

Research Paper

# More attention should be paid to adult gastric cancer patients younger than 35 years old: extremely poor prognosis was found

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## Abstract

**Purpose:** Several studies have reported controversial results about prognosis of gastric cancer in young age patients. The difference may partially result from variable definitions of young age. The aim of this study was to find out the relation between age and prognosis of gastric cancer patients, and to analyze the clinicopathological features and prognostic factors in young gastric cancer patients.

**Methods:** Data queried for this analysis included GC patients from the Surveillance, Epidemiology, and End Results Program database from 1973 to 2014. Gastric cancer patients (N=79,505) diagnosed with an age $\geq$ 18 were included. By combining patients with similar prognosis, we figured out 3 cutoff values of age, 35 years old, 65 years old and 75 years old. We divided patients into 4 groups: young age patients: 18-34 years; middle-age patients: 35-64 years; elderly patients: 65-74 years; extremely elderly patients: >74 years. GC patients from Sun Yat-sen University Cancer Center (SYSUCC) were used as external validation data.

**Results:** The clinicopathological features of young age gastric cancer patients included: poor-differentiated, diffuse type of cancer, and advanced stage at diagnosis. The median survival of patients <35 years old was significantly lower than middle-age patients (35-64 years) and elderly patients (65-74 years) (12 months vs. 15 and 16 months, respectively, both  $p < 0.001$ ). Location of tumor, ethnicity, tumor size, surgery and TNM stage were independent prognostic factors by multivariate analysis in young patients. The poor prognosis for young patients remained valid in the SYSUCC database.

**Conclusions:** Our results demonstrated that gastric cancer patients <35 years old had an extremely poor prognosis. Early detection of gastric cancer is of paramount importance in young age people.

Key words: Age, Clinic-pathologic features, Gastric cancer, Prognosis, Young, Clinic-pathologic features

## Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related

death in the world (1). Although GC mostly occurs in the 50-70 age groups and the overall incidence of GC has declined in last decade, the incidence rate in younger patients has increased (2, 3). Compared to the older age group, the clinicopathological features and prognosis of young GC patients remain controversial. Some studies have revealed that the prognosis of GC is worse in younger patients due to delayed diagnosis or more advanced stage (4-6). However, other studies state that the prognosis in the young patients is comparable to the older patients (7-9), or even better (10, 11). The controversy findings may result from many reasons, including sample size, ethnicity, and different definitions of young age group. Most literatures defined young age as below 40 or 45 years (5-7, 9, 12-19), while others used 30, 50, 60 or even 70 (4, 8, 10, 11, 20-23). The difference of cut-off value for ages may lead to different outcomes of analysis. Besides, in clinical practice, we found that the proportion of extremely young patients (20-30 years old) was increasing, and prognosis of this age group was poor. To investigate the association between age and prognosis, we reviewed the epidemiologic and clinicopathological characteristics of GC patients based on Surveillance, Epidemiology, and End Results (SEER) population-based data.

## Methods

### Database

The SEER database is the largest publicly available cancer dataset. It is a population-based cancer registry across several disparate geographic regions. The SEER research data include cancer incidence and prevalence as well as demographic information tabulated by age, sex, race / ethnicity, year of diagnosis and Tumor-Node-Metastasis (TNM) stage. The exact dataset we used for this analysis was SEER Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) Research Data (1973-2014), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, based on the November 2016 submission.

Another cohort from the Sun Yat-sen University Cancer Center (SYSUCC) was used as external validation data. It included all the gastric adenocarcinoma cancer patients who received therapy and had full record of follow-up in SYSUCC during 2000 and 2013 (Supplementary table 1). The study protocol for the Chinese cohort was approved by the independent Ethics Committees at SYSUCC.

### Outcome variables

Variable definitions information on age at diagnosis, sex, year of diagnosis, race/ethnicity, primary site, tumor grade and differentiation, histology, lymph node involvement, AJCC 7<sup>th</sup> TNM

stage, insurance status and overall survival were coded and available in SEER database.

