Journal of Advanced Research 75 (2025) 697–705

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Trends, clinicopathological features, surgical treatment patterns and prognoses of early-onset versus late-onset gastric cancer: A retrospective cohort study

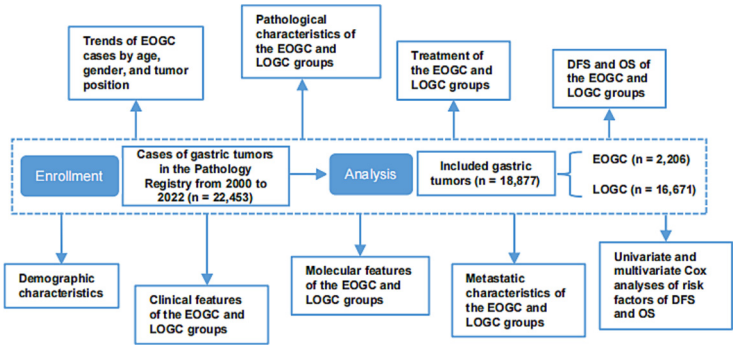
Yingxue Liu [a,b,c,1], Xiaoyan Zhang [a,b,c,1], Lu Gan [d,1], Zhikai Chen [e,1], Xin Wang [a,b,c], Jiayu Zhang [a,b,c], Jie Chen [b,f], Cong Tan [a,b,c], Weiqi Sheng [a,b,c,*], Midie Xu [a,b,c,*]

[a] Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai 200032, China
[b] Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China
[c] Institute of Pathology, Fudan University, Shanghai 200032, China
[d] Department of Medical Oncology, Fudan University Zhongshan Hospital, Shanghai 200032, China
[e] Shanghai Medical College, Fudan University, Shanghai 200032, China
[f] Second Department of Gastric Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China

HIGHLIGHTS

- From 2000 to 2022, the numbers of EOGC and LOGC have shown a steady increase.
- Compared to LOGC, the EOGC group generally exhibits more aggressive clinical and pathological characteristics.
- The EOGC group undergoes more thorough preoperative and intraoperative treatments.
- The EOGC group has a better prognosis in the early stage but a poorer prognosis in the advanced stage.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 5 September 2024
Revised 19 November 2024
Accepted 22 November 2024
Available online 24 November 2024

Keywords:
Early-onset gastric cancer
Late-onset gastric cancer
Characteristics and prognosis
Disease-free survival
Overall survival

ABSTRACT

Introduction: This study investigates the differences between early-onset gastric carcinoma (EOGC) and late-onset gastric carcinoma (LOGC) by examining trends, demographics, clinical and molecular features, treatments, and outcomes at a leading cancer center in China.
Objectives: To delineate the distinctions between EOGC and LOGC in terms of patient characteristics, disease progression, and treatment outcomes, and to suggest appropriate screening strategies.
Methods: We analyzed 18,877 gastric carcinoma cases treated at Fudan University Shanghai Cancer Center (FUSCC) from 2000 to 2022. Descriptive statistics were performed using IBM SPSS. Survival rates were assessed via the Kaplan-Meier method and log-rank test, while COX regression analysis identified factors affecting disease-free survival (DFS) and overall survival (OS).
Results: The average age of gastric cancer diagnosis has increased slightly since 2000, with a steady rise in both EOGC and LOGC cases, though EOGC's proportion has slightly decreased. EOGC had a higher proportion of female patients and was more common in the gastric body and antrum pylorus. EOGC cases showed lower levels of cancer biomarkers, HER2 expression, vascular and lymphatic invasion, and lower differentiation and invasion depth. They also exhibited more advanced N and TNM staging, Borrmann IV type, and low adhesive carcinoma. EOGC underwent more extensive D2 lymphadenectomy and

* Corresponding authors at: Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai 200032, China.
E-mail addresses: shengweiqi2006@163.com (W. Sheng), xumd27202003@sina.com (M. Xu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jare.2024.11.028
2090-1232/

neoadjuvant chemotherapy. There were no significant differences in Claudin18.2 and MMR protein status between EOGC and LOGC. EOGC had higher rates of ovarian and peritoneal metastases, with a better early prognosis but faster late-stage progression.
Conclusion: EOGC and LOGC cases have increased over the past two decades. EOGC presents unique clinical and pathological features, requiring thorough surgical treatment and has a better early prognosis but more rapid late-stage progression. Enhanced screening for younger adults is recommended to address the rising EOGC trend.

Introduction

With the implementation of gastric cancer (GC) prevention and screening strategies, between 1990 and 2019, a notable decline has been observed in the global incidence and mortality rates of GC. However, the decline in early-onset GC (EOGC) rates has not matched that of late-onset GC (LOGC), as evidenced by China's decrease in LOGC incidence rates by approximately 79 % contrasted with an alarming 28 % increase in EOGC incidence rates. Projections suggest that by 2035, the incidence rate of EOGC will nearly double globally, with China and South Korea bearing the brunt of this rise [1].

Given the significant growth trend of EOGC in China, it is imperative to clarify the distinctive characteristics of EOGC in the Chinese population to develop more personalized prevention and treatment strategies. This study aims to conduct a comprehensive comparison between EOGC and LOGC cohorts treated at a major cancer center in China.

Methods

Study design

In this study, we standardized the definition of EOGC as a diagnosis made at the age of 45 years or younger, following established criteria in previous research [2–4]. Patients aged over 45 years were classified into the LOGC group. Our initial analysis focused on the trends in EOGC and LOGC over the past 23 years, with particular attention to changes within subgroups of EOGC. Subsequently, we compared various aspects including clinical and pathological characteristics, sites of metastasis, molecular profiles, treatment strategies, and prognosis between the two cohorts. Finally, we conducted separate analyses of the factors influencing disease-free survival (DFS) and overall survival (OS) for EOGC and LOGC subsets. This study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center. Informed consent was obtained from patients and their families. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. All experiments involving human patients were conducted according to the ethical policies and procedures approved by the ethics committee of the Fudan University (Approval no. 2407-ZZK-124).

Study population

We conducted a single-center retrospective cohort study from the pathology registry at Fudan University Shanghai Cancer Center (FUSCC) between January 1, 2000, and December 31, 2022.

