A nomogram for predicting recurrence-free survival in patients with high-risk GIST receiving adjuvant imatinib: A nationwide registry study

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Abstract. Despite adjuvant imatinib therapy, a substantial proportion of patients with high-risk gastrointestinal stromal tumor (GIST) experience disease recurrence. This study aimed to identify prognostic factors associated with poor recurrence-free survival (RFS) and develop a predictive nomogram for personalized clinical decision-making. In the present study, a retrospective analysis was conducted of 269 patients with modified Armed Forces Institute of Pathology-classified high-risk GIST who underwent macroscopically complete resection and received adjuvant imatinib therapy at 11 Taiwanese centers between 2013 and 2023. All patients were intended to receive 3 years of adjuvant imatinib and were

categorized into disease-free (n=204) and recurrence (n=65) cohorts. Independent predictors of poor RFS were identified through multivariate Cox regression analysis and incorporated into a nomogram. Model performance was assessed using concordance index (C-index) and calibration plots. The cohort comprised 149 males and 120 females with a median age of 60.9 years (range, 29-88 years). At a median follow-up of 62.6 months, the 1-, 3- and 5-year disease-free survival rates were 97.0, 91.7 and 76.4%, respectively. Multivariate analysis identified male sex [hazard ratio (HR): 1.76, P=0.039], non-gastric tumor origin with duodenum showing highest risk (HR: 6.15, P<0.0001) and shorter imatinib duration with <1 year treatment showing HR: 3.91 (P=0.002) as independent predictors of poor RFS. The resulting nomogram demonstrated robust predictive performance with good calibration and C-index of 0.72. Nomogram-based prognostic stratification identified three distinct groups with 5-year survival rates of 99.2% (favorable prognosis), 68.1% (moderate prognosis) and 16.7% (poor prognosis). In the present study, a clinically applicable nomogram was developed that accurately predicts poor RFS in patients with high-risk GIST following surgery and adjuvant imatinib therapy. While external validation is needed before clinical implementation, this prognostic tool may facilitate individualized treatment strategies and patient counseling.

Introduction

Gastrointestinal stromal tumor (GIST) represents the most common mesenchymal neoplasm of the gastrointestinal tract (1,2). The pathogenesis of GIST is predominantly driven by activating mutations in the KIT proto-oncogene, receptor tyrosine kinase (KIT) or platelet-derived growth factor receptor alpha (PDGFRA) genes (1). Approximately 70-80% of GISTs harbor KIT mutations, with exon 11 being the most frequently affected site, followed by less common mutations in exons 9, 13 or 17 (1). PDGFRA mutations account for approximately one-third of KIT-wild-type GISTs (3,4). Tumors lacking mutations in both KIT and PDGFRA, termed wild-type GISTs, may harbor alterations in other genes, including succinate dehydrogenase, B-Raf proto-oncogene, serine/threonine kinase or KRAS proto-oncogene, GTPase (1).

Complete surgical resection remains the primary treatment modality for localized GIST (2-4). However, disease recurrence frequently occurs in patients with high-risk features, including large tumor size, elevated mitotic index, non-gastric location, tumor rupture or specific molecular profiles (8,5-9). While numerous patients achieve a cure through surgery alone (2-4), adjuvant imatinib therapy for a minimum of three years is recommended for those at substantial risk of recurrence (5,6).

Recent advances in GIST research have focused on developing prognostic tools that integrate clinical and pathological factors to improve risk stratification beyond traditional classification systems. However, most existing prognostic models were developed for surgical cohorts or metastatic disease settings, with limited tools specifically designed for patients receiving adjuvant therapy (10-12).

This recommendation is supported by three pivotal randomized controlled trials: ACOSOG Z9001 (NCT00041197) (7), EORTC 62024 (8) and SSG XVIII (5). These studies demonstrated that adjuvant imatinib significantly improves recurrence-free survival (RFS) compared to placebo (7) or observation alone (8), with 3 years of therapy proving superior to 1 year in enhancing both RFS and overall survival in patients with KIT-positive high-risk GIST (5). Although an 800-mg dose represents an option for patients with KIT exon 9 mutations in advanced disease, retrospective analyses of adjuvant therapy showed no superiority over the standard 400-mg daily dose (5).

Despite optimal treatment, a substantial proportion of patients experience disease recurrence following completion of the standard 3-year imatinib course (4). The PERSIST-5 study investigated extending adjuvant therapy to 5 years, reporting a 90% 5-year RFS rate, though nearly half of participants discontinued treatment prematurely (9). Whether prolonging treatment beyond 3 years provides an additional clinical benefit remains unestablished in randomized trials. The ongoing IMADGIST study, initiated in 2014, seeks to determine whether an additional three years of adjuvant imatinib improves outcomes compared to the standard 3-year duration in high-risk patients (8,13,14).

While numerous studies have evaluated recurrence risk following surgery alone (8,9), limited data exist regarding prognostic factors in patients treated with combined surgical resection and adjuvant imatinib. Such insights are essential for individualized surveillance strategies and patient counseling.

Therefore, the present study aims to evaluate prognostic factors and long-term outcomes of adjuvant imatinib therapy using national registry data to develop a practical nomogram for risk stratification in this treatment setting.

Patients and methods

Study design and patient population. This retrospective, multicenter registry study was conducted using the Taiwan Cooperative Oncology Group protocol T1218 with participation from 11 hospitals across Taiwan: i) National Taiwan University Hospital (Taipei City); ii) Taipei Veterans General Hospital (Taipei City); iii) Mackay Memorial Hospital (Taipei City); iv) Tri-Service General Hospital (Taipei City); v) Linkou Chang Gung Memorial Hospital (Taoyuan City); vi) China Medical University Hospital (Taichung City); vii) Changhua Christian Hospital (Changhua City); viii) National Cheng Kung University Hospital (Tainan City); ix) Kaohsiung Medical University Hospital (Kaohsiung City); x) Kaohsiung Veterans General Hospital (Kaohsiung City); and xi) Kaohsiung Chang Gung Memorial Hospital (Kaohsiung City, Taiwan).

