Japanese Journal of
Oncology and Clinical Research

JScholar
Fostering Scholarly Communication

Research Article Open Access

Clinicopathological Characteristics and Prognosis of Cardia Adenocarcinoma: A SEER-Based Study

Jie Jie Jin[1,2], Ziwen Long[1,2*] and Yanong Wang[1,2*]

[1]Department of Gastric surgery, Fudan university Shanghai Cancer Center, Shanghai, China

[2]Department of Oncology, Shanghai Medical College, Fudan university, Shanghai, China

***Corresponding authors:** Yanong Wang, Department of Gastric surgery, Fudan university Shanghai Cancer Center, Shanghai China; Department of Oncology, Shanghai Medical College, Fudan university, Shanghai, China. Tel: 021-65642662, E-mail wangyn11111@hotmail.com

Ziwen Long, Department of Gastric surgery, Fudan university Shanghai Cancer Center, Shanghai China; Department of Oncology, Shanghai Medical College, Fudan university,Shanghai, China, Tel: 021-65642662, E-mail： ziwenlog@163.com

Received Date: September 06, 2021 **Accepted Date:** October 06, 2021 **Published Date:** October 08, 2021

Citation: Jie Jie Jin (2021) Clinicopathological Characteristics and Prognosis of Cardia Adenocarcinoma: ASEER-Based Study. JJ Oncol Clin Res 1: 1-12.

Abstract

Background: Whether patients suffering from cardia gastric cancer (CGC) have a worse prognosis than those with non-cardia gastric cancer (NCGC).

To compare the cancer-specific survival (CSS) of CGC with that of NCGC in USA patients who had undergone gastrectomy and regional lymph node dissection.

Materials & Methods: The data from the Surveillance, Epidemiology, and End Results Program (SEER) database regarding patients with GC diagnosed with GC, who underwent gastrectomy and regional lymph node dissection, and with complete data were obtained. CSS and overall survival (OS) were compared between CGC and NCGC after propensity score matching (PSM) based on the Kaplan-Meier estimator of inverse probability of treatment weight (IPTW).

Results: There were 2366 patients with CGC and 4912 with NCGC. Median CSS of CGC patients was 23 months shorter than that of NCGC patients (34 vs. 57 months, P<0.001). The 5-year CSS rate was 39% and 48% for CGC and NCGC patients, respectively (P<0.001). The results remained consistent after PSM and IPTW. Stratified analyses were performed by the TNM stage. There were significant differences between CGC and NCGC for patients diagnosed at stages I and II. The Cox multivariable regression analysis showed that CGC was an independent prognostic factor compared with NCGC, a hazard ratio of 1.33 (95% confidence interval: 1.23-1.45, P<0.001).

Conclusion: CGC patients present a significantly worse prognosis than NCGC patients. CGC is an independent prognostic factor for GC patients, especially those at stages I and II.

Keywords: Cardia; Gastric Cancer; Prognosis; Cancer-Specific Survival; SEER Program

Introduction

Gastric cancer (GC) is the fifth most common cancer, and the third leading cause of cancer death worldwide [1]. The GC incidence rates are high in Eastern/Southeastern and Central Asia, Eastern Europe, and parts of Central and Southern America, while thefigures are relatively low in North America and Western Europe [2]. Since World WarII, the incidence of GC has been declining globally, and now it is one of the least common cancers in North America, but it nevertheless remains a heavy burden of publichealth worldwide because the incidence of GC remains high in East Asia [1]. In 2020,an estimated 27,600 people will be diagnosed, and 11,010 people will eventually die ofGC in the United States [3]. The prognosis of patients with GC is dismal since the 5- year relative survival rate was 30.1% for GC patients in the United States from 2005 to2009 [4].

Most GCs include tumors of the noncardia and the subcardia (Siewert type III), with their center starting 2-5 cm below the esophagogastric junction, while cardia GC (CGC) is more proximal to the junction and is managed like esophageal and esophagogastric tumors [5-7]. In developed countries, the CGC incidence follows the distribution of esophageal cancer [8-10], while non-cardia GC shows marked geographic variation with countries in Eastern Asia and South America [11]. In 2012, non-cardia GC occurred more frequently than CGC, with an average ratio of 2:1, while in certain populations where non-cardia GC incidence rates are lower than the global average, CGC rates are similar to or higher than non-cardia GC rates [12].

Though both CGC and non-cardia GC are reported to be influenced by cigarette smoking [13-15] and high salt intake [16,17], and possibly by low intake of fruits and vegetables [18-20], the other risk factors differ between the two GC types. Indeed, therisk factors for CGC are similar to those for oesophageal adenocarcinoma, including obesity [21,22] and gastroesophageal reflux disease [23,24]. On the other hand, non- cardia GC is strongly associated with *Helicobacter pylori* infection [25,26]. Some evidence suggests that *H. pylori* infection might even be inversely associated with both esophageal adenocarcinoma and CGC [27,28], while studies in some populations have suggested a positive association between the *H. pylori* and CGC [29,30].

