ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2025.108.4.245
Annals of Surgical Treatment and Research

Proposal of age definition for early-onset gastric cancer based on the Korean Gastric Cancer Association nationwide survey data: a retrospective observational study

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Purpose: This study aimed to define an optimal age cutoff for early-onset gastric cancer (EOGC) and compare its characteristics with those of late-onset gastric cancer (LOGC) using nationwide survey data.
Methods: Using data from a nationwide survey, this comprehensive population-based study analyzed data spanning 3 years (2009, 2014, and 2019). The joinpoint analysis and interrupted time series (ITS) methodology were employed to identify age cutoffs for EOGC based on the sex ratio and tumor histology. Clinicopathologic characteristics and surgical outcomes were compared between the EOGC and LOGC groups.
Results: The age cutoff for defining EOGC was suggested to be 50 years, supported by joinpoint and ITS analyses. Early gastric cancer was predominantly present in the EOGC and LOGC groups. Patients with EOGC comprised 20.3% of the total study cohort and demonstrated a more advanced disease stage compared to patients with LOGC. However, patients with EOGC underwent more minimally invasive surgeries, experienced shorter hospital stays, and had lower postoperative morbidity and mortality rates.
Conclusion: This study proposes an age of ≤50 years as a criterion for defining EOGC and highlights its features compared to LOGC. Further research using this criterion should guide tailored treatment strategies and improve outcomes for young patients with gastric cancer.
[Ann Surg Treat Res 2025;108(4):245-255]

Key Words: Diagnosis; Early-onset gastric cancer; Interrupted time series analysis; Joinpoint trend analysis; Stomach neoplasms

INTRODUCTION

Gastric cancer (GC) ranks fifth in incidence and fourth in mortality worldwide [1]. Incidence rates of GC are twice as high in males as in females, and a higher prevalence has been observed in East Asian countries. According to a recent

Received November 4, 2024, **Revised** December 30, 2024, **Accepted** January 7, 2025

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comprehensive analysis of the global annual burden of GC, this malignancy is estimated to increase by up to 66% for new cases and 71% for the death ratio by 2040 [2]. GC incidence among the young population has recently increased in low- and high-risk countries. It has been suggested that the increase in autoimmune gastritis and dysbiosis of the gastric microbiome may contribute to the rising prevalence of GC in the young population [3,4].

Early-onset gastric cancer (EOGC) is more prevalent in females and is characterized by poorly differentiated tumor histology, including poorly cohesive or signet ring cell carcinoma, which tends to metastasize to the peritoneum and shows a higher incidence of lymph node metastasis. Moreover, younger patients often present with a higher number of positive estrogen receptors, potentially linked to bone metastasis [5-7]. These findings suggest that EOGC is associated with more aggressive tumor progression and a consequent worse prognosis. However, despite clinical implications, there are still ongoing debates regarding the issues of EOGC, primarily the undetermined age criterion for this disease [5,8-10].

Previous studies have suggested different ages based on single-institution data or findings from other studies [5-7,10]. The absence of a universally accepted definition for EOGC has been limiting comprehensive research. As attention to EOGC increases, it is crucial to identify specific criteria for understanding the distinctive attributes of this subset. The establishment of an age definition facilitates in-depth disease characterization, survival analysis, and contributes to the exploration of appropriate treatment strategies for young patients.

Herein, we used joinpoint trend and interrupted time series (ITS) analyses to define the optimal age cutoff and investigate the unique characteristics of EOGC compared to late-onset gastric cancer (LOGC) using data from a nationwide survey conducted by the Korean Gastric Cancer Association (KGCA).

METHODS

Ethics considerations

All surveys were approved by the Institutional Review Boards (IRBs) of each participating institution and the protocol of this study received IRB approval from the Gangneung Asan Hospital (No. GNAH 2023-06-017). The IRB waived the requirement for informed consent to participate in the study because of the study design.

Study design

This retrospective study analyzed nationwide survey data for surgically treated patients with GC collected by the KGCA in South Korea.

Data source

The KGCA has been collecting data every 5 years since 1999. For this analysis, we utilized recent data from the years 2009, 2014, and 2019 for identification and validation of age cutoffs and comparison of clinicopathologic characteristics.

The survey in 2009 collected information on patient demographics (age and sex), pathological results including tumor size, location, gross type, number of resected lymph nodes, depth of invasion, lymph node metastasis, distant metastasis, tumor, node, and metastasis (TNM) staging [11], the World Health Organization and Lauren classifications [12,13], and the operative methods (surgical approaches, curability, and reconstruction methods) of 59 institutions with 14,658 patients [14]. The survey in 2014 supplemented information on operations (type of stapler used for anastomosis, estimated blood loss, and operating time) from 69 institutions with 15,613 patients [15]. The survey in 2019 introduced more detailed data on patient demographics (height, weight, body mass index, the American Society of Anesthesiologist physical status classification, Eastern Cooperative Oncology Group performance score, familial history, comorbidities, previous endoscopic treatment or chemotherapy prior to the operation, previous abdominal surgery, and other cancer treatment histories) from 68 institutions with 14,076 patients. In addition, it included surgical information on combined resections, the number of trocars used in minimally invasive surgery, extent of lymph node dissection, omentectomy, and postoperative morbidity and mortality [16]. The TNM stage was based on the American Joint Committee on Cancer/Union for International Cancer Control, 8th edition [11].

We included all patients for whom data were available and excluded cases with incorrect or missing data on age.