Inclusion criteria: 1. Patients who histologically confirmed primary gastric adenocarcinoma (GAD) through surgery or gastroscopy; 2. Patients with relatively complete clinical and pathological data. Exclusion criteria: 1. Patients with unknown histology; 2. Patients with benign gastric lesions; 3. Patients concurrent with other cancer; 4. Patients with residual, metastatic or recurrent GC.

According to the inclusion and exclusion criteria, totaling 18,877 cases were included. (**Figure S1**).

Data collection

The data obtainable through hospital medical record systems mainly include:

1) Demographic data: gender, age, height, weight, place of origin, and Body Mass Index (BMI), calculated by dividing weight (in kilograms) by the square of height (in meters).
2) Clinical data: family history, serum hemoglobin, albumin, prealbumin, tumor marker levels (including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA)), fecal occult blood, blood type, days of hospitalization, volume of intraoperative blood transfusion, days of tube placement.
3) Pathological data: degree of differentiation, tumor location, tumor size, T satge, N stage, M stage, TNM stage, vascular invasion, lymphatic invasion, perineural invasion, expression status of mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2), Claudin18.2 status ($\geq$ 2 + membrane staining intensity in $\geq$ 50 % of tumor cells are considered as positive status), human epidermal growth factor receptor 2 (HER2) expression (3 + membrane staining intensity and 2 + membrane staining intensity with positive FISH are considered as positive expression), pathological type, and Borrmann classification of advanced GC.
4) Treatment information: preoperative chemotherapy, surgical method, surgical approach, postoperative chemotherapy and postoperative radiotherapy etc.

Follow up

Prognosis follow-up was primarily conducted by professional personnel through telephone interviews combined with outpatient medical record reviews. The follow-up period was set until October 31, 2023. The follow-up content focused on postoperative recurrence or metastasis, including sites and dates, as well as occurrences of GC-related deaths and their dates. The primary study endpoint was OS (time from surgery to GC-related death or follow-up deadline), and the secondary endpoint was DFS (time from surgery to recurrence or metastasis or follow-up deadline). The follow-up duration ranged from 305 to 8,695 days, with a median follow-up time of 2,707 days and an average follow-up time of 3,116 days. Cases with OS less than 30 days was excluded. As of the end of follow-up, data from 13,464 patients with prognosis information were available, with OS and DFS ranging from 30 to 8,146 days.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 27.0.1, with continuous variables presented as mean ± standard deviation and compared using the Mann-Whitney *U* test; categor-

ical variables were presented as counts and percentages and compared using the chi-square test. Survival analysis was conducted using the Kaplan-Meier method and log-rank test, plotted using R (version 4.3.1). Univariate and multivariate COX regression analyses were employed to identify factors influencing DFS and OS. A significance level of P-value < 0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 18,253 cases of pathologically confirmed GAD were included in this study. A flowchart of the patient selection process is shown in **Figure S1**. **Figure S2** depicts the provincial distribution of patients' permanent residential addresses. The age distribution at the time of diagnosis is detailed in **Table S1**, with an average age of 59.3 years and a standard deviation of 11.3 years. Patients were categorized into two groups based on their age at diagnosis: EOGC (n = 2,206) and LOGC (n = 16,671).

Trends of EOGC cases by age, gender, and tumor position

The numbers of newly diagnosed cases of EOGC, LOGC, and GC at our hospital from 2000 to 2022 are shown in **Table S2**. Overall, there was a significant increase in EOGC, LOGC, and GAD cases during this period (**Table S2,** Fig. 1**A**). Notably, there were significant decreases in the numbers of GC cases across all three groups between 2021 and 2022, possibly due to the impact of the Shanghai COVID-19 Omicron outbreak and related lockdown policies. The distribution of age at diagnosis, gender, and tumor positions of EOGC from 2000 to 2022 by year is shown in Fig. 1**B-D** and **Table S3**. The proportions of EOGC in different age intervals (≤ 30 years, 31–35 years, 36–40 years, and 41–45 years) have been steadily increasing (Fig. 1**B**). Gender-wise, females have consistently outnumbered males since 2014 (Fig. 1**C**). Additionally, there has been a consistent rise in EOGC cases in the gastric antrum and body, while the proportion in the cardia region has shown a general decrease (Fig. 1**D**).

Clinical features of the EOGC and LOGC groups

EOGC is more common in females (53.0 %), while LOGC is more prevalent among males (72.7 %, P < 0.001; Fig. 2**A**). The EOGC group exhibited lower BMI (P < 0.001), CEA (P < 0.001), CA199 (P = 0.001), CA50 (P = 0.005), and CA242 (P < 0.001) levels, along with shorter total hospitalization days (P = 0.001) and postoperative hospitalization days (P = 0.001) compared to the LOCRC group. Additionally, they showed higher levels of albumin (P < 0.001), CA125 (P < 0.001), and higher ratio of blood type A (P = 0.017) (Table 1). The potential of fecal occult blood (89.0 % vs. 88.1 %) was significantly higher in the EOGC group than that in the LOGC group (P = 0.030; Table 1). The risks of cardiovascular disease, cerebrovascular disease, hypertension, diabetes, and respiratory diseases were higher in LOGC compared to EOGC (P < 0.001).

Pathological characteristics of the EOGC and LOGC groups

The EOGC group exhibited lower differentiation (P < 0.001), less vascular (P < 0.001) and lymphatic (P < 0.001) invasion, shallower invasion depth (P < 0.001), more lymph node metastasis (P < 0.001), low adhesive carcinoma (including signet ring cell carcinoma and its variants) (P < 0.001), and higher TNM staging (P < 0.001) compared to the LOGC group (Table 2**,** Fig. 2**B-F**). Among the included patients, 22.3 % had fundus cardia cancer, 19.5 % had stomach body cancer, 46.8 % had antrum pylorus cancer, and 11.4 % had multiple stomach cancer. Regarding tumor position, stomach body and antrum pylorus cancer were more prevalent in EOGC than in the LOGC group (83.8 % vs. 64.0 %, Fig. 2**G**). For advanced-stage GC, the Borrmann IV type is more common in EOGC than in LOGC group (P < 0.001; Fig. 2**H**).