It is reported that CGC has more aggressive biological behavior than non-cardia GC. Data from Japanese [28] and Korean [30] studies have noted that patients with CGC are more likely to have advanced T and N stages at diagnosis. Data from a Chinese population revealed that compared with patients with non-cardia GC, patients with CGC tend to be diagnosed at a more advanced stage and have a worse prognosis after R0 resection [31]. On the other hand, data based on a USA population [32] suggested that the disease-free survival (DFS) and overall survival (OS) were similar between patients with CGC and those with non-cardia GC. Nevertheless, both studies are limited by small sample size, and whether non-cardia GC and CGC have different prognosis remains uncertain.

A large-scale study on the prognosis of GC patients and non-cardia GC is needed. Theaim of this study is to compare the cancer-specific survival (CSS) of CGC with that ofnon-cardia GC in USA patients who had undergone gastrectomy and regional lymph node dissection.

Patients and Methods

Database

The patient population was based on the Surveillance, Epidemiology, and End Results (SEER) cancer registry (www.seer.cancer.gov). Sponsored by National Cancer Institute, the SEER program collects and publishes incidence, mortality, prevalence, survival, and lifetime risk statistics, which can be used to assess the impact of cancer in the general population. The current SEER database consists of 18 population-based registries, which cover approximately 26% of the United States population. It is the largest publicly available cancer database, including information on prevalence, incidence, age, sex, race and ethnicity, year of diagnosis, marital status, insurance, TNMstage, geographic region, and mortality.

Patient selection

The SEER-stat software (SEER*Stat 8.1.6) was used for data extraction and patient selection.

The inclusion criteria were 1) patients with a diagnosis of invasive adenocarcinoma ofthe stomach (International Classification of Disease [ICD]-O-3 code in the range of 8000-8152, 8154-8231, 8243-8245, 8250-8576, 8940-8950, and 8980-8990), 2) diagnosed from 2004 to 2010, 3) underwent gastrectomy, and 4) have recorded numbersof lymph nodes. The exclusion criteria were 1) multiple cancers, 2) unknown TNM stage, 3) M1 disease, 4) local tumor destruction, 5) local tumor excision; 6) unknown whether cancer-directed surgery was performed 7) no cancer-directed surgery of the primary tumor; or 8) primary site recorded as “stomach, NOS” and “overlapping lesionof the stomach”. Cause

of death (COD) and follow-up were restricted to "Alive or dead due to cancer" and "Active follow-up".

Variables

According to the SEER database, tumor location is described as cardia, fundus, body, greater curvature, lesser curvature, gastric antrum, pylorus, "stomach, NOS", and overlapping lesion of the stomach. We divided the patients into two groups by tumor location: CGC and non-cardia GC (NCGC). The NCGC subgroup includes fundus, body, greater curvature, lesser curvature, gastric antrum, and pylorus. The race was classified as white, African-American, and others (including American Indian/AK Native, Asian/Pacific Islander), as determined by SEER. Marital status was identified as married, single, widowed, separated, divorced, and unknown. Single, widowed, separated, and divorced was collected as unmarried, so marital status was classified intothree subgroups (married, unmarried, and unknown) in this study. According to the SEER database, cause-specific survival is a net survival measure representing survivalto a specified cause of death in the absence of other causes of death. Estimates are calculated by specifying the cause of death. Individuals who died of causes other than the specified cause were censored. In this study, GC is the specified cause of death. Theseventh American Joint Classification of Cancer (AJCC) TNM staging system was adopted [33].

Outcomes

The outcomes were OS (time from diagnosis to death from any cause) and CSS (time from diagnosis to GC-related death). Patients alive at last contact were censored at thelast contact. For CSS, patients who died from non-GC causes were censored on the dateof death.

Statistical analysis

Categorical variables are presented as n (%) and were analyzed using the chi-square test or Fisher's exact test. Continuous data are presented as means ± standard deviationsand were analyzed using Wilcoxon's rank-sum test. Multivariable Cox regression analysis was used to determine the factors independently associated with CSS after adjustment for demographic and therapeutic factors. All P-values were two-sided, and P-values <0.05 were considered statistically significant. All confidence intervals (CIs)were stated at the 95% confidence level. All analyses were conducted using SPSS 22.0(IBM, Armonk, NY, USA).

For the survival analysis, two models of the association between CSS and tumor location were constructed using a propensity score-matched (PSM) univariable Cox proportional hazards model and an unmatched univariable analysis based on the Kaplan-Meier estimator of inverse probability of treatment weight (IPTW). To construct the PSM model of OS, NCGC patients were matched 1:2 to CGC patients onpropensity score by using a greedy, nearest neighbor matching algorithm, with maximum allowed differences of ±0.1% for propensity scores. Kaplan-Meier estimators were calculated for each group and were compared using the log-rank test. For the final model of OS, IPTW Kaplan-Meier estimators were calculated across all patients and compared between the two groups using the log-rank test. All calculationswere performed with R software, version 3.6.3 (The R Project for Statistical Computing,www.r-project.org).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In the SEER database, all data are anonymized.