Statistical analysis

The joinpoint trend and ITS analyses were conducted to identify the age criterion for EOGC. The joinpoint analysis identifies the age when a trend change occurs and was used to evaluate trends in the proportions of males and poorly differentiated tumor histology over age. Histology with poor differentiation included poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, and poorly cohesive carcinoma reported from surgical pathology.

The joinpoint analysis describes changes in data trends by connecting several different line segments. The analysis starts with the minimum number of joinpoints (i.e., 0 joinpoints, representing a straight line) and tests for model fit with a maximum of 4 joinpoints. The Monte Carlo permutation method was used to test for significance. In addition, an annual percent change (APC) for each line segment and the corresponding 95% confidence interval (CI) were estimated. The APC is tested to determine whether a difference exists from the

null hypothesis of no change (0%) [17].

ITS analysis was employed to assess changes in both factors. In the ITS analysis, the time series of interest was used as the outcome measure with dummy variables entered as model predictors to indicate the pre- and post-interruption or intervention phases of the series following a segmented regression analysis. The single-ITS analysis model follows the regression: $y = \alpha + \beta 1\ T + \beta 2\ X + \beta 3\ XT + \varepsilon$, where y = outcome variable, α = intercept, β = coefficients, T = age group (1, 2, 3, …, N), X = study phase (0 during pre-interruption and 1 during post-interruption), XT = age group after interruption (0 during pre-interruption and 1, 2, 3, …, N during post-interruption), and ε = error or residual [18]. Using the cutoff value derived from the joinpoint analysis, we validated the significance of the criterion in surveyed data with ITS analysis.

Statistical analyses were performed to compare the clinicopathologic characteristics and TNM stage distribution between the EOGC and LOGC groups for each survey year. Missing values were treated as "unclassified" in categorical data analysis and were excluded from continuous data analysis. The data were presented as counts and percentages for categorical variables and means ± standard deviations for continuous values. The chi-square test, Fisher exact test, and Student t-test were used to assess the differences between the 2 groups.

Statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc.) and IBM SPSS Statistics ver. 25.0 (IBM Corp.). For the joinpoint analysis, we used the Joinpoint Regression Program (ver. 5.0.2, Statistical Research and Applications Branch, National Cancer Institute). A P-value of <0.05 was considered statistically significant for all analyses.

RESULTS

Age criterion to define early- *vs.* late-onset gastric cancer regarding sex ratio and tumor histology

For analysis, we included 14,655, 15,612, and 14,076 patients from the surveys in 2009, 2014, and 2019, respectively. Using large-scale nationwide data, we demonstrated the age distribution of GC occurrence in Korea (Fig. 1). The most prevalent age group across all surveys was the 60s. The mean age at surgery was 59.2, 60.9, and 62.9 years in 2009, 2014, and 2019, respectively. Over the course of the serial surveys, there was a steady increase in patients aged over 80 years, rising from 2.2% to 7.7%. Conversely, patients under 50 years showed a consistent decrease from 24.5% to 15.5%.

Age cutoff was investigated through the joinpoint analysis with the proportion of male and poorly differentiated histology (Fig. 2). There were 2 significant joinpoints in the ratio of males to all patients, 50 and 65 years. APC for a group aged <50 years was 12.7 (95% CI, 10.1–81.7) and decreased to 5.9 (95% CI, 1.1–8.8) and –5.2 (95% CI, –8.1 to –3.9) in the groups aged 50–65 years and ≥65 years, respectively. Regarding tumor histology, 2 joinpoints of 45 and 70 years were observed with significant APC changes. The highest proportion of poorly differentiated tumor histology was seen in patients aged <45 years (APC, –5.0; 95% CI, –7.7 to –4.0), followed by the group aged between 45 and 65 (APC, –12.3; 95% CI, –15.9 to –11.0) and those ≥65 years (APC, –0.7; 95% CI, –7.0 to –8.2). Therefore, we assumed that 45 and 50 years could be the cutoff values for EOGC, which were younger joinpoints in the analysis.

For further investigation, we adopted ITS analysis for cutoff values of 45 and 50 years (Figs. 3, 4). The male-to-female ratio showed significant changes at the age of 45 years in 2009, 2014, and all series data (Fig. 3A, B, and D) (P = 0.017, P = 0.031, and P = 0.027, respectively). The 50-year assessment demonstrated significant changes in sex ratio across most patient populations,

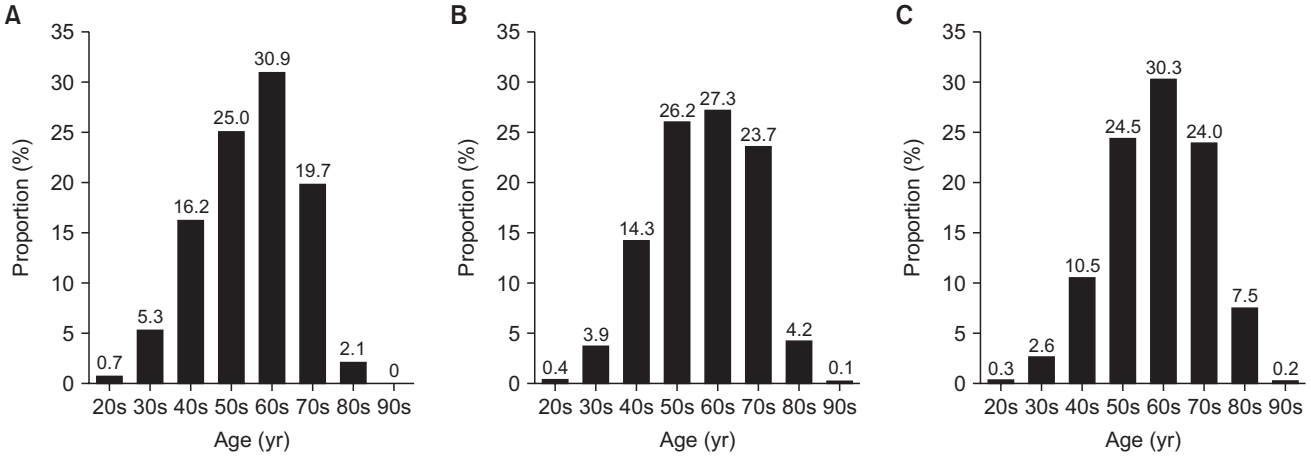

Fig. 1. The age group histogram for patients with gastric cancer in 2009 (A), 2014 (B), and 2019 (C).