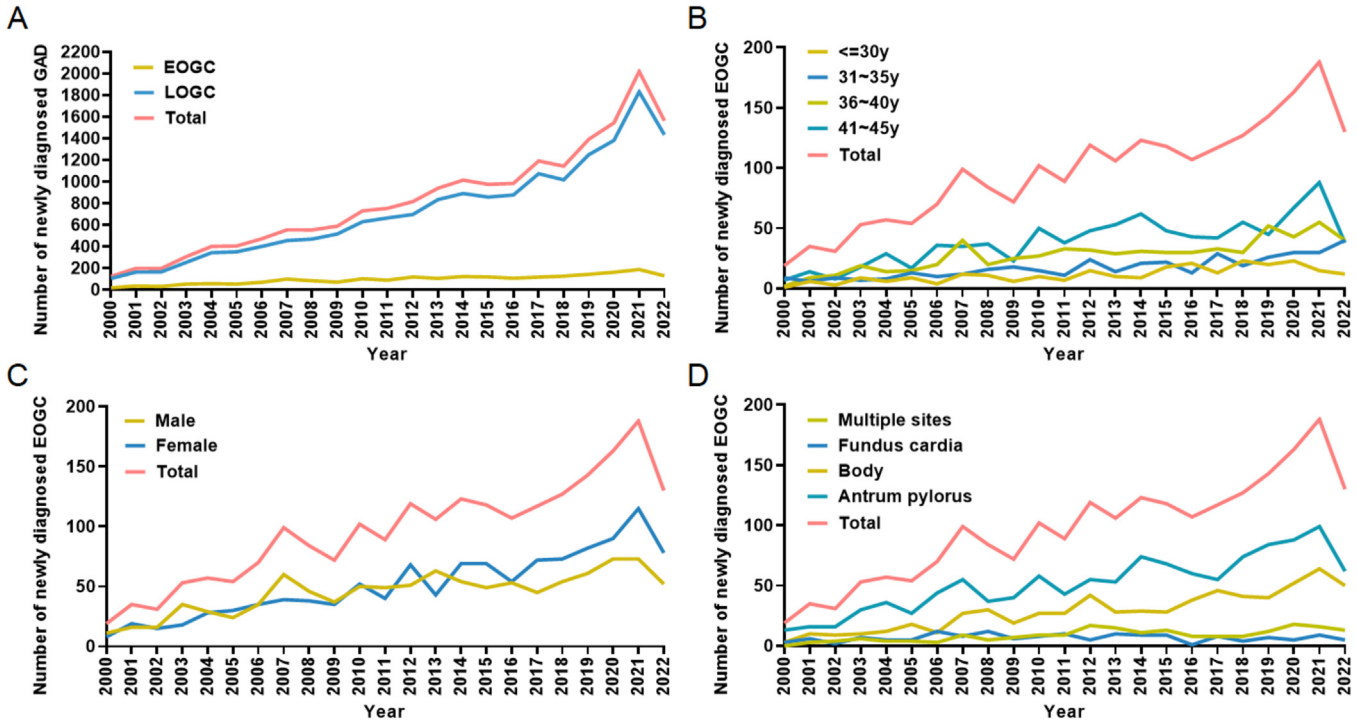


Fig. 1. The trend changes in subgroups of EOGC from 2000 to 2022. Annual Changes in Total Gastric Cancer Cases, Early-Onset Gastric Cancer (EOGC), and Late-Onset Gastric Cancer (LOGC) at FUSCC from 2000 to 2022 (A), with Subgroup Analyses of EOGC by Age (B), Gender (C), and Site (D).