Results

Clinicopathological characteristics of the patients

From the SEER, 17,623 GC cases were extracted, but those patients included patients with stage I to IV cancer, and detailed medical records are not available for some patients. Therefore, to obtain more convincing results and reduce bias, only patients who had undergone surgery, with the type of surgery and number of examined lymph nodes being reported, were included. Finally, 7278 GC patients who had undergone gastrectomy and regional lymph nodes dissection were eligible for this study from January 2004 to December 2010 (Figure 1).

Among total of 7278 patients, there were 2366 (32.5%) and 4912 (67.5%) patients withCGC and NCGC, respectively. Their characteristics are listed in Table 1. Matching bypropensity score achieved an adequate balance between the two groups for age, marital status, race, differentiated grade, and tumor stage (Appendix Table A1, online only).Patients diagnosed with cardia adenocarcinoma were younger (63.0 vs. 66.3 years,P<0.001), more frequently white compared to African-Americans/others, and had ahigher percentage of males (79.2% vs. 54.9%, P<0.001). The CGC group

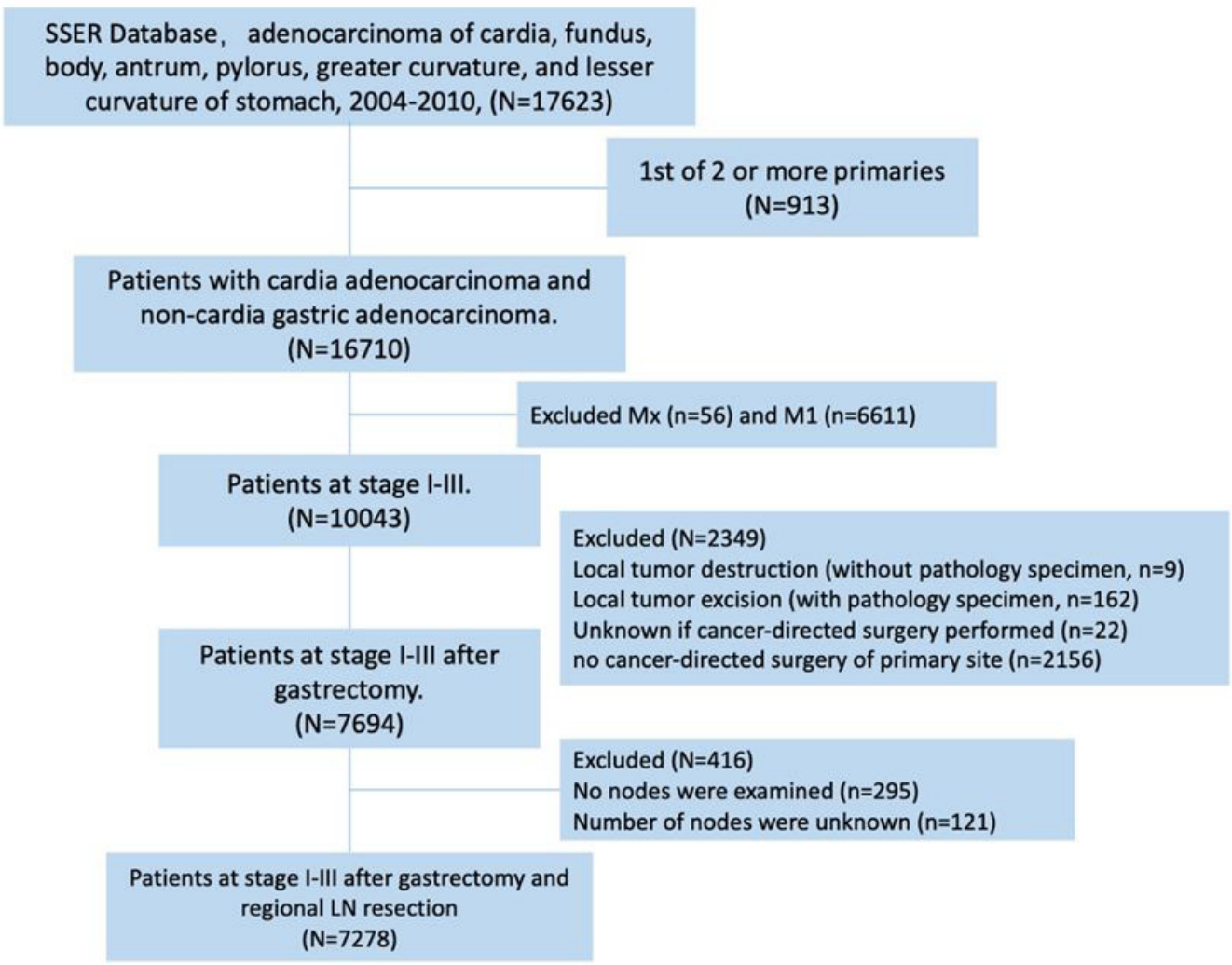


Figure 1. Inclusion and exclusion diagram

also hadlarger proportion of well/moderate differentiated tumors (36.8% vs. 27.3%, P<0.001),higher lymph node metastasis rates (66.3% vs. 59.5%, P<0.001), relatively higherpercentage of advanced T stage (T3/T4a/T4b, 68.6% vs. 64.4%, P<0.001), and more advanced TNM stage (stage II/III, 75.2% vs. 70.7%, P<0.001) than the NCGC group.

