Original Article

Characteristics and clinical outcomes of early-onset gastrointestinal stromal tumors: a population-based study

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Background: The incidence of gastrointestinal stromal tumors (GISTs) has risen, but early-onset GISTs (age <50 years) remain underexplored. This study aims to compare the clinical characteristics and prognostic outcomes of early-onset GISTs with later-onset cases (age ≥50 years).

Methods: We conducted a retrospective study using data on GISTs diagnosed from 2000 to 2021 in the Surveillance, Epidemiology, and End Results (SEER) database. Prognostic factors for overall survival (OS) and cancer-specific survival (CSS) were analyzed using Cox regression and competing risk analysis. Kaplan-Meier and cumulative risk curves assessed survival disparities, and forest plots were used for subgroup analyses. Bias was minimized through multiple imputation, propensity score matching (PSM), and stratified regression.

Results: Among 12,608 GIST cases, 2,271 (18%) were early-onset, and 10,337 (82%) were later-onset. Median age and survival for early-onset cases were 43 years and 70 months, respectively, *vs.* 66 years and 48 months for later-onset cases. Early-onset patients had larger tumor diameters, higher liver metastasis rates, higher mitotic rates, and higher risk stratification at diagnosis. They also underwent surgery more frequently than later-onset patients. Cox and competing risk analyses indicated a survival advantage for early-onset patients. Kaplan-Meier and cumulative risk curves confirmed better OS and CSS for early-onset patients before and after matching (P<0.001). This advantage persisted across stages, risk strata, and subgroups.

Conclusions: Early-onset GISTs have distinct clinicopathological features and better OS and CSS compared to later-onset patients.

Keywords: Gastrointestinal stromal tumor (GIST); Surveillance, Epidemiology, and End Results (SEER); age; prognosis

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common soft-tissue sarcomas of the gastrointestinal tract, with an incidence rate of approximately 1.1 per 100,000 individuals, accounting for roughly 1–3% of all gastrointestinal tumors (1). Despite the relatively low incidence of GISTs, early diagnosis is challenging due to their diverse clinical manifestations and their tendency to be confused with other gastrointestinal diseases. Most tumors are large at the time of diagnosis, and about 15% of patients already have metastases, primarily in the liver and peritoneal cavity (2,3). Surgery is the primary treatment for GISTs. Although most confined GISTs are amenable to complete surgical resection, metastatic recurrence occurs in approximately 40% of patients after surgery (4). Metastasis

and recurrence are significant causes of death in patients with GISTs. For patients with advanced or metastatic tumors, chemotherapy or radiotherapy is the most common treatment. However, GISTs are resistant to traditional systemic chemotherapeutic drugs and radiation therapy, often resulting in unsatisfactory treatment outcomes. With the in-depth study of the pathogenesis of GISTs, it is found that they are mainly caused by oncogenic activating mutations in the KIT proto-oncogene, receptor tyrosine kinase (*KIT*) or platelet-derived growth factor receptor alpha (*PDGFRA*) genes (5). Consequently, the introduction of tyrosine kinase inhibitors (TKIs) (imatinib), a targeted drug for gastrointestinal mesenchymal tumors, has greatly improved the prognosis of patients and even increased the overall survival (OS) of some patients from less than 12 months to more than 5 years (6). TKIs have now become the standard of care for patients with advanced or metastatic GISTs.

Recent epidemiological studies have indicated that while the overall incidence of colorectal cancer has significantly decreased compared to previous years, there has been a notable increase in cases of early-onset colorectal cancer. This increasing trend has been demonstrated across various tumors, including gastric, liver, gallbladder, and pancreatic cancers (7,8). More importantly, compared to patients with later-onset tumors, some authors have found that patients with early-onset cancers are usually diagnosed at a later stage and have a worse prognosis (9,10). Similar to other early-onset tumors, early-onset GISTs are defined as those diagnosed in patients younger than 50 years of age, while patients aged 50 years and older are classified as having later-onset GISTs. Previous studies have shown that GISTs occur mainly in middle-aged and older adults, with a median age at diagnosis of about 60–65 years, and are very rare in children, adolescents, and young adults (1,11).

There are no studies in the literature specifically addressing early-onset GISTs. We hypothesized that the clinical features and prognosis of early-onset GISTs may differ from those of later-onset GISTs. Therefore, the main objective of this article was to compare the clinicopathologic features and long-term prognosis of early- and later-onset GISTs. Given the low incidence of gastrointestinal mesenchymal tumors, we utilized the large sample size of the Surveillance, Epidemiology, and End Results (SEER) database for our study. The SEER database is the authoritative source of cancer data in the United States, covering approximately 28% of the U.S. population and including demographic data, important clinicopathologic information, and follow-up information. Through this study, we aimed to deepen our understanding of the characteristics of early-onset GISTs to guide clinical practice, advance oncology research, and ultimately improve the prognosis and quality of life for patients. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1942/rc).

Highlight box

Key findings

- Early-onset gastrointestinal stromal tumors (GISTs) exhibit distinct clinicopathological characteristics and demonstrate a significant survival advantage.

What is known and what is new?

- Age is a key factor influencing the prognosis of GIST patients.
- Despite presenting with more aggressive tumor characteristics, early-onset GIST patients exhibit better survival outcomes compared to those with later-onset GISTs.

What is the implication, and what should change now?