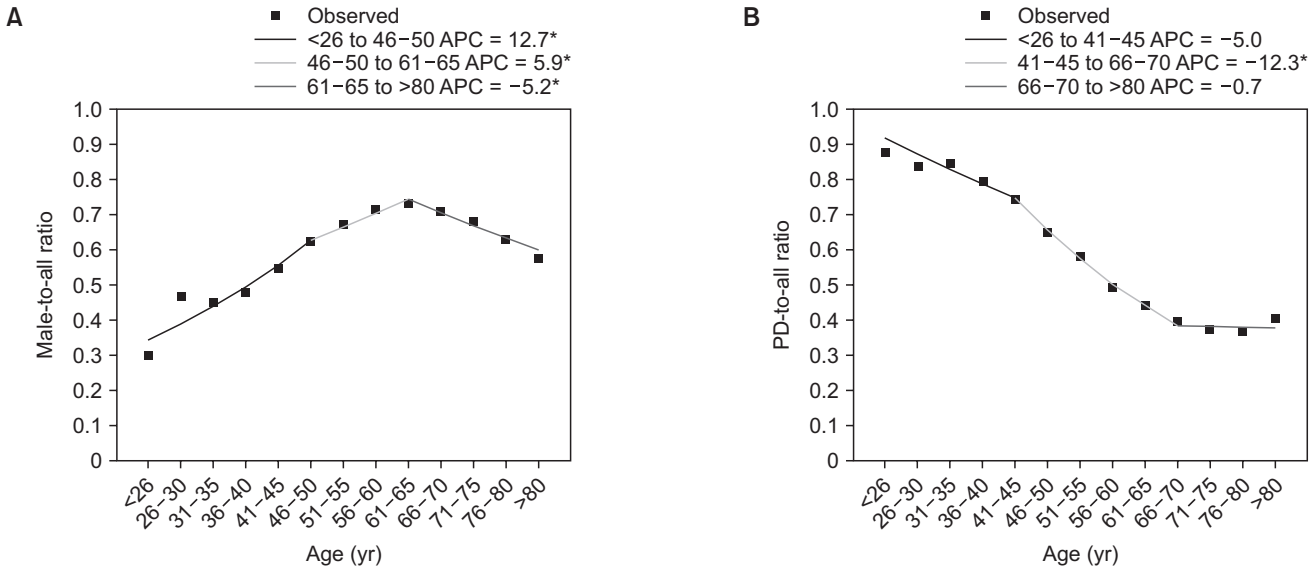

Fig. 2. Jointpoint graphs. (A) Trend in the proportion of male patients to all patients. (B) Trend in the proportion of poorly-differentiated (PD) patients with gastric cancer to all patients. APC, annual percent change. *APC is significantly different from zero at $\alpha = 0.005$.

with statistical significance being more consistent than that of 45 years (Fig. 3E–H) (P = 0.005, P = 0.008, P = 0.054, and P = 0.006, respectively). Regarding the proportion of poorly differentiated tumor histology, similar results were found when we analyzed based on the ages of 45 and 50 years. The ITS analysis at the age of 50 years demonstrated more consistent and significant differences than the results based on the age of 45 years (Fig. 4). Therefore, we suggested 50 years to define EOGC.

Comparisons of clinicopathologic characteristics between early- and late-onset gastric cancer

We compared the clinicopathologic characteristics and surgical information between the EOGC and LOGC groups.

The demographic characteristics of the study population are presented in Table 1. In all patient populations, there was a significant difference in the sex distribution and age at surgery between both groups. In the 2019 patient groups, data regarding GC familial history were newly collected; however, there were no statistically significant differences in the familial history between the 2 groups.

Compared with LOGC, EOGC was significantly characterized by smaller tumor sizes and predominance of the diffuse type in the Lauren classification (Table 2). There was a consistently significant difference in the tumor location in all surveys (P < 0.001). By longitudinal location, EOGC more frequently occurred in the middle third of the stomach or encompassed the entire stomach unlike LOGC. By circular location, the greater curvature and anterior wall of the stomach were frequently encompassed by GC in patients aged <50 years. A higher incidence of tumor multiplicity and the presence of lymphovascular invasion by cancer cells were observed in the LOGC group (both P < 0.001).

Comparisons of surgical information and tumor staging between early- and late-onset gastric cancer

Total gastrectomy, pylorus-preserving gastrectomy, and exploration were frequently performed in younger patients across the surveys (P < 0.001), and the incidence of Roux-en-Y gastrojejunostomy was higher than other anastomoses after distal gastrectomy (P < 0.001) (Table 3). A minimally invasive approach was also favored in the EOGC group (P < 0.001). Regarding surgical outcomes, hospital stay after surgery was shorter (9.3 days *vs.* 11.1 days) and the incidence of postoperative morbidity was significantly lower in the EOGC group (2.7 % *vs.* 4.3%). In addition, there was a significant difference in mortality within 30 days after surgery (0.1% in the EOGC group *vs.* 0.4% in the LOGC group).