Prognostic factors for cancer-specific survival in GC patients

The median follow-up for the entire cohort was 72 months (interquartile range, 53 to94 months). CSS was compared among the different subgroups (Table 2). Patients ≤60

years displayed better survival than those of 61-74 and the ≥75 years group (5-year CSS:

51% vs. 47% vs. 34%, P<0.001). Patients in marriage had longer survival than those who were unmarried (including single, widowed, separated, and divorced) (5-year CSS: 48% vs. 40%, P<0.001). White patients and African-American patients displayed worsesurvival than patients of other races (5-year CSS: 42% vs. 44% vs. 56%, P<0.001). Patients diagnosed in 2009-2010 had a better survival than those diagnosed in 2007- 2008 and 2004-2006 (5-year CSS: 53% vs. 45% vs. 41%, P<0.001). Patients with CGCshowed significantly worse survival than NCGC patients (5-year CSS: 39% vs. 48%, P<0.001). Patients who had undergone partial/subtotal/hemi- gastrectomy showedbetter survival than those who had undergone gastrectomy with the removal of a portionof the esophagus and those who had undergone gastrectomy with en bloc resection of other organs (5-year CSS: 50% vs. 40% vs. 40%, P<0.001). From the multivariable Coxregression analysis, age, marital status, race, year of diagnosis, tumor location (cardia and non-cardia), differentiated grade, and tumor stage were independent prognostic factors for GC.

CGC patients had a worse prognosis than NCGC patients

Among the 7278 cases, the median CSS of CGC patients was 23 months shorter than in NCGC patients (34 vs. 57 months, P<0.001). The 5-year CSS rate was 39% for CGC and

Characteristics	NCGC (n= 4912)	CGC (n= 2366)	P
Sex			<0.001
Female	2217 (45.1%)	492 (20.8%)	
Male	2695 (54.9%)	1874 (79.2%)	
Age (y)			<0.001
≤60	1589 (32.3%)	970 (41.0%)	
61-74	1806 (36.8%)	972 (41.1%)	
≥75	1517 (30.9%)	424 (17.9%)	
Marital status			<0.001
Married	2972 (60.5%)	1679 (71.0%)	
Unmarried *	1809 (36.8%)	641 (27.1%)	
Unknown	131 (2.7%)	46 (1.9%)	
Race			<0.001
White	2751 (56.0%)	2086 (88.2%)	
African-American	761 (15.5%)	94 (4.0%)	
Other	1400 (28.5%)	186 (7.9%)	
Year of diagnosis			0.241
2004-2006	2066 (42.1%)	949 (40.1%)	
2007-2008	1417 (28.8%)	719 (30.4%)	
2009-2010	1429 (29.1%)	698 (29.5%)	
Grade			<0.001
Well/moderate	1343 (27.3%)	869 (36.7%)	
Poor/undifferentiated	3390 (69.0%)	1381 (58.4%)	
Unknown	179 (3.6%)	116 (4.9%)	
Surgery			<0.001
Gastrectomy (partial, subtotal, hemi-)	3093 (63.0%)	360 (15.2%)	
Near-total or total gastrectomy	737 (15.0%)	199 (8.4%)	
Gastrectomy with the removal of a portion of the esophagus	534 (10.9%)	1493 (63.1%)	
Gastrectomy with enbloc resection of other organs	538 (11.0%)	286 (12.1%)	
Gastrectomy or surgery	10 (0.2%)	28 (1.2%)	
T stage			<0.001
T1	1125 (22.9%)	481 (20.3%)	
T2	620 (12.6%)	262 (11.1%)	
T3	1706 (34.7%)	942 (39.8%)	
T4a	1087 (22.1%)	549 (23.2%)	
T4b	374 (7.6%)	132 (5.6%)	
N stage			0.001>
N0	1991 (40.5%)	797 (33.7%)	
N1	1765 (35.9%)	1139 (48.1%)	
N2	860 (17.5%)	321 (13.6%)	
N3	296 (6.0%)	109 (4.6%)	
Stage			0.001>
IA/IB	1443 (29.4%)	587 (24.8%)	
IIA/IIB	1693 (34.5%)	969 (41.0%)	
IIIA/IIIB/IIIC	1776 (36.2%)	810 (34.2%)	

Table 1: Comparison of clinicopathologic characteristics between patients with CGC and NCGC