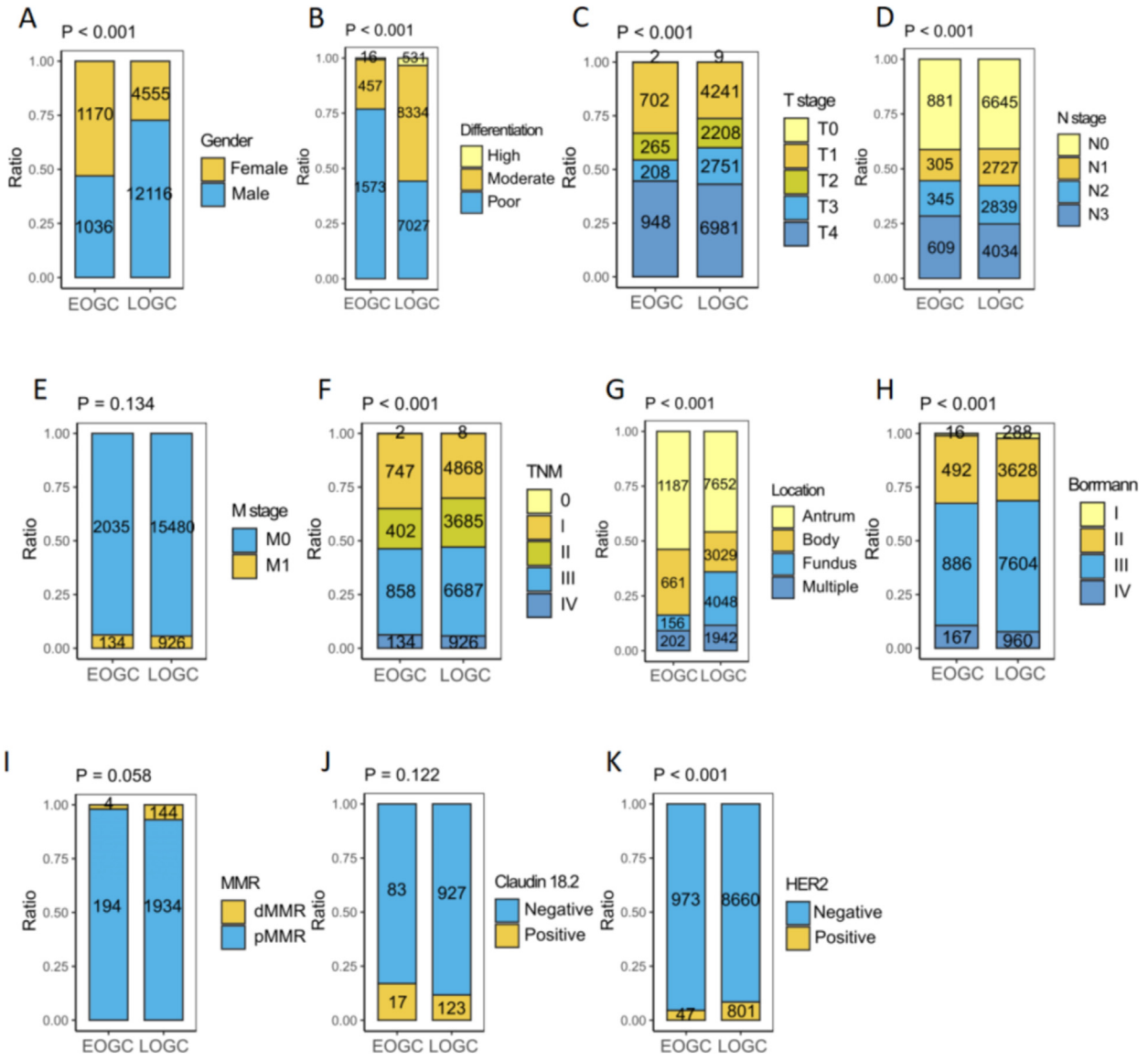


Fig. 2. Comparison of the clinical pathological characteristics between EOGC and LOGC. Comparative analysis between Early-Onset Gastric Cancer (EOGC) and Late-Onset Gastric Cancer (LOGC) includes gender (A), differentiation degree (B), T stage (C), N stage (D), M stage (E), TNM stage (F), tumor location (G), Borrmann classification of advanced stage (H), MMR status (I), Claudin 18.2 status (J), and HER2 status (K).

Molecular features of the EOGC and LOGC groups

Our analysis of molecular features, including MMR status, HER2, and Claudin18.2 protein expression, focused on patients diagnosed with GC between 2012 and 2022. No significant intergroup differences were identified in dMMR (2.02 % vs. 6.93 %, P = 0.058) and Claudin18.2 (20.48 % vs. 11.71 %, P = 0.122; Fig. 2**I-J**). However, the EOGC group had a significantly lower incidence of HER2 expression than the LOGC group (4.61 % vs. 9.25 %, P < 0.001; Fig. 2**K**).

Treatment of the EOGC and LOGC groups

The treatment analysis revealed distinct patterns between the EOGC and LOGC groups. EOGC was associated with a higher frequency of distal subtotal gastrectomy (P < 0.001) due to the tumor's predominant occurrence in the middle to lower parts of the stomach. Additionally, the EOGC group showed a higher likelihood of midline upper abdominal incision (P < 0.001), epidural anesthesia (P < 0.001), extensive lymphadenectomy (P = 0.013), and neoadjuvant chemotherapy utilization (P = 0.019) compared to LOGC (**Table S4**).

Metastatic characteristics of the EOGC and LOGC groups

A total of 2,013 cases of EOGC underwent curative gastrectomy, among which 183 cases experienced postoperative metastasis, primarily to the peritoneum, ovaries, liver, and bones. In contrast, a total of 15,593 cases of LOGC underwent curative gastrectomy, among which 1,103 cases experienced postoperative metastasis, predominantly to the liver, peritoneum, lungs, and lymph nodes. Notably, EOGC exhibited higher rates of peritoneum, ovarian, and bone metastases compared to LOGC, while pulmonary metastases were less frequent (**Table S5**).

Table 1
Comparison of Clinical features between early-onset gastric cancer (EOGC) and late-onset gastric cancer (LOGC) patients.

Variables[a]	GAD (n = 18,877)	EOGC (n = 2,206)	LOGC (n = 16,671)	P-value
Cardiovascular diseases				< 0.001
Yes	673 (3.57 %)	21 (0.95 %)	652 (3.91 %)	
No	18,204 (96.43 %)	2,185 (99.05 %)	16,019 (96.09 %)	
Cerebrovascular diseases				< 0.001
Yes	223 (1.18 %)	2 (0.09 %)	221 (1.33 %)	
No	18,654 (98.82 %)	2,204 (99.91 %)	16,450 (98.67 %)	
Hypertension				< 0.001
Yes	3,662 (19.40 %)	63 (2.86 %)	3,599 (21.59 %)	
No	15,215 (80.60 %)	2,143 (97.14 %)	13,072 (78.41 %)	
Diabetes				< 0.001
Yes	1,291 (6.84 %)	28 (1.27 %)	1,263 (7.58 %)	
No	17,586 (93.16 %)	2,178 (98.73 %)	15,408 (92.42 %)	
Respiratory diseases				< 0.001
Yes	194 (1.03 %)	5 (0.23 %)	189 (1.13 %)	
No	18,683 (98.97 %)	2,201 (99.77 %)	16,482 (98.87 %)	
Liver dysfunction				0.148
Yes	269 (1.43 %)	39 (1.77 %)	230 (1.38 %)	
No	18,608 (98.57 %)	2,167 (98.23 %)	16,441 (98.62 %)	
Renal dysfunction				0.675
Yes	32 (0.17 %)	5 (0.23 %)	27 (0.16 %)	
No	18,845 (99.83 %)	2,201 (99.77 %)	16,644 (99.84 %)	
Neurological diseases				0.140
Yes	56 (0.30 %)	3 (0.14 %)	53 (0.32 %)	
No	18,821 (99.70 %)	2,203 (99.86 %)	16,618 (99.68 %)	
Smoke				< 0.001
Yes	1,952 (36.70 %)	201 (27.80 %)	1,751 (38.10 %)	
No	3,367 (63.30 %)	522 (72.20 %)	2,845 (61.90 %)	
Unknow	13,558	1,483	12,075	
Alcohol				0.002
Yes	1,445 (27.31 %)	162 (22.53 %)	1,283 (28.06 %)	
No	3,847 (72.69 %)	557 (77.47 %)	3,290 (71.94 %)	
Unknow	13,585	1,487	12,098	
Albumin (g/l)				< 0.001
Mean ± SD	41.48 ± 5.15	42.87 ± 5.18	41.29 ± 5.12	
Prealbumin (mg/dl)				0.651
Mean ± SD	0.42 ± 2.18	0.45 ± 2.15	0.42 ± 2.19	
AFP (ug/l)				0.077
Mean ± SD	8.78 ± 78.57	5.27 ± 60.43	9.25 ± 80.69	
CEA (ug/l)				< 0.001
Mean ± SD	7.6 ± 35.14	3.32 ± 17.97	8.17 ± 36.81	
CA19-9 (u/ml)				0.001
Mean ± SD	39.63 ± 127.85	31.19 ± 115.89	40.76 ± 129.32	
CA50 (u/ml)				0.005
Mean ± SD	18.24 ± 55.11	15.93 ± 51.54	18.55 ± 55.56	
CA125 (u/ml)				< 0.001
Mean ± SD	14.26 ± 23.30	19.48 ± 39.77	13.64 ± 20.39	
CA72-4 (u/ml)				0.386
Mean ± SD	8.92 ± 30.55	7.37 ± 27.88	9.12 ± 30.88	
CA242 (u/ml)				< 0.001
Mean ± SD	14.21 ± 34.17	10.09 ± 22.31	14.74 ± 35.37	
Length of stay				0.001
Mean ± SD	16.39 ± 7.64	16.02 ± 7.44	16.44 ± 7.66	
Postoperative hospital stay				0.001
Mean ± SD	10.77 ± 6.36	10.44 ± 5.80	10.81 ± 6.43	
Intraoperative Blood Transfusion (ml)				0.764
Mean ± SD	572.52 ± 247.23	577.37 ± 318.85	572.08 ± 239.78	
Days of abdominal drainage tube placement				< 0.001
Mean ± SD	7.87 ± 4.25	7.57 ± 3.38	7.91 ± 4.35	
Days of chest tube placement				0.278
Mean ± SD	7.17 ± 6.98	6.1 ± 5.56	7.24 ± 7.06	
Days of gastric tube placement				< 0.001
Mean ± SD	4.09 ± 3.87	3.65 ± 2.39	4.15 ± 4.03	
Examined lymph node number				0.033
Mean ± SD	25.65 ± 10.88	25.05 ± 10.67	25.73 ± 10.90	
Family history of tumor				0.974
Absent	15,668 (83.00 %)	1,830 (82.96 %)	13,838 (83.01 %)	
Present	3,209 (17.00 %)	376 (17.04 %)	2,833 (16.99 %)	
Fecal occult blood				0.030
Negative	16,642 (96.59 %)	1,963 (97.42 %)	14,679 (88.82 %)	
Positive	587 (3.41 %)	52 (2.58 %)	535 (3.24 %)	
Unknown	1,648	191	1,457	