Between 2013 (when adjuvant imatinib was incorporated into Taiwan's National Health Insurance reimbursement program) and 2023, a total of 269 patients with pathologically confirmed, primary resectable, c-KIT-positive modified Armed Forces Institute of Pathology (AFIP)-classified high-risk GISTs who received adjuvant imatinib therapy were enrolled from institutional databases (15). Patient data were collected retrospectively for cases treated between 2013 and the date of institutional review board (IRB) approval at each institution, and prospectively thereafter through 2023 as part of the ongoing national registry (16).

Inclusion criteria as per a previous study (17) required patients to have undergone tumor resection as primary treatment with complete macroscopic resection confirmed,

received adjuvant imatinib therapy as per institutional guidelines, no prior tyrosine kinase inhibitor therapy before surgery, no evidence of metastatic disease before or during surgery and AFIP-classified high recurrence risk as determined by the treating physician using modified National Institutes of Health criteria (18). Patient data were collected retrospectively through chart review using standardized data collection forms (Data SI).

Data collection encompassed baseline demographics, pathological characteristics, mutation profiles, imatinib treatment duration and dosing, and RFS outcomes. The study protocol received approval from the IRB of each participating hospital with the following approval numbers: (Institution 1: IRB-201806048RSC), (Institution 2: IRB-2018-09-004CC), (Institution 3: IRB-20CT002be), (Institution 4: IRB-C202005012), (Institution 5, 11: IRB-201801966A2), (Institution 6: IRB-CMUH107-REC1-108), (Institution 7: IRB-181203), (Institution 8: IRB-A-ER-107-271), [Institution 9: IRB-F(II)-20200081] and (Institution 10: IRB-KSVGH22-CT2-08), and written informed consent was obtained from all living patients prior to enrollment (16). Chang Gung Memorial Hospital Linkou (Institution 5) and Chang Gung Memorial Hospital Kaohsiung (Institution 11) share the same IRB approval number under their unified institutional review system.

Treatment assessment. Adjuvant imatinib therapy duration was systematically documented from medical records. The treatment duration was categorized as time (T) <1 year, 1<T≤2 years, 2<T≤3 years and T>3 years. The standard dose of imatinib was 400 mg daily unless modified for toxicity. Treatment completion was based on documented treatment periods in the medical records.

Follow-up protocol. Patients underwent regular follow-up assessments, including physical examinations, performance status evaluation, body weight monitoring, complete blood counts and comprehensive serum biochemistry testing. Imatinib administration details and adverse events were systematically documented throughout the treatment period.

Surveillance imaging with abdominal computed tomography scans was performed according to institutional protocols, typically every 3 months during the initial 3 years of follow-up, followed by 6-monthly intervals for an additional 2 years. Disease recurrence was defined by radiological evidence of new lesions or clinical progression based on multidisciplinary team assessment. RFS was defined as the interval from adjuvant imatinib initiation to documented tumor recurrence or last follow-up visit.

Molecular analysis. Tumor specimens obtained through surgical resection or biopsy were processed as formalin-fixed, paraffin-embedded tissue blocks. Molecular testing was performed when available during the study period. Tumor-enriched sections underwent genomic DNA extraction, followed by PCR amplification of KIT and PDGFRA gene regions. Mutation analysis was conducted according to previously established protocols (19,20). However, mutation testing was not systematically performed across all centers and time periods, resulting in missing molecular data for 126 patients (46.8%).

The anatomical tumor location was classified into four distinct categories based on surgical considerations and anatomical differences in operative approach: i) Stomach; ii) duodenum; iii) small bowel (jejunum and ileum); and iv) colorectum. While the duodenum is anatomically part of the small intestine, it was classified separately due to the fundamentally different surgical procedures required for duodenal vs. jejunal/ileal GISTs. Duodenal GISTs often require pancreaticoduodenectomy or complex duodenal reconstruction, whereas small bowel GISTs typically undergo segmental resection with primary anastomosis (21).

Statistical considerations for missing data. Given the retrospective registry nature of the present study, mutation data were unavailable for 126 patients (46.8% of the cohort). This missing data pattern reflects the evolution of molecular testing practices during the study period (2013-2023) rather than random missingness. The mutation status was analyzed as an available category and sensitivity analyses were conducted to assess the impact of missing molecular data on nomogram performance.

Nomogram development and validation. A prognostic nomogram was constructed using R software (version 4.3.1) with the rms package and supporting libraries. Point assignments were based on Cox regression coefficients from the final multivariate model. Nomogram performance was evaluated using the concordance index (C-index), and calibration was assessed by comparing predicted vs. observed disease-free survival probabilities. Internal validation was performed using 1,000 bootstrap resamples to ensure model robustness.

Statistical analysis. Categorical variables were compared using Chi-square or Fisher's exact tests, as appropriate. Continuous variables were analyzed using independent-samples t-tests or Mann-Whitney U-tests based on data distribution characteristics. Survival distributions were estimated using Kaplan-Meier methodology, with group comparisons performed using log-rank tests.

Univariate Cox proportional hazards regression was used to identify factors associated with disease-free survival. Variables with statistical significance or clinical relevance were included in multivariate Cox regression modeling.

To assess the prognostic significance of nomogram total points, recursive partitioning analysis was utilized to determine optimal cut-off values and stratify patients into distinct risk groups (22).

Statistical significance was defined as $P<0.05$ for all analyses. All statistical analyses were performed using R software version 4.3.1.