Marital status			**<0.001**			
Married	4651	48%		Reference		
Unmarried*	2450	40%		1.158	1.082-1.238	**<0.001**
Unknown	177	49%		0.983	0.794-1.216	0.837
Race			**<0.001**			
White	4837	42%		Reference		
African-American	855	44%		1.026	0.928-1.135	0.618
Other	1586	56%		0.755	0.693-0.823	**<0.001**
Year of diagnosis			**<0.001**			
2004-2006	3015	41%		Reference		
2007-2008	2136	45%		0.922	0.856-0.992	**0.030**
2009-2010	2127	53%		0.773	0.714-0.837	**<0.001**
Tumor location			**<0.001**			
Non-cardia	4912	48%		Reference		
Cardia	2366	39%		1.303	1.216-1.397	**<0.001**
Grade			**<0.001**			
Well/moderate	2212	55%		Reference		
Poor/undifferentiated	4771	40%		1.328	1.234-1.430	**<0.001**
Unknown	295	58%		1.058	0.879-1.275	0.550
Surgery			**<0.001**			
Gastrectomy (partial, subtotal, hemi-)	3453	50%		Reference		
Near-total or total gastrectomy	936	44%		1.012	0.642-1.595	0.960
Gastrectomy with the removal of a portion of the esophagus	2027	40%		1.208	0.762-1.914	0.421
Gastrectomy WITH en bloc resection-of other	824	40%		1.183	0.752-1.863	0.467
organs						
Gastrectomy or surgery	38	49%		1.170	0.738-1.854	0.504
Lymph nodes examined#				0.987	0.984-0.990	**<0.001**
T stage			**<0.001**	**NI**		
T1	1606	79%				
T2	882	63%				
T3	2648	36%				
T4a	1636	24%				
T4b	506	20%				
N stage			**<0.001**	**NI**		
N0	2788	70%				
N1	2904	37%				
N2	1181	19%				
N3	405	9%				
Stage			**<0.001**			
IA/IB	2030	79%		Reference		
IIA/IIB	2662	44%		3.131	2.813-3.485	**<0.001**
IIIA/IIIB/IIIC	2586	20%		6.476	5.826-7.197	**<0.001**

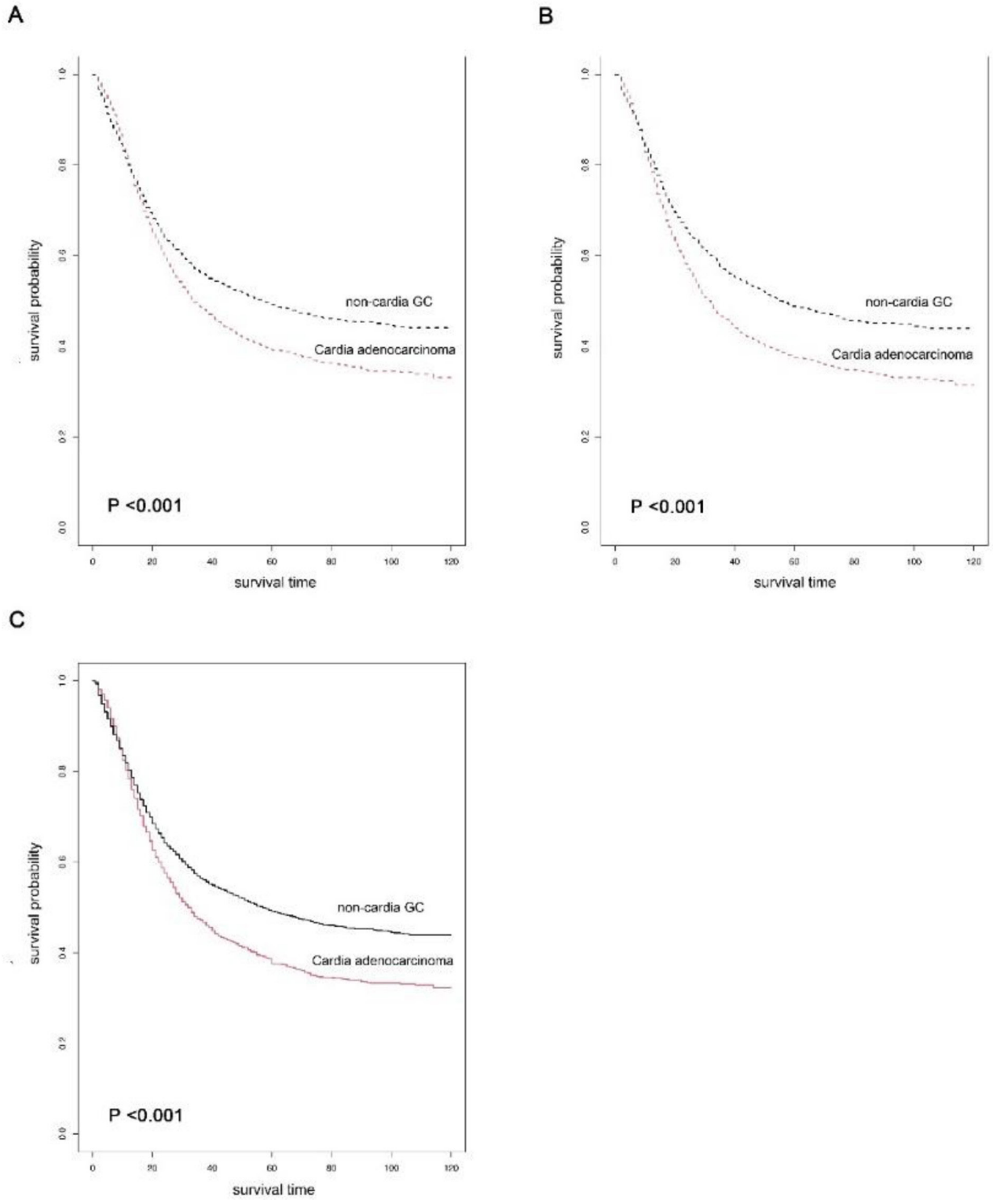
CSS: cancer-specific survival; HR: hazard ratio; NI, not included; CI: confidence interval

*Including single (never married), widowed, separated, and divorce.

