



Clinicopathological features and prognosis of younger patients with gastric carcinoma

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Background: The incidence rate of gastric carcinoma (GC) in young patients has increased in recent decades in China. The objective of this study was to examine the clinicopathological features and prognosis of younger patients with GC and to investigate the impact of younger age (≤ 50 years) on the presentation and survival outcomes of patients with GC.

Methods: A total of 411 GC patients, whose operations were performed by the same surgeon, were selected at Fudan University Shanghai Cancer Center. Differences in demographic distribution and clinicopathological features were analysed between 102 younger (≤ 50 years of age, young group, YG) and 290 old (51–70 years of age, old group, OG) GC patients. In addition, the surgical features and prognosis of the two groups were retrospectively investigated.

Results: The percentage of females in the YG was significantly higher than that in the OG (45.1% and 24.5%, respectively; $P < 0.001$). The distinguishing clinicopathological features between the two groups included gender, depth of invasion, differentiation grade, carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA19-9) level and delayed diagnosis. The 5-year disease-specific survival rate of patients in the YG was significantly higher than that in the OG (67.7% and 55.8%, respectively; $P = 0.048$). In the YG, female patients with GC showed a significantly lower disease-specific survival than males ($P = 0.021$). Male patients with GC in the YG showed a significantly higher 5-year disease-specific survival rate compared to female ones ($P = 0.009$), while the same was not found in the OG ($P = 0.633$). Multivariate analysis revealed that tumor size (≥ 5 cm), N classification (N2/3), elevated CA19-9 level and sex (Female) were independent negative prognostic factors of GC patients aged ≤ 50 years old.

Conclusions: In comparison with old patients, young patients with GC show unique features, including a higher percentage of females, a higher percentage of the T1 depth of invasion, undifferentiated histological grade, normal preoperative CA19-9 level and normal preoperative CEA level. In particular, males ≤ 50 years showed a higher rate of early stage disease with better survival than males aged > 50 years, while the prognosis of females aged ≤ 50 years was as poor as that of females aged > 50 years.

Keywords: Gastric carcinoma (GC); young age; clinicopathological features; prognosis

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Introduction

Gastric carcinoma (GC) is the fourth most prevalent type of cancer with a low survival rate, and therefore, it places an enormous burden on societies worldwide (1,2). GC occurs most frequently in the 50–70 year age group (2-5). Many studies have shown that younger GC patients (≤ 50 years old) constitute a different clinical entity with its own specific clinicopathological features (6,7). Although young people are less commonly affected by GC, researchers have proposed that young patients show a worse prognosis than older patients. Specifically, GC has demonstrated more aggressive behaviour in patients under 50 years of age than in those over 50 years of age, with a median survival duration of 11 to 16 months versus 33 months, respectively (8). However, recent studies have suggested that younger GC patients have a better prognosis than older GC patients (6), and the number of studies performed on young GC patients is increasing. However, the impact of younger age (≤ 50 years) on the presentation and survival outcomes of GC patients remains controversial (3,6-10). Because of this lack of data on the biological and clinicopathological features of GC in young patients, we selected 487 patients with GC from one surgical team and performed a retrospective cohort study to identify the reasons for the different biological behaviour and prognosis in younger patients. The objective of this study was to assess the clinicopathological features and prognosis of GC patients younger than or equal to 50 years of age compared with the more typical GC population of older patients (51–70 years old).

Methods

Patients

From June 2009 to August 2011, 1,704 patients with GC underwent stomach surgery at Fudan University Shanghai Cancer Center. Four hundred and sixty-three patients underwent surgeries performed by the same chief surgeon. All patients were diagnosed using barium meal, endoscopy, and pathological examination. Clinical data were acquired from the medical records through our computerised documentation system (ChiBASE) and telephone investigation. Four hundred and eleven of the patients were chosen and categorized into the following two groups: the young group, YG (≤ 50 years old, 102 patients), and the old group, OG (51–70 years old, 290 patients). Seventy-one patients older than 70 years of age were excluded. The inclusion criteria consisted of the following: (I) patients with

GC who were pathologically confirmed; (II) patients who underwent radical or palliative surgeries without previous gastric surgery or neoadjuvant chemotherapy; (III) patients who died from other diseases (not GC or related to GC) were excluded. This study was approved by the local ethic committee, and the clinical features analysed included patient age, pathogenesis prior to hospital visit, gender, tumor size, tumor location, histological grade, tumor-node-metastasis (TNM) stage, Borrmann type, anaemia, angiolymphatic invasion, carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA19-9) level, surgical approach and survival.