Regarding tumor staging, despite the gradual increment of stage I GC over survey periods, there was still a significant number of patients diagnosed with stage IV tumors, and more patients underwent surgery in the EOGC groups (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study to reveal a consistent optimal age cutoff value for defining EOGC based on a large-scale nationwide multicenter database. We suggest that ≤50 years could be adopted as a reliable criterion for EOGC.

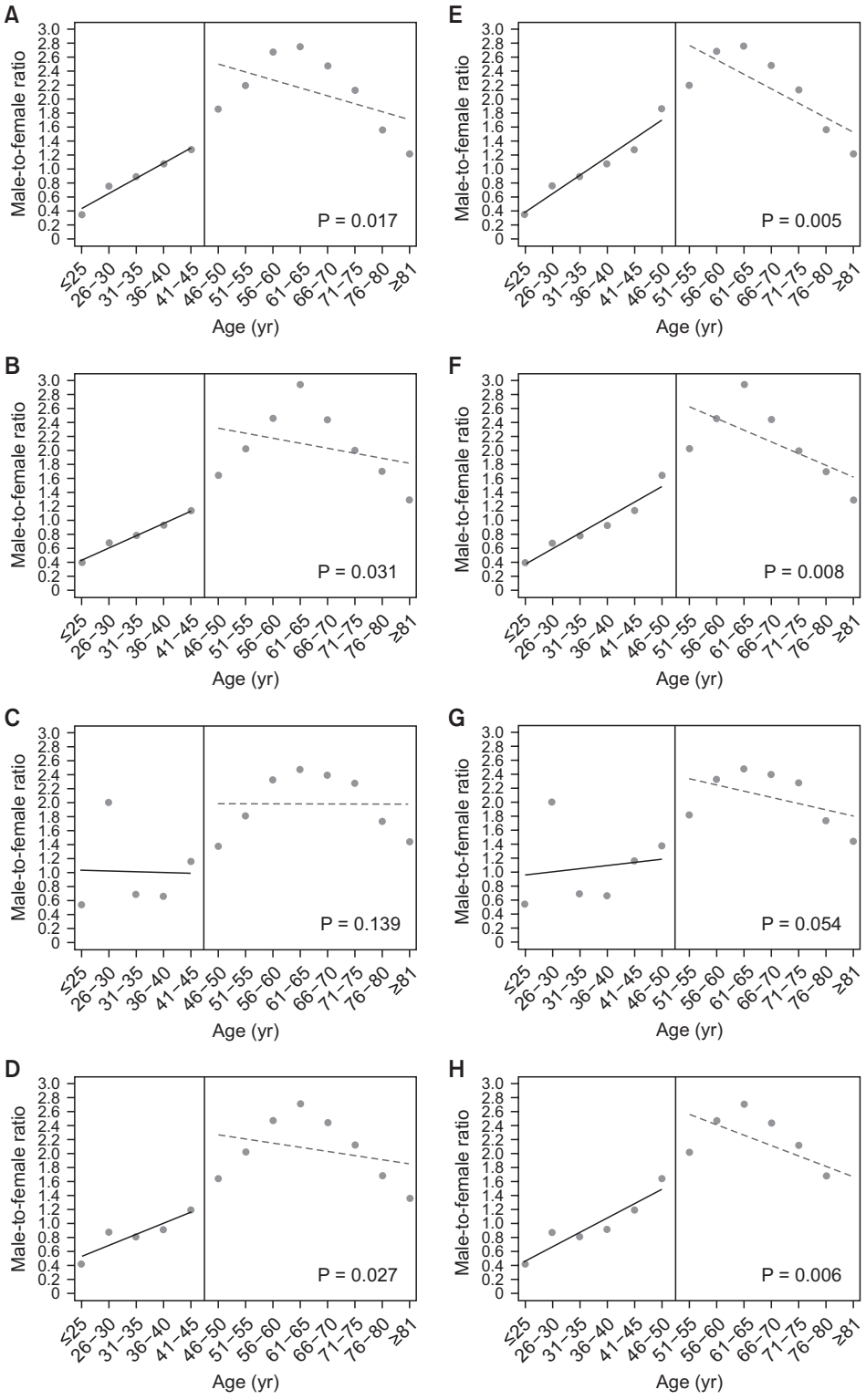

Fig. 3. Interrupted time series analysis for the male-to-female ratio in the study population: (A) in 2009 at the age of 45 years, (B) in 2014 at the age of 45 years, (C) in 2019 at the age of 45 years, (D) all series at the age of 45 years, (E) in 2009 at the age of 50 years, (F) in 2014 at the age of 50 years, (G) in 2019 at the age of 50 years, and (H) all series at the age of 50 years.

Although previous studies on EOGC have suggested various ages from 30 to 60 years as a criterion, those studies applied the age criterion based on arbitrarily determined percentiles within the data or adopted it from other studies [5,7-9]. We believe that this study provides more solid evidence than other research because the optimal cutoff age was evaluated based on 2 known characteristics of EOGC, which are female dominance and a high proportion of poorly differentiated tumor histology.