(*continued on next page*)

Table 1 (*continued*)

Variables[a]	GAD (n = 18,877)	EOGC (n = 2,206)	LOGC (n = 16,671)	P-value
Blood type				0.017
O	5,808 (30.79 %)	674 (30.58 %)	5,134 (30.82 %)	
A	6,598 (34.98 %)	828 (37.57 %)	5,770 (34.64 %)	
B	4,583 (24.30 %)	485 (22.01 %)	4,098 (24.60 %)	
AB	1,872 (9.93 %)	217 (9.85 %)	1,655 (9.94 %)	
Unknown	16	2	14	

Note: GAD: gastric adenocarcinoma; EOGC: early-onset gastric cancer; LOGC: late-onset gastric cancer; BMI: body mass index; AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; CA19-9: cancer antigen 19–9; CA50: cancer antigen 50; CA125: cancer antigen 125; CA72-4: cancer antigen 72–4; CA242: cancer antigen 242; SD: standard deviation.

[a] Continuous data was showed as mean ± SD and categoric data as number (%).

Table 2
Comparison of pathological characteristics between early-onset gastric cancer (EOGC) and late-onset gastric cancer (LOGC) patients.

Variables	GAD (n = 18,877)	EOGC (n = 2,206)	LOGC (n = 16,671)	P-value
Differentiation degree				<0.001
High	547 (3.05 %)	16 (0.78 %)	531 (3.34 %)	
Moderate	8,791 (48.97 %)	457 (22.33 %)	8,334 (52.40 %)	
Poor	8,600 (47.90 %)	1,573 (76.84 %)	7,027 (44.18 %)	
Mixed	15 (0.08 %)	1 (0.05 %)	14 (0.08 %)	
Unknown	924	159	765	
Pathological type				<0.001
Papillary adenocarcinoma	106 (0.56 %)	5 (0.23 %)	101 (0.62 %)	
Tubular adenocarcinoma	822 (4.35 %)	51 (2.33 %)	771 (4.69 %)	
Adenocarcinoma	11,913 (63.11 %)	1,019 (46.61 %)	10,894 (66.34 %)	
Mucinous adenocarcinoma	944 (5.00 %)	66 (3.02 %)	878 (5.35 %)	
Low adhesive carcinoma (including signet ring cell carcinoma and its variants)	4,767 (25.25 %)	1,034 (47.30 %)	3,733 (22.73 %)	
Poorly differentiated and undifferentiated carcinoma	56 (0.30 %)	11 (0.50 %)	45 (0.27 %)	
Mixed adenocarcinoma	269 (1.43 %)	32 (1.45 %)	237 (1.42 %)	
Intravascular invasion				<0.001
Absent	9,680 (52.46 %)	1,219 (57.02 %)	8,461 (51.86 %)	
Present	8,772 (47.54 %)	919 (42.98 %)	7,853 (48.14 %)	
Unknown	425	68	357	
Lymphatic invasion				<0.001
Absent	10,640 (57.95 %)	1,329 (62.34 %)	9,311 (57.37 %)	
Present	7,722 (42.05 %)	803 (37.66 %)	6,919 (42.63 %)	
Unknown	515	74	441	
Perineural invasion				0.292
Absent	9,974 (54.09 %)	1,132 (53.02 %)	8,842 (54.23 %)	
Present	8,466 (45.91 %)	1,003 (46.98 %)	7,463 (45.77 %)	
Unknown	437	71	366	

Note: GAD: gastric adenocarcinoma.