- Early-onset GISTs may constitute a biologically distinct subgroup with unique behaviors and a more favorable long-term prognosis.
- Treatment protocols for early-onset GISTs should be individualized, with more aggressive monitoring and surgical interventions potentially offering continued benefit to these patients.

Methods

Data sources

We extracted diagnoses of GISTs from January 2000 to December 2021 using SEER*Stat 8.4.3 software from the SEER database {Research Data 17 Registries Nov 2023 Sub [2000–2021]}. Inclusion criteria were: (I) International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) code: 8936/3 malignant tumor; and (II) location codes: esophagus (C15.0–C15.9), stomach (C16.0–C16.9), duodenum (C17.0), small intestine (C17.1–C17.2, C17.8, C17.9), appendix (C18.1), colon (C18.0, C18.2–C19.9), rectum (C20.9), and peritoneum (C48.0–C48.3, C48.8). Exclusion criteria included: (I) unknown pathology; (II) unknown survival time; (III) non-first primary malignancy; (IV) unknown surgery; and (V) unknown staging. The flow chart for screening patients is detailed in *Figure 1*. It's noteworthy that this study did not involve interactions with human subjects nor utilized personally identifiable

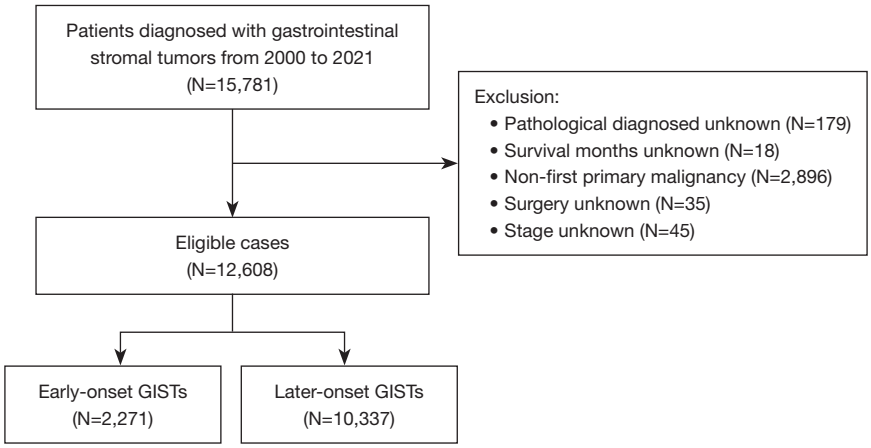

Figure 1 Flowchart of patient selection. GIST, gastrointestinal stromal tumor.

information from the SEER data, thus obviating the necessity for institutional review board approval and informed patient consent. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables and outcomes

Clinical indicators collected in this study included age, sex, race, year of diagnosis, household income, city of residence, tumor size, tumor site, mitotic count, tumor stage, liver metastasis, surgery, survival status, and follow-up time. Hazard stratification was calculated according to the modified National Institutes of Health (NIH) criteria (12), using three variables: tumor size, mitotic count, and tumor site. The variable "collaborative staging (CS) site-specific factor 6" was used to assess the mitotic rate. A mitotic rate ≤5/50 high power field (HPF) was considered low risk, while >5/50 HPF was considered high risk. Race was categorized as White, Black, and others (including American Indian/Alaska Native, Asian/Pacific Islander). Median household income was categorized as low (<$55,000), moderate ($55,000–$70,000), and high (>$70,000) (13). Rural and urban classifications were based on proximity to metropolitan areas. Endoscopic treatment included local tumor excisions (such as polypectomy, excisional biopsy, laser excision) and local tumor destruction methods (including photodynamic therapy, electrocautery, fulguration, cryosurgery, and laser procedures). The primary endpoint of the study was OS, and the secondary endpoint was cancer-specific survival (CSS). The last follow-up was on December 31, 2021. OS was defined as the time from the date of diagnosis to the date of death from any cause or the date of the last follow-up. CSS was defined as the time from diagnosis to cancer-specific mortality (CSM) or the date of the last follow-up.

Multiple imputation

Due to missing data for several variables, including race (1.1%), marital status (4.9%), tumor size (17.6%), liver metastasis (30.6%), and mitotic counts (71.3%), polyreg interpolation in R was used to address these gaps. Specifically, race and marital status were interpolated using the polyreg interpolation method, liver metastasis and mitotic counts were interpolated using the logreg method, and tumor size was interpolated using the predictive mean matching (pmm) method. The consistency of the data was found to be good following interpolation.

Propensity score matching (PSM)

Significant differences were observed in the baseline characteristics between the early- and later-onset groups (*Table 1*). To address this, PSM was employed using a 1:1 nearest-neighbor matching method, with a caliper value of 0.1 and without replacement. Variables included in the matching process were age, gender, race, year of diagnosis, household income, city of residence, tumor size, tumor site, mitotic rate, tumor stage, liver metastasis, and treatment. After matching, 2,269 patient pairs were successfully matched, resulting in no significant differences in baseline characteristics between the two groups (*Table 1*).

