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# Effect of Age on Prognosis of Gastric Signet-Ring Cell Carcinoma: A SEER Database Analysis

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**Background:** Age is a prognostic factor for multiple malignancies. In this study, we aimed to assess the effect of age on the cancer-specific survival (CSS) of patients with gastric signet-ring cell carcinoma (SRC).

**Material/Methods:** Information on patients with gastric SRC was extracted from the Surveillance, Epidemiology, and End Results database. Chi-squared tests were used to demonstrate distribution differences, and Kaplan-Meier analysis and Cox regression models were used to analyze the impact of age on CSS.

**Results:** A total of 4596 patients were enrolled and divided into 3 subgroups according to age (<45, 45–74, and >74 years old). Higher percentages of T4, N2, and M1 disease were observed in the <45-year-old group (all  $P < 0.001$ ). Kaplan-Meier plots showed that the youngest group had the most favorable 5-year CSS rate (36.3%), which remained true after stratification according to tumor stage. Multivariate Cox regression models demonstrated a poorer survival outcome for >74-year-old than for <45-year-old patients (hazard ratio 1.841, 95% confidence interval 1.636–2.071;  $P < 0.001$ ).

**Conclusions:** Young age is associated with improved survival, even though younger patients generally present with a more advanced-stage disease.

**MeSH Keywords:** **Age Factors • Carcinoma, Signet Ring Cell • SEER Program • Stomach Neoplasms**

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## Background

Gastric cancer (GC) is the fourth most common malignancy and is the third leading cause of cancer-associated mortality worldwide [1]. Signet-ring cell carcinoma (SRC) is a histological subtype of adenocarcinoma, with cells containing high levels of intracytoplasmic mucins [2]. SRC is seen most commonly in the stomach (95%) and occasionally in the colon, rectum, ovary, breast, and gallbladder. Approximately 15–28% of GCs are SRCs [3,4]. SRC of the stomach was classified as an undifferentiated type according to the Japanese Gastric Cancer Association [5].

Age at diagnosis is an indispensable adjusted element in observational studies, as well as a promising prognostic factor for survival in multiple cancers [6–8]. In GC, the data are conflicting regarding survival outcomes among younger patients. For example, Wang et al. reported overall 5-year survival rates in younger and older groups of 60.8% and 53.7%, respectively ( $P=0.017$ ). When stratified by TNM stage, the younger group at stage IV exhibited better 5-year survival compared with the older group (26.9% vs. 10.3%,  $P=0.003$ ) [9]. Kim et al. [10] reported overall 5-year survival rates in younger and older groups of 84.3% and 89.6%, respectively ( $P=0.172$ ), while another study found that the 5-year survival rates did not differ significantly between younger ( $\leq 45$  years) and older ( $> 45$  years) GC patients (69.97% vs. 69.03%,  $P=0.534$ ). However, in curatively resected patients, the 5-year survival rate was significantly better in the younger group (80.81% vs. 75.42%;  $P=0.002$ ) [11].

GC patients with SRC tend to be younger than non-SRC patients [12,13]. Some studies investigated the effect of age on the survival of patients with gastric SRC. Yokota et al. [14] carried out a retrospective analysis of 93 patients with SRC of the stomach who were operated on between 1985 and 1995. They reviewed the clinicopathologic characteristics and found that vascular invasion and tumor location were statistically significant prognostic factors, whereas age, tumor size, and lymph node metastasis were not. Jiang et al. used multivariate Cox regression analysis to demonstrate that sex, age, lymph node metastatic ratio, pTNM stage, curative operation, and distant metastasis were independent prognostic factors; in addition, a younger age predicted worse cancer-specific survival (CSS) [15]. Moreover, using multivariate analysis, Liu et al. [16] found higher 5-year overall survival rates in younger than in older patients with gastric SRC. Therefore, the effects of younger age on the prognosis of gastric SRC are controversial, and these studies have been generally limited by small numbers of patients and a limited ability to assess CSS accurately.