DFS and OS of the EOGC and LOGC groups

A comprehensive survival analysis included 13,464 patients, with 1,410 in the EOGC group and 12,054 in the LOGC group. EOGC exhibited superior DFS and OS ($P < 0.001$, $P < 0.001$; Fig. 3**A**) compared to LOGC overall. Subgroup analysis based on TNM staging revealed that in stages I and II, EOGC demonstrates significant advantages in both DFS ($P < 0.001$; $P = 0.019$) and OS ($P < 0.001$; $P < 0.001$) (Fig. 3**B-C**). However, in stage III, only OS showed an advantage for EOGC ($P = 0.024$), with no significant difference in DFS ($P = 0.886$) (Fig. 3**D**). Interestingly, in stage IV, OS was worse for EOGC compared to LOGC ($P < 0.001$) (Fig. 3**E**).

Univariate and multivariate Cox analyses of risk factors of DFS and OS in patients with GAD, EOGC, and LOGC

For EOGC patients, both univariate and multivariate COX regression analysis identified advanced T stage, N stage, and TNM stage, BMI < 18.5 kg/m^2, elevated CEA level (> 5 ng/ml), CA242 level (> 20u/ml), total gastrectomy, tumor size > 4 cm, and lymphatic invasion as independent risk factors for both OS and DFS. CA50 level > 20 u/ml was identified as an independent risk factor for OS only. Conversely, preoperative neoadjuvant chemotherapy and postoperative adjuvant radiotherapy emerged as independent protective factors (**Table S6 and Figure S3A-B**).

For LOGC patients, both univariate and multivariate COX regression analysis identified advanced T stage, N stage, and TNM stage, BMI < 18.5 kg/m^2, elevated CEA level (> 5 ng/ml), CA125 level (> 35u/ml), tumor size > 4 cm, vascular, lymphatic, and perineural invasion, and poorer differentiation grade as independent risk factors for both OS and DFS. Conversely, BMI $\geq$ 25, retrieved lymph nodes $\geq$ 16, and preoperative neoadjuvant chemotherapy were identified as independent protective factors. AFP level > 8 ng/ml and CA724 level > 6u/ml were independent risk factors for DFS only (**Table S7 and Figure S4A-B**).

Discussion

Recent data from China in 2020, reveals that GC ranks third among all malignancies in terms of incidence and mortality rates.

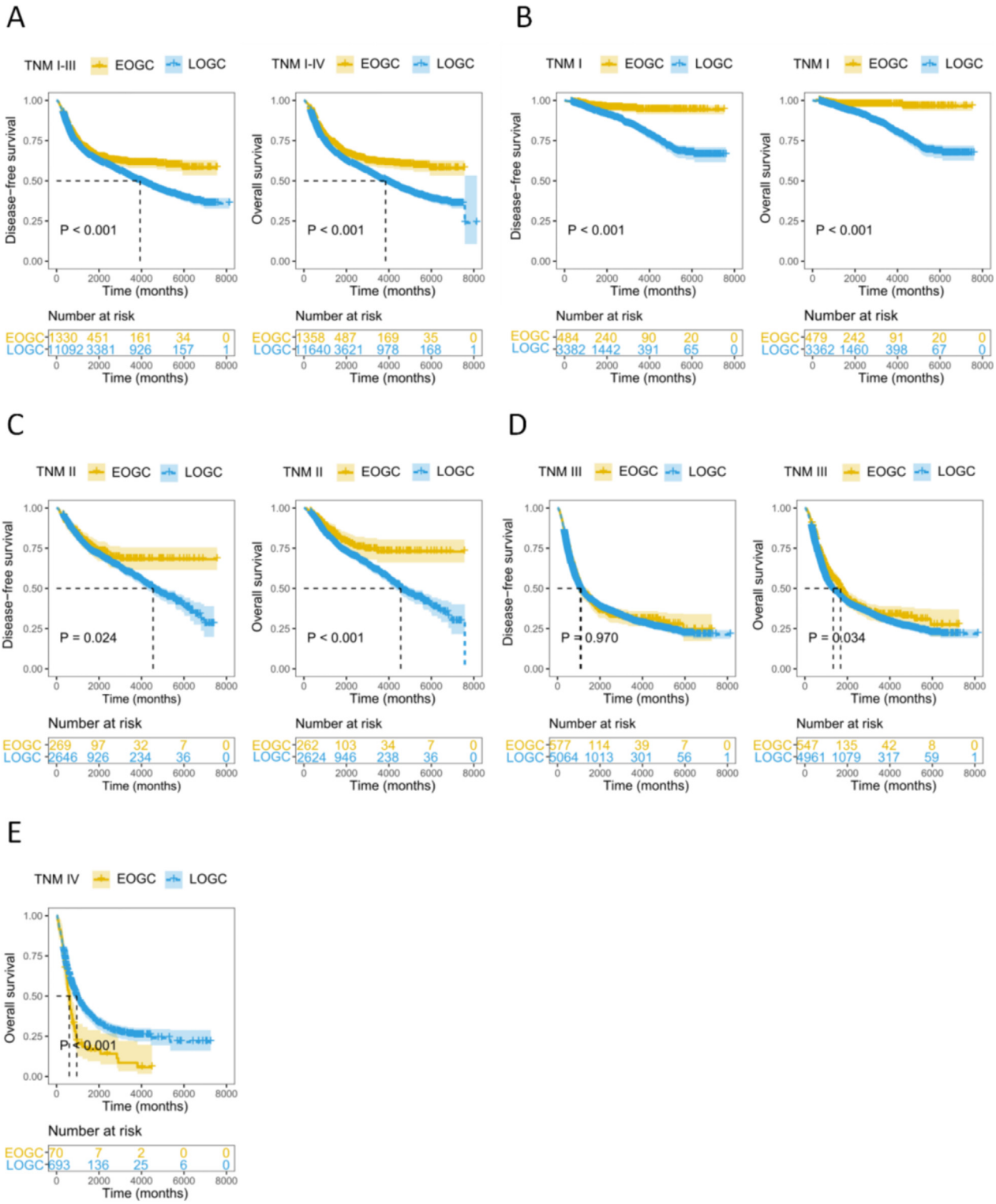


Fig. 3. Comparative analysis of the overall and substages prognosis between EOGC and LOGC. Comparing overall survival (OS) and disease-free survival (DFS) between Early-Onset Gastric Cancer (EOGC) and Late-Onset Gastric Cancer (LOGC) across overall stages (A), as well as specifically for Stage I (B), Stage II (C), Stage III (D), and Stage IV (E) subgroups.