The primary site was defined by the following International Classification of Diseases for Oncology (ICD-O-2) codes: C16.0-C16.9. Cardia, (C16.0), fundus (C16.1), body (C16.2), antrum (C16.3), pylorus (C16.4), lesser curvature (C16.5), greater curvature (C16.6), overlapping lesion (C16.7) and stomach, NOS (C16.9).

Grade and differentiated was defined by the following ICD-O-2 codes; well differentiated (Code 1), moderate differentiated (Code 2), poorly differentiated (Code 3) and undifferentiated (Code 4).

Histological types were defined by the following ICD-O-3 codes: 8140 to 8147, 8210 to 8211, 8220 to 8221, and 8260 to 8263 for adenocarcinoma, 8480 and 8481 for mucinous adenocarcinoma, and 8490 for Signet ring cell carcinoma.

For the Race/Ethnicity, we reclassified the patients into 5 groups: "Caucasian", "African American", "Asian", "Others" and "Unknown".

### Patient Population

The study population was based on the SEER cancer registry. We restricted eligibility to patients with gastric adenocarcinoma (including mucinous adenocarcinoma and signet ring cell carcinoma) from 1973 to 2014 with an age  $\geq 18$ . We excluded cases without follow-up records (survival time code of 0 months).

### Statistical Methods

The patients' demographic and tumor characteristics were summarized with descriptive statistics. Comparisons of categorical variables were performed using the Chi square test, and continuous variables were compared using Student's t test. The primary endpoint of this study was 5-year cause specific survival (CSS), which was calculated from the date of diagnosis to the date of cancer specific death. Deaths attributed to gastric cancer were treated as events and deaths from other causes were treated as censored observations. Survival function estimation and comparison among different variables were performed using Kaplan-Meier estimates and the log-rank test. The independence of the prognostic factors was adjusted for other known factors including age at diagnosis and tumor stage. All of statistical analyses were performed using the Intercooled Stata 13.0 (Stata Corporation, College Station, TX). Statistical significance was set at two-sided  $P < 0.05$ .

### Informed consent and Protection of Human Subjects

This study with SEER data was deemed exempt from institutional review board approval by Sun

Yat-sen University Cancer Center and informed consent was waived. The study protocol for the Chinese cohort was approved by the independent Ethics Committees at SYSUCC.

## Results

### Cut-off points of age groups

We identified 79,505 GC patients diagnosed between 1973 and 2014 with an age $\geq$ 18. The median age of the whole population was 68 years old (mean $\pm$ SD: 66.43 $\pm$ 13.74). We divided the patients into 11 age groups (every 5 years of age). Since the number of patients younger than 30 was small, we combined these patients into one group. If the median overall survival between two adjacent groups were significantly different, the youngest age of the latter group was set as the cut-off value (Table 1). Based on the cut-off points, all the patients were divided into 4 groups as follows: young age patients: 18-34 years; middle-age patients: 35-64 years; elderly patients: 65-74 years; extremely elderly patients: >74 years. Young age patients accounted for 1.72% (1369/79505) of all GC patients.

**Table 1.** Survival analysis among different age groups

Age group	Age	Number (%)	Median CSS (Months)	5-year CSS rate (%)	95% CI (%)	P value
Group 1	<30	499 (0.63)	14	21.53	17.55-25.79	0.0872
	30-34	870 (1.09)	15	25.46	22.31-28.71	0.0166
Group 2	35-39	1539 (1.94)	17	30.56	28.09-33.06	0.3868
	40-44	2623 (3.30)	17	28.68	26.80-30.58	0.3833
	45-49	4097 (5.15)	18	29.87	28.37-31.39	0.6340
	50-54	6065 (7.63)	18	28.75	27.51-30.01	0.1731
Group 3	55-59	7821 (9.84)	19	29.49	28.39-30.61	0.2634
	60-64	9470 (11.91)	19	29.27	28.26-30.29	0.0086
	65-69	10887 (13.70)	19	31.75	30.80-32.72	0.2732
Group 4	70-74	11212 (14.10)	20	31.37	30.43-32.32	0.0071
	75+	24422 (30.72)	16	27.34	26.70-27.98	

CSS: Cause specific survival, CI: Confidential Interval.