Follow-up

The follow-up for all patients was regularly performed by telephone or periodic review, and 93.4% of patients received full follow-up. The follow-up period was defined as beginning from the date of treatment to the date of death or final follow-up. The final follow-up date was September 1, 2015.

Evaluation

Pathogenesis prior to hospital visit was defined as ranging from the time alarm symptoms developed to the time at which patients visited the doctor. The TNM classification of GC stage was based on the 7th edition of TNM staging (UICC 2009). Surgical and clinicopathological features were recorded on the basis of the Japanese Classification of Gastric Carcinoma. The following two histological types were included: differentiated (papillary adenocarcinoma and well/moderately differentiated adenocarcinomas) and undifferentiated (poorly or undifferentiated adenocarcinoma, mucinous carcinoma or signet ring cell). For calculation of the survival curves and 5-year disease-specific survival rate, patients who did not undergo tumor resection were excluded because they lacked complete histopathological examination or staging.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 statistical software (SPSS IBM USA). The figures were constructed using GraphPad Prism 5.0 (La Jolla, CA). The data are presented as the mean \pm SD. The chi square test and independent T test were used to compare the clinicopathological data. The Kaplan-Meier method was used to calculate the OS rates. The log-rank test was used

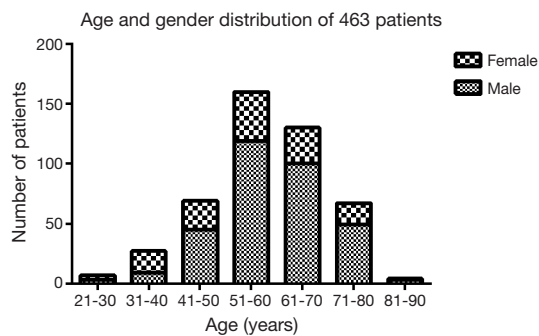


Figure 1 The age and gender distribution of 463 patients with GC. GC, gastric carcinoma.

for the univariate analysis of the relationship between the clinical features and prognosis. Multivariate cox proportional hazards models were used when meaningful factors ($P < 0.05$ in univariate analysis) and features with prognostic value were selected to identify the clinicopathological features that were independent predictive markers of the YG. $P < 0.05$ was considered statistically significant for all methods.

Results

Demographic distribution and clinicopathological features

The demographic distribution and clinicopathological features of all subjects enrolled in this study are summarized in *Figure 1* and *Table 1*. The YG consisted of 102 patients ≤ 50 years of age, while the OG consisted of the remaining 290 patients (> 50 and ≤ 70 years of age). In the YG, 56 patients were male (54.9%) and 46 patients were female (45.1%), while in the OG, 219 were male (75.5%) and 71 were female (24.5%). The age and gender distributions are shown in *Figure 1*. Most patients were 51–70 years old, accounting for 74.0% of all patients. The male-to-female ratio of all GC patients was 2.35:1, but it was 1.22:1 in the YG and 3.08:1 in the OG. The mean age was significantly different in the two study groups at 42.50 ± 6.74 years in the YG versus 60.11 ± 5.14 years in the OG ($P < 0.001$). Regarding time when alarm symptoms began, the YG remained untreated for a significantly longer duration in comparison to the OG (7.33 ± 17.06 days versus 4.50 ± 7.20 days, respectively; 0.022), indicating the YG received a more delayed diagnosis. The YG also differed significantly from the OG in terms of a higher percentage of the T1 depth of invasion (0.034), undifferentiated histological grade ($P < 0.001$), normal preoperative CA19-9 level ($P = 0.07$) and normal preoperative CEA level ($P = 0.017$). However,

no significant differences were found between the two groups in tumor size ($P = 0.059$), tumor location ($P = 0.599$), TNM stage ($P = 0.062$), Borrmann type ($P = 0.144$), lymph node metastasis ($P = 0.731$), distant metastasis ($P = 0.372$), angiolymphatic invasion ($P = 0.347$) and anaemia ($P = 0.231$). *Table 2* shows the surgical features of the GC patients. The YG had a shorter hospital stay after surgery but without significance (11.84 ± 4.26 vs. 12.56 ± 11.57 days; $P = 0.540$), and there were no significant differences for the other surgical features between the two groups.