Table 1 Baseline characteristics of patients before and after PSM

Characteristics	Before PSM			After PSM		
	Later-onset (n=10,337)	Early-onset (n=2,271)	P	Later-onset (n=2,269)	Early-onset (n=2,269)	P
Race			0.001			>0.99
Other	1,550 (15.0)	305 (13.4)		305 (13.4)	305 (13.4)	
White	6,907 (66.8)	1,483 (65.3)		1,485 (65.4)	1,483 (65.4)	
Black	1,880 (18.2)	483 (21.3)		479 (21.1)	481 (21.2)	
Marital			<0.001			0.84
Divorced	944 (9.1)	161 (7.1)		157 (6.9)	161 (7.1)	
Married	6,305 (61.0)	1,296 (57.1)		1,319 (58.1)	1,296 (57.1)	
Separated	99 (1.0)	29 (1.3)		20 (0.9)	29 (1.3)	
Single	1,596 (15.4)	756 (33.3)		746 (32.9)	754 (33.2)	
Unmarried	27 (0.3)	14 (0.6)		12 (0.5)	14 (0.6)	
Widowed	1,366 (13.2)	15 (0.7)		15 (0.7)	15 (0.7)	
Household income			0.24			0.93
High	7,431 (71.9)	1,669 (73.5)		1,656 (73.0)	1,667 (73.5)	
Low	986 (9.5)	195 (8.6)		199 (8.8)	195 (8.6)	
Middle	1,920 (18.6)	407 (17.9)		414 (18.2)	407 (17.9)	
Rural/urban			0.002			0.74
Rural	1,037 (10.0)	179 (7.9)		173 (7.6)	179 (7.9)	
Urban	9,300 (90.0)	2,092 (92.1)		2,096 (92.4)	2,090 (92.1)	
Sex			0.08			0.57
Female	5,134 (49.7)	1,082 (47.6)		1,099 (48.4)	1,080 (47.6)	
Male	5,203 (50.3)	1,189 (52.4)		1,170 (51.6)	1,189 (52.4)	
Tumor site			<0.001			0.12
Colon	233 (2.3)	51 (2.2)		42 (1.9)	51 (2.2)	
Duodenum	603 (5.8)	193 (8.5)		196 (8.6)	193 (8.5)	
Esophagus	56 (0.5)	9 (0.4)		2 (0.1)	9 (0.4)	
Other	185 (1.8)	41 (1.8)		30 (1.3)	41 (1.8)	
Rectum	281 (2.7)	73 (3.2)		54 (2.4)	72 (3.2)	
Small intestine	2,138 (20.7)	607 (26.7)		619 (27.3)	607 (26.8)	
Stomach	6,841 (66.2)	1,297 (57.1)		1,326 (58.4)	1,296 (57.1)	
Tumor size			<0.001			0.97
≤2 cm	1,278 (12.4)	300 (13.2)		308 (13.6)	300 (13.2)	
2.1–5 cm	3,217 (31.1)	582 (25.6)		569 (25.1)	582 (25.7)	
5.1–10 cm	3,261 (31.5)	777 (34.2)		782 (34.5)	777 (34.2)	
>10 cm	2,581 (25.0)	612 (26.9)		610 (26.9)	610 (26.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Before PSM			After PSM		
	Later-onset (n=10,337)	Early-onset (n=2,271)	P	Later-onset (n=2,269)	Early-onset (n=2,269)	P
Stage			0.03			0.54
Distant	1,860 (18.0)	429 (18.9)		421 (18.6)	428 (18.9)	
Localized	6,687 (64.7)	1,401 (61.7)		1,421 (62.6)	1,401 (61.7)	
Regional	1,221 (11.8)	311 (13.7)		319 (14.1)	311 (13.7)	
Unstaged	569 (5.5)	130 (5.7)		108 (4.8)	129 (5.7)	
Treatment			<0.001			0.25
No	2,063 (20.0)	335 (14.8)		320 (14.1)	335 (14.8)	
ER	1,087 (10.5)	217 (9.6)		189 (8.3)	217 (9.6)	
Surgery	7,187 (69.5)	1,719 (75.7)		1,760 (77.6)	1,717 (75.7)	
Liver metastases			0.001			0.93
No	9,386 (90.8)	2,011 (88.6)		2,013 (88.7)	2,011 (88.6)	
Yes	951 (9.2)	260 (11.4)		256 (11.3)	258 (11.4)	
Mitotic rate			0.02			0.79
≤5/50 HPF	7,957 (77.0)	1,695 (74.6)		1,686 (74.3)	1,694 (74.7)	
>5/50 HPF	2,380 (23.0)	576 (25.4)		583 (25.7)	575 (25.3)	
Risk stratification			<0.001			0.66
Very low	1,173 (11.3)	259 (11.4)		279 (12.3)	259 (11.4)	
Low	2,709 (26.2)	482 (21.2)		465 (20.5)	482 (21.2)	
Moderate	1,966 (19.0)	396 (17.4)		413 (18.2)	396 (17.5)	
High	4,489 (43.4)	1,134 (49.9)		1,112 (49.0)	1,132 (49.9)	

ER, endoscopic resection; HPF, high power field; PSM, propensity score matching.

Statistical analysis

Analyses were conducted using R software version 4.3.3 and GraphPad Prism 9.5. Categorical data comparisons were performed using the χ^2 test. Prognostic factors associated with OS were evaluated using univariate and multivariate Cox regression models, while those associated with CSS were assessed using univariate and multivariate competing risks regression models. Variables with a P value <0.05 in the univariate analysis were included in the multivariate analysis. To minimize bias and enhance the robustness of the results, stratified regression was employed with gradual adjustments of variables. OS was estimated using the Kaplan-Meier method and compared using the log-rank test. CSM was calculated using the cumulative incidence function (CIF) and compared using Gray's test. Subgroup analyses were depicted through forest plots. A P value <0.05 was considered to indicate statistical significance.