To perform a comprehensive analysis of gastric SRC, we used data from the Surveillance, Epidemiology, and End Results

(SEER) database to investigate the impact of age on clinicopathological features and identify independent prognostic factors for gastric SRC using a multivariate approach.

## Material and Methods

### Patient selection

The SEER database is a population-based cancer registry containing data from 18 sites that cover approximately 30% of the United States population [17]. We used SEER Stat software (Surveillance Research Program, National Cancer Institute SEER Stat software, [www.seer.cancer.gov/seerstat](http://www.seer.cancer.gov/seerstat), version 8.3.4) to identify patients who were diagnosed with gastric SRC. Data regarding age, sex, race, marital status, histological type, American Joint Committee on Cancer (AJCC) stage, tumor site, number of positive lymph nodes, and gastric CSS were extracted from the SEER database for further analysis.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: the tumor site was limited to the stomach (C16.0–16.9), which was further categorized as the proximal third (cardia and fundus), mid-third (body and lesser curvature), distal third (antrum and pylorus), greater curvature, and overlapping lesions of the stomach; histological type was limited to SRC (ICD-03, 8490/3); diagnosis was made between 2004 and 2012; and the diagnostic confirmation method was limited to microscopic. The exclusion criteria were incomplete patient information regarding sex, race, marital status, histological type, AJCC stage, tumor site, number of positive lymph nodes, or survival time. The timeframe of 2004–2012 was selected because AJCC TNM staging became available in 2004, and patients diagnosed after 2012 were excluded to ensure an adequate follow-up time. Cases diagnosed before 2010 were restaged according to the criteria described in the 7th edition of the AJCC staging manual (2010).

### Statistical analysis

The study endpoint was gastric CSS, which was calculated from the date of diagnosis to the date of GC-specific death. Deaths caused by GC were treated as events; surviving patients at the last follow-up or deaths from other causes were treated as censored observations. To investigate the impact of age on the prognosis of gastric SRC, age was classified into a categorical variable consisting of 3 groups:  $< 45$ , 45–74, and  $> 74$  years. Patient demographics and tumor factors were compared among the age groups using the chi-square test to evaluate proportions. CSS was assessed using the Kaplan-Meier method. Univariate differences among groups were analyzed using log-rank tests, and the significant variables ( $P < 0.05$ ) were

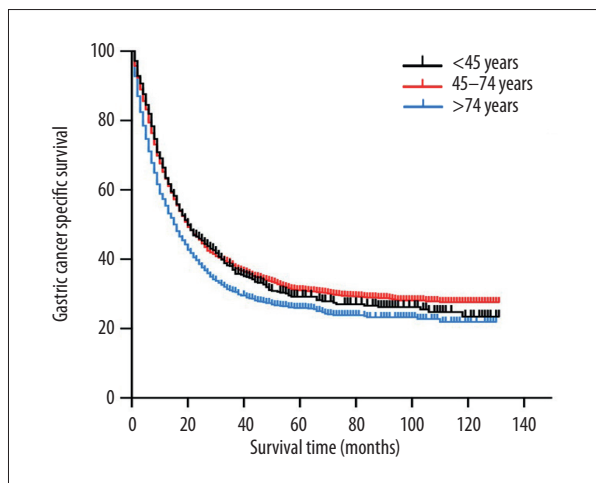
**Table 1.** Characteristics of patients with signet-ring cell carcinoma of the gastric from the SEER database by age at diagnosis.