Results

Patient characteristics. The demographic and clinicopathological characteristics of the 269 patients with modified AFIP high-risk GIST receiving adjuvant imatinib are presented in Table I. The cohort comprised 149 males (55.4%) and 120 females (44.6%) with a mean age of 60.9±11.4 years. The median follow-up duration was 62.7 months (range: 7.2-151.9 months).

Table I. Baseline characteristics (n=269).

Characteristics	No. of cases	Mean ± SD or %
Age, yr		60.9±11.4
≤65	179	66.5
>65	90	33.5
Sex		
Male	149	55.4
Female	120	44.6
Site		
Stomach	133	49.4
Colorectum	17	6.3
Small bowel	104	38.7
Duodenum	15	5.6
Tumor size, cm		9.3 ± 4.9
>2,≤5	40	14.8
>5,≤10	132	49.1
>10	97	36.1
Mitotic counts/50 HPFs		
≤5	75	27.9
6-10	77	28.6
>10	117	43.5
Rupture		
No	227	84.4
Yes	42	15.6
Mutation		
Exon 9	15	5.6
Exon 10	1	0.4
Exon 11	119	44.2
Exon 12	1	0.4
Exon 13	2	0.8
Exon 18	3	1.1
Wild type	2	0.7
N/A	126	46.8
Duration of Imatinib treatment, yr		
<1	38	14.1
1<T≤2	37	13.8
2<T≤3	59	21.9
>3	135	50.2

SD, standard deviation; yr, years; N/A, information not available; HPF, high-power field.

The stomach was the most common tumor location (133/269; 49.4%), followed by the small bowel (104/269; 38.7%), with fewer cases originating from the colorectum (17/269; 6.3%) and duodenum (15/269; 5.6%). The mean tumor size was 9.3±4.9 cm, with 36.1% of tumors >10 cm. Among the 269 patients, 119 (44.2%) harbored KIT exon 11 mutations; however, mutation data were unavailable for 126 patients (46.8%). Tumor rupture was present in 42 patients (15.6%).

Treatment duration distribution. The treatment duration (T) distribution was as follows: T<1 year (n=38, 14.1%), 1<T≤2 years (n=37, 13.8%), 2<T≤3 years (n=59, 21.9%) and T>3 years (n=135, 50.2%). The majority of patients (50.2%) completed >3 years of adjuvant therapy.

Factors associated with disease recurrence. Table II presents the relationship between recurrence status and clinicopathologic features. Univariate analysis showed significant associations with male sex (P=0.010) and tumor site (P<0.001), and a duodenal location was associated with the highest recurrence rate (60.0 vs. 15.8% for gastric tumors).

Table III and Fig. 1 present the data of multivariate logistic regression, which identified three independent risk factors for recurrence: Male sex [adjusted odds ratio (OR): 2.24, 95% CI: 1.20-4.17, P=0.011], and the tumor locations with the highest risk were the duodenum (OR: 8.37, 95% CI: 2.58-27.13, P<0.001) and small bowel (OR: 2.19, 95% CI: 1.15-4.19 P=0.018) compared to a gastric location.

Univariate analysis for RFS. Table IV presents the univariate Cox regression analysis. Significant factors associated with unfavorable RFS were male sex [hazard ratio (HR): 1.89, 95% CI: 1.12-3.21, P=0.018] and treatment duration <1 year (HR: 3.03, 95% CI: 1.52-6.05, P=0.002), and the tumor locations with the highest risk were the duodenum (HR: 4.68, 95% CI: 2.14-10.24, P<0.001) and small bowel (HR: 1.75, 95% CI: 1.01-3.06, P=0.049).

Multivariate Cox regression and final model. Table V presents the final multivariate Cox regression analysis. A total of 3 independent predictors of poor RFS were confirmed: Male sex (HR: 1.76, 95% CI: 1.03-3.00, P=0.039), non-gastric tumor origin with duodenum showing the highest risk (HR: 6.15, 95% CI: 2.71-13.95, P<0.0001), followed by the small bowel (HR: 1.92, 95% CI: 1.09-3.38, P=0.025), and treatment duration <1 year (HR: 3.91, 95% CI: 1.91-8.01, P=0.002). These variables were incorporated into the nomogram construction.

Nomogram-based prognostic stratification. A prognostic nomogram was constructed based on the final multivariable model (Fig. 2A). The model demonstrated good discriminative ability with a concordance index of 0.72. Bootstrap validation confirmed model stability. Calibration curves for 1-, 3- and 5-year RFS probabilities showed good agreement between nomogram predictions and actual observations (Fig. 2B).

Table VI shows the nomogram scoring system with survival probabilities at different total point scores. The scoring system assigned points based on Cox regression coefficients: Gender (male: 31 points, female: 0 points), tumor location (stomach: 0 points, colorectum: 22 points, small bowel: 36 points, duodenum: 100 points), and imatinib duration (≥3 years: 0 points, 2-3 years: 8 points, 1-2 years: 35 points, <1 year: 75 points) (Fig. 2A).

Recursive partitioning analysis (Fig. 3A) was used to establish optimal cut-off points for prognostic stratification based on nomogram scores. This analysis identified three distinct prognostic groups among the AFIP-classified high-risk GIST cohort of the present study. The favorable-prognosis group included 139 patients with nomogram

Table II. Relationship between recurrence status and clinicopathologic features of gastrointestinal stromal tumor with imatinib adjuvant treatment.

