accuracy of the RFS prediction model through comparison with the modified NIH consensus criteria, the AFIP criteria, and Gold's nomogram. In terms of the epidemiological features, our study showed an almost-balanced sex ratio (male:female = 1.01). Most of the tumors were located in the stomach, followed by the small intestine and colorectum. These results are consistent with previous studies.[3]

Our study revealed that Chinese GIST patients had a better prognosis than has been reported in Western countries. In our study cohort, the 5-year RFS and DSS rates were 78.8% and 88.9%, respectively. On the other hand, in an analysis of pooled population-based cohorts, Joensuu et al. reported a 5-year RFS of 70.5%.[19] Additionally, Mucciarini et al. reported that the 5-year DSS was 84.6% for patients treated with radical surgery.[25]

As for this discrepancy, this is partly because, on the one hand, the percentage of small GISTs (≤ 2 cm) in our cohort (22.9%) was a little higher than those in the cohorts of Joensuu et al. (12.3%) and Mucciarini et al. (17.5%). On the other hand, it is possible that the differences in prognosis result from genetic differences associated with ethnicity, although additional research would be needed to investigate this explanation and to determine whether it is valid.

We determined that male sex, non-gastric GISTs, large tumor size, high mitotic count, and ruptured tumors were adverse, independent prognostic factors. On the other hand, female sex, gastric GISTs, small tumor size, low mitotic count, and unruptured tumors were associated with better survival.

Tumor size and mitotic count are the recognized independent prognostic factors. In 2002, Fletcher et al. first published a consensus approach (the NIH consensus) for predicting GIST outcomes.[14] Using this approach, the risk of aggressive behavior in GISTs is staged according to tumor size and mitotic count. Similarly, in the current study, these two factors were independently related to patient outcomes in both univariate analyses and multivariate Cox regression.

In 2006, the AFIP criteria[15] were developed by Miettinen et al. based on four long-term follow-up studies.[26–29] The suggested guidelines indicate that the clinical behavior of GISTs varies by site; this suggestion agrees with our results. In the current study, significant RFS differences were observed between esophageal GISTs and gastric GISTs; however, no significant difference was observed in terms of DSS or OS. Esophageal GISTs were associated with better survival in univariate analysis, a finding that may be related to the pathological features of tumors in our database. In addition, we observed that the prognosis of small intestinal GISTs, colorectal GISTs, and E-GISTs was worse than that of gastric GISTs.

In 2007, Rutkowski et al.[30] and Takahashi et al.[31] suggested that tumor rupture was a significant prognostic factor. The following year, Joensuu et al.[17] modified the NIH consensus though the addition of two factors—tumor site and rupture. Consistent with this modification, our analyses of RFS showed that the presence of tumor rupture was associated with an HR of 3.52.

However, it is controversial whether sex is an independent risk factor among GIST patients. The results of the current study were consistent with previous reports from Joensuu et al.[19], Rutkowski et al.[30], and Lv et al.[5] that male sex may be associated with a worse prognosis; however, Huang et al.[16] observed no relationship between sex and survival. These discrepancies deserve further study.

TABLE 2 Multivariate analysis of recurrence-free survival

Variable	Category	HR	95% CI	p-Value
Sex	Female	1.000	–	0.016
	Male	1.310	1.052–1.632	
Tumor size		1.100	1.081–1.120	< 0.001
Mitotic count	≤5 per 50 HPFs	1.000	–	< 0.001
	6–10 per 50 HPFs	4.231	3.261–5.489	< 0.001
	>10 per 50 HPFs	7.585	5.678–10.134	< 0.001
Tumor rupture	Unruptured	1.000	–	< 0.001
	Ruptured	3.522	2.573–4.822	
Tumor site	Gastric GIST	1.000	–	< 0.001
	Non-gastric GIST	1.419	1.144–1.760	