### Epidemiologic and clinicopathological characteristics

General epidemiologic and clinicopathological characteristics among different age groups were summarized in Table 2. The proportion of young age patients had increased faster than the other 3 groups during the last decade. The proportion of female was significantly higher in young age group, compared to the middle-age and the elderly (46.8%, 31.6% and 32.4%, respectively.  $P<0.001$ ). The ethnic composition

and location of lesions were different between young age group and the other 3 groups (All  $P<0.001$ ). The diffuse type GC was much more common in the young age group (47.6%) than in the other 3 age groups (26.8%, 17.6%, 12.8%, respectively, all  $P<0.001$ ). Besides, poorly differentiated tumors were remarkably more common in the young age group (66.9%), and signet-ring cell carcinoma was more frequently seen in the young age patients (40.8%). Moreover, less patients in the young age group received surgery (45.4%) than the middle-age and the elderly groups ( $P<0.001$ ), which was similar with the extremely elderly group. More young patients were diagnosed with distant metastasis (28.1%) than the other 3 groups.

**Table 2.** Comparison of clinic-pathologic features among different age groups

	<35 (%) (N=1369)	35-64 (%) (N=31615)	65-74 (%) (N=22099)	>74 (%) (N=24422)	P value
Sex					
Male	728 (53.18)	21618 (68.38)	14935 (67.58)	13169 (53.92)	
Female	641 (46.82)	9997 (31.62)	7164 (32.42)	11253 (46.08)	<0.001
Year					
1973-1983	115 (8.40)	4295 (13.59)	3292 (14.90)	3328 (13.63)	
1984-1993	175 (12.78)	4305 (13.62)	3826 (13.71)	3752 (15.36)	
1994-2003	399 (29.15)	8145 (25.76)	6118 (27.68)	7208 (29.51)	
2004-2014	680 (49.67)	14870 (47.03)	8863 (40.11)	10134 (41.50)	<0.001
Lauren					
Diffuse	652 (47.63)	8473 (26.80)	3883 (17.57)	3138 (12.85)	
Intestinal	668 (48.79)	21927 (69.36)	17330 (78.42)	20469 (83.81)	
Unknown	49 (3.58)	1215 (3.84)	886 (4.01)	815 (3.34)	<0.001
Grade					
Well	31 (2.26)	1162 (3.68)	1117 (5.05)	1376 (5.63)	
Moderate	123 (8.98)	6233 (19.72)	5363 (24.27)	6724 (27.53)	
Poorly	916 (66.91)	17728 (56.07)	11414 (51.65)	11202 (45.87)	
Undifferentiated	44 (3.21)	779 (2.46)	493 (2.23)	426 (1.74)	
Unknown	255 (18.63)	5713 (18.07)	3712 (16.80)	4694 (19.22)	<0.001
Ethnicity					
Caucasian	888 (64.86)	22027 (69.67)	15654 (70.84)	17795 (72.86)	
African-American	180 (13.15)	4306 (13.62)	2592 (11.73)	2404 (9.84)	
Asian	225 (16.44)	4399 (13.91)	3353 (15.17)	3849 (15.76)	
Others	76 (5.55)	883 (2.79)	500 (2.26)	374 (1.53)	<0.001
Primary site					
Cardia	295 (21.55)	10469 (33.11)	6611 (29.92)	5228 (21.41)	
Fundus	43 (3.14)	1065 (3.37)	795 (3.60)	949 (3.89)	
Body	133 (9.72)	2165 (6.85)	1598 (7.23)	2019 (8.27)	
Antrum	229 (16.73)	5556 (17.57)	4471 (20.23)	6026 (24.67)	
Pylorus	46 (3.36)	987 (3.12)	764 (3.46)	982 (4.02)	
Lesser curvature	121 (8.84)	2894 (9.15)	2225 (10.07)	2537 (10.39)	
Greater curvature	61 (4.46)	1234 (3.90)	906 (4.10)	1014 (4.15)	
Overlapping	153 (11.18)	2629 (8.32)	1728 (7.82)	1923 (7.87)	
NOS	288 (21.04)	4616 (14.60)	3001 (13.58)	3744 (15.33)	<0.001
Surgery					
Yes	720 (52.60)	19799 (62.63)	14516 (65.69)	13149 (53.84)	
No	621 (45.36)	11245 (35.57)	7112 (32.18)	10642 (43.58)	
Unknown	28 (2.05)	571 (1.81)	471 (2.13)	631 (2.58)	<0.001
Histology					
Adenocarcinoma	786 (57.41)	23721 (75.03)	18372 (83.13)	21403 (87.64)	
Signet Ring cell	558 (40.76)	7169 (22.68)	3208 (14.52)	2548 (10.43)	