Parameter	Total N	No recurrence, n (%)	Recurrence, n (%)	P-value	Odds ratio	95% CI	P-value
Age, yr				0.407			
≤65	179	133 (74.3)	46 (25.7)		1.29	0.70-2.37	0.408
>65	90	71 (78.9)	19 (21.1)		1		
Sex				0.010			
Male	149	104 (69.8)	45 (30.2)		2.16	1.20-3.92	0.011
Female	120	100 (83.3)	20 (16.7)		1		
Site				<0.001			
Stomach	133	112 (84.2)	21 (15.8)		1		
Colorectum	17	12 (70.6)	5 (29.4)		2.22	0.71-6.97	0.171
Small bowel	104	74 (71.2)	30 (28.8)		2.16	1.15-4.06	0.016
Duodenum	15	6 (40.0)	9 (60.0)		8.00	2.58-24.85	<0.001
Tumor size, cm				0.093			
>2, ≤5	40	35 (87.5)	5 (12.5)		1		
>5, ≤10	132	101 (76.5)	31 (23.5)		2.15	0.78-5.96	0.142
>10	97	68 (70.1)	29 (29.9)		2.99	1.06-8.39	0.038
Mitotic counts/ 50 HPFs				0.543			
≤5	75	58 (77.3)	17 (22.7)		1		
6-10	77	61 (79.2)	16 (20.8)		0.90	0.41-1.94.	0.778
>10	117	85 (72.6)	32 (27.4)		1.28	0.65-2.53	0.468
Rupture				0.468			
No	227	174 (76.7)	53 (23.3)		1		
Yes	42	30 (71.4)	12 (28.6)		1.31	0.63-2.74	0.469
Mutation				0.133			
Exon 9	15	8 (53.3)	7 (46.7)		2.83	0.97-8.24	0.061
Exon 11	119	91 (76.5)	28 (23.5)		1		
Others	7	7 (100)	0		0.21	0.01-3.86	0.195
Wild type	2	2 (100)	0		0.64	0.03-13.77	0.767
N/A	126	96 (76.2)	30 (23.8)		1.01	0.57-1.82	0.961
Duration of treatment, yr				0.771			
≤1	38	27 (71.1)	11 (28.9)		1.31	0.59-2.94	0.510
1<T≤2	37	27 (73.0)	10 (27.0)		1.19	0.52-2.73	0.677
2<T≤3	59	47 (79.7)	12 (20.3)		0.82	0.39-1.74	0.607
>3	135	103 (76.2)	32 (23.7)		1		

CI, confidence interval; yr, years; N/A, information not available; HPF, high-power field.

scores indicating excellent long-term outcomes and achieved a 5-year RFS rate of 84.9%. The moderate-prognosis group comprised 120 patients with moderate risk scores and demonstrated a 5-year RFS rate of 70.4%. Most concerning, the poor-prognosis group consisted of 10 patients whose nomogram scores predicted markedly inferior outcomes, with these patients achieving only a 16.7% 5-year RFS rate despite all being AFIP-classified as high-risk and receiving adjuvant imatinib therapy (Fig. 3B). The survival differences between these nomogram-based prognostic groups were highly significant (P<0.0001) (Fig. 3B, Tables VII and VIII).

Discussion

The present study evaluated prognostic factors and long-term outcomes in a large national cohort of 269 patients with modified AFIP-classified high-risk GIST who received adjuvant imatinib over a median follow-up period of 62.7 months. A total of 3 independent predictors

Table III. Relationship between recurrence status and clinicopathologic features of gastrointestinal stromal tumor with imatinib adjuvant treatment.

Parameter	Odds ratio	95 % CI	P-value	Adjusted odds ratio	95% CI	P-value
Sex (female vs. male)	2.16	1.20-3.92	0.011	2.24	1.20-4.17	0.011
Site						
Stomach	1			1		
Colorectum	2.22	0.71-6.97	0.171	2.40	0.74-7.85	0.146
Small bowel	2.16	1.15-4.06	0.016	2.19	1.15-4.19	0.018
Duodenum	8.00	2.58-24.85	<0.001	8.37	2.58-27.13	<0.001
Tumor size, cm						
>2, ≤5	1			1		
>5, ≤10	2.15	0.78-5.96	0.142	2.23	0.76-6.58	0.147
>10	2.99	1.06-8.39	0.038	3.31	1.11-9.85	0.032

CI, confidence interval.

Table IV. Impact of the clinicopathologic features on recurrence-free survival in univariate Cox regression analysis.

Parameter	Total N	Events, n (%)	Hazard ratio	95% CI	P-value
Age, yr					
≤65	179	46 (25.7)	1		
>65	90	19 (21.1)	0.99	0.58-1.68	0.956
Sex					
Male	149	45 (30.2)	1.89	1.12-3.21	0.018
Female	120	20 (16.7)	1		
Site					
Stomach	133	21 (15.8)	1		
Colorectum	17	5 (29.4)	1.64	0.61-4.36	0.325
Small bowel	104	30 (28.8)	1.75	1.01-3.06	0.049
Duodenum	15	9 (60.0)	4.68	2.14-10.24	<0.001
Tumor size, cm					
>2, ≤5	40	5 (12.5)	1		
>5, ≤10	132	31 (23.5)	2.01	0.78-5.18	0.147
>10	97	29 (29.9)	2.40	0.93-6.21	0.070
Mitotic counts/50 HPFs					
≤5	75	17 (22.7)	1		
6-10	77	16 (20.8)	0.89	0.45-1.76	0.733
>10	117	32 (27.4)	1.41	0.78-2.55	0.252
Rupture					
No	227	53 (23.3)	1		
Yes	42	12 (28.6)	1.55	0.83-2.90	0.173
Mutation[a]					
Exon 9	15	7 (46.7)	2.22	0.92-4.73	0.073
Exon 11	119	28 (23.5)	1		
Others	7	0	0.24	0.01-NA	0.204
Wild type	2	0	0.69	0.01-NA	0.780
N/A	126	30 (23.8)	1.17	0.70-1.95	0.555

Table IV. Continued.

