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RESEARCH

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Comparison among Early-Onset, Late-Onset, and Conventional-Onset Adenocarcinoma of Stomach and Esophagogastric Junction: a Retrospective Study

Yidi Liang[1,2], Kai Liu[1,2], Valentin Kudriashov[1,2], Lifei Sun[3,4], Weihan Zhang[1,2], Xiaolong Chen[1,2], Linyong Zhao[1,2], Xiaohai Song[1,2], Kun Yang[1,2] and Jiankun Hu[1,2*]

Abstract

Background The incidence of EOGC has been increasing, while COGC has decreased over the past few decades. The objective of this study was to identify differences in clinical characteristics and prognosis and to verify survival results among early-onset gastric cancer (EOGC), conventional-onset gastric cancer (COGC), late-onset gastric cancer (LOGC), and within the adenocarcinoma of the esophagogastric junction (AEG) group.

Materials and Methods A retrospective trend analysis was conducted on patients diagnosed with gastric adenocarcinoma between 2002 and 2021. Additionally, 3,940 patients who underwent radical gastrectomy between January 2009 and December 2019 were included in a further analysis. The patients were categorized into three groups based on their age: EOGC, COGC, and LOGC. The study compared the three groups' demographic parameters, surgical details, pathological characteristics, and survival rates.

Results From 2002 to 2021, there was a fluctuating decrease in the surgical population of EOGC from 18.0% to 9.4% ($p < 0.0001$). 3940 patients were included in this analysis, EOGC ($n = 572$), COGC ($n = 2816$), and LOGC ($n = 552$). The EOGC group indicated a higher proportion of females ($p < 0.0001$), poorer differentiation $p < 0.0001$), higher proportion of signet-ring cell cancer (SRCC) ($p < 0.0001$), and lower Her-2 expression ($p = 0.0038$) than the COGC and LOGC groups. EOGC patients showed the best overall survival rate compared to COGC ($p = 0.0110$) and LOGC ($p < 0.0001$). After stratified by TNM stage, LOGC patients had the worst survival among all stages. When considering the patients with AEG, the EOGC group showed the worst survival outcome ($p = 0.0130$). Only patients with COGC showed improved survival with chemotherapy compared to those without it (stage II: $p = 0.0051$; stage III: $p = 0.0160$).

Conclusion A decreasing trend in the EOGC surgical population has been observed over the past 20 years at West China Hospital. Compared to COGC patients, EOGC patients had a higher proportion of females, SRCC cases, poorer differentiation, and lower Her-2 expression, but demonstrated a better survival outcome. Conversely, the worst prognosis outcome was observed in EOGC patients within the AEG subgroup. LOGC was an independent negative factor for survival results. Chemotherapy did not improve the prognosis for EOGC and LOGC patients at stage II and III.

Keywords Early-onset, Gastric cancer, Esophagogastric junction, Adenocarcinoma, Prognosis, Trend

*Correspondence:
Jiankun Hu
hujkwch@126.com
Full list of author information is available at the end of the article

Background

Gastric cancer (GC) is the fifth most common malignant tumor worldwide, and the second most common digestive system cancer in China [1]. Although the overall incidence of gastric cancer (GC) has decreased over the past decades, it remains a leading cause of cancer-related mortality worldwide [2, 3]. A global rise in the incidence of esophagogastric junction (EGJ) cancer, particularly adenocarcinoma of the esophagogastric junction (AEG), has been observed [1, 4].

Furthermore, there was a concerning increase in the incidence of GC in young individuals during this period [5, 6]. With different cutoff points of age, the incidence of GC in young patients has increased from 1.7%—7.6% in 1973 to 3.5%—12.5% in 2015 [7]. The GC diagnosed in young individuals was defined as early-onset gastric cancer (EOGC) in this study. This study aimed to identify similarities and differences between EOGC and conventional-onset gastric cancer (COGC). Additionally, the study examined the difference between older patients and the conventional population, which we referred to as late-onset gastric cancer (LOGC) patients. The survival outcomes of young GC patients remain controversial, some studies indicated a poorer prognosis in EOGC [8, 9], while others reported that it was better than in the elderly [10, 11]. Moreover, few studies have focused on the AEG, so it is uncertain whether the survival trend is in accordance with the GC population.

This study retrospectively analyzes the clinicopathological features, prognosis, chemotherapy benefit, postoperative staging, and pathology-related antibody expression among patients with EOGC, LOGC, and COGC. This study aims to discern disparities in clinicopathological features, chemotherapy effectiveness, and survival outcomes in EOGC, LOGC, and COGC patients. Furthermore, survival differences within the AEG group are also researched.

Materials and methods

Definition of EOGC, COGC, and LOGC

The age range of EOGC varies from 40 to 50, according to different studies [12, 13]. There is no consensus on the specific age limit, therefore, in this study, patients with EOGC were defined as those younger than 45 years old who were diagnosed with GC according to a recommended optimum age for initiation of screening in Aisa [14]. Then we describe the gastric cancer diagnosed in those patients older than 70 years old as LOGC, the rest part of the patients (46–70 years old) were categorized as COGC patients.

Data source and patient selection

We retrospectively analyzed surgical population trends from 2002 to 2021 using the Gastrointestinal Surgery Department's database at West China Hospital. Additionally, we identified patients with a pathologic diagnosis of gastric adenocarcinoma who underwent treatment between January 2009 and December 2019. Patients were included according to the following criteria: (1) the pathological diagnosis was gastric adenocarcinoma, (2) ECOG score ≤ 2 and ASA score ≤ 3, and (3) radical gastrectomy (R0 resection). The exclusion criteria were: (1) lack of patients' age, requisite clinicopathological and survival outcome data, (2) combined with other malignant tumors or previous malignant tumor history, (3) multiple gastric cancer, recurrent gastric cancer, malignant tumors originating from other sites metastasized to the stomach and stump gastric cancer, (4) combined with other organ resection (except cholecystectomy) for treatment, and (5) palliative excision. Finally, 3940 patients who met the criteria were included in the analysis. We retrospectively collected the patient's demographic parameters, surgical details, and pathological and survival characteristics.