#Continuous variable.Bold: P<0.05.

Table 2. Prognostic factors for cause-specific survival in GC patients

48% for NCGC (Figure 2A, P<0.001). The result remained after PSM (Figure 2B, P<0.001). In the PSM Cox proportional hazard regression analysis, cardia adenocarcinoma was associated with a significantly worse CSS (hazard ratio [HR], 1.33;95% CI: 1.228-1.447, P<0.001); the 5-year CSS was 37% in the CGC group versus 48% in the NCGC group (P<0.001). The IPTW analysis revealed similar results (Figure 2C;P<0.001). The survival rates of the cohort were stratified by TNM stage (Table 3), and the



Overall survival in (A) the unmatched, (B) the propensity score-matched, and (C) the inverse probability of treatment weight-adjusted analysis in cardia adenocarcinoma patients and non-cardia GC patients after surgery.

Figure 2: Overall survival of cardia adenocarcinoma and non-cardia GC patients

results showed that the survival disadvantage remained for CGC diagnosed at stageI/II (stage I, 68% vs. 83%, P<0.001; stage II, 37% vs. 48%, P<0.001), but for patients diagnosed at stage III, the survival rates between the two groups were similar (20% vs.20%, P=0.520). The results remained consistent after PSM (Table 3).

	Unadjusted			After PSM		
	n	5-y CSS (%)	P	n	5-y CSS (%)	P
Stage I *			<0.001			<0.001
Non-cardia	1443	83%		463	84%	
Cardia Stage II #	587	68%	<0.001	479	64%	<0.001
Non-cardia	1693	48%		739	48%	
Cardia	969	37%		705	35%	
Stage III			0.520			0.566
Non-cardia	1776	20%		610	21%	
Cardia	810	20%		628	19%	

PSM: propensity score matching; CSS, cancer-specific survival; CI, confidence interval; HR, hazard ratio.

* Adjusted for age, LN examined, surgery, marital status, year of diagnosis, grade.

Adjusted for age, LN examined, surgery, marital status, year of diagnosis, grade, and radiation.

Table 3: Prognostic value of tumor site on cause-specific survival of GC patients by TNM stage

Discussion

Whether patients suffering from CGC have a worse prognosis than those with NCGC remained controversial. Therefore, this study aimed to compare the CSS of CGC with that of NCGC in USA patients who had undergone gastrectomy and regional lymph node dissection. The results showed that CGC patients present a significantly worse prognosis than NCGC patients. CGC is an independent prognostic factor for GC patients, especially those at stages I and II.

This study included a large number of patients with GC. The results showed that CGC

patients were younger than NCGC patients at diagnosis. This finding is consistent withthe findings of studies of populations from western countries, Japan, and Korea [30,32,34,35], but not those of populations from China and another population from Korea [29,36-38]. In addition, compared with NCGC, CGC was more common in men, as supported by previous studies from Korea, Japan, and China [34,36,38], while threestudies from Korea and Japan reported no substantial differences in sex between the two groups [30,35,37]. The data displayed a higher percentage of married people in theCGC group than in the NCGC group. A previous study demonstrated that married patients with GC displayed better survival than those unmarried [39]. The prevalence of white people in the CGC cohort was significantly higher than in the NCGC cohort, keeping with the trend of a high incidence of CGC in western countries [40-44].

The pathological features of CGC patients were compared with those of NCGC patients.The results showed that CGC had a higher percentage of tumors with a well/moderately differentiated grade than NCGC. In a study with large sample size, the CGC patients had a significantly lower rate of poor-to-moderate tumor grade than the NCGC [31], supporting the present study. In this study, CGC patients had higher lymph node metastasis rates than NCGC patients. A previous study based on a US population demonstrated a similar lymph node metastasis rate between CGC and NCGC [32], while studies from Japan, Korea, and China reported higher rates of lymph node metastasis in CGC than that in NCGC [31,34,35,37].

The most significant finding from this study is that CGC is an independent prognostic factor for patients with GC. CGC patients had a worse prognosis than NCGC patients,and the results remained significant in stages I and

II, even after being adjusted for clinicopathological characteristics and therapeutic management. A previous study based on a US population demonstrated a similar prognosis between CGC and NCGC, but the authors declared that long-term outcome was worse among patients with CGC and early-stage disease [32], which is partly consistent with the present study. Moreover, a study based on a Singapore population demonstrated that the R0 resection rates were similar, but the systemic recurrence rate was higher in CGC, and survival was poorer for CGC compared with NCGC. A study from a Korean population demonstrated that, regardless of curative probability, survival was worse for proximal GC than for distal GC. A study in Chinese patients revealed that CGC patients had a worse prognosis after R0 resection [31]. A study based on a single Japanese center reported that CGC patients had a worse survival than NCGC patients after curative resection [34]. In comparison to a previous US study [32], the present study confirmed that CGC patients had a worse prognosis than NCGC patients after gastrectomy and regional lymph node dissection in a US population.