HR hazard ratio, *CI* confidence interval, *GIST* gastrointestinal stromal tumor, *HPFs* high-power fields
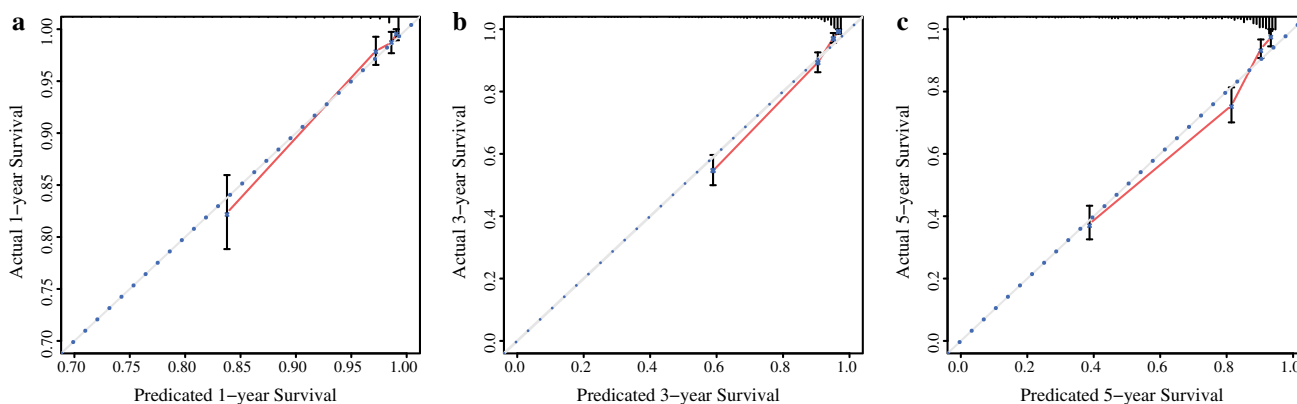
FIG. 4 Calibration of the RFS prediction model. Actual RFS is shown compared with the RFS prediction model at (**a**) 1, (**b**) 3, and (**c**) 5 years. *RFS* recurrence-free survival
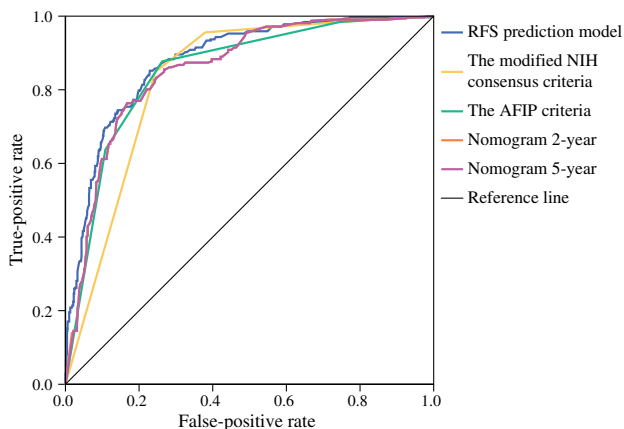
FIG. 5 Receiver operating characteristic curve analysis comparing our RFS prediction model with the modified NIH consensus criteria, the AFIP criteria, and Gold's nomogram. *RFS* recurrence-free survival, *NIH* National Institutes of Health, *AFIP* Armed Forces Institute of Pathology

This study had a multicenter retrospective design with a large patient population. Compared with the modified NIH consensus criteria and the AFIP criteria, the new RFS prediction model can predict the risk of the individual patient. It may be appropriate for doctors to treat certain GIST patients with adjuvant imatinib. Importantly, it is both difficult and valuable to acquire detailed, large-scale data on GIST patients who are not treated with imatinib, and these data reflect the original clinical and pathological features of GIST in Chinese patients. Moreover, our results revealed that Chinese patients with GIST had a better prognosis than GIST patients from Europe and America, indicating that the clinicopathological features and prognosis of GIST varies geographically or ethnically. These results also verify that it is necessary to establish specific standards for monitoring and treating GIST in different areas of the world.

This study is subject to some limitations. First, gene mutations and SDHB protein expression were not included in the prediction model. In 2013, a National Comprehensive Cancer Network (NCCN) guideline first pointed out that genetic analysis of the tumor should be assessed if planned treatment involves tyrosine kinase inhibitors. Previously, genetic analysis was not routinely performed.[32] In 2014, another NCCN guideline suggested that if no

mutations were observed in KIT or PDGFR-α, SDHB immunohistochemistry should be further evaluated. Since our database included patient data from 2001 to 2014, most of these cases did not examine SDHB immunohistochemistry;[33] therefore, we did not evaluate the effects of gene mutations and SDHB protein expression on prognosis because of incomplete mutation data. Prospective studies and long-term follow-up are needed to address these issues. As this study was a retrospective study, which had inevitable limitations, the missing data of mitotic count might influence the stability of the results. Second, no other cohort was available for validation, therefore we were not able to perform a validation study using an external cohort; however, the internal validation has suggested a good prediction power.