Results

Patients' characteristics

A total of 12,608 patients with GISTs were enrolled in this study, of whom 2,271 (18%) had early-onset GISTs and 10,337 (82%) had later-onset GISTs. The number of GIST diagnoses increased progressively with age, as shown in *Figure 2A*. The annual incidence of later-onset GISTs was significantly higher than that of early-onset GISTs from 2000 to 2021 (*Figure 2B*). The median age for patients with early-onset GISTs was 43 years (range, 8–49 years), while for later-onset GISTs, the median age was 66 years

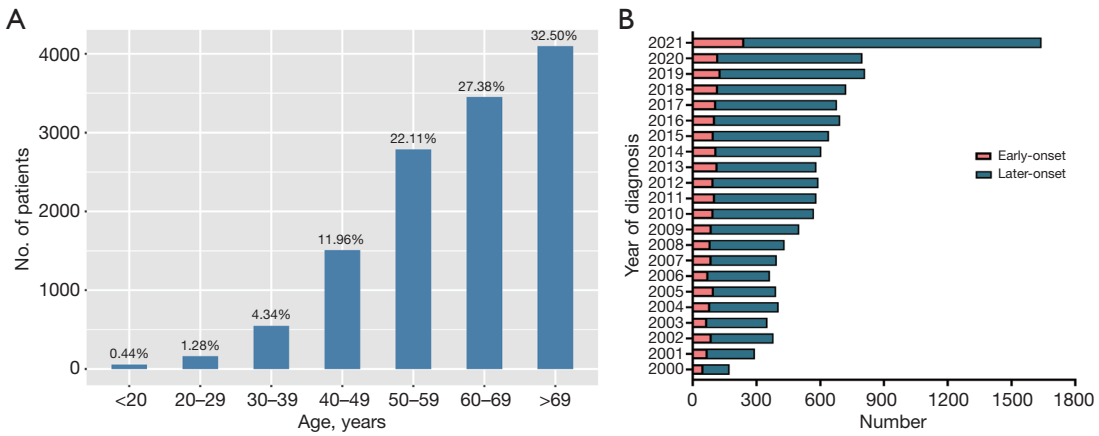

Figure 2 The proportion of patients with GISTs in different age groups, as well as early- and late-onset types, from 2000 to 2021. (A) A progressive increase in the incidence of GISTs with advancing age. (B) The annual incidence of GISTs was significantly greater in the later-onset group than in the early-onset group. GIST, gastrointestinal stromal tumor.

(range, 50–90+ years). The median survival time was 70 months (range, 0–263 months) for patients with early-onset GISTs and 48 months (range, 0–263 months) for those with later-onset GISTs. *Table 1* compares the clinicopathologic characteristics of early- and later-onset GISTs. No significant difference was found in gender distribution between the two groups (P=0.08). The most common tumor location for both early- and later-onset GISTs was the stomach, accounting for 57.1% and 66.2%, respectively. However, early-onset tumors were more frequently located in the duodenum (8.5% *vs.* 5.8%), small intestine (26.7% *vs.* 20.7%), and rectum (3.2% *vs.* 2.7%) than later-onset tumors (P<0.001). Early-onset GISTs had a higher proportion of tumors larger than 50 mm in diameter at the time of diagnosis compared to later-onset GISTs (61.1% *vs.* 56.5%). The most common stage for both early- and later-onset GISTs was localized (61.7% and 64.7%), but early-onset GISTs were more often diagnosed at regional (13.7% *vs.* 11.8%) and distant (18.9% *vs.* 18.0%) stages than later-onset GISTs (P=0.03). Early-onset GISTs were also more frequently associated with liver metastases compared to later-onset GISTs (11.4% *vs.* 9.2%). A higher percentage of early-onset GISTs had high mitotic rates (25.4% *vs.* 23.0%) and were classified as high-risk (49.9% *vs.* 43.4%) compared to later-onset GISTs. Additionally, more patients with early-onset GISTs underwent surgery (75.7% *vs.* 69.5%), whereas more patients with later-onset GISTs underwent endoscopic treatment (10.5% *vs.* 9.6%).

Prognostic factors of OS and CSS

Multifactorial Cox regression analysis identified age, sex, race, marital status, family income, tumor location, stage, mitotic rate, and surgical intervention as prognostic factors affecting patients' OS. Factors such as male gender, Black race, widowhood, middle-income and low-income status, and a mitotic count >5/50 were associated with increased risk of death. Similarly, multifactorial competing risk analysis revealed the same factors as significant predictors of CSS, with male gender, widowhood, middle-income status, and mitotic counts >5/50 contributing to higher risk of CSM. Notably, early-onset GISTs demonstrated significant survival benefits in both OS and CSS compared to later-onset GISTs [hazard ratio (HR) =0.46, 95% confidence interval (CI): 0.42–0.51, P<0.001 for OS; HR =0.79, 95% CI: 0.71–0.88, P<0.001 for CSS], as shown in *Table 2*.