As suggested for determining the EOGC criteria, 2 main trends were usually observed through many studies. First, there

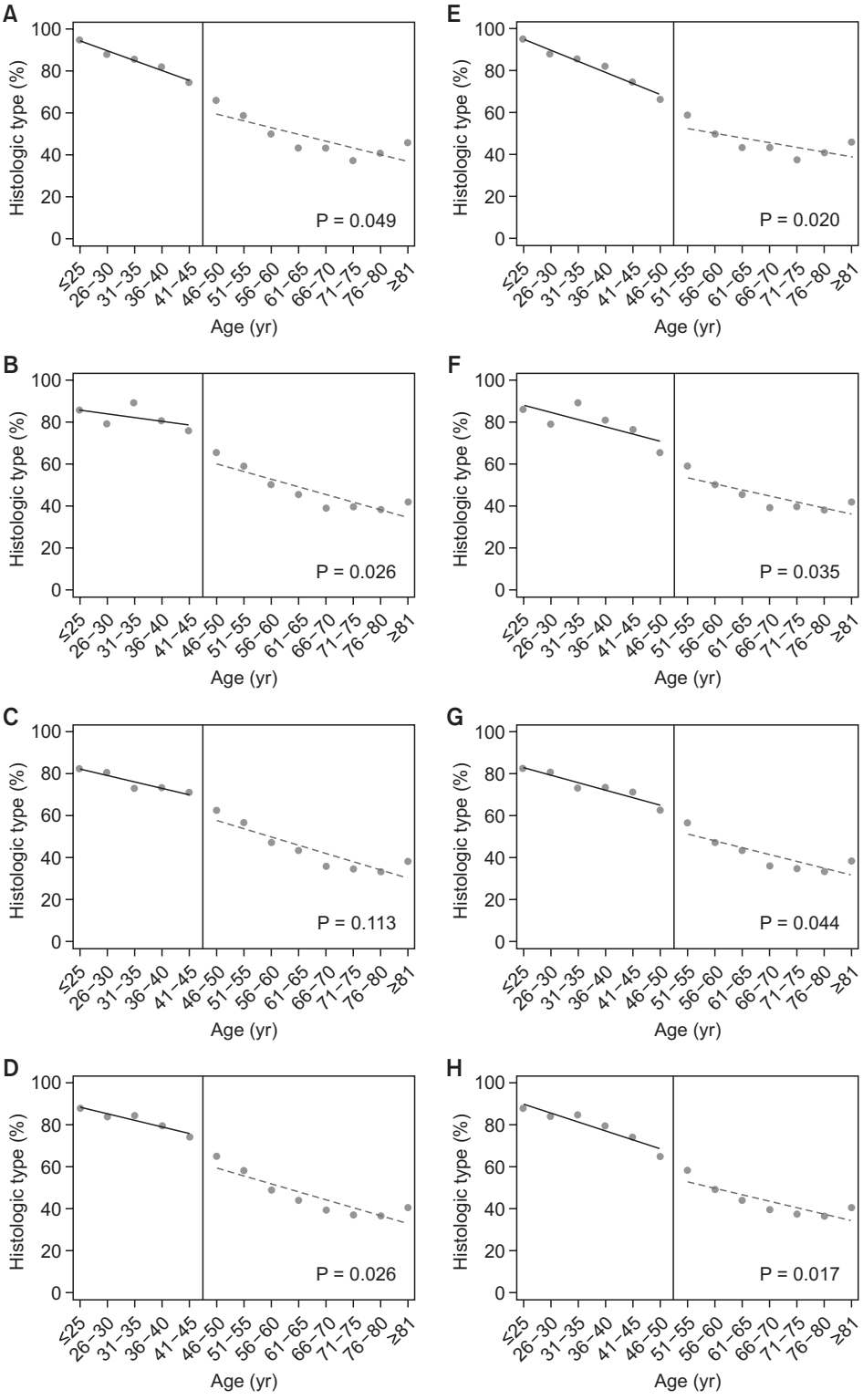

Fig. 4. Interrupted time series analysis for the histologic type in the study population: (A) in 2009 at the age of 45 years, (B) in 2014 at the age of 45 years, (C) in 2019 at the age of 45 years, (D) all series at the age of 45 years, (E) in 2009 at the age of 50 years, (F) in 2014 at the age of 50 years, (G) in 2019 at the age of 50 years, and (H) all series at the age of 50 years.

was a higher number of female patients compared to LOGC. Second, EOGC had a higher prevalence of undifferentiated histology [7-9,19,20]. It was observed that younger patients were more likely to develop a diffuse type carcinoma, and older patients tended to have intestinal histology. Intestinal cancers are usually associated with chronic atrophic gastritis and subsequent intestinal metaplasia. Since younger patients have fewer years to develop intestinal metaplasia, genetic factors and *Helicobacter pylori* infection may play a significant role in the development of undifferentiated GC types [21-23]. While *H.*

Table 1. Epidemiologic characteristics of the study population in the Korean Gastric Cancer Association nationwide survey

Characteristic	2009			2014			2019		
	EOGC (n = 3,595)	LOGC (n = 11,060)	P-value	EOGC (n = 3,211)	LOGC (n = 12,401)	P-value	EOGC (n = 2,175)	LOGC (n = 11,901)	P-value
Age (yr)	43.1 ± 5.7	64.5 ± 8.0	<0.001	43.4 ± 5.4	65.5 ± 8.8	<0.001	43.8 ± 5.4	66.4 ± 9.1	<0.001
Sex			<0.001			<0.001			<0.001
Female	1,514 (42.1)	3,326 (30.1)		1,442 (44.9)	3,873 (31.2)		1,028 (47.3)	3,820 (32.1)	
Male	2,080 (57.9)	7,733 (69.9)		1,769 (55.1)	8,528 (68.8)		1,147 (52.7)	8,081 (67.9)	
Missing	1 (0.0)	1 (0.0)		0 (0)	0 (0)		0 (0)	0 (0)	
Familial history of GC	NA	NA	NA	NA	NA	NA	265 (12.2)	1,375 (11.6)	0.560

Values are presented as mean ± standard deviation or number (%).
EOGC, early-onset gastric cancer; LOGC, late-onset gastric cancer; GC, gastric cancer; NA, not applicable.