Endpoints

The primary endpoint of our study was 5-year overall survival (OS) and the clinicopathologic characteristics difference in different age groups. The second endpoint was chemotherapy benefit, which was assessed based on the improvement in OS.

Statistical analysis

Categorical variables were shown as numbers and percentages (%) and were compared using the Chi-Square test to identify significant differences between patient groups. Continuous variables were expressed as the mean (standard deviation) and used for variance analysis if necessary. The Kruskal–Wallis test could be operated when comparing the Her-2 status. A time trend analysis for the proportion was conducted using the Cochran-Armitage trend test. Kaplan–Meier method was used to calculate overall survival, and the log-rank test was used to compare. The associations between different factors and patients'overall survival (OS) were evaluated using univariate and multivariate Cox proportional hazards regression analyses. Variables with a p-value < 0.05 in the univariate analysis were considered confounders in the multivariable analysis. The results for significant prognostic factors were presented as hazard ratios (HR) for each category along with their 95% confidence intervals (CI). To further assess the chemotherapy benefits within different age groups, propensity score matching (PSM)

was conducted to mitigate selection bias and potential confounding. PSM used the 1:1 nearest neighbor matching and set the distance metric to logical distance to ensure more accurate and reliable matching results. R software performed all the above evaluations (Version 4.3.2. https://www.r-project.org/). A p-value <0.05 was defined to be statistically significant.

Results

Trends in Age Group Proportions of Surgical GC Patients (2002–2021)

A time trend analysis was conducted to ascertain the proportionate change trend of different age groups of surgical GC patients over 20 years, from 2002 to 2021. The changes in the proportion of GC in various age groups are shown in Fig. 1. The 20 years were divided into 10 sections for analysis. The proportion of EOGC decreased with a fluctuating tendency from 18.0% to 9.4%, and a downward trend was observed in EOGC from 2002 to 2021 ($p < 0.0001$). The proportion of COGC ($p = 0.0275$) and LOGC ($p < 0.0001$) exhibited an increasing trend during the past 20 years.

Demographic characteristics

Finally, 3940 eligible patients (572 EOGC, 2816 COGC, and 522 LOGC) were included in the analysis. The demographic characteristics of the three groups are shown in Table 1. The mean age was 38.77 years old in the EOGC group, 58.81 years old in the COGC group, and 74.99 years old in the LOGC group. Compared with the COGC and LOGC groups, the EOGC group indicated a higher proportion of females (EOGC 51.4% vs. COGC 28.9% vs. LOGC 20.8%, $p < 0.0001$) and lower body mass index ($p = 0.0007$). Additional demographic information is also shown in Table 1.

Clinicopathological characteristics

The clinicopathological characteristics are also displayed in Table 1. The LOGC patients displayed a larger tumor size according to the tumor diameter than the COGC and EOGC group (LOGC 5.21 (2.68) cm vs. COGC 4.74 (2.66) cm vs. EOGC 4.80 (2.76) cm, $p < 0.001$). The EOGC group exhibited a significantly higher proportion of tumor sites in the lower third of the stomach ($p < 0.0001$), while the upper third part accounted for more in the COGC and LOGC groups. This trend was also observed in AEG, with COGC and LOGC patients more likely to have Siewert-II adenocarcinoma ($p < 0.0001$). Compared to the COGC and LOGC patients, EOGC patients displayed a higher proportion of JGCA TNM stage IV ($p = 0.0141$), diffuse type ($p < 0.0001$), poorer differentiated degree (G3) ($p < 0.0001$), and more frequent with SRCC ($p < 0.0001$). EOGC patients presented a significantly lower Her-2 status, but COGC and LOGC patients were more likely to have Her-2 (2–3 +) than the EOGC group ($p = 0.0038$).