Among these cases, EOGC accounts for approximately 10 % of the total GC population [5]. Considering the significant role of young people in society, thorough research on the unique clinical and pathological features of EOGC can help propose targeted preventive measures. The age range defining EOGC varies across literature [6–8]; here, we define adult GC patients aged 45 and below as EOGC. Our study, based on 18,877 cases of GAD at FUSCC from 2000 to 2022, provides comprehensive insights into EOGC in China.

Our data reveals a steady increase in both EOGC and LOGC cases since the turn of the 21st century, although the proportion of EOGC cases has slightly decreased. This contrasts with some previous studies suggesting a faster growth rate of EOGC in China compared

to LOGC [1]. A possible explanation for this discrepancy could be the regional representation of our center, limited to the southeastern region of China. Overall speaking, the average age at diagnosis of GC patients has increased. Unlike LOGC, we observed a higher proportion of females among EOGC cases. This could be attributed to higher estrogen levels in young females, known to promote GC development through various pathways [9,10].

We observed a higher prevalence of Borrmann type IV and low-adhesive cancer in EOGC, aligning with previous findings [6,11]. Borrmann type IV, characterized by poorly differentiated adenocarcinoma and signet ring cell carcinoma, exhibits aggressive behavior, which may contribute to the poorer prognosis of late-stage EOGC. K Haruma's research confirmed a high correlation between H. pylori infection and histological poor differentiation [12], with young GC patients showing higher infection rates than elderly patients [13]. Therefore, measures to eradicate H. pylori are essential for improving EOGC prognosis. Another notable aspect is the shifting predilection site of GC upward with age, as evidenced by Shiro Imagama's study [6]. The main reason is the increased gastroesophageal reflux disease prevalence in the elderly, leading to precancerous lesions like gastritis and intestinal metaplasia [14–16]. Tumors in the gastric antrum are often detected early due to pyloric obstruction, resulting in better outcomes, while tumors in the gastric fundus and cardia have relatively poorer prognosis. EOGC's common occurrence in the gastric antrum may contribute to its favorable early prognosis.

We observed lower dMMR in the EOGC group, which may limit the effectiveness of immune checkpoint inhibitors [17]. In contrast, Claudin18.2 expression were higher in the EOGC group, making it a promising therapeutic target, particularly for HER2-negative GC patients who may benefit from Zolbetuximab [18]. Although the HER2 levels in EOGC patients are lower, monitoring HER2 status should not be neglected, as the standard treatment regimen for HER2-positive advanced GC (trastuzumab combined with chemotherapy) significantly improves patient prognosis [19].

Regarding metastatic patterns, both EOGC and LOGC exhibit high pelvic and abdominal cavity metastasis rates, with EOGC showing a higher propensity for ovarian, peritoneal, and bone metastases. This underscores the importance of thorough examinations for relevant sites by clinical practitioners. Treatment comparisons reveal more distal subtotal gastrectomies in EOGC, aligning with its predilection sites. EOGC patients undergo comprehensive treatment strategies. Multivariate COX regression analysis highlights the benefits of preoperative chemotherapy and postoperative radiotherapy for EOGC patients, recommending active consideration of these treatments for eligible patients.

There is still controversy regarding the prognosis differences between EOGC and LOGC [8,20,21]. Our study adds to this discussion by highlighting that EOGC patients in early stages have a notably better prognosis. However, once distant metastasis occurs, EOGC progresses faster than LOGC, leading to a poorer prognosis. One of the challenges contributing to delayed diagnosis and treatment in EOGC is the misinterpretation of symptoms as benign conditions like gastric ulcers due to low health awareness among young individuals. We emphasize the importance of early diagnosis and urge young patients to undergo thorough examinations when experiencing gastric discomfort. For EOGC patients, especially in advanced stages, radical surgery is recommended whenever feasible. Young patients generally tolerate surgery well and experience fewer postoperative complications [6], potentially offering better long-term outcomes with a wider range of surgical clearance to reduce disease burden. Advancements in diagnostic technology have significantly benefited the detection and treatment of gastric cancer. For example, Mehran et al. present insights into the formation of controllable silicon nano-grass through hydrogenation-assisted reactive ion etching, a technique that could be leveraged for substrate preparation in cancer diagnostic [22], which may support early detection and tailored treatment approaches in oncology research.

Despite these insights, our study has limitations. The long-time span of the study may have impacted follow-up rates due to practical issues like phone number cancellations. The lack of testing data, including H. pylori status, and information on adjuvant chemotherapy and radiotherapy regimens has hindered our comprehensive analysis of the disease characteristics of EOGC. Additionally, the inclusion of patients from outside the local area and potential differences in postoperative treatments across centers introduce some selection bias and affect the analysis of prognostic factors.

Conclusion

Our study has found that compared to LOGC, patients with EOGC exhibit more invasive clinical and pathological characteristics, making them more prone to metastasis in the ovaries and pelvic area. However, they also display a higher tolerance to surgery and a more thorough curative effect, potentially resulting in better prognosis for early-stage EOGC patients compared to LOGC. Nevertheless, the disease progression in late-stage EOGC tends to be faster.

Compliance with ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (approved by the ethics committee of the Fudan University (Approval no. 2407-ZZK-124)) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

CRediT authorship contribution statement

Yingxue Liu: Conceptualization, Supervision, Validation, Investigation, Methodology, Writing – review & editing, Project administration, Formal analysis, Visualization, Writing – original draft, Data curation. **Xiaoyan Zhang:** Project administration, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Investigation. **Lu Gan:** Methodology, Data curation. **Zhikai Chen:** Methodology, Data curation. **Xin Wang:** Visualization, Validation, Writing – review & editing. **Jiayu Zhang:** Visualization, Validation, Writing – review & editing. **Jie Chen:** Visualization, Validation, Writing – review & editing, Investigation. **Cong Tan:** Writing – review & editing. **Weiqi Sheng:** Funding acquisition, Data curation, Writing – review & editing. **Midie Xu:** Conceptualization, Supervision, Validation, Investigation, Methodology, Writing – review & editing, Funding acquisition.