Characteristics	All patients	<45 years	45–74 years	>74 years	P value
N (%)	4596 (100)	625 (13.6)	2532 (55.1)	1439 (31.3)	
Median follow-up, months	15	16	17	10	
Sex, n (%)					0
Male	2422 (52.7)	277 (44.3)	1430 (56.5)	715 (49.7)	
Female	2174 (47.3)	348 (55.7)	1102 (43.5)	724 (50.3)	
Race, n (%)					0
White	3149 (68.5)	403 (64.5)	1694 (66.9)	1052 (73.1)	
Black	573 (12.5)	108 (17.3)	340 (13.4)	125 (8.7)	
Others*	854 (18.6)	110 (17.6)	487 (19.2)	257 (17.9)	
Unknown	20 (0.4)	4 (0.6)	11 (0.4)	5 (0.3)	
Marital status					0
Married	3310 (72.0)	385 (61.6)	1763 (69.6)	1162 (80.8)	
Unmarried	1125 (24.5)	220 (35.2)	688 (27.2)	217 (15.1)	
Unknown	161 (3.5)	20 (3.2)	81 (3.2)	60 (4.2)	
Tumor location					0
Proximal third	924 (20.1)	79 (12.6)	557 (22.0)	288 (20.0)	
Mid third	994 (21.6)	140 (22.4)	551 (21.8)	303 (21.1)	
Distal third	1317 (28.7)	186 (29.8)	706 (27.9)	425 (29.5)	
Greater curvature	247 (5.4)	42 (6.7)	133 (5.3)	72 (5.0)	
Overlapping lesions	546 (11.9)	91 (14.6)	289 (11.4)	166 (11.5)	
Unknown	568 (12.4)	87 (13.9)	296 (11.7)	185 (12.9)	
Tumor size (cm)					0.093
≤5	1576 (34.3)	184 (29.4)	879 (34.7)	513 (35.6)	
>5	1436 (31.2)	208 (33.3)	789 (31.2)	439 (30.5)	
Unknown	1584 (34.5)	233 (37.3)	864 (34.1)	487 (33.8)	
PLNH					0.604
<15	4148 (90.3)	571 (91.4)	2281 (90.1)	1296 (90.1)	
≥15	448 (9.7)	54 (8.6)	251 (9.9)	143 (9.9)	
Grade					0.096
Low	127 (2.8)	11 (1.8)	67 (2.6)	49 (3.4)	
High	4469 (97.2)	614 (98.2)	2465 (97.4)	1390 (96.6)	
T-stage					0
T1	973 (21.2)	109 (17.4)	495 (19.5)	369 (25.6)	
T2	423 (9.2)	44 (7.0)	237 (9.4)	142 (9.9)	
T3	1273 (27.7)	180 (28.8)	724 (28.6)	369 (25.6)	
T4	1927 (41.9)	292 (46.7)	1076 (42.5)	559 (38.8)	

**Table 1 continued.** Characteristics of patients with signet-ring cell carcinoma of the gastric from the SEER database by age at diagnosis.

Characteristics	All patients	<45 years	45–74 years	>74 years	P value
N-stage					0
N0	1846 (40.2)	236 (37.8)	950 (37.5)	660 (45.9)	
N1	1443 (31.4)	201 (32.2)	844 (33.3)	398 (27.7)	
N2	737 (16.0)	115 (18.4)	421 (16.6)	201 (14.0)	
N3	570 (12.4)	73 (11.7)	317 (12.5)	180 (12.5)	
M-stage					0
M0	3323 (72.3)	380 (60.8)	1807 (71.4)	1136 (78.9)	
M1	1273 (27.7)	245 (39.2)	725 (28.6)	303 (21.1)	
AJCC stage					0
I	933 (20.3)	89 (14.2)	471 (18.6)	373 (25.9)	
II	889 (19.3)	98 (15.7)	497 (19.6)	294 (20.4)	
III	1501 (32.7)	193 (30.9)	839 (33.1)	469 (32.6)	
IV	1273 (27.7)	245 (39.2)	725 (28.6)	303 (21.1)	

\* Native Americans, Asians, Pacific Islanders. PLNH – number of positive lymph nodes harvested; AJCC – American Joint Committee on Cancer.



**Figure 1.** Survival curves for patients with signet-ring cell carcinoma of the gastric according to 3 age subgroups.  $\chi^2=46.838$ ,  $P<0.001$ .

further analyzed using a Cox regression model. Multivariate Cox regression models were used to evaluate risk factors for survival outcomes in GC patients. All statistical analyses were performed using Statistical Package for Social Sciences for Mac IOS, version 24 (SPSS Inc., Chicago, IL, USA). A 2-sided  $P$  value of  $<0.05$  was considered statistically significant.