Survival and subgroup analysis

Patients with early-onset GISTs exhibited a 3-year OS rate of 91.1%, a 5-year OS rate of 85.1%, and a 10-year OS rate of 73.6%. In contrast, patients with later-onset GISTs had a 3-year OS rate of 81.6%, a 5-year OS rate of 72.1%, and a 10-year OS rate of 52.1%. Kaplan-Meier survival curves and cumulative risk curves indicate that patients with early-onset GISTs had better OS and CSS rates compared to those with later-onset GISTs, both before and after PSM

Table 2 Multivariate Cox and competing analysis of prognostic factors for GIST patients before PSM

Characteristics	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
Age				
Later-onset	Reference		Reference	
Early-onset	0.46 (0.42–0.51)	<0.001	0.79 (0.71–0.88)	<0.001
Race				
Other	Reference		Reference	
White	1.09 (0.99–1.20)	0.07	0.95 (0.84–1.08)	0.43
Black	1.22 (1.09–1.37)	<0.001	1.05 (0.90–1.22)	0.56
Marital				
Divorced	Reference		Reference	
Married	0.92 (0.82–1.03)	0.16	0.88 (0.76–1.02)	0.09
Separated	1.20 (0.88–1.63)	0.26	0.98 (0.65–1.49)	0.94
Single	1.11 (0.97–1.26)	0.13	1.01 (0.86–1.19)	0.89
Unmarried	0.39 (0.13–1.22)	0.11	0.52 (0.22–1.20)	0.12
Widowed	2.03 (1.78–2.31)	<0.001	1.32 (1.10–1.58)	0.002
Household income				
High	Reference		Reference	
Low	1.14 (1.01–1.28)	0.03	1.07 (0.91–1.26)	0.43
Middle	1.19 (1.10–1.28)	<0.001	1.15 (1.04–1.28)	0.009
Rural/urban				
Rural	Reference		Reference	
Urban	1.00 (0.89–1.12)	0.96	1.00 (0.85–1.17)	0.99
Sex				
Female	Reference		Reference	
Male	1.36 (1.27–1.45)	<0.001	1.22 (1.12–1.33)	<0.001
Tumor site				
Colon	Reference		Reference	
Duodenum	0.71 (0.57–0.87)	0.002	0.75 (0.55–1.01)	0.06
Esophagus	0.88 (0.58–1.33)	0.54	1.11 (0.64–1.94)	0.71
Other	1.00 (0.78–1.28)	0.99	0.92 (0.66–1.30)	0.65
Rectum	0.55 (0.43–0.71)	<0.001	0.57 (0.40–0.82)	0.002
Small intestine	0.72 (0.60–0.87)	0.001	0.72 (0.56–0.94)	0.02
Stomach	0.70 (0.59–0.84)	<0.001	0.65 (0.50–0.84)	0.001
Tumor size				
≤2 cm	Reference		Reference	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
2.1–5 cm	0.94 (0.65–1.34)	0.73	0.86 (0.55–1.35)	0.52
5.1–10 cm	1.15 (0.81–1.64)	0.42	1.17 (0.76–1.82)	0.47
>10 cm	1.23 (0.86–1.78)	0.26	1.39 (0.88–2.19)	0.15
Stage				
Distant	Reference		Reference	
Localized	0.45 (0.41–0.50)	<0.001	0.35 (0.30–0.40)	<0.001
Regional	0.64 (0.57–0.72)	<0.001	0.62 (0.54–0.72)	<0.001
Unstaged	0.57 (0.50–0.66)	<0.001	0.58 (0.49–0.69)	<0.001
Treatment				
No	Reference		Reference	
ER	0.47 (0.42–0.53)	<0.001	0.45 (0.37–0.54)	<0.001
Surgery	0.42 (0.39–0.46)	<0.001	0.48 (0.43–0.53)	<0.001
Liver metastases				
No	Reference		Reference	
Yes	1.01 (0.91–1.13)	0.85	1.1 (0.96–1.27)	0.15
Mitotic rate				
≤5/50 HPF	Reference		Reference	
>5/50 HPF	1.38 (1.27–1.49)	<0.001	1.73 (1.56–1.92)	<0.001
Risk stratification				
Very low	Reference		Reference	
Low	1.09 (0.74–1.61)	0.68	1.43 (0.84–2.43)	0.19
Moderate	1.10 (0.76–1.58)	0.62	1.79 (1.10–2.93)	0.02
High	1.23 (0.83–1.82)	0.31	2.17 (1.28–3.70)	0.004

CI, confidence interval; CSS, cancer-specific survival; ER, endoscopic resection; GIST, gastrointestinal stromal tumor; HPF, high power field; HR, hazard ratio; OS, overall survival; PSM, propensity score matching.

(P<0.001 and P<0.001) (*Figure 3*). The OS advantage of early-onset GISTs was observed across different stages and risk strata (*Figure 4*). This survival benefit persisted even after stepwise adjustment of variables in multiple models, using propensity-matched data (P<0.001) (*Table 3*). Further subgroup analyses confirmed the robustness of these findings (*Figure 5*).