Parameter	Total N	Events, n (%)	Hazard ratio	95% CI	P-value
Duration of treatment, yr					
<1	38	11 (28.9)	3.03	1.52-6.05	0.002
1<T≤2	37	10 (27.0)	1.91	0.94-3.90	0.076
2<T≤3	59	12 (20.3)	1.25	0.64-2.43	0.514
>3	135	32 (23.7)	1		

[a]Cox regression model using Firth's bias correction for solution the occurrence of monotone likelihood in small samples. CI, confidence interval; yr, years; N/A, information not available; HPF, high-power field.

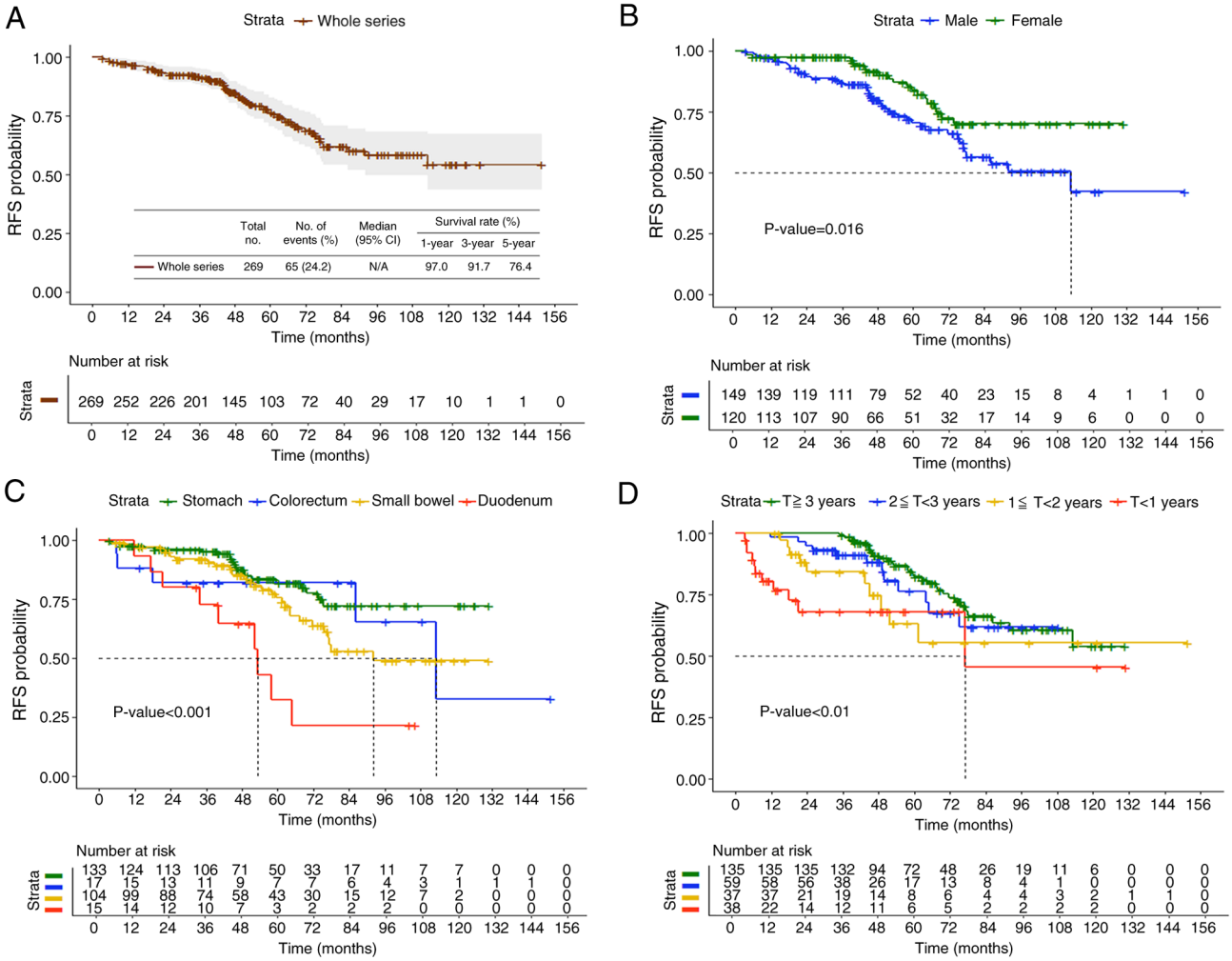

Figure 1. RFS after adjuvant imatinib use in patients with high-risk gastrointestinal stromal tumor. (A) Overall RFS for the entire cohort (n=269) showing 1, 3 and 5-year survival rates of 97.0, 91.7 and 76.4%, respectively. (B) RFS by gender showing significantly worse outcomes for male patients (P=0.016). (C) RFS by tumor location demonstrating poorest outcomes for duodenal tumors ($P=7x10^{-4}$). (D) RFS by treatment duration showing inferior outcomes for patients with shorter treatment courses (P=0.0076). RFS, recurrence-free survival; yr, year(s).

of unfavorable RFS were identified: Male sex, non-gastric tumor origin and shorter duration of imatinib therapy. A nomogram incorporating these clinicopathological variables demonstrated good predictive accuracy and calibration, enabling further prognostic stratification within this already high-risk population into three distinct groups with markedly different outcomes.

The present study provides specific insights for the adjuvant therapy setting that complement existing knowledge from surgical cohorts. An important clarification for readers is that the entire cohort of the present study consists of patients with modified AFIP-classified high-risk GIST who received adjuvant therapy, and the nomogram provides additional prognostic stratification within this population. The three 'prognostic

Table V. Impact of the clinicopathologic features on recurrence-free survival in multivariate analysis.