## Results

### Demographic and baseline characteristics of SRC patients

A total of 4596 patients with gastric SRC were identified in the SEER database during the 9-year study period (2004–2012). Of these, 625 (13.6%), 2532 (55.1%), and 1439 (31.3%) were aged  $<45$ , 45–74, and  $>74$  years, respectively. The median follow-up time was 16 months (interquartile range [IQR], 7–39.5 months) in the  $<45$ -year-old group, 17 months (IQR, 6–41 months) in the 45–74-year-old group, and 10 months (IQR, 3–29 months) in the  $>74$ -year-old group. Female patients accounted for a greater proportion (55.7%) of the  $<45$ -year-old group, while there was a male predominance in those aged 45–74 years (56.5%). The most common ethnicity was white in all groups (Table 1).

The distal third gastric region was the most frequent primary tumor location in each age group of GC patients. No differences in the grade of differentiation or number of positive lymph nodes harvested were found among the age groups. The  $<45$ -year-old group had significantly higher proportions of patients with AJCC T4, N2, and M1 stages compared with the other 2 groups ( $P<0.001$  for all); thus, these patients presented with a more advanced AJCC clinical stage (IV,  $P<0.001$ ). However, the  $<45$ -year-old group had fewer patients with stage I, II, or III disease compared with the other 2 groups ( $P<0.001$ ).

**Table 2.** Univariate and multivariate Cox analyses of determinants of cancer-specific survival (CSS) of patients with signet-ring cell gastric carcinoma.

Variable	No. of patients	5-year GCSS(%)	Univariate		Multivariate		
			Log-rank test	P	Hazard Ratio	95% CI	P
Age			46.838	0			
<45	625	36.30%			1	Reference	
45-74	2532	35.74%			1.144	1.025-1.276	0.016
>74	1439	31.83%			1.841	1.636-2.071	0
Sex			0.057	0.811			
Male	2422	34.72%					
Female	2174	34.45%					
Race			71.23	0			
White	3149	31.53%			1		
Black	573	33.86%			1.08	0.967-1.205	0.173
Others*	854	45.55%			0.825	0.746-0.913	0
Unknown	20	70.00%			0.435	0.195-0.97	0.042
Marital status			1.263	0.532			
Married	3310	34.29%					
Unmarried	1125	34.76%					
Unknown	161	39.75%					
Tumor location			187.904	0			
Proximal third	924	25.97%			1		
Mid third	994	41.65%			0.82	0.733-0.916	0
Distal third	1317	41.91%			0.819	0.738-0.909	0
Greater curvature	247	41.70%			0.826	0.689-0.99	0.038
Overlapping lesions	546	23.08%			0.931	0.824-1.053	0.255
Unknown	568	27.29%			1.037	0.917-1.174	0.563
Tumor size (cm)			688.588	0			
≤5	1576	55.46%			1		
>5	1436	28.20%			1.324	1.198-1.464	0
Unknown	1584	19.63%			2.096	1.899-2.314	0
PLNH			84.323	0			
<15	4148	36.55%			1		
≥15	448	16.52%			1.197	1.067-1.342	0.002
Grade			5.762	0.016			
Low	127	45.67%			1		
High	4469	34.28%			1.046	0.827-1.323	0.708

**Table 2 conitued.** Univariate and multivariate Cox analyses of determinants of cancer-specific survival (CSS) of patients with signet-ring cell gastric carcinoma.

Variable	No. of patients	5-year GCSS(%)	Univariate		Multivariate		
			Log-rank test	P	Hazard Ratio	95% CI	P
T-stage			488.878	0			
T1	973	55.91%					
T2	423	51.54%					
T3	1273	34.72%					
T4	1927	20.03%					
N-stage			127.5	0			
N0	1846	44.47%					
N1	1443	30.35%					
N2	737	28.90%					
N3	570	20.70%					
M-stage			1252.535	0			
M0	3323	44.00%					
M1	1273	10.05%					
AJCC stage			1578.803	0			
I	933	68.17%			1		
II	889	47.24%			1.898	1.644–2.191	0
III	1501	27.05%			3.237	2.827–3.705	0
IV	1273	10.05%			6.791	5.921–7.788	0

\* Native Americans, Asians, Pacific Islanders. PLNH – number of positive lymph nodes harvested; AJCC – American Joint Committee on Cancer.

for all). There were no significant differences in tumor size among the groups ( $P=0.093$ ; Table 1).