Discussion

In recent years, the incidence of early-onset cancers has been increasing worldwide, a trend that may be associated with various factors such as genetic predispositions, environmental changes, lifestyle choices (e.g., smoking, alcohol consumption, physical inactivity, dietary habits), and advancements in diagnostic techniques (7,14). Our study demonstrated a gradual increase in the number of diagnosed cases of early-onset GISTs from 2000 to 2021. Despite comprising only 18% of all GISTs, as opposed to the 82% accounted for by later-onset GISTs, early-onset cases showed distinctive clinicopathologic characteristics. Patients with early-onset GISTs were more likely to present

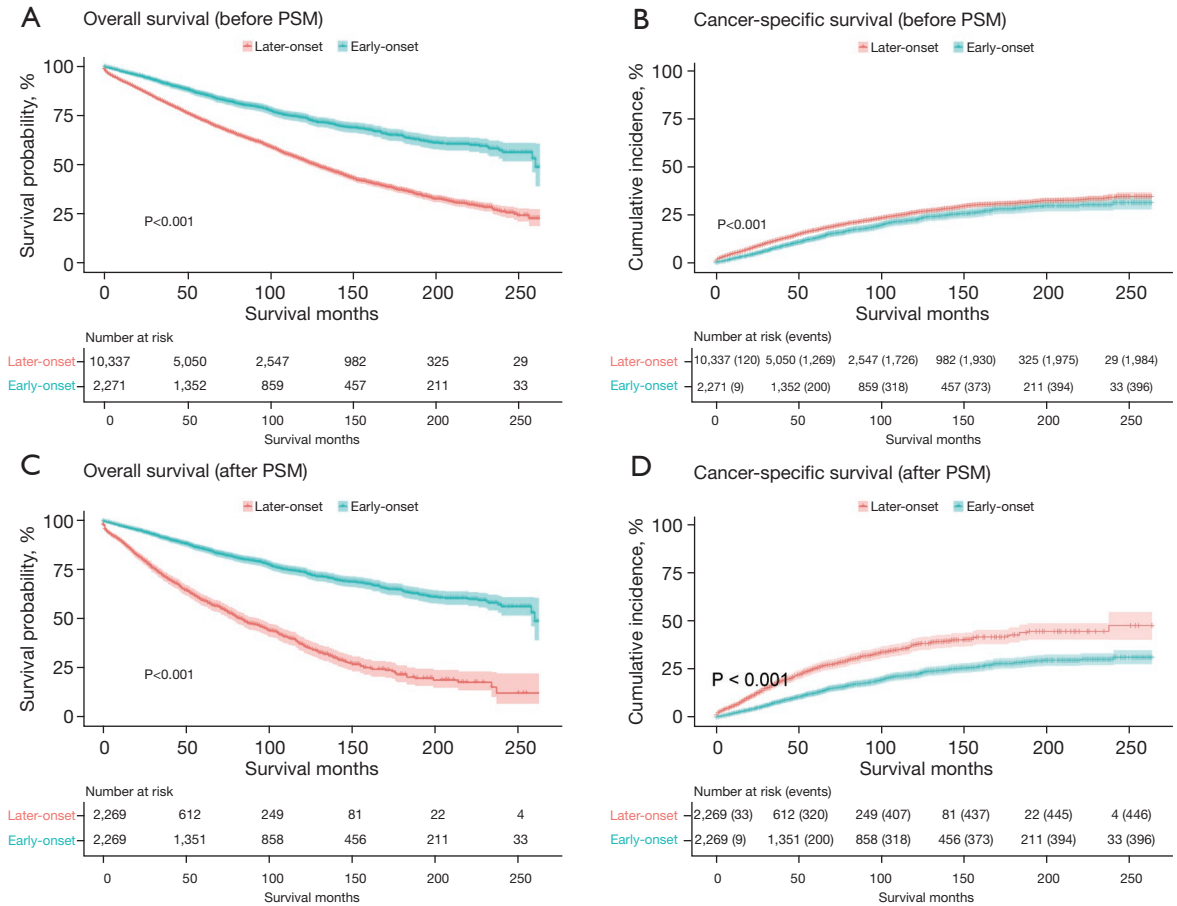

Figure 3 Comparison of OS and CSS in patients with GISTs between early- and later-onset groups. CSS, cancer-specific survival; GIST, gastrointestinal stromal tumor; OS, overall survival; PSM, propensity score matching.