CGC has a tendency to have different risk factors than NCGC. Similar to oesophageal adenocarcinoma, CGC is associated with obesity [21,22] and gastro-oesophageal refluxdisease [23,24], while NCGC is strongly associated with *Helicobacter pylori* infection [25,26]. Moreover, the surgical approach, extent of resection, lymph node dissection, digestive tract reconstruction, and neoadjuvant therapy of CGC is still under debate [6,7]. Subtotal esophageal and proximal gastric resection with gastric pull-up or distal esophageal resection with total gastrectomy and esophagojejunostomy are competing procedures for advanced CGC, and gastrectomy maybe not adequate for tumorsinvading the lower esophagus [6,7,45,46]. Furthermore, the Japanese Gastric Cancer Association (JGCA) recommend that the dissection of the lymph nodes at stations 4, 5,and 6 is not necessary for AEG tumors [47,48] because the lymphatic metastases of CGC are found mainly in stations 1, 2, 3, and 7 [47,48]. In addition, lymph nodes at stations 19 and 20 are recommended to be dissected for T2-4 CGC. According to the NCCN guidelines [6,7], patients with CGC are recommended to be treated as described in the NCCN Guidelines for Esophageal and EGJ Cancers [7]. Neoadjuvant therapy is increasingly used in advanced GC. Since a survival difference was observed between the two groups in patients diagnosed at stages I and II, this could be explained, at leastin part, by the omission of neoadjuvant therapy in stage I-II patients.

The multivariable Cox regression model in this study showed that age, marital status, race, year of diagnosis, cardia GC, differentiated grade, tumor stage, radiation therapy, number of examined lymph nodes, and number of positive lymph nodes were independent prognostic factors for GC. We found that married patients had a better prognosis than unmarried patients, which is consistent with another SEER-based study [39]. Patients classified as other races (which included a certain number of Asian patients) had a better prognosis than the white and African-American patients, as supported by another SEER-based study [45]. Patients diagnosed in 2009 and 2010 hadbetter survival than those diagnosed in 2004-2008, which could be attributed to the improvement of medical treatments. Patients with poorly differentiated tumors had worse survival compared with those with well/moderately differentiated tumors. In this study, the number of examined lymph nodes and the number of positive lymph nodes were also prognostic factors for GC patients, which is in keeping with the AJCC stagingsystem [33].

To the best of our knowledge, this report describes the first SEER-based study focusingon the differences in clinicopathological characteristics and cancer-specific survival between CGC and NCGC. Nevertheless, there are some limitations due to the retrospective nature of this study. First, the SEER database lacks information about body mass index, smoking, drinking, and *H. pylori* infection, which are important riskfactors for CGC and NCGC. Second, the database has no record of whether the surgery is an R0 resection or not. Finally, further details regarding the use of systematic treatments and respective responses should be considered, but the SEER database lackssuch information.

In conclusion, based on 7278 GC cases who had undergone gastrectomy and regional lymph node dissection, CGC is more likely to be T3-T4 lesions and has higher lymph node metastasis rates than NCGC tumors. Following gastrectomy, the CSS of CGC patients is significantly worse than that of NCGC. CGC is an independent prognostic factor for GC patients, especially for those diagnosed at stages I-II.

References

1. Bray F, Ferlay J, Soerjomataram I (2018) Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424.

2. Hartgrink HH, Jansen EP, van Grieken NC, van de Velde CJ (2009) Gastric cancer. Lancet 374: 477-90.

3. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA Cancer J Clin 70: 7- 30.

4. Allemani C, Matsuda T, Di Carlo V (2018) Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391: 1023-75.

5. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 388: 2654-64.

6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) (2020) Gastric Cancer. Version 3.2020. Fort Washington: National Comprehensive Cancer Network.

7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) (2020) Esophageal and Esophagogastric Junction Cancers. Version 4.2020. Fort Washington: National Comprehensive Cancer Network.

8. Crew KD, Neugut AI (2004) Epidemiology of upper gastrointestinal malignancies. Semin Oncol. 31: 450-64.

9. Kubo A, Corley DA (2002) Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. Cancer 95: 2096-102.

10. Powell J, McConkey CC, Gillison EW, Spychal RT (2002) Continuing rising trend in oesophageal adenocarcinoma. Int J Cancer 102: 422-7.

11. Corley DA, Buffler PA (2001) Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. Int J Epidemiol 30: 1415-25.

12. Colquhoun A, Arnold M, Ferlay J (2015) Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut 64: 1881-8.

13. Ladeiras-Lopes R, Pereira AK, Nogueira A (2008) Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 19: 689-701.

14. Cook MB, Kamangar F, Whiteman DC (2010) Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst 102: 1344-53.

15. Freedman ND, Abnet CC, Leitzmann MF (2007) A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 165: 1424-33.

16. Wang XQ, Terry PD, Yan H (2009) Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. World J Gastroenterol 15: 2204-13.

17. Yang WG, Chen CB, Wang ZX (2011) A case-control study on the relationship between salt intake and salty taste and risk of gastric cancer. World J Gastroenterol 17: 2049-53.