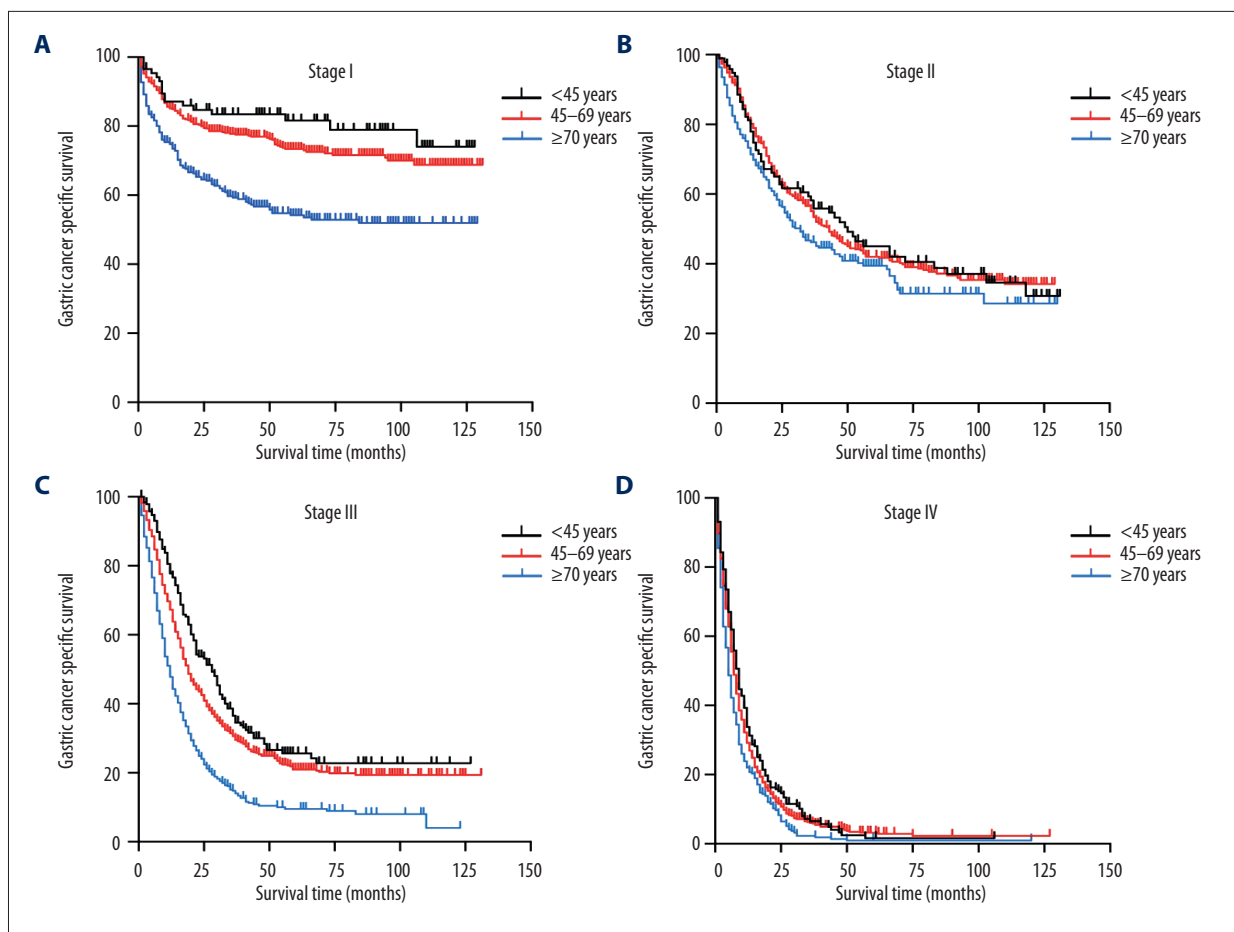
### Impact of age on CSS in SRC patients