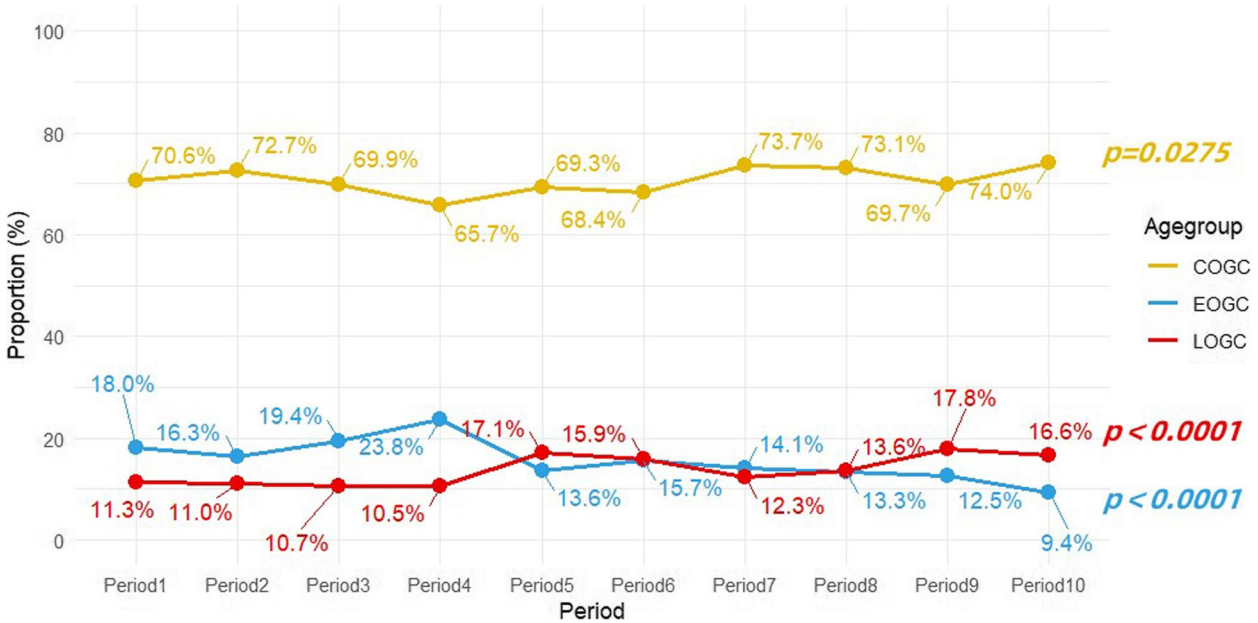

Fig. 1 Trends of gastric adenocarcinoma in surgical patients across age groups from 2002 to 2021. The *P*-value was calculated using the Cochran-Armitage trend test. Period1: 2002–2003, Period2: 2004–2005, Period3: 2006–2007, Period4: 2008–2009, Period5: 2010–2011, Period6: 2012–2013, Period7: 2014–2015, Period8: 2016–2017, Period9: 2018–2019, Period10: 2020–2021

Table 1 Demographics and Clinicopathologic Characteristics of COGC, EOGC, and LOGC group

	Overall	COGC	EOGC	LOGC	*p*
n	3940	2816	572	552	
Age (Mean (SD))					< 0.0001
	58.17 (11.55)	58.81 (6.77)	38.77 (5.48)	74.99 (3.50)	
Gender (%)					< 0.0001
Female	1222 (31.0)	813 (28.9)	294 (51.4)	115 (20.8)	
Male	2718 (69.0)	2003 (71.1)	278 (48.6)	437 (79.2)	
Body Mass Index (Mean (SD))					0.0007
	22.59 (3.20)	22.69 (3.15)	22.08 (3.35)	22.60 (3.28)	
#Tumor site (%)					< 0.0001
Lower	2258 (57.8)	1573 (56.4)	389 (68.4)	296 (53.8)	
Middle	636 (16.3)	435 (15.6)	114 (20.0)	87 (15.8)	
Upper	945 (24.2)	729 (26.1)	58 (10.2)	158 (28.7)	
UML	68 (1.7)	51 (1.8)	8 (1.4)	9 (1.6)	
Adenocarcinoma of the esophagogastric junction (%)					< 0.0001
No	3228 (81.9)	2264 (80.4)	536 (93.7)	428 (77.5)	
Siewert-I	25 (0.6)	20 (0.7)	2 (0.3)	3 (0.5)	
Siewert-II	416 (10.6)	328 (11.6)	16 (2.8)	72 (13.0)	
Siewert-III	271 (6.9)	204 (7.2)	18 (3.1)	49 (8.9)	
Esophageal invasion (%)					< 0.0001
No	493 (36.6)	327 (33.0)	82 (64.1)	84 (36.7)	
Yes	855 (63.4)	664 (67.0)	46 (35.9)	145 (63.3)	
Tumor diameter (cm) (Mean (SD))					0.0009
	4.81 (2.68)	4.74 (2.66)	4.80 (2.76)	5.21 (2.68)	
Borrmann type (%)					0.0065
Borr-1	93 (2.6)	70 (2.7)	12 (2.4)	11 (2.2)	
Borr-2	1302 (36.6)	949 (37.2)	173 (34.3)	180 (35.6)	
Borr-3	1408 (39.5)	1000 (39.2)	192 (38.1)	216 (42.8)	
Borr-4	221 (6.2)	135 (5.3)	46 (9.1)	40 (7.9)	
Early	537 (15.1)	398 (15.6)	81 (16.1)	58 (11.5)	
Signet-Ring cell cancer (%)					< 0.0001
No	3204 (81.3)	2317 (82.3)	402 (70.3)	485 (87.9)	
Yes	736 (18.7)	499 (17.7)	170 (29.7)	67 (12.1)	
Differentiation (%)					< 0.0001
G1	33 (0.9)	23 (0.9)	2 (0.4)	8 (1.6)	
G2	1193 (34.0)	890 (35.5)	85 (16.8)	218 (44.0)	
G3	2280 (65.0)	1592 (63.6)	419 (82.8)	269 (54.3)	
Lauren classification (%)					< 0.0001
Diffuse	1153 (41.3)	772 (39.2)	271 (64.8)	110 (27.2)	
Intestinal	960 (34.4)	691 (35.1)	66 (15.8)	203 (50.2)	
Mixed	679 (24.3)	507 (25.7)	81 (19.4)	91 (22.5)	
!TNM stage (%)					0.0141
I	966 (26.5)	717 (27.5)	135 (25.9)	114 (22.0)	
II	928 (25.4)	643 (24.7)	132 (25.3)	153 (29.5)	
III	1663 (45.6)	1181 (45.3)	236 (45.2)	246 (47.4)	
IV	92 (2.5)	67 (2.6)	19 (3.6)	6 (1.2)	
*Her2 (%)					0.0038
0	1308 (53.9)	926 (52.5)	201 (60.7)	181 (54.8)	
1 +	666 (27.5)	484 (27.4)	90 (27.2)	92 (27.9)	
2 +	333 (13.7)	263 (14.9)	28 (8.5)	42 (12.7)	
3 +	119 (4.9)	92 (5.2)	12 (3.6)	15 (4.5)	