Survival and prognostic factor

As of September 1, 2015, the 5-year disease-specific survival rate for all 302 patients was 51.3%. The median observation periods were 46.4 months in the YG (range, 4–72 months) versus 43.1 months in the OG (range, 1–68 months). Thirty of our younger patients died during the study period. The 5-year disease-specific survival rate was 67.7% in the YG and 55.8% in the OG. The survival curves of the two groups are shown in *Figure 2A*. The 5-year disease-specific survival rate of the YG was better than that of the OG ($P = 0.048$, *Figure 2A*). In the YG, a significantly lower survival rate was observed for female patients with GC compared to males with GC, as presented in *Figure 2B* (56.1% and 77.6%, respectively; $P = 0.021$). Male patients with GC in the YG showed a significantly higher 5-year disease-specific survival rate compared to those in the OG (77.6% and 57.6%, respectively; $P = 0.009$; *Figure 2C*), while females did not present this difference with age (56.1% and 49.4%, respectively; $P = 0.633$; *Figure 2D*).

Of all 109 younger GC patients analysed in this study, univariate analysis showed that the tumor size, depth of invasion, lymph node involvement, distant metastatic spread, Lymphatic infiltration, venous invasion, CA19-9 level and sex were prognostic factors (*Table 3*). Furthermore, multivariate analysis using Cox regression demonstrated that the tumor size (≥ 5 cm), N classification (N2/3), elevated CA19-9 level and sex (Female) were independent negative prognostic factors of GC patients aged ≤ 50 years old (*Table 3*). In contrast, T classification (T3/4) and N classification (N2/3) were independent negative prognostic factors of GC patients aged > 50 years old ($P = 0.023$, $P = 0.001$, respectively, *Table 4*) and sex (female) had no effect on their prognosis ($P = 0.370$, *Table 4*).

TNM stage distribution

Table 1 Demographic and clinicopathological characteristics of younger and old GC patients (Age, pathogenesis before hospital, tumor size: mean \pm SD)

Variable	Younger group (n=102)	Old group (n=290)	P value
Age (year)	42.50 \pm 6.74	60.11 \pm 5.14	<0.001*
Pathogenesis prior to hospital visit (day)†	7.33 \pm 17.06	4.50 \pm 7.20	0.022*
Gender			<0.001*
Male	56	219	
Female	46	71	
Tumour size			0.059
<5 cm	71	167	
\geq 5 cm	31	116	
Tumour location			0.599
Upper third	47	149	
Middle third	18	48	
Lower third	35	91	
Diffuse	2	2	
Depth of invasion			
T1	35	60	0.034*
T2	9	29	
T3	48	153	
T4	10	48	
Lymph node metastasis			0.731
N0	46	107	
N1	32	98	
N2	14	41	
N3	7	22	
Distant metastasis			0.372
M0	93	255	
M1	9	35	
TNM stage‡			0.062
I	40	73	
II	15	52	
III	38	130	
IV	9	35	
Borrmann type			0.144
I	4	16	
II	35	66	
III	49	162	
IV	0	1	

Table 1 (continued)

Table 1 (continued)

Variable	Younger group (n=102)	Old group (n=290)	P value
Angiolymphatic invasion			0.347
No	63	156	
Yes	36	112	
Differentiation			<0.001*
Well and Moderate	7	75	
Poor	78	167	
Anaemia (Hb <10 g/dL)	10	42	0.231
Preoperative, CA19-9 (µg/mL)			0.007*
Elevated	5	44	
Normal	97	246	
Preoperative, CEA (µg/L)			0.017*
Elevated	9	55	
Normal	93	235	

†, pathogenesis prior to hospital visit ranges from the time alarm symptoms begin to the time patients visit the doctor; ‡, TNM, pathological tumor-node-metastasis; *, significant difference. GC, gastric carcinoma; CA, carbohydrate antigen; CEA, carcinoembryonic antigen.

Table 2 Surgical characteristics of GC patients (Hospital stay after surgery: mean ± SD)

Variable	Younger group (n=102)	Old group (n=290)	P value
Hospital stay after surgery (days)	11.84±4.26	12.56±11.57	0.540
Type of gastrectomy			0.091
Subtotal	71	172	
Total	28	95	
No gastrectomy	3	23	
Curative resection			0.153
Yes	96	259	
No	6	31	
Lymphadenectomy			0.103
D0	3	23	
D1	10	17	
≥D2	89	250	
Radicality			0.434
R0	96	266	
R1 and R2	6	24	
Cancer-related combined resection			0.481
No	92	254	
Yes	10	36	

*, significant difference. GC, gastric carcinoma.