Mucinous adenocarcinoma	25 (1.83)	725 (2.29)	519 (2.35)	471 (1.93)	<0.001
Tumor size (mm)					
Median	50	45	40	40	
Mean±SD	158.0±300.3	91.6±197.1	71.9±156.7	65.2±138.8	<0.001
AJCC 7 <sup>th</sup> T stage					
T1	119 (8.69)	3011 (9.52)	2194 (9.93)	2951 (12.08)	
T2	42 (3.07)	1225 (3.87)	863 (3.91)	967 (3.96)	
T3	129 (9.42)	3545 (11.21)	2160 (9.77)	2020 (8.27)	
T4	222 (16.22)	4404 (13.93)	2233 (10.10)	1987 (8.14)	
Tx	857 (62.60)	19430 (61.46)	14649 (66.29)	16497 (67.55)	<0.001
AJCC 7 <sup>th</sup> N stage					
N0	216 (15.78)	5273 (16.68)	3629 (16.42)	4851 (19.86)	
N1	243 (17.75)	5511 (17.43)	3114 (14.09)	2773 (11.35)	
N2	64 (4.67)	1659 (5.25)	845 (3.82)	708 (2.90)	
N3	30 (2.19)	666 (2.11)	363 (1.64)	254 (1.04)	
Nx	816 (59.61)	18506 (58.54)	14148 (64.02)	15836 (64.84)	<0.001
AJCC 7 <sup>th</sup> M stage					
M0	276 (20.16)	9010 (28.50)	6184 (27.98)	7512 (30.76)	
M1	385 (28.12)	5452 (17.24)	2403 (10.87)	1955 (8.01)	
MX	708 (51.72)	17153 (54.26)	13512 (61.14)	14955 (61.24)	<0.001
AJCC 7 <sup>th</sup> TNM stage					
IA	36 (2.63)	1290 (4.08)	1132 (5.12)	1364 (5.59)	
IB	15 (1.10)	755 (2.39)	612 (2.77)	730 (2.99)	
IIA	21 (1.53)	844 (2.67)	660 (2.99)	761 (3.12)	
IIB	38 (2.78)	1531 (4.84)	999 (4.52)	987 (4.04)	
IIIA	51 (3.73)	1490 (4.71)	934 (4.23)	744 (3.05)	
IIIB	40 (2.92)	1207 (3.82)	629 (2.85)	543 (2.22)	
IIIC	28 (2.05)	710 (2.25)	434 (1.96)	320 (1.31)	
IV	385 (28.12)	5452 (17.24)	2403 (10.87)	1955 (8.01)	
Unknown	755 (55.15)	18336 (58.00)	14296 (64.69)	17018 (69.69)	<0.001

NOS: Not otherwise specified; SD: Standard Deviation; AJCC: The American Joint Committee on Cancer; TNM: Tumor Node Metastasis

### Survival analysis

The median CSS of the young age group was 12 months, which was significantly lower than the middle-age and the elderly groups (15 and 16 months, respectively, both  $P < 0.001$ ). The median overall survival between young age group and extremely elderly group was comparable (12 months vs. 13 months,  $P = 0.153$ ) (Fig 1). To explore the prognostic factor for young age GC patients, we carried out the univariate and multivariate analysis in young GC group (Table 3). There were 952 deaths (69.54%) in this group with a 5-year CSS of 14.61% (95%CI: 12.80%-16.54%).