Table 2. Tumor characteristics in the Korean Gastric Cancer Association nationwide survey

Characteristic	2009			2014			2019		
	EOGC (n = 3,595)	LOGC (n = 11,060)	P-value	EOGC (n = 3,211)	LOGC (n = 12,401)	P-value	EOGC (n = 2,175)	LOGC (n = 11,901)	P-value
Tumor size (cm)	4.0 ± 3.1	4.0 ± 3.0	0.435	3.8 ± 3.0	4.0 ± 2.9	<0.001	3.7 ± 3.2	3.9 ± 2.9	0.005
Lauren classification			<0.001			<0.001			<0.001
Intestinal type	972 (27.0)	5,594 (50.6)		689 (21.5)	5,766 (46.5)		407 (18.7)	5,389 (45.3)	
Diffuse type	1,913 (53.2)	3,205 (29.0)		1,858 (57.9)	4,026 (32.5)		1,250 (57.5)	3,592 (30.2)	
Mixed type	346 (9.6)	1,089 (9.8)					271 (12.5)	1,383 (11.6)	
Unclassified	364 (10.1)	1,172 (10.6)		653 (20.3)	2,609 (21.0)		247 (11.4)	1,537 (12.9)	
Location, longitudinal			<0.001			<0.001			<0.001
Upper third	557 (15.5)	1,810 (16.4)		463 (14.4)	1,902 (15.3)		422 (19.4)	2,417 (20.3)	
Middle third	1,204 (33.5)	2,829 (25.6)		1,092 (34.0)	3,141 (25.3)		821 (37.7)	3,268 (27.5)	
Lower third	1,593 (44.3)	5,854 (52.9)		1,414 (44.0)	6,544 (52.8)		806 (37.1)	5,614 (47.2)	
Whole stomach	95 (2.6)	199 (1.8)		64 (2.0)	180 (1.5)		45 (2.1)	225 (1.9)	
Unclassified	146 (4.1)	368 (3.3)		178 (5.5)	634 (5.1)		81 (3.7)	377 (3.2)	
Location, circular	NA	NA	NA			<0.001			<0.001
Lesser curvature				1,162 (36.2)	4,920 (39.7)		722 (33.2)	4,540 (38.1)	
Greater curvature				539 (16.8)	1,773 (14.3)		432 (19.9)	1,873 (15.7)	
Anterior wall				524 (16.3)	1,803 (14.5)		375 (17.2)	1,855 (15.6)	
Posterior wall				614 (19.1)	2,397 (19.3)		434 (20.0)	2,387 (20.1)	
Circular				144 (4.5)	636 (5.1)		89 (4.1)	633 (5.3)	
Unclassified				228 (7.1)	872 (7.0)		123 (5.7)	613 (5.2)	
Multiplicity	NA	NA	NA			<0.001			<0.001
Single				2,947 (91.8)	11,103 (89.5)		2,082 (95.7)	11,102 (93.3)	
Multiple				78 (2.4)	565 (4.6)		46 (2.1)	530 (4.5)	
Unclassified				186 (5.8)	733 (5.9)		47 (2.2)	269 (2.3)	
Lymphovascular invasion	NA	NA	NA	811 (27.2)	4,079 (32.9)	<0.001	500 (23.0)	3,796 (31.9)	<0.001
Perineural invasion	NA	NA	NA	NA	NA	NA	453 (20.8)	2,414 (20.3)	0.579

Values are presented as number (%).
EOGC, early-onset gastric cancer; LOGC, late-onset gastric cancer; NA, not applicable.

pylori is associated with poorly differentiated gastric carcinoma in young individuals [21], it usually requires several decades to induce histological changes and subsequent neoplastic transformation, suggesting that different mechanisms might be used in young populations [24]. Although the molecular biology of GC is heterogeneous, common genetic mutations were observed in the *CDH1* gene or *RHOA* gene, characterized by a higher rate of diffuse histological variants [5]. We expect that proper genetic screening for patients with EOGC would suggest more regarding tumor biology.

The reasons underlying the higher female proportion of patients with GC in the younger groups remain unclear. Some

Table 3. Surgical characteristics in the Korean Gastric Cancer Association nationwide survey