18. Larsson SC, Bergkvist L, Wolk A (2006) Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 15: 1998-2001.

19. Lunet N, Valbuena C, Vieira AL (2007) Fruit and vegetable consumption and gastric cancer by location and histological type: case-control and meta-analysis. Eur J Cancer Prev 16: 312-27.

20. Freedman ND, Subar AF, Hollenbeck AR (2008) Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. Cancer Causes Control 19: 459-67.

21. Hoyo C, Cook MB, Kamangar F (2012) Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 41: 1706-718.

22. Yang P, Zhou Y, Chen B (2009) Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. Eur J Cancer 45: 2867-73.

23. Whiteman DC, Sadeghi S, Pandeya N (2008) Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus Gut 57: 173-80.

24. Ye W, Chow WH, Lagergren J, Yin L, Nyren O (2001) Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. Gastroenterology 121: 1286-93.

25. An international association between Helicobacter pylori infection and gastric cancer (1993) The EUROGAST Study Group. Lancet 341: 1359-62.

26. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C (2015) Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer 136: 487-90.

27. Helicobacter, Cancer Collaborative G (2001) Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 49: 347-53.

28. Kamangar F, Dawsey SM, Blaser MJ (2006) Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with Helicobacter pylori seropositivity. J Natl Cancer Inst 98: 1445-52.

29. Limburg P, Qiao Y, Mark S (2001) Helicobacter pylori seropositivity and subsite- specific gastric cancer risks in Linxian, China. J Natl Cancer Inst 93: 226-33.

30. Cho SJ, Choi IJ, Kim CG (2010) Helicobacter pylori Seropositivity Is Associated with Gastric Cancer Regardless of Tumor Subtype in Korea. Gut Liver 4: 466-74.

31. Wang Y, Liu S, Zhang Y (2014) Helicobacter pylori infection and gastric cardia cancer in Chaoshan region. Microbes Infect. 16: 840-4.

32. Amini N, Spolverato G, Kim Y (2015) Clinicopathological features and prognosis of gastric cardia adenocarcinoma: a multi-institutional US study. J Surg Oncol 111: 285-92.

33. Edge SB, Byrd DR, Compton CC (2010) AJCC Cancer Staging Manual, Seventh Edition. Chicago: American Joint Committee on Cancer.

34. Saito H, Fukumoto Y, Osaki T (2006) Distinct recurrence pattern and outcome of adenocarcinoma of the gastric cardia in comparison with carcinoma of other regions of the stomach. World J Surg 30: 1864-9.

35. Maeda H, Okabayashi T, Nishimori I (2008) Clinicopathologic features of adenocarcinoma at the gastric cardia: is it different from distal cancer of the stomach? J Am Coll Surg 206: 306-10.

36. Zhou Y, Zhang Z, Zhang Z (2008) A rising trend of gastric cardia cancer in Gansu Province of China. Cancer Lett. 269: 18-25.

37. Park JC, Lee YC, Kim JH () Clinicopathological features and prognostic factors of proximal gastric carcinoma in a population with high Helicobacter pylori prevalence: a single-center, large-volume study in Korea. Ann Surg Oncol. 17(3),829-837 (2010).

38. Chung JW, Lee GH, Choi KS et al. Unchanging trend of esophagogastric junction adenocarcinoma in Korea: experience at a single institution based on Siewert's classification. Dis Esophagus 22: 676-81.

39. Jin JJ, Wang W, Dai FX (2016) Marital status and survival in patients with gastric cancer. Cancer Med 5: 1821-9.

40. Dassen AE, Lemmens VE, van de Poll-Franse LV (2010) Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer 46: 1101-10.

41. Kubo A, Corley DA (2004) Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol 99: 582-588.

42. Orengo MA, Casella C, Fontana V (2006) Trends in incidence rates of oesophagus and gastric cancer in Italy by subsite and histology, 1986-1997. Eur J Gastroenterol Hepatol 18: 739-46.

43. Steevens J, Botterweck AA, Dirx MJ, van den Brandt PA, Schouten LJ (2010) Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol 22: 669-78.

44. Vial M, Grande L, Pera M (2010) Epidemiology of adenocarcinoma of the esophagus, gastric cardia, and upper gastric third. Recent Results Cancer Res 182: 1-17.

45. Reddavid R, Strignano P, Sofia S (2019) Transhiatal distal esophagectomy for Siewert type II cardia cancer can be a treatment option in selected patients. Eur J Surg Oncol 45: 1943-49.

46. Holscher AH, Law S (2020) Esophagogastric junction adenocarcinomas: individualization of resection with special considerations for Siewert type II, and Nishi types EG, E=G and GE cancers. Gastric Cancer 23: 3-9.

47. Yamashita H, Seto Y, Sano T (2017) Results of a nation-wide retrospective study of lymphadenectomy for esophagogastric junction carcinoma. Gastric Cancer 20: 69-83.

48. Koyanagi K, Kato F, Kanamori J (2018) Clinical significance of esophageal invasion length for the prediction of mediastinal lymph node metastasis in Siewert type II adenocarcinoma: A retrospective single-institution study. Ann Gastroenterol Surg. 2: 187-96.