Abbreviations: *UML* Upper & middle & lower

Tumor locations classified as upper (U), middle (M), and lower (L) thirds by trisecting the lesser and greater curvatures, according to the Japanese Classification of Gastric Carcinoma (3rd English Edition) [15]. *Ordinal data was tested using the Kruskal–Wallis test.!TNM stage IV included lymph node metastasis at No.8p, No.14v, and others

Surgical characteristics

The surgical characteristics are demonstrated in Table 2. The LOGC and COGC patients underwent a higher proportion of total gastrectomy (COGC 31.0% vs. LOGC 32.5% vs. EOGC 21.9%, $p < 0.001$) while EOGC patients received more distal gastrectomy. However, regarding the positive lymph nodes, EOGC had significantly higher amounts than the other two groups (EOGC 6.16 (7.81) vs. COGC 5.38 (8.04) vs. LOGC 4.75 (7.08), $p = 0.0153$). No significant difference was observed in the operation duration time among these three groups ($p = 0.4286$). The LOGC patients seemed to have a higher occurrence rate of surgical complications than EOGC and COGC patients (LOGC 7.2% vs. COGC 5.2% vs. EOGC 4.0%, $p = 0.0474$). LOGC patients took a lower proportion of undergoing postoperative chemotherapy when compared to the other two groups ($p < 0.0001$).

Survival outcomes

Out of 3940 patients, 3757 were included in the survival analysis, with 183 patients lost to follow-up (a follow-up loss rate of 4.64%). The analysis for overall survival (OS) using the Kaplan–Meier and log-rank test was shown in Fig. 2, age was associated with a significant difference in overall survival time ($p < 0.0001$). The overall survival rates at 1, 3, and 5 years for the COGC group were 94.3%, 81.8%, and 74.6%, respectively. In comparison, the EOGC group demonstrated rates of 93.7%, 83.8%, and 78.2% for the corresponding time intervals, while the LOGC group reported 91.7%, 74.0%, and 65.6% for the same periods. The median survival time in the LOGC group was 117 months, whereas the overall survival rates in the EOGC and COGC groups did not exceed 50%. After using the log-rank test to conduct pairwise comparisons, we found that the LOGC patients had the lowest OS rate than the COGC ($p < 0.0001$) and EOGC groups ($p < 0.0001$). Furthermore, the EOGC group held a better prognosis than

Table 2 Surgical characteristics of COGC, EOGC, and LOGC group

	Overall	COGC	EOGC	LOGC	*p*
Positive lymph node (Mean (SD))					0.0153
	5.40 (7.89)	5.38 (8.04)	6.16 (7.81)	4.75 (7.08)	
Excision extent (%)					< 0.0001
DG	2294 (59.8)	1585 (57.7)	405 (73.9)	304 (56.2)	
PG	393 (10.2)	309 (11.3)	23 (4.2)	61 (11.3)	
TG	1148 (29.9)	852 (31.0)	120 (21.9)	176 (32.5)	
Lymph node dissection (%)					0.0196
D1	24 (0.6)	12 (0.4)	4 (0.7)	8 (1.5)	
D1 +	51 (1.3)	37 (1.4)	9 (1.7)	5 (0.9)	
D2	3572 (94.0)	2555 (94.2)	501 (92.3)	516 (95.2)	
D2 +	151 (4.0)	109 (4.0)	29 (5.3)	13 (2.4)	
Operation duration time (Mean (SD))					0.4286
	234.61 (58.20)	235.12 (58.53)	231.14 (55.78)	235.55 (58.92)	
Surgical complications (%)					0.0474
No	3731 (94.7)	2670 (94.8)	549 (96.0)	512 (92.8)	
Yes	209 (5.3)	146 (5.2)	23 (4.0)	40 (7.2)	
Postoperative chemotherapy (%)					< 0.0001
No	1022 (37.9)	709 (36.1)	126 (33.4)	187 (52.2)	
Yes	1675 (62.1)	1253 (63.9)	251 (66.6)	171 (47.8)	

Abbreviations: *DG* Distal gastrectomy. *TG* Total gastrectomy. *PG* Proximal gastrectomy