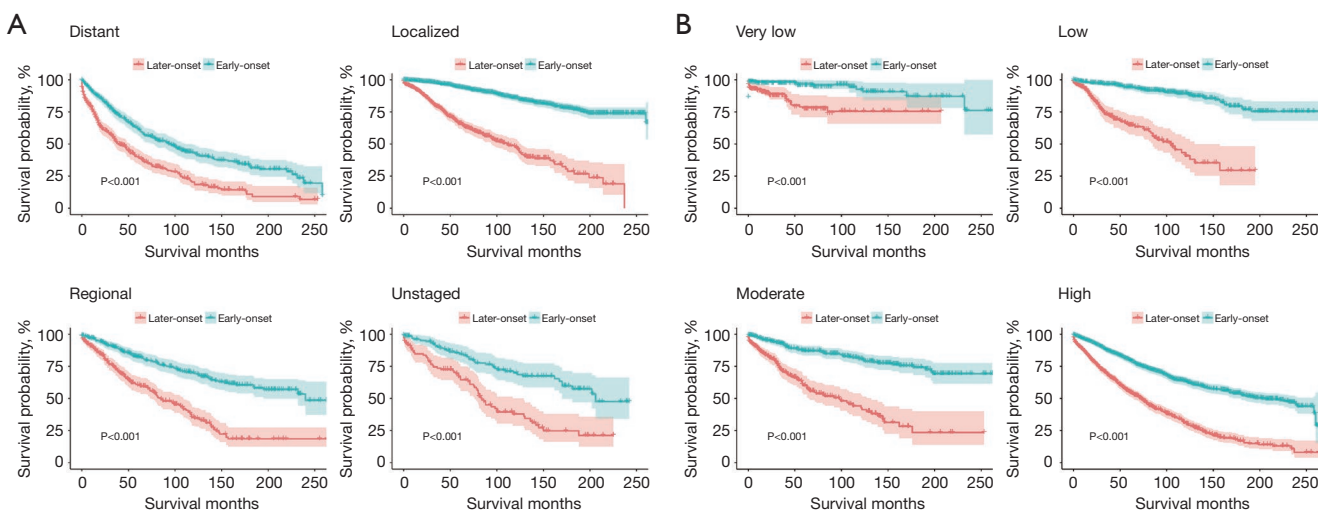

Figure 4 Comparison of OS between early- and later-onset patients in different staging (A) and risk stratification (B) groups after PSM. OS, overall survival; PSM, propensity score matching.

Table 3 The relationship between early- and later-onset and OS and CSS

Outcome	Group	Non-adjusted		Model 1		Model 2		Model 3		After PSM	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
OS	Later-onset	Reference		Reference		Reference		Reference		Reference	
	Early-onset	0.45 (0.41–0.50)	<0.001	0.48 (0.43–0.52)	<0.001	0.33 (0.29–0.37)	<0.001	0.46 (0.42–0.51)	<0.001	0.30 (0.26–0.33)	<0.001
CSS	Later-onset	Reference		Reference		Reference		Reference		Reference	
	Early-onset	0.81 (0.73–0.91)	<0.001	0.83 (0.74–0.92)	<0.001	0.76 (0.69–0.85)	<0.001	0.80 (0.71–0.89)	<0.001	0.54 (0.47–0.61)	<0.001

Model 1: adjusted demographic information (sex, martial, race, income, rural/urban); model 2: adjusted demographic and oncological information (stage, size, mitotic rate, site, liver metastases, risk stratification); model 3: adjusted demographic, oncological, and treatment. CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival; PSM, propensity score matching.

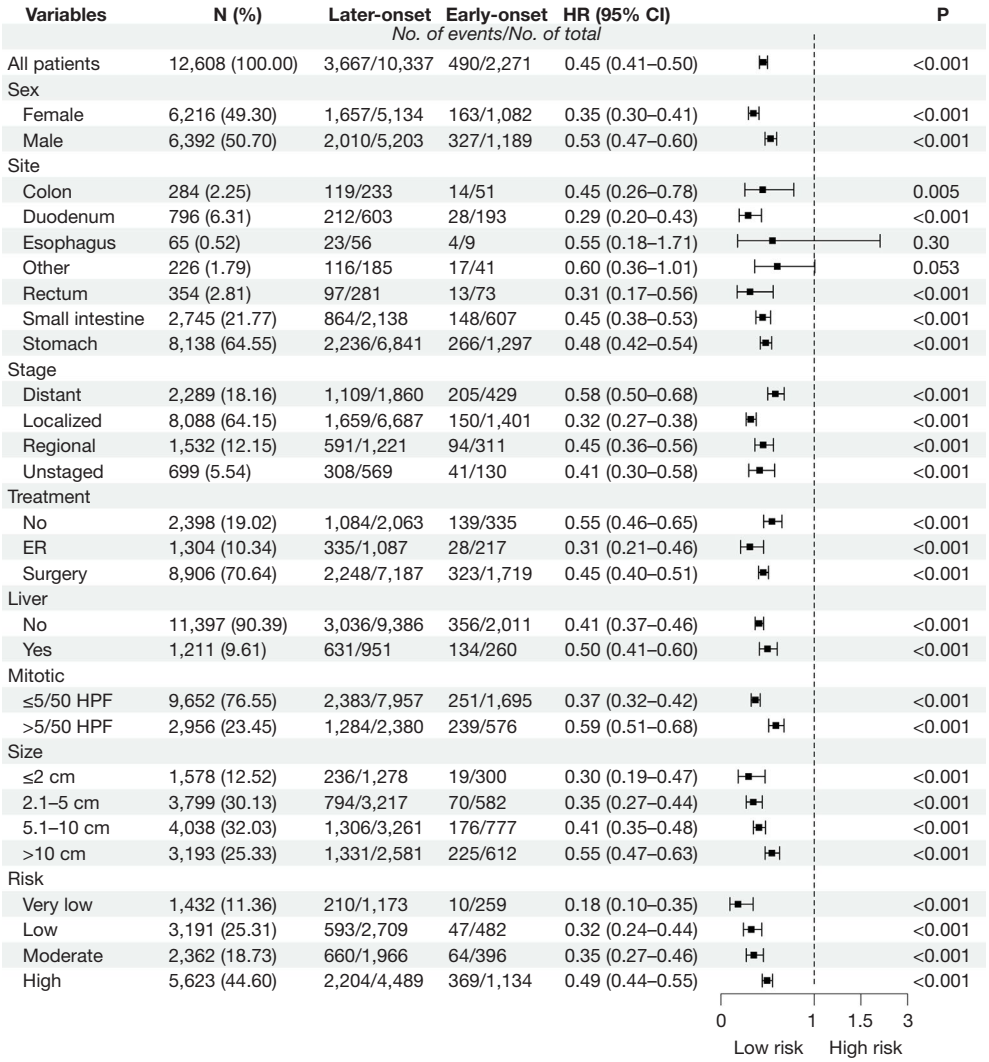

Figure 5 Subgroup analyses of OS in the early- and later-onset groups according to baseline characteristics. CI, confidence interval; ER, endoscopic resection; HPF, high power field; HR, hazard ratio; OS, overall survival.