The 5-year CSS was 36.3% in patients aged <45 years, 35.74% in patients aged 45–74 years, and 31.83% in patients aged >74 years, suggesting that survival outcomes were more favorable among the youngest age group of patients (Figure 1; Table 2). Moreover, when CSS was further stratified according to AJCC stage, these observations remained true for all stage strata (Figure 2; Table 3). In univariate survival analyses, grade ( $P=0.016$ ), age, race, tumor size, tumor location, number of positive lymph nodes, AJCC TNM stage, and clinical stage (all  $P<0.001$ ) were significant risk factors for poor survival (Table 2).

The multivariate Cox proportional model further demonstrated age to be an independent prognostic factor for CSS. The hazard

ratio (HR) increased steadily with age, and the >74-year-old group had the poorest survival outcome compared with the other 2 age groups (HR, 1.841; 95% confidence interval [CI], 1.636–2.071,  $P<0.001$ ). Five other variables were also independent prognostic factors: ethnicity (using white as a reference; others: HR 0.825, 95% CI 0.746–0.913,  $P<0.001$ ; unknown: HR 0.435, 95% CI 0.195–0.97,  $P=0.042$ ; there was no significant difference in risk between black and white,  $P=0.173$ ); tumor location (using the proximal third as the reference; mid-third: HR 0.82, 95% CI 0.733–0.916,  $P<0.001$ ; distal third: HR 0.819, 95% CI 0.738–0.909,  $P<0.001$ ; greater curvature: HR 0.826, 95% CI 0.689–0.99,  $P=0.038$ ); tumor size (using  $\leq 5$  cm as the reference; >5 cm: HR 1.324, 95% CI 1.198–1.464,  $P<0.001$ ); positive lymph nodes (using <15 as the reference;  $\geq 15$ : HR 1.197, 95% CI 1.067–1.342,  $P=0.002$ ); clinical stage (using stage I as the reference; stage II: HR 1.898, 95% CI 1.644–2.191,  $P<0.001$ ; stage III: HR 3.237, 95% CI 2.827–3.705,  $P<0.001$ ; stage IV: HR 6.791, 95% CI 5.921–7.788,  $P<0.001$ ) (Table 2).





**Figure 2.** Survival curves for patients with signet-ring cell carcinoma of the gastric in tumor stage subgroups. (A) Stage I:  $\chi^2=54.738$ ,  $P<0.001$ ; (B) Stage II:  $\chi^2=8.339$ ,  $P=0.015$ ; (C) Stage III:  $\chi^2=91.76$ ,  $P<0.001$ ; (D) Stage IV:  $\chi^2=32.425$ ,  $P<0.001$ .

## Discussion

Although the incidence and mortality of GC have decreased in many countries over the past 50 years, the rate of gastric SRC-type cancer has increased sharply. Donald et al. used the SEER database to identify an increase in the incidence of the diffuse type of GC from 0.3 cases per 100 000 persons in 1973 to 1.8 cases per 100 000 persons in 2000, and the predominant increase occurred in the SRC subtype [18]. Some other investigators have also reported an obvious increase in the occurrence of SRC subtype GC worldwide [18–20]. Furthermore, Postlewaite et al. [21] recently found that the SRC subtype was present in 40.6% of 768 gastric adenocarcinoma patients and was associated with a younger age.

Compared with non-signet-ring cell carcinoma, gastric SRC patients have worse outcomes, different prognostic factors, a tendency for metastases, and reduced sensitivity to chemotherapy [22–25]. As a subtype of GC associated with poor survival, gastric SRC has an intrinsic genetic basis that is responsible for its high rate of malignancy. It was reported that SRC

cells rarely adhere to each other because of downregulated E-cadherin expression, which is important for cell adhesion; therefore, SRC cells are more likely to metastasize [23,26]. Yang et al. [27] revealed that >80.0% of gastric SRCs express the oestrogen receptor (ER), and SRC cells are prone to metastasize to the ovary or uterine cervix in the presence of high levels of oestrogen. Gastric SRC expresses heparanase (HPA) during the very early stages of progression; high levels of HPA and cyclooxygenase-2 (whose expression is induced by HPA and other factors) stimulate angiogenesis, tumor growth, and tumor invasion. However, the exact genetic mechanism behind young-onset gastric SRC is still largely unknown. Therefore, further comparative studies are needed to delineate the genetic peculiarity of young-onset gastric SRC.