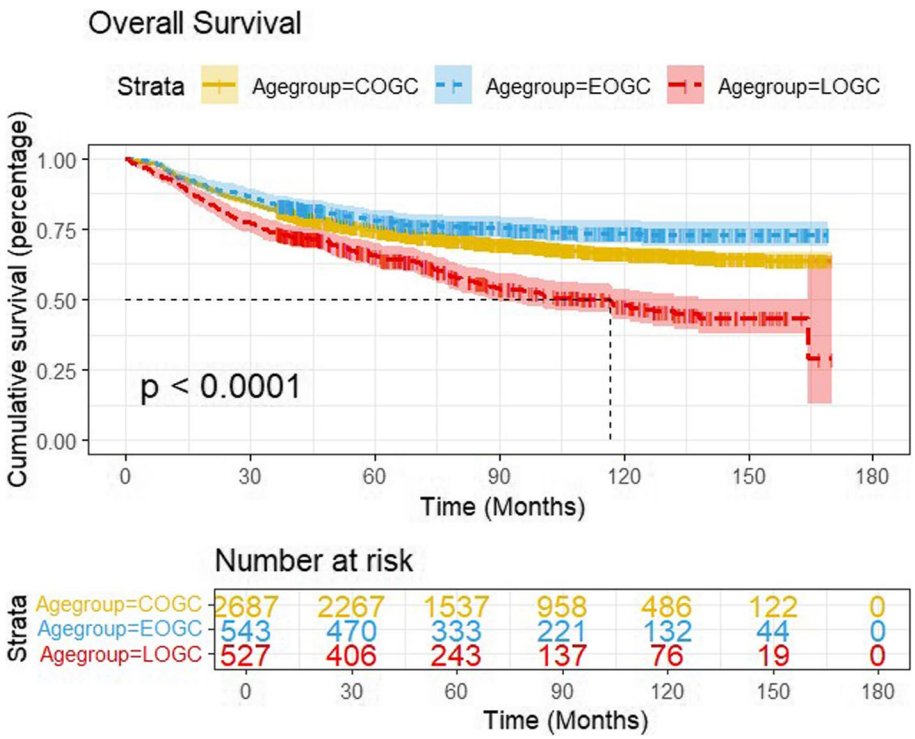

Fig. 2 Kaplan–Meier survival curves comparing overall survival in COGC, EOGC, and LOGC groups. The *P*-value was calculated using the log-rank test

the COGC group ($p = 0.0110$). Kaplan–Meier curves were also performed for OS stratified by TNM stage (stage I, stage II, stage III), and the results are shown in Fig. 3. Compared to the COGC and EOGC group, the OS rate of the LOGC was still significantly lower in 1-year, 3-year, and 5-year, this difference was most significant in the early stage (stage I and stage II). Concerning stage III, there was no statistical difference between COGC and EOGC groups in OS ($p = 0.4656$). The survival rates for 1-, 3-, and 5-year intervals were compared among three age groups, as shown in Supplementary Table 1. Pairwise comparisons for survival analysis were demonstrated in Supplementary Table 2.

Univariate and multivariate analysis

Univariate and multivariate analysis were performed to evaluate the risk factors of overall survival, and the results were displayed in Table 3. Significantly associated risk factors influencing prognosis included EOGC, LOGC, gender, tumor site, AEG, esophageal invasion, tumor diameter, Borrmann type, SRCC, differentiation degree, TNM stage, and positive lymph node in the univariate analysis. The multivariate analysis demonstrated that LOGC (Hazard Ratio (HR) = 1.63, 95%CI = 1.39–1.92, $p < 0.0001$), tumor diameter (HR = 1.09, 95%CI = 1.06–1.12, $p < 0.0001$), Grade 3 of differentiation (HR = 1.25, 95%CI = 1.07–1.45, $p = 0.0044$) and advanced TNM stage were the independent negative prognostic factors.

AEG in Different Age-Group

Furthermore, we selected AEG patients from the total study population as a subgroup for analysis. The characteristics of AEG patients are shown in Supplementary Table 3. There was no statistical difference in gender among the three groups ($p = 0.2019$). EOGC patients showed bigger tumor size (EOGC 6.79 (3.13) cm vs. COGC 5.09 (2.61) cm vs. LOGC 5.47 (2.35) cm, $p = 0.0004$), a higher proportion of SRCC (EOGC 25.0% vs. COGC 11.4% vs. LOGC 14.5%, $p = 0.0467$), poorer differentiation (G3) (EOGC 77.1% vs. COGC 58.8% vs. LOGC 46.4%, $p = 0.0127$), higher proportion of stage III-IV patients (EOGC 77.8% vs. COGC 58.4% vs. LOGC 55.6%, $p = 0.0188$) when compared with LOGC and COGC patients. The result of the Kaplan–Meier and log-rank test was shown in Supplementary Fig. 2, the EOGC patients showed worse survival outcomes than COGC ($p = 0.0320$), and there was no significant difference between LOGC and EOGC ($p = 0.2070$). The overall survival rates at 1, 3, and 5 years for the COGC group were 93.9%, 78.5%, and 67.2%, respectively. In comparison, the EOGC group exhibited rates of 78.1%, 56.2%, and 46.9% for the corresponding time intervals, while the LOGC group reported 94.9%, 71.8%, and 60.4% for the same periods. The median survival time in the EOGC group was 51.9 months, and 87.7 months in the LOGC group, while the COGC group did not exceed 50%.

Chemotherapy Benefits in Different Age-Group

Additionally, we established subgroups based on postoperative chemotherapy receipt to evaluate chemotherapy benefits by the improvement of survival time among the three groups in Fig. 4. PSM was performed to mitigate baseline characteristics bias between groups, with differentiation grade and tumor diameter selected as covariates based on the results of multivariate analysis for OS. We conducted a survival analysis stratified by JGCA TNM stage to enhance comparability across groups and evaluate chemotherapy benefits. In COGC stage II or III patients, those who received chemotherapy demonstrated a significantly better prognosis than those who did not ($p = 0.0051$; $p = 0.0160$). However, this difference was not observed in EOGC and LOGC patients with TNM stage II and III. The survival rates for 1-, 3-, and 5-year intervals were compared between patients who received chemotherapy and those who did not, as shown in Supplementary Table 4.