Prognostic variable	Adjusted HR	95% CI of HR		P-value	Points assigned in nomogram
		Lower	Upper		
Gender					
Male	1.76	1.03	3.00	0.039	31
Female	1				0
Site					
Stomach	1				0
Colorectum	1.50	0.56	4.01	0.417	22
Small bowel	1.92	1.09	3.38	0.025	36
Duodenum	6.15	2.71	13.95	<0.0001	100
Duration of treatment, years					
<1	3.91	1.91	8.01	0.002	75
1<T≤2	1.89	0.91	3.92	0.089	35
2<T≤3	1.16	0.59	2.28	0.665	8
>3	1	0.17	0.66		0

CI, confidence interval; HR, hazard ratio.

Table VI. The prognostic scoring system.

A, 1-year RFS

Nomogram points	Probability
178	0.80
137	0.90
97	0.95
8	0.99

B, 3-year RFS

178	0.50
161	0.60
141	0.70
116	0.80
74	0.90
35	0.95

C, 5-year RFS

193	0.05
178	0.10
159	0.20
143	0.30
128	0.40
112	0.50
95	0.60
76	0.70
50	0.80
9	0.90

RFS, recurrence-free survival.

groups' identified by the nomogram (favorable, moderate and poor-prognosis) represent further risk refinement among patients already classified as high-risk by conventional criteria.

The association between male sex and inferior RFS has been observed in multiple GIST cohorts and warrants further investigation. This sex-based disparity may reflect biological differences in tumor behavior, hormonal influences on GIST pathogenesis, or variations in treatment adherence and tolerance patterns (23). The underlying mechanisms driving this observation merit further research to inform personalized treatment strategies.

The findings of the present study confirm that tumor location remains a critical prognostic determinant even in the era of adjuvant imatinib therapy. Non-gastric GISTs, particularly those arising from the duodenum with a 60.0% recurrence rate and small bowel with a 28.8% recurrence rate, demonstrated significantly worse outcomes compared to gastric tumors with a 15.8% recurrence rate. This observation aligns with established knowledge regarding the more aggressive biological behavior of non-gastric GISTs and may reflect underlying molecular differences specific to anatomical location (24).

Historical studies from the pre-imatinib era identified *KIT* exon 11 deletions, particularly those involving codons 557-558, as harboring adverse prognostic significance compared to other mutation types. Wozniak *et al* (24) previously highlighted the poor outcomes associated with *KIT* del557/558 mutations in gastric GISTs. Furthermore, our group has demonstrated that *KIT* exon 11 557-558 deletions promote liver metastasis through C-X-C motif chemokine receptor 4 upregulation via enhanced ETV1 promoter binding (25). Unfortunately, our registry lacked detailed exon-level mutation data, precluding examination of these specific molecular correlates. Future studies incorporating comprehensive genotyping may provide additional prognostic insights and guide preoperative risk assessment.

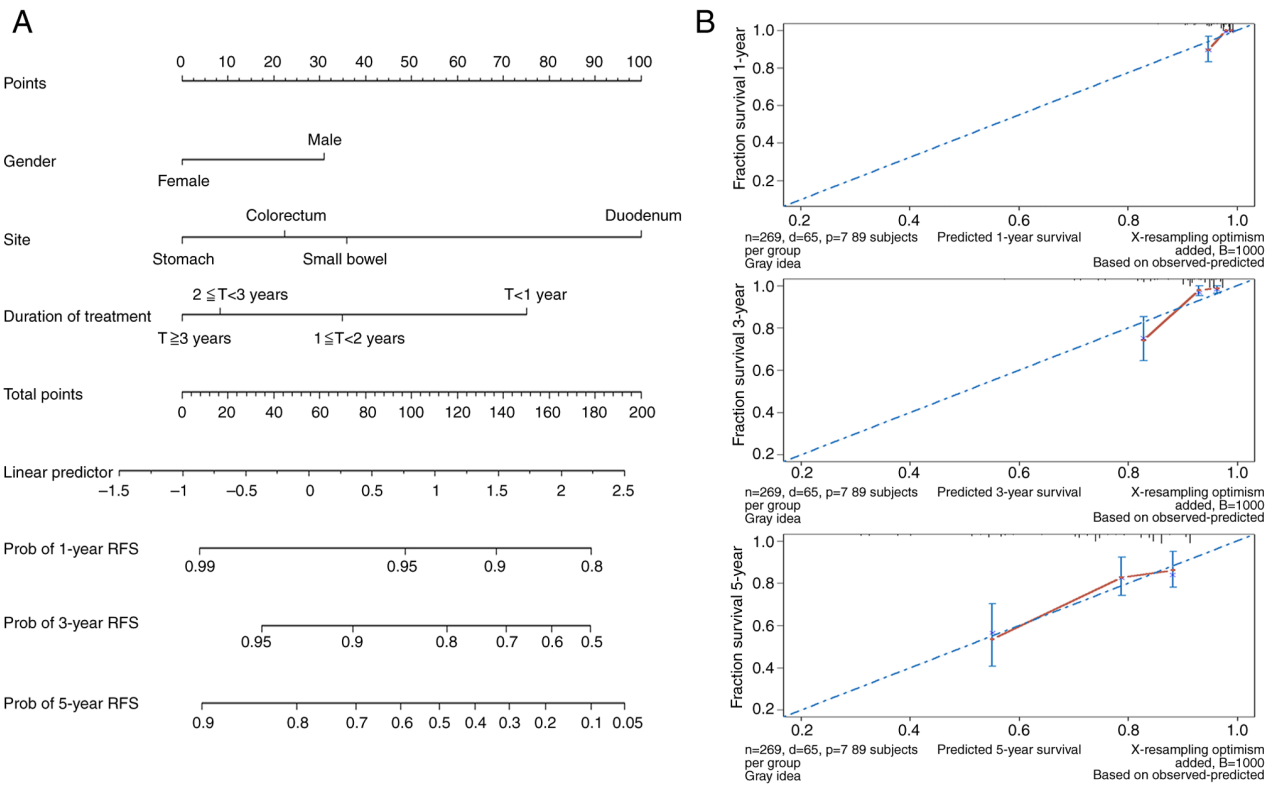

Figure 2. Predictive nomogram for RFS. (A) Nomogram based on the final multivariate Cox model incorporating gender, tumor location and treatment duration with point assignments based on regression coefficients. (B) Calibration plots for 1, 3 and 5-year disease-free survival showing good agreement between nomogram predictions and observed outcomes. RFS, recurrence-free survival; yr, year(s).