Variables showing a trend for association with survival ( $P < 0.05$ ) were selected in the cox proportional hazards model. Tumor location, ethnicity, tumor size ( $\geq 5$ cm), surgery and TNM stage were identified as independent prognostic factors in young GC patients by both univariate and multivariate analysis.

### Validation using GC patients from SYSUCC

We found that patients younger than 35 years old still had the worst prognosis among the four age groups (Figure 2). The median survival for these 4 groups patients were as follow: 25 months for patients

younger than 35 years old, 57 months for patients who were 35-64 years, 43 months for patients who were 65-74 years and 38 months for patients  $>74$  years old,  $P = 0.0003$ .

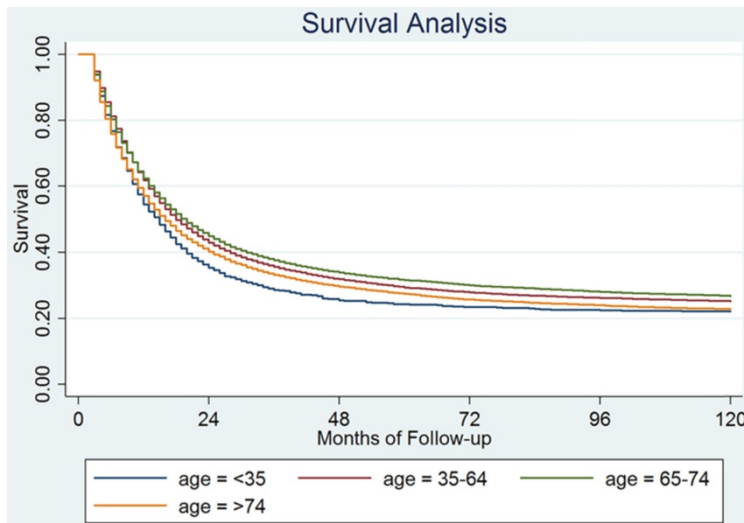
**Table 3.** Survival analysis for young patients with gastric cancer

	Univariate analysis			Multivariate analysis		
	Median CSS (months)	5-year CSS	P value	Hazard ratio	95% confidence interval	P value
Sex						
Male	14	22.09%		--		
Female	16	26.45%	0.0667	--		
Location						
Cardia	13	16.26%		Reference		
Fundus	10	14.64%		0.989	0.887-1.103	0.845
Body	16	28.66%		0.986	0.912-1.067	0.735
Antrum	22	35.72%		0.974	0.918-1.032	0.373
Pylorus	22	32.83%		1.042	0.930-1.167	0.478
Lesser curvature	26	33.57%		0.870	0.806-0.939	<0.001
Greater curvature	17	31.61%		1.060	0.958-1.173	0.261
Overlapping	10	10.38%		1.094	1.013-1.180	0.021
NOS	12	21.68%	<0.001	1.056	0.977-1.142	0.171
Race/Ethnicity						
Caucasian	14	22.57%		Reference		
African-American	11	20.29%		0.987	0.928-1.050	0.684
Asian	22	30.15%		0.805	0.760-0.853	<0.001
Others	13	32.33%	0.0005	0.931	0.807-1.074	0.327
Tumor size						
<5cm	40	38.47%		Reference		
$\geq 5$ cm	15	18.27%	<0.001	1.124	1.078-1.172	<0.001
Lauren						
Diffuse	15	23.94%		--		
Intestinal	14	23.99%	0.5443	--		
Histology subgroup						
Adenocarcinoma	15	24.21%		--		
Signet Ring cell	15	23.48%		--		
Mucinous adenocarcinoma	13	34.89%	0.9155	--		
Grade						
Well differentiated	21	31.52%		--		
Moderately differentiated	17	26.35%		--		
Poorly differentiated	15	23.88%		--		
Undifferentiated	11	16.35%	0.0951	--		
Surgery						
Yes	25	34.50%		Reference		
No	9	11.51%	<0.001	2.082	1.970-2.200	<0.001
AJCC 7 <sup>th</sup> TNM stage						
IA	NR	93.15%		Reference		
IB	NR	60%		2.007	1.744-2.311	<0.001
IIA	80	54.62%		2.733	2.402-3.109	<0.001
IIB	60	50.51%		4.325	3.845-4.864	<0.001
IIIA	27	21.50%		5.837	5.191-6.564	<0.001
IIIB	27	40.19%		7.311	6.481-8.247	<0.001
IIIC	19	31.28%		10.190	8.971-11.574	<0.001
IV	9	4.97%		10.640	9.473-11.951	<0.001