To our knowledge, this study included the largest cohort of Asian GIST patients that has been investigated to date. In this large, multicenter, retrospective study, we determined that sex, tumor location, size, mitotic count, and rupture were independent prognostic factors. Based on the independent prognostic factors and the estimated regression coefficients, we developed an RFS prediction model that was capable of estimating the risks of recurrence and metastasis at 1, 3, and 5 years.

CONCLUSIONS

Our RFS prediction model is able to predict the risk among individual patients. In the meantime, this can be of use to health policymakers and doctors in the formulation of treatment strategies. The RFS prediction model is available for use at the following URL: http://www.gistriskcalculator.com/.

REFERENCES

1. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer.* 2005;103(4):821–29.

2. Chan KH, Chan CW, Chow WH, et al. Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong. *World J Gastroenterol.* 2006;12(14):2223–28.

3. Soreide K, Sandvik OM, Soreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol.* 2016;40:39–46.

4. Chiang NJ, Chen LT, Tsai CR, Chang JS. The epidemiology of gastrointestinal stromal tumors in Taiwan, 1998–2008: a nationwide cancer registry-based study. *BMC Cancer.* 2014;14:102.

5. Lv M, Wu C, Zheng Y, Zhao N. Incidence and survival analysis of gastrointestinal stromal tumors in shanghai: a population-based study from 2001 to 2010. *Gastroenterol Res Pract.* 2014;2014:834136.

6. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol.* 1983;7(6):507–19.

7. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 1998;279(5350):577–80.

8. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer.* 2011;11(12):865–78.

9. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science.* 2003;299(5607):708–10.

10. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology.* 2003;125(3):660–67.

11. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol.* 2008;26(4):620–25.

12. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2009;373(9669):1097–1104.

13. Joensuu H, Eriksson M, Sundby Hall K, et al. One versus three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA.* 2012;307(12):1265–72.

14. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Int J Surg Pathol.* 2002;10(2):81–9.

15. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70–83.

16. Huang HY, Li CF, Huang WW, et al. A modification of NIH consensus criteria to better distinguish the highly lethal subset of primary localized gastrointestinal stromal tumors: a subdivision of the original high-risk group on the basis of outcome. *Surgery.* 2007;141(6):748–56.

17. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol.* 2008;39(10):1411-19.

18. Sobin LH, Gospodarowicz MK, Wittekind C, International union against cancer. *TNM classification of malignant tumours.* 7th ed. Chichester: Wiley-Blackwell; 2010.

19. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. *Lancet Oncol.* 2012;13(3):265–74.

20. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Oncol.* 2009;10(11):1045–52.

21. Rossi S, Miceli R, Messerini L, et al. Natural history of imatinib-naive GISTs: a retrospective analysis of 929 cases with long-term follow-up and development of a survival nomogram based on mitotic index and size as continuous variables. *Am J Surg Pathol.* 2011;35(11):1646–56.

22. Bischof DA, Kim Y, Behman R, et al. A nomogram to predict disease-free survival after surgical resection of GIST. *J Gastrointest Surg.* 2014;18(12):2123–29.

23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996;15(4):361–87.

24. Moons KG, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. *Heart.* 2012;98(9):683–90.

25. Mucciarini C, Rossi G, Bertolini F, et al. Incidence and clinico-pathologic features of gastrointestinal stromal tumors. A population-based study. *BMC Cancer.* 2007;7:230.

26. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol.* 2006;30(4):477–89.

27. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol.* 2005;29(1):52–68.

28. Miettinen M, Kopczynski J, Makhlouf HR, et al. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical, and molecular genetic study of 167 cases. *Am J Surg Pathol.* 2003;27(5):625–41.

29. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. *Am J Surg Pathol.* 2001;25(9):1121–33.

30. Rutkowski P, Nowecki ZI, Michej W, et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. *Ann Surg Oncol.* 2007;14(7):2018–27.

31. Takahashi T, Nakajima K, Nishitani A, et al. An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. *Int J Clin Oncol.* 2007;12(5):369–74.

32. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Soft Tissue Sarcoma, Version 1. 2013. https://www.nccn.org/. Accessed 30 Sep 2019.

33. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Soft Tissue Sarcoma, Version 2. 2014. https://www.nccn.org/. Accessed 30 Sep 2019.