Characteristic	2009			2014			2019		
	EOGC (n = 3,595)	LOGC (n = 11,060)	P-value	EOGC (n = 3,211)	LOGC (n = 12,401)	P-value	EOGC (n = 2,175)	LOGC (n = 11,901)	P-value
Surgical extent			<0.001			<0.001			<0.001
Distal gastrectomy	2,490 (69.3)	7,988 (72.2)		2,179 (67.9)	8,747 (70.5)		1,566 (72.0)	8,525 (71.6)	
Total gastrectomy	881 (24.5)	2,466 (22.3)		791 (24.6)	2,868 (23.1)		409 (18.8)	2,446 (20.6)	
Proximal gastrectomy	28 (0.8)	113 (1.0)		23 (0.7)	145 (1.2)		54 (2.5)	311 (2.6)	
PPG	31 (0.9)	55 (0.5)		71 (2.2)	162 (1.3)		49 (2.3)	193 (1.6)	
Segmental resection				0 (0)	10 (0.1)				
Wedge resection	13 (0.4)	38 (0.3)		17 (0.5)	41 (0.3)		5 (0.2)	32 (0.3)	
Bypass	29 (0.8)	167 (1.5)		16 (0.5)	147 (1.2)		15 (0.7)	142 (1.2)	
Exploration	98 (2.7)	153 (1.4)		99 (3.1)	201 (1.6)		60 (2.8)	179 (1.5)	
Others	25 (0.7)	80 (0.7)		9 (0.3)	62 (0.5)		17 (0.8)	69 (0.6)	
Unclassified	0 (0)	0 (0)		6 (0.2)	18 (0.1)		0 (0)	4 (0.0)	
Reconstruction			0.021			<0.001			<0.001
Billroth 1	1,547 (43.0)	5,063 (45.8)		1,119 (34.8)	4,382 (35.3)		558 (25.7)	2,789 (23.4)	
Billroth 2	852 (23.7)	2,672 (24.2)		681 (21.2)	3,350 (27.0)		527 (24.2)	3,950 (33.2)	
RYGJ				357 (11.1)	1,185 (9.6)		448 (20.6)	1,590 (13.4)	
Uncut RYGJ				129 (4.0)	339 (2.7)		18 (0.8)	72 (0.6)	
RYGJ, RYEJ	980 (27.3)	2,746 (24.8)							
RYEJ				674 (21.0)	2,349 (18.9)		398 (18.3)	2,389 (20.1)	
Loop EJ				4 (0.1)	15 (0.1)		5 (0.2)	7 (0.1)	
Jejunal interposition	11 (0.3)	37 (0.3)		16 (0.5)	38 (0.3)		1 (0.0)	4 (0.0)	
DTR				15 (0.5)	80 (0.6)		47 (2.2)	239 (2.0)	
Esophagogastrostomy				7 (0.2)	66 (0.5)		7 (0.3)	59 (0.5)	
Gastrogastrostomy				52 (1.6)	145 (1.2)		47 (2.2)	188 (1.6)	
Others	89 (2.5)	240 (2.2)		27 (0.8)	103 (0.8)		95 (4.4)	416 (3.5)	
Unclassified	116 (3.2)	302 (2.7)		130 (4.0)	349 (2.8)		24 (1.1)	198 (1.7)	
Surgical approach			<0.001			<0.001			<0.001
Laparoscopy	887 (24.7)	2,491 (22.5)		1,678 (52.3)	5,814 (46.9)		1,403 (64.5)	7,894 (66.3)	
Open	2,083 (57.9)	7,289 (65.9)		1,406 (43.8)	6,354 (51.2)		497 (22.9)	3,357 (28.2)	
Robot				118 (3.7)	207 (1.7)		205 (9.4)	582 (4.9)	
Others	78 (2.2)	98 (0.9)		1 (0.0)	0 (0)		57 (2.6)	201 (1.7)	
Unclassified	547 (15.2)	1,182 (10.7)		8 (0.2)	26 (0.2)		13 (0.6)	112 (0.9)	
Hospital stay (day)	NA	NA	NA	NA	NA	NA	9.3 ± 11.5	11.1 ± 14.2	<0.001
Morbidity	NA	NA	NA	NA	NA	NA	58 (2.7)	506 (4.3)	<0.001
Mortality	NA	NA	NA	NA	NA	NA			0.007
No							2,078 (95.5)	11,206 (94.2)	
Yes, before POD 30							1 (0.1)	44 (0.4)	
Yes, after POD 30							21 (1.0)	70 (0.6)	
Unclassified							75 (3.4)	581 (4.9)	

Values are presented as number (%).
EOGC, early-onset gastric cancer; LOGC, late-onset gastric cancer; RYGJ, Roux-en Y gastrojejunostomy; RYEJ, Roux-en Y esophagojejunostomy; EJ, esophagojejunostomy; DTR, double tract reconstruction; POD, postoperative day; NA, not applicable.

researchers speculate that this might be partially attributed to the higher expression of estrogen receptors in young female patients with GC [25,26]. A large case-control study also found that frequent use of oral contraceptives, older age at first delivery, no history of lactation, and nulliparity were significantly associated with an increased risk of GC in females [27]. Higher bone metastasis in young patients may also be associated with estrogen receptor positivity, as has been demonstrated in other cancer types [28,29].

Joinpoint analysis has been usually used for detecting changes in trend data, such as cancer mortality and incidence. This method proposes the best-fitting set of joinpoints over the entire data range [17]. We adopted it to analyze the GC trend changes over the age groups. ITS analysis is an optimal method for evaluating the impact of a policy change or intervention on the rate of an outcome in a population. Investigators expect to understand the impact of quality improvement efforts using observational data after the intervention [18]. We used ITS

Table 4. TNM stage for all patients with gastric cancer according to the 8th edition of the American Joint Committee on Cancer guidelines