Although several studies have evaluated the prognostic value of various factors in GC, the prognostic determinants of gastric SRC are largely undefined [28], and the impact of age on the prognosis of gastric SRC remains controversial. In the current study, a total of 4596 patients with gastric SRC were included to evaluate the impact of age on prognosis. The lowest HR

**Table 3.** Univariate analysis of age on gastric cancer-specific survival by disease stage.

Variable	No. of patients	5-year GCSS(%)	Log-rank test	P
<b>Stage 1</b>				
Age			54.738	0
<45	89	83.15		
45–74	471	74.73		
>74	373	56.3		
<b>Stage 2</b>				
Age			8.339	0.015
<45	98	48.98		
45–74	497	47.69		
>74	294	45.92		
<b>Stage 3</b>				
Age			91.76	0
<45	193	34.72		
45–74	839	29.68		
>74	469	19.19		
<b>Stage 4</b>				
Age			32.425	0
<45	245	15.51		
45–74	725	9.24		
>74	303	7.59		

was observed in the younger group (<45 years), and the risk increased with age and was highest for the older group (>74 years). Moreover, younger patients with gastric SRC presented with more frequent deep invasion and distant metastasis, which was consistent with other studies. We believe that this could be attributed to the following factors. First, the morbidity of GC is lower among younger patients, and the clinical symptoms of early GC and common benign diseases overlap; therefore, GC in younger people may not be considered at the time of presentation. Second, there has been less incentive to establish surveillance endoscopy programs to identify younger patients at an earlier stage. However, our data showed that the 5-year CSS of the younger group exceeded those of the older cohorts. The worse survival in older patients is in part due to poor tolerance to extensive lymphadenectomy and adjuvant chemotherapy because of a poorer performance status and presence of many more comorbidities compared with younger patients [29]. In addition, poorer tolerance to surgical complications and adjuvant treatments and greater difficulty restoring gastrointestinal function may be evident in older patients compared with younger patients [30,31].

In the present study, Asians, Native Americans, and Pacific Islanders had better prognoses than those of white and black patients. These findings are consistent with previous studies. For example, a study in the United States found that Asians had a better prognosis than those of African Americans, whites, and Hispanics with gastric SRC [20]. Gill et al. [32] found more favorable outcomes after curative surgery in Asians than in non-Asians with GC. The present study also found that tumor location was associated with CSS, which is consistent with other studies showing a worse prognosis for tumors located in the proximal third compared with the antrum or pylorus [24,32]. Not surprisingly, tumor size, positive lymph nodes, and clinical stage at diagnosis were powerful independent prognostic factors for gastric SRC. Furthermore, our analyses found no significant association between sex or marital status and CSS. In the univariate analyses, we found that pathological grade was associated with CSS; however, no significant difference was detected in the multivariate analysis, indicating that pathological grade was not an independent prognostic factor.



Although our analysis is convincing because it was a large population-based study, it still has several potential limitations. First, the SEER database lacks important chemotherapy-related information such as the specific chemotherapy regimens used, adjuvant versus neoadjuvant treatment, and the treatment duration. Second, the SEER database does not separate palliative from curative surgeries. Finally, the SEER database does not include information on comorbidities, nutritional status, or family history. Thus, our study could not adjust for these potential confounding factors.

## Conclusions

In conclusion, our analysis used the SEER database to demonstrate that younger patients (<45 years) with gastric SRC

presented with more advanced disease. However, their survival outcomes were more favorable than those of the older cohorts, and these observations remained true after stratification by AJCC stage. Clinicians should include age in their assessments and treatment decisions for patients with gastric SRC.

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## Conflicts of interest

None.

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