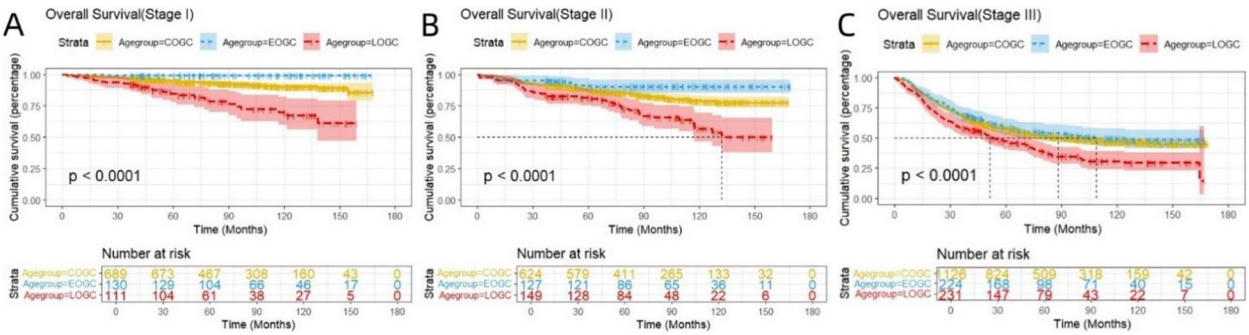

Fig. 3 Kaplan–Meier curves comparing overall survival in COGC, EOGC, and LOGC by TNM stage. **A**: TNM stage I; **B**: TNM stage II; **C**: TNM stage III. The *P*-value was calculated using the log-rank test

Table 3 Univariate and multivariate analysis of overall survival (OS)

	Univariable Cox Regression Analysis		Multivariable Cox Regression Analysis	
	Hazard Ratio [95%CI]	**p**	**Hazard Ratio [95%CI]**	**p**
Age-group				
COGC	reference		reference	
EOGC	0.78 (0.65–0.94)	0.0095	0.81 (0.66–0.99)	0.0430
LOGC	1.63 (1.41 –1.89)	< 0.0001	1.63 (1.39–1.92)	< 0.0001
Gender				
Female	reference			
Male	1.23 (1.08—1.40)	0.0022	1.14 (0.99—1.32)	0.0756
Tumor site				
Lower	reference		reference	
Middle	1.18 (0.99—1.39)	0.0564	1.02 (0.85—1.22)	0.8401
Upper	1.46 (1.28—1.67)	< 0.0001	1.13 (0.89—1.43)	0.3272
UML	2.93 (2.11—4.06)	< 0.0001	1.09 (0.73—1.64)	0.6623
Adenocarcinoma of the esophagogastric junction				
No	reference		reference	
Yes	1.54 (1.35—1.76)	< 0.0001	1.04 (0.82—1.32)	0.7648
Tumor diameter				
	1.19 (1.17—1.21)	< 0.0001	1.09 (1.06—1.12)	< 0.0001
Borrmann type				
Borr-1	reference		reference	
Borr-2	1.80 (1.09—2.96)	0.0218	1.52 (0.91—2.55)	0.1124
Borr-3	2.60 (1.58—4.27)	0.0002	1.57 (0.94—2.64)	0.0850
Borr-4	4.09 (2.42–6.91)	< 0.0001	1.54 (0.88—2.68)	0.1273
Early	0.36 (0.20—0.66)	0.0008	0.94 (0.49—1.79)	0.8507
Signet-Ring cell cancer				
No	reference		reference	
Yes	1.21 (1.05—1.40)	0.0086	1.00 (0.85—1.18)	0.9616
Differentiation				
G1—G2	reference		reference	
G3	1.49 (1.30–1.70)	< 0.0001	1.25 (1.07–1.45)	0.0044
TNM Stage				
I	reference		reference	
II	2.24 (1.71—2.94)	< 0.0001	1.56 (1.13—2.14)	0.0070
III	7.98 (6.31—10.09)	< 0.0001	4.59 (3.40–6.21)	< 0.0001
IV	14.74 (10.52—20.67)	< 0.0001	7.34 (4.80–11.24)	< 0.0001
Surgical complications				
No	reference			
Yes	1.25 (0.97—1.60)	0.0797		

Discussion

Many previous studies have revealed that EOGC is a distinct disease compared to COGC, with a higher prevalence in female patients, poorer differentiation, and more proportion of signet ring cell [7, 16, 17]. In this study, we divided gastric cancer patients into three age groups and analyzed the characteristics and survival outcomes of EOGC, COGC, and LOGC, aiming to distinguish the differences among these three groups.

In the past decades, we have observed an overall decrease in the proportion of EOGC among all GC surgical patients from 2002 to 2021. The overall trend of EOGC exhibited an initial increase but was followed by a subsequent decline. Although the EOGC trend in our study was inconsistent with previous studies that reported an increasing trend in EOGC incidence. The SEER has reported that the incidence rate of stomach cancer in Asian people under 50 years showed the same