	2009			2014			2019		
	EOGC (n = 3,595)	LOGC (n = 11,060)	P-value	EOGC (n = 3,211)	LOGC (n = 12,401)	P-value	EOGC (n = 2,175)	LOGC (n = 11,901)	P-value
T stage			<0.001			<0.001			<0.001
Tx				67 (2.1)	168 (1.4)		12 (0.6)	56 (0.5)	
Tis	14 (0.4)	39 (0.4)		24 (0.7)	140 (1.1)		7 (0.3)	71 (0.6)	
1a	1,246 (34.7)	3,225 (29.2)		1,231 (38.3)	3,513 (28.3)		877 (40.3)	3,644 (30.6)	
1b	738 (20.5)	2,879 (26.0)		641 (20.0)	3,294 (26.6)		498 (22.9)	3,447 (29.0)	
2	371 (10.3)	1,354 (12.2)		264 (8.2)	1,404 (11.3)		168 (7.7)	1,159 (9.7)	
3	500 (13.9)	1,537 (13.9)		350 (10.9)	1,472 (11.9)		212 (9.7)	1,546 (13.0)	
4a	458 (12.7)	1,341 (12.1)		384 (12.0)	1,506 (12.1)		272 (12.5)	1,339 (11.3)	
4b	87 (2.4)	301 (2.7)		95 (3.0)	326 (2.6)		31 (1.4)	195 (1.6)	
Unclassified	181 (5.0)	381 (3.5)		155 (4.8)	578 (4.7)		98 (4.5)	444 (3.7)	
N stage			0.006			0.002			0.002
0	2,252 (62.6)	6,928 (62.6)		2,177 (67.8)	8,023 (64.7)		1,539 (70.8)	7,997 (67.2)	
1	657 (18.3)	2,249 (20.3)		319 (9.9)	1,310 (10.6)		178 (8.2)	1,192 (10.0)	
2	282 (7.8)	883 (8.0)		233 (7.3)	1,043 (8.4)		131 (6.0)	913 (7.7)	
3a	9 (0.3)	12 (0.1)		186 (5.8)	886 (7.1)		124 (5.7)	742 (6.2)	
3b	216 (6.0)	554 (5.0)		149 (4.6)	644 (5.2)		90 (4.1)	477 (4.0)	
Unclassified	179 (5.0)	434 (3.9)		147 (4.6)	495 (4.0)		113 (5.2)	580 (4.9)	
M stage			0.007			<0.001			0.002
0	3,284 (91.4)	10,287 (93.0)		2,942 (91.6)	11,472 (92.5)		2,010 (92.4)	11,157 (93.7)	
1	224 (6.2)	564 (5.1)		179 (5.6)	505 (4.1)		140 (6.4)	571 (4.9)	
Unclassified	87 (2.4)	209 (1.9)		90 (2.8)	424 (3.4)		25 (1.1)	173 (1.5)	
TNM stage			0.024			<0.001			0.001
Stage I	1,810 (50.3)	5,520 (49.9)		2,010 (62.6)	7,506 (60.5)		1,426 (65.6)	7,568 (63.6)	
Stage II	920 (25.6)	3,068 (27.7)		405 (12.6)	1,704 (13.7)		301 (13.8)	1,719 (14.4)	
Stage III	502 (14.0)	1,563 (14.1)		467 (14.5)	2,079 (16.8)		269 (12.4)	1,728 (14.5)	
Stage IV	224 (6.2)	564 (5.1)		179 (5.6)	505 (4.1)		140 (6.4)	571 (4.8)	
Unclassified	139 (3.9)	345 (3.1)		150 (4.7)	607 (4.9)		39 (1.8)	315 (2.6)	

Values are presented as number (%).
EOGC, early-onset gastric cancer; LOGC, late-onset gastric cancer.

analysis to check whether the trend change was significant before and after the age values derived from joinpoint analysis.

Joinpoint analysis exhibited 2 different age values: 50 years from the male proportion and 45 years from tumor histology. Additionally, a significant shift was observed in the age range of 60–65 years. However, as this range exceeds the median age of GC, 59.2–62.9 years in this study, it was deemed less appropriate as a criterion for EOGC compared to the younger cutoff values. To obtain more robust evidence, we independently conducted ITS analysis, and the results demonstrated that more consistent and significant statistical values were acquired when the age was 50 years.

An unclear definition of EOGC has led to conflicting results in previous studies. Some studies have reported a low prevalence of GC in the upper third of the stomach in younger patients [7,19], whereas others have shown a high incidence in the proximal stomach [5,20] or no significant difference between EOGC and LOGC [30]. Additionally, there is ambiguity regarding tumor size in EOGC compared to LOGC [19,20]. From the oncological perspective, EOGC, compared to LOGC, is generally diagnosed at an advanced stage [5,8,10]. However, the comparison of survival outcomes between both groups has yielded varying results [7,8,10,19,20]. Due to better general condition and tolerance for cancer-directed therapies, patients with EOGC showed better stage-specific survival in some studies [8,30], whereas other studies showed no survival difference between the 2 groups [7,19] and a higher incidence of peritoneal recurrence [20].

Using an age criterion of 50 years, we identified a higher prevalence of metastatic cases in the EOGC group than in the LOGC group. After surgery, they showed shorter hospital stays and lower postoperative morbidity and mortality. However, the current study did not demonstrate a survival outcome because of the absence of data in the survey. More prospective research is needed to show the survival outcomes.

This study has some limitations. First, the study is

retrospective, implying the occurrence of biases and missing information. The data collected from the survey were anonymized, which makes it challenging to collect additional information regarding the patients included. Second, the survey only involved patients who underwent surgery for GC, excluding those who received endoscopic treatment or palliative chemotherapy. However, >70% of patients with GC are treated by surgery in Korea, thus, these results could reflect most patients suffering from GC [28]. Third, as previous nationwide surveys did not contain survival data, we could not compare the prognosis between the EOGC and LOGC groups. Future research should aim to address these limitations and validate our study findings through prospective studies that involve larger sample sizes and longer follow-up periods.

In conclusion, this study adds to our knowledge of EOGC by proposing an age criterion for classifying it and comparing its characteristics to LOGC. With an age criterion of ≤50 years, more research is needed on GC in young patients. Recognizing the unique clinicopathological features of EOGC assists in developing appropriate treatment strategies and enhancing outcomes for these patients.

ACKNOWLEDGEMENTS

Fund/Grant Support

This research was supported by a nationwide survey project of the information committee funded by the Korean Gastric Cancer Association (grant number: KGCA2022IC13).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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