Funding

This work was supported by National Natural Science Foundation of China (82273370, 82202899, 82172702), Natural Science Foundation of Shanghai (22ZR1413000, 21ZR1414900), Shanghai Science and technology development fund (19MC1911000), Shanghai Municipal Key Clinical Specialty (shslczdzk01301), Shanghai Science and Technology Innovation Action Plan Basic research project subproject (20JC1419303) and Shanghai Municipal Health Commission Youth Projects(20214Y0394).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2024.11.028.

References

[1] Ning F, Zhang N, Zhao Z, Du W, Zeng Y, Abe M, et al. Regional, and National Burdens with Temporal Trends of Early-, Intermediate-, and Later-Onset Gastric Cancer from 1990 to 2019 and Predictions up to 2035. Cancers 1990;2022. doi: https://doi.org/10.3390/cancers14215417.

[2] Milne AN, Offerhaus GJ. Early-onset gastric cancer: Learning lessons from the young. World J Gastro Oncol 2010. doi: https://doi.org/10.4251/wjgo.v2.i2.59.

[3] Milne AN, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJ. Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. Curr Mol Med 2007. doi: https://doi.org/10.2174/156652407779940503.

[4] Milne AN, Carvalho R, Morsink FM, Musler AR, de Leng WW, Ristimaki A, et al. Early-onset gastric cancers have a different molecular expression profile than conventional gastric cancers. Modern Pathol 2006. doi: https://doi.org/10.1038/modpathol.3800563.

[5] Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 2020. doi: https://doi.org/10.3390/ijms21114012.

[6] Takatsu Y, Hiki N, Nunobe S, Ohashi M, Honda M, Yamaguchi T, et al. Clinicopathological features of gastric cancer in young patients. Gastric Cancer 2016. doi: https://doi.org/10.1007/s10120-015-0484-1.

[7] Park HJ, Ahn JY, Jung HY, Lim H, Lee JH, Choi KS, et al. Clinical characteristics and outcomes for gastric cancer patients aged 18–30 years. Gastric Cancer 2014. doi: https://doi.org/10.1007/s10120-013-0331-1.

[8] Santoro R, Carboni F, Lepiane P, Ettorre GM, Santoro E. Clinicopathological features and prognosis of gastric cancer in young European adults. Brit J Surg 2007. doi: https://doi.org/10.1002/bjs.5600.

[9] Ur RM, Cao J. Estrogen receptors in gastric cancer: Advances and perspectives. World J Gastroentero 2016. doi: https://doi.org/10.3748/wjg.v22.i8.2475.

[10] Nishi K, Tokunaga A, Shimizu Y, Yoshiyuki T, Wada M, Matsukura N, et al., Immunohistochemical study of intracellular estradiol in human gastric cancer. Cancer-Am Cancer Soc (1987). Doi: 10.1002/1097-0142(19870401)59:7<1328::aid-cncr2820590716>3.0.co;2-c.

[11] Bamboat ZM, Tang LH, Vinuela E, Kuk D, Gonen M, Shah MA, et al., Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. ANN SURG ONCOL (2014).dio:10.1245/s10434-013-3466-8.

[12] Haruma K, Komoto K, Kamada T, Ito M, Kitadai Y, Yoshihara M, et al. Helicobacter pylori infection is a major risk factor for gastric carcinoma in young patients. Scand J Gastroentero 2000. doi: https://doi.org/10.1080/003655200750024100.

[13] Hirahashi M, Yao T, Matsumoto T, Nishiyama K, Oya M, Iida M, et al. Intramucosal gastric adenocarcinoma of poorly differentiated type in the young is characterized by Helicobacter pylori infection and antral lymphoid hyperplasia. Modern Pathol 2007. doi: https://doi.org/10.1038/modpathol.3800714.

[14] Imagama S, Hasegawa Y, Wakao N, Hirano K, Hamajima N, Ishiguro N. Influence of lumbar kyphosis and back muscle strength on the symptoms of gastroesophageal reflux disease in middle-aged and elderly people. Eur Spine J 2012. doi: https://doi.org/10.1007/s00586-012-2207-1.

[15] Heading RC. Review article: diagnosis and clinical investigation of gastro-oesophageal reflux disease: a European view. Aliment Pharm Ther 2004. doi: https://doi.org/10.1111/j.1365-2036.2004.02221.x.

[16] Yagi K, Nakamura A, Sekine A, Oyamatsu M, Tamiya Y, Watanabe H. An early cancer of the gastric cardia arising from carditis after long-term gastroesophageal reflux disease in the absence of Helicobacter pylori infection. J Gastroen Hepatol 2002. doi: https://doi.org/10.1046/j.1440-1746.2002.02749.x.

[17] Chang L, Chang M, Chang HM, Chang F, Microsatellite Instability: A Predictive Biomarker for Cancer Immunotherapy. Appl Immunohisto M M (2018). doi. 10.1097/PAI.0000000000000575.

[18] Lordick F, Thuss-Patience P, Bitzer M, Maurus D, Sahin U, Tureci O. Immunological effects and activity of multiple doses of zolbetuximab in combination with zoledronic acid and interleukin-2 in a phase 1 study in patients with advanced gastric and gastroesophageal junction cancer. J Cancer Res Clin 2023. doi: https://doi.org/10.1007/s00432-022-04459-3.

[19] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010. doi: https://doi.org/10.1016/S0140-6736(10)61121-X.

[20] Zhang J, Gan L, Xu MD, Huang M, Zhang X, Gong Y, et al. The prognostic value of age in non-metastatic gastric cancer after gastrectomy: a retrospective study in the U.S. and China. J Cancer 2018. doi: https://doi.org/10.7150/jca.22085.

[21] Nakamura R, Saikawa Y, Takahashi T, Takeuchi H, Asanuma H, Yamada Y, et al. Retrospective analysis of prognostic outcome of gastric cancer in young patients. Int J Clin Oncol 2011. doi: https://doi.org/10.1007/s10147-011-0185-7.

[22] Mehran M, Sanaee Z, Abdolahad M, Mohajerzadeh S. Controllable silicon nano-grass formation using a hydrogenation assisted deep reactive ion etching. Mat Sci Semicon Proc 2011. doi: https://doi.org/10.1016/j.mssp.2011.02.014.