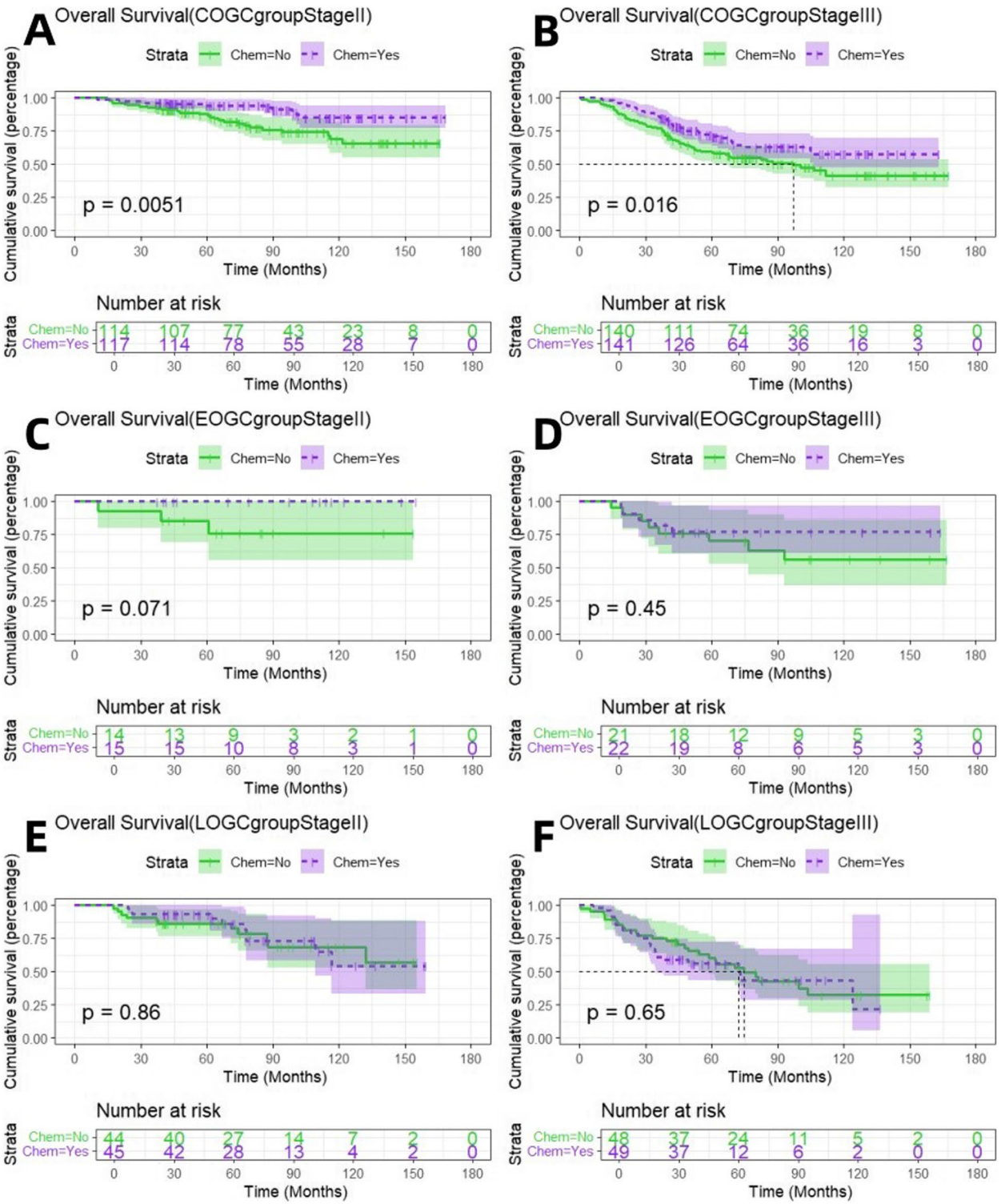

Fig. 4 Kaplan–Meier curves comparing overall survival in COGC, EOGC, and LOGC by chemotherapy status. **A**: TNM stage I-II in COGC; **B**: TNM stage III in COGC; **C**: TNM stage I-II in EOGC; D: TNM stage III in EOGC; E: TNM stage I-II in LOGC; F: TNM stage III in LOGC. The *P*-value was calculated using the log-rank test

trend as ours, with an initial increase and subsequent decrease [18].

GC was more frequent in males than females across all age groups worldwide [19]. In our study, the EOGC patients demonstrated different gender features versus patients with COGC and LOGC. We found a higher proportion of female patients in the EOGC group than in the other two groups, which is in accordance with some prior studies [20, 21]. However, it is noteworthy that some studies have also indicated a trend toward a higher proportion of male patients in EOGC [22]. We speculated that young female GC patients express a higher estrogen receptor positivity, which may be the reason for this gender difference [23, 24]. Moreover, a study conducted by Yi et al. demonstrated an association between estrogen receptor expression and diffuse cancer type [25], which could also explain the higher proportion of diffuse type observed in our EOGC patients. Current studies demonstrated a discrepancy regarding tumor sites in EOGC patients, some have suggested a preponderance of tumors in the middle third part of the stomach among young patients [26, 27], while other studies claimed higher incidence in the lower third part [28]. Our results indicate that the EOGC showed a higher proportion of lower third site GC, while the COGC and LOGC are more likely to occur in the upper third site. A study conducted by Qiu et al. reported that diffuse type GC was significantly associated with distal location [29]. Therefore, we suppose that the discrepancy in tumor location is more likely driven by the histological type rather than age.

The treatment strategy for GC displays no difference among EOGC, COGC, and LOGC. However, notable disparities emerge in survival outcomes. Despite EOGC patients being more inclined to present with advanced-stage cancer, poorer differentiation, and higher lymph node metastasis which were risk factors of GC patients' prognosis in our proportional hazards model, their overall survival rate was not inferior to that of other groups. In contrast to a prior study [30], EOGC patients in our study exhibited a significantly higher 3- and 5-year survival rate compared to the elderly and conventional patients, while the LOGC patients demonstrated the lowest OS rate. Patients diagnosed with EOGC might exhibit superior physical conditions, yet display inferior prognostic indicators, including SRCC and a greater prevalence of positive lymph nodes, among other factors. Moreover, the multivariate analysis conducted in this study revealed a significant association between EOGC and a more favorable prognosis. The same result was expressed in earlier stages when the TNM stage was stratified for analysis. However, the results differ slightly when considering stage III. In this context, no statistically significant difference in OS exists between the EOGC and COGC groups in stage III. We speculate this situation according to a previous study that the young patients were SRCC-dominated and could demonstrate a better survival outcome compared to non-SRCC at the early stage [31]. However, this trend disappeared in the advanced stage. Our study also reveals that the LOGC and COGC groups demonstrated a higher Her-2 status. Based on the previous studies, Her-2 could be an indicator of poor prognosis [32], this could be another reasonable explanation for EOGC's better survival outcomes. We can infer from another study conducted by Takashima et al. [33] that the lower third of the stomach which was prevalent in EOGC patients could lead to a favorable prognosis. Additionally, Petrelli et al. study showed that primary tumor location in the upper third of the stomach which was common in LOGC appeared to be a poor risk factor for survival [34]. The tumor sites were found to be statistically significant prognostic factors in the context of a univariate analysis. However, this was not observed in the multivariate analysis. We supposed that the tumor sites were not the primary determinant of survival. With regard to patients diagnosed with LOGC, it can be reasonably assumed that elderly patients exhibit a more compromised physical condition as we have conducted the OS as our study endpoint. A greater number of surgical complications and comorbidities were observed in patients with LOGC who had a lower tolerance for surgery compared to younger individuals. In our multivariate analysis, the presence of LOGC was also identified as an independent negative factor in prognosis. Furthermore, a larger tumor size, measured by diameter in the LOGC group, was identified as an independent risk factor for prognosis, which is consistent with the findings of Jun KH et al [35]. Consequently, elderly patients require a longer recovery period and are associated with the most unfavorable prognosis at each TNM stage.