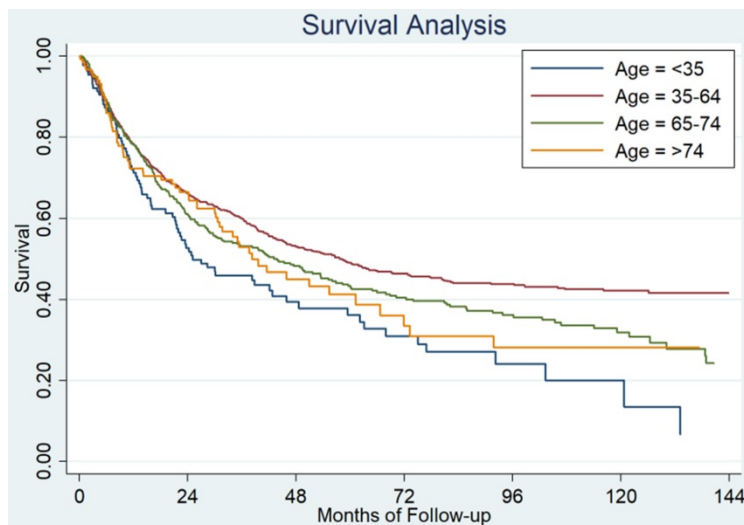
NOS: Not otherwise specified; CSS: Cause Specific Survival; AJCC: The American Joint Committee on Cancer; TNM: Tumor Node Metastasis

### Discussion

The prognosis of GC in different age groups is still controversial. This may result from different definitions of young age. Most literatures defined



**Figure 1.** Cause specific survival among patients with different age groups from SEER data.



**Figure 2.** Cause specific survival among patients with different age groups from Sun Yat-sen University Cancer Center.

young age as below 40 or 45 years(5-7, 9, 12-19), while others used 30, 50, 60 or even 70 (4, 8, 10, 11, 20-23). Some studies simply used median age as the cutoff value to analyze the prognosis of age in GC patients (24-27). Most of the studies come to the conclusion that young patients had a better prognosis than elderly patients with the possible explanation that young patients had better performance status and better tolerance to therapy, while elderly patients might have more complication and could not stand effective therapy (10). In our clinical practice, we realized that young patients should be treated as two distinct types, pretty young patients who actually had worse prognosis than older patients and middle-age patients who had better prognosis. How can we figure out the young patients who have poor prognosis? In our study, we compared the survival of different groups GC patients according to their ages with an

interval of 5 years. By combining patients with similar prognosis, we figured out 3 cutoff values, 35 years old, 65 years old and 75 years old. By this, we divided patients into 4 groups: young age patients: 18-34 years; middle-age patients: 35-64 years; elderly patients: 65-74 years; extremely elderly patients: >74 years. Young patients had the worst prognosis, while the elderly group had the best prognosis. The median survivals for these two groups were 12months and 16months, respectively,  $P < 0.001$ . The poor prognosis for young patients remained valid in the SYSUCC database.