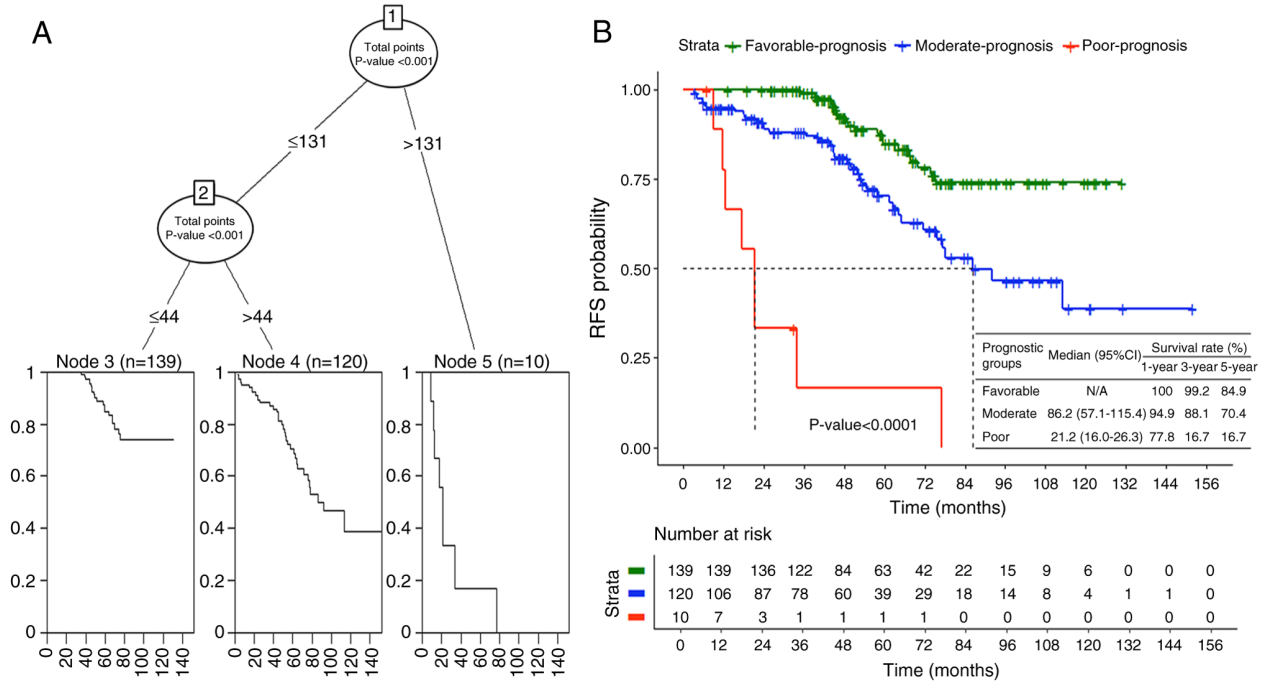

Figure 3. Recursive partitioning analysis and risk stratification. (A) Recursive partitioning analysis identifying optimal cut-off points for nomogram scores. (B) Kaplan-Meier curves for the three risk groups showing marked differences in outcomes: Favorable prognosis (n=139, 5-year survival: 99.2%), moderate prognosis (n=120, 5-year survival: 68.1%) and poor prognosis (n=10, 5-year survival: 16.7%) with P<0.0001. yr, year(s).

The substantial proportion of missing mutation data (46.8%) in the present cohort reflects the evolution of molecular testing practices during the study period rather than systematic study bias. In Taiwan, comprehensive mutation testing transitioned from research-based to routine clinical practice between 2013 and 2023. While this represents a study limitation, the

Table VII. Prognostic model discrimination in the Taiwan GISTs registry dataset.

	Taiwan GISTs registry	
Measures of discrimination	Estimate	95% CI
Harrell's C-index	0.72	0.65-0.79
Gonen and Heller's K	0.67	0.62-0.72
Royston & Sauerbrei's D-statistic	1.19	0.77-1.62

Taiwan GISTs Registry prognostic group was categorized using RPA to establish optimal cutoff points on the PI determined by Cox's model. GIST, gastrointestinal stroma tumor; CI, confidence interval.

Table VIII. Survival analysis by prognostic group.

Prognostic group	HR	95% CI of HR	P-value
Favorable	1		
Moderate	2.63	1.52-4.52	0.001
Poor	18.62	8.02-43.25	<0.0001

CI, confidence interval; HR, hazard ratio.

sensitivity analyses demonstrate that the nomogram maintains prognostic utility without molecular data, making it applicable in clinical settings where comprehensive genetic testing may not be routinely available. This practical consideration enhances the global applicability of our prognostic tool.

Notably, tumor rupture was present in 15.6% of patients but did not emerge as an independent prognostic factor in the multivariate analysis of the present study, despite being traditionally considered a high-risk feature requiring adjuvant therapy. This finding may reflect that all patients with rupture in our cohort received adjuvant therapy, potentially mitigating its prognostic impact compared to historical surgical-only cohorts. Data from the SSG XVIII trial similarly suggest that standard 3-year adjuvant therapy may not adequately address the elevated recurrence risk associated with tumor rupture, supporting European Society for Medical Oncology guideline recommendations for extended imatinib in this subset (5,26).