with larger tumors (diameter >5 cm), concomitant liver metastases, high mitotic rates, high-risk stratification, and advanced staging (e.g., regional and distant metastases). Interestingly, although these patients exhibited more severe clinical features at diagnosis, their long-term OS and CSS were superior to those of patients with later-onset GISTs. These findings are consistent with other studies, such as the work of Corless *et al.* (15), which noted that GISTs in younger patients often possess unique genetic mutations and biological characteristics that may lead to better prognoses.

The favorable prognosis observed in young GIST patients may be attributable to several factors. Firstly, younger patients generally possess greater physiological reserves and immune function, enabling them to more effectively combat disease progression and treatment-related complications. Secondly, younger patients are more likely to undergo multiple therapies, potentially leading to more comprehensive tumor removal and improved prognoses. This observation is supported by our findings, which indicated a higher percentage of early-onset patients undergoing surgical treatment. Additionally, genetic factors and molecular features may play a significant role in the prognosis of early-onset GISTs (16). It has been shown that patients with early-onset GISTs are more likely to harbor specific genetic mutations, such as *KIT* and *PDGFRA*, which are closely linked to GIST development and may enhance tumor sensitivity to treatment, thereby improving patient survival (17).

Our study identified several factors closely associated with the prognosis of GISTs, including age, gender, tumor location, tumor stage, and mitotic rate. Among these, mitotic rate, tumor size, and tumor location emerged as the most valuable prognostic factors (18). Mitotic rate serves as a key indicator of tumor proliferative activity, with higher rates typically predicting rapid tumor growth, aggressiveness, and increased risk of recurrence and metastasis. A higher mitotic rate is also correlated with a higher incidence of adverse treatment effects (19). Tumor size is another crucial prognostic factor; larger mesenchymal tumors are generally associated with higher aggressiveness and poorer prognoses. Studies have shown that patient survival is significantly reduced when tumor size exceeds 5 cm, a trend particularly evident in long-term survival analyses, suggesting that larger tumors often carry a greater risk of recurrence and metastasis (12,20). Tumor location also significantly impacts prognosis. In general, gastric GISTs have a better prognosis, while GISTs from the small intestine and other locations are associated with worse outcomes. This disparity may be due to the fact that gastric GISTs typically exhibit lower mitotic rates and smaller tumor sizes at detection. In contrast, small bowel GISTs are often detected at more advanced stages due to their occult location and are characterized by higher mitotic rates and larger tumor sizes, leading to poorer prognoses (21).

Currently, the main treatments for GISTs include surgery, endoscopic therapy, and targeted drug therapy (22). The choice of treatment is influenced by factors such as tumor size and location, patient age, comorbid conditions, and the presence of symptoms or complications (2). For smaller, localized GISTs, especially those under 2 cm, endoscopic treatment can be effective in removing tumors while minimizing damage to surrounding tissues (23). However, surgery is generally considered the standard treatment for larger GISTs or those at risk of metastasis. Targeted drug therapies, such as imatinib and sunitinib, are primarily used for controlling residual lesions post-surgery or treating advanced, recurrent GISTs (24). For patients unable to tolerate surgery or endoscopic treatment, as well as those with metastases, targeted drug therapy offers a crucial treatment option, significantly improving survival and quality of life. Our study found that a higher proportion of later-onset GIST patients opted for endoscopic therapy compared to early-onset patients, possibly due to the preference of elderly patients for less invasive treatment options. Endoscopic therapy offers a viable option to reduce surgical trauma while preserving organ function, making it a relatively safe and effective choice for elderly GIST patients, thereby reducing perioperative risks and improving their quality of life.

This study has some limitations. Firstly, as a retrospective study, there is an inherent risk of selection bias. Although we employed propensity matching, multiple imputations, and stratified regression to minimize bias, complete elimination was not possible. Secondly, the data used in this study were sourced primarily from the U.S. population via the SEER database, which may limit the generalizability of our findings to other ethnic and regional populations. Thirdly, despite the large sample size of the SEER database, it lacks certain critical data, such as patients' underlying disease conditions, which could have influenced our findings. Additionally, the database does not provide information on tumor recurrence indicators and specific targeted drug treatments, preventing us from comparing the effects of these factors on the survival prognosis of early- and later-onset GIST patients.

Conclusions

In summary, this study is the first to systematically compare the clinicopathologic characteristics and survival prognosis of early- and later-onset GIST patients. Our findings suggest that early-onset GIST patients exhibit unique clinicopathologic features and have superior OS and CSS compared to later-onset patients. These results provide a crucial foundation for the clinical management and prognostic assessment of early-onset GISTs. Despite the limitations of our study, we believe that further research, particularly in-depth exploration of molecular and genetic factors, will offer a more comprehensive understanding of the pathogenesis and therapeutic strategies for early-onset GISTs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1942/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1942/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As SEER database is publicly available to researchers worldwide, no ethics approval was required.

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