During the last few decades, the incidence of GC has declined in most countries. However, there is a rising trend in the incidence of GC in young age patients (2). Our study also showed that the proportion of young GC patients had increased in the last 4 decades. It has been suggested that GC in young patients has different clinical features and tumor behavior from older gastric cancer. Most common reported features by literatures included female dominance, location in upper third area, undifferentiated and diffuse histologic types, advanced stage at diagnosis (5-7, 9, 10, 15, 23, 28, 29). In our study, the percentage of female patients in the young patient subgroup was higher than that in other age groups. The male-to-female ratio in the young age group was 1.14, in contrast to 2.16 in middle age group and 2.08 in elderly group. The reason for higher proportion of female in the young age group remains controversial. Sex hormone especially estrogen has been suggested to play a role in pathogenesis of GC (14, 30-33). Some studies reported the protective effect of estrogen in GC (30, 32, 33), while others claimed the opposite (14, 31). Chung et.al suggested that the excessive exposure of estrogen without the counter effect of progesterone may increase the risk of GC (14). Further studies are needed to clarify the underlying mechanism of female dominance in young age GC patients.

Regarding histologic classifications, previous studies have showed poor-differentiated or undifferentiated and diffuse-type gastric cancer predominated in young age patients (7, 9, 14, 15, 23, 34). Our study also showed a higher proportion of diffuse type and poor differentiated gastric cancer in the young age group. Previous studies indicated that intestinal-type and well differentiated GC originates from intestinal metaplasia or atrophic gastritis, which is associated with infection by *Helicobacter pylori*. This

progression from infection of *H.pylori* to pre-malignant stage and finally malignant tumor may take many years (35-37). However, the diffuse-type adenocarcinoma or poor-differentiated gastric cancer may develop without passing all these stages. Young age patients have fewer years to pass through these stages, which may partially explain why diffuse-type and poor-differentiated is more common in the young age group. Moreover, it has been reported that diffuse type GC is associated with E-cadherin deregulation upon genetic alterations (38), and E-cadherin gene (CDH1) mutations are more common in young age GC (39). According to the definition of hereditary diffuse gastric cancer, diffuse gastric cancer patients who are younger than 40 years old have met the criteria (40). Hence the genetic factors may play an important role in the development of GC in young age patients.

To explore the factors that contribute to the worse survival in pretty young GC patients, we carried out the univariate and multivariate analysis. We found that location of tumor, ethnicity, tumor size, surgery and TNM stage were independent risk factors in young age patients. Previous studies have suggested various clinicopathological factors, including tumor location, tumor size, depth of invasion, lymphovascular invasion, peritoneal metastasis, distant metastasis, curative resection, CEA and CA125 level, and TNM stage (5-7, 10, 14, 17-19, 23, 34, 41). Curative resection was the most common risk factor seen in these studies. Several studies found that the prognosis of young age patients after curative surgery was comparable or better than the old age patients (5, 23, 41, 42), and prognosis of advanced stages was worst in young age patients than the old age patients (29, 43). However, few young age patients present with alarm symptoms and they do not receive regular screen by gastroscopy. More patients in young age group were diagnosed at stage IV and lost the chance for curative resection. Considering genetic factors may play a role in development of early gastric cancer, it is reasonable to offer earlier screening to young people with family history. Further studies are warranted to figure out the high risk factor for gastric cancer and based on these to design the screen strategy in high risk young people. It is also important to find out more effective screen methods, such as liquid biopsy or superfine gastroscopy.

There were some limitations to this study. Firstly, it was a retrospective study. Secondly, as this study overlapped long time frame and AJCC staging system for gastric cancer changed, the current study couldn't reflect the stages and clinical practice of gastric cancer in previous years. Thirdly, the SEER

database does not include data on signs and symptoms, family history, level of tumor markers, chemotherapy, and other factors that might affect prognosis. Further studies are needed to elucidate the mechanism for poor prognosis of young age patients.

## Conclusion

This study demonstrated that gastric cancer patients <35 years old had a poor prognosis. Location of tumor, ethnicity, tumor size, surgery and TNM stage were independent risk factors on prognosis for young patients. Early detection of gastric cancer is very important in all patients but in young patients it is of paramount importance.

## Supplementary Material

Supplementary table.

<http://www.jcancer.org/v10p0472s1.pdf>

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## Competing Interests

The authors have declared that no competing interest exists.

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