The present analysis of treatment duration as a prognostic factor addresses important methodological considerations about potential reverse causation. While it is acknowledged that some early discontinuations may result from disease progression, the landmark analyses at multiple time-points demonstrate that treatment duration maintains prognostic significance even after accounting for time-dependent effects. This suggests that treatment completion, when medically feasible, has important implications for long-term outcomes, though the complex relationship between duration and prognosis requires careful clinical interpretation. The clinical message remains that achieving adequate treatment duration is associated with better outcomes in patients who can tolerate therapy.

The nomogram developed herein provides a practical tool for individualized risk assessment in the adjuvant setting (10). Its demonstrated discriminative ability (C-index: 0.72) and clear risk stratification into three prognostic groups with dramatically different survival outcomes (84.9, 70.4 and 16.7% 5-year survival rates) may assist clinicians in patient counseling, surveillance planning and treatment decision-making.

The present study has several important limitations that require acknowledging. The retrospective registry design reflects real-world clinical practice but lacks the standardization of prospective trials, with clinical practices varying across the 11 participating centers over the 10-year study period. This variation potentially introduces heterogeneity in treatment decisions and follow-up protocols that may affect the present results.

Selection bias represents another significant limitation, as the present cohort includes only patients with modified AFIP-classified high-risk GIST who actually received adjuvant imatinib therapy. This represents a selected subset of the broader high-risk GIST population, since some high-risk patients do not receive adjuvant therapy due to age, comorbidities, patient preference or other factors. The present findings may therefore not be generalizable to all patients with high-risk GIST, particularly those who did not receive adjuvant therapy.

The substantial proportion of missing mutation information (46.8%) represents a significant methodological limitation. While these missing data reflect the evolution of molecular testing practices during the study period and the sensitivity analyses suggest the nomogram maintains utility without molecular data, the absence of comprehensive genetic information limits our ability to develop more sophisticated molecular-integrated prognostic models.

The limited number of patients in certain subgroups, particularly duodenal tumors (n=15) and the poor-prognosis nomogram category (n=10), results in wide confidence intervals and limits the precision of survival estimates for these subsets. While these numbers reflect the true epidemiological rarity of duodenal GISTs, which represent only 3-5% of all GISTs (27), they constrain our ability to make definitive conclusions about these specific populations.

The interpretation of treatment duration as a prognostic factor requires careful consideration due to the complex bidirectional relationship between treatment completion and outcomes. While our landmark analyses suggest that treatment duration has genuine prognostic significance beyond simple reverse causation, early discontinuation may reflect both patient factors and underlying disease biology, making clinical interpretation nuanced.

Most importantly, external validation in independent cohorts from different populations and healthcare systems is essential before routine clinical implementation of our nomogram. The single-country design and specific healthcare context may limit generalizability to other populations.

The present findings carry important clinical implications. The identification of a poor-prognosis subgroup within AFIP-classified high-risk patients, with only 16.7% 5-year survival despite standard adjuvant therapy, highlights that current treatment paradigms may be insufficient for this population. These patients may benefit from more

intensive surveillance protocols, extended adjuvant therapy or novel therapeutic approaches currently under investigation. Additionally, the present results emphasize the importance of long-term follow-up extending beyond conventional surveillance periods, particularly for patients identified as having poor prognosis by nomogram assessment.

Future research priorities should include prospective validation of our nomogram in external cohorts, investigation of strategies to optimize treatment completion rates and integration of comprehensive molecular profiling as it becomes more widely available. Clinical trials evaluating extended adjuvant therapy duration or novel approaches specifically in nomogram-identified poor-prognosis patients may help improve outcomes in this challenging population.

In conclusion, this large retrospective registry analysis identified male sex, non-gastric tumor origin and shorter imatinib duration as independent predictors of poor disease-free survival in patients with modified AFIP high-risk GIST receiving adjuvant therapy. The resulting nomogram provides a practical tool for risk stratification, enabling identification of three distinct prognostic groups with markedly different outcomes. While external validation is essential before routine clinical implementation, this prognostic tool may enhance clinical decision-making and patient counseling in the adjuvant setting. These findings highlight the need for personalized approaches to surveillance and treatment planning, particularly for nomogram-identified poor-prognosis patients who may benefit from intensified monitoring or extended imatinib adjuvant use.

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Availability of data and materials

All data generated or analyzed during the current study are included in this published article. The DNA mutations identified in this study have been deposited at ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/submitters/509598).

Authors' contributions

CNY was responsible for the design of the study, provision of the patients, assembly of the data, data analysis, interpretation of the results and manuscript writing. LTC and HJT participated in the conception and design of the study, provision of the patients, data analysis and interpretation of the results, and reviewed the manuscript. YSS, CYY, CHT, CCW, DCC and CCY were responsible for provision of the patients, data analysis and interpretation of the results, and reviewed the manuscript. MTL, CFT, THC, YYC, HYL, TSY, CLH, TYS, LYB, JTH and ISC were responsible for provision of the patients, interpretation of the results and review of the manuscript. CFH assembled the data, performed data analysis and interpretation of the results, and reviewed the manuscript. CNY and HJT checked and confirmed the authenticity of the raw data. All authors reviewed the manuscript and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the IRB of each participating institution, including National Taiwan University Hospital Ethics Center Research Ethics Section, IRB of Taipei Veterans General Hospital, the IRB of Tri-Service General Hospital, Mackay Memorial Hospital IRB, Chang Gung Medical Foundation IRB, China Medical University Hospital Research Ethics Committee, IRB of Changhua Christian Hospital, National Cheng Kung University Hospital IRB, Kaohsiung Medical University Hospital IRB and Department of Medical Education and Research Kaohsiung Veterans General Hospital. All patients provided written informed consent and those who had died provided consent before they died.

Patient consent for publication

Not applicable.

Competing interests

LTC has received research funding from Pfizer to National Health Research Institutes for National Registry Study. All other authors declare that they have no competing interests.

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