We conducted a subgroup analysis for AEG patients, and we observed that EOGC patients showed the worst prognosis, which was opposite to previous studies [10, 16, 36]. We hypothesize that the poorer differentiation and more advanced TNM stage, which were known as risk factors for worse prognosis in our multivariate analysis, played a significant role in the EOGC subgroup. Moreover, the mean tumor diameter in our EOGC group was 6.64 cm, which was significantly bigger than the other two groups. This aligns with the findings of Takeda et al. [37] showed that tumor size > 5 cm was significantly associated with a worse prognosis compared to smaller tumor sizes. The early-onset group displayed a significantly higher frequency of alterations in CCNE1 and CDH1 as previously reported [16]. CCNE1 was involved in the oncogenic process [38], and its overexpression

was associated with an unfavorable prognosis in cancer patients [39]. CDH1 was a tumor suppressor gene that could transcribe a protein called E-cadherin. Reduction or loss of E-cadherin would affect epithelial architecture, cell adhesion, and increased invasiveness through epithelial-mesenchymal transition [40, 41]. Hu et al. showed that low expression of E-cadherin could be associated with poor prognosis in AEG patients [42]. These factors may collectively contribute to the unfavorable prognosis in our EOGC group. Nevertheless, the small overall sample size and uneven distribution among the three age groups in our study may have led to an inaccurate interpretation of the results.

In this study, we assessed the chemotherapy benefit among groups by comparing whether there was an improvement with chemotherapy in OS. To mitigate variations attributed to different age ranges and baseline bias, we performed a survival analysis stratified by age group and TNM stage with PSM. The chemotherapy group showed superior overall survival in the COGC patients with stage II and III. Moreover, in other groups, particularly in the EOGC and LOGC groups, there is no significant discrepancy in OS regardless of chemotherapy. In our study, the EOGC group demonstrated a higher proportion of SRCC, and SRCC is associated with less chemosensitivity in accordance with previous studies [31]. We assume that is why we could not observe the survival improvement in the EOGC patients. Moreover, the chemotherapy-associated toxicities could potentially impact the post-chemotherapy quality of life in the elderly [43], contributing to the non-superiority in survival analysis within the chemotherapy group in LOGC in our study. We suppose that patients with EOGC and LOGC exhibit lower chemotherapy sensitivity to the current chemotherapy strategies compared to those with COGC.

This study has several limitations. First, as a single-center retrospective study, it is subject to selection bias. Second, controlling for confounding variables was challenging, potentially influencing the results. Third, incomplete or missing data may have affected the robustness of certain findings. Fourth, the retrospective design limited the sample size and data types available for comprehensive analysis. Lastly, although recurrence-free survival (RFS) better reflects tumor-specific outcomes, only OS data were available due to limited follow-up. We acknowledge this as a limitation and aim to include RFS in future prospective studies.

Conclusions

EOGC surgical patients showed a downward trend in proportion from 2002 to 2021. In conclusion, while EOGC patients demonstrated several unfavorable prognostic factors compared to COGC patients, including cases of SRCC, poorer differentiation, and more advanced TNM stage, they paradoxically exhibited a better survival outcome in survival analysis. However, EOGC patients showed the most unfavorable outcomes within the AEG subgroup. Furthermore, LOGC emerged as an independent negative factor for survival outcomes. Additionally, both EOGC and LOGC patients seemed to have lower sensitivity to chemotherapy than COGC patients.

Abbreviations

EOGC	Early-onset gastric cancer
COGC	Conventional-onset gastric cancer
LOGC	Late-onset gastric cancer
AEG	Adenocarcinoma of the esophagogastric junction
SRCC	Signet-ring cell cancer
GC	Gastric cancer
EGJ	Esophagogastric junction
OS	Overall survival
PSM	Propensity score matching
HR	Hazard Ratio

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Not applicable

Authors' contributions

YDL, KL, and JKH designed the study; YDL drafted the manuscript; YDL, KL, and VK collected the data; LFS, XLC, WHZ and LYZ analyzed the data; KY, KL and JKH revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The retrospective database was approved by the Special Committee on Clinical Trials and Biomedical Ethics at West China Hospital (Approval No. 215 of 2014).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of General Surgery and Laboratory of Gastric Cancer, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang Street, Chengdu 610041, Sichuan Province, China. [2]Gastric

Cancer Center, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang Street, Chengdu 610041, Sichuan Province, China. [3]Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan Province, China. [4]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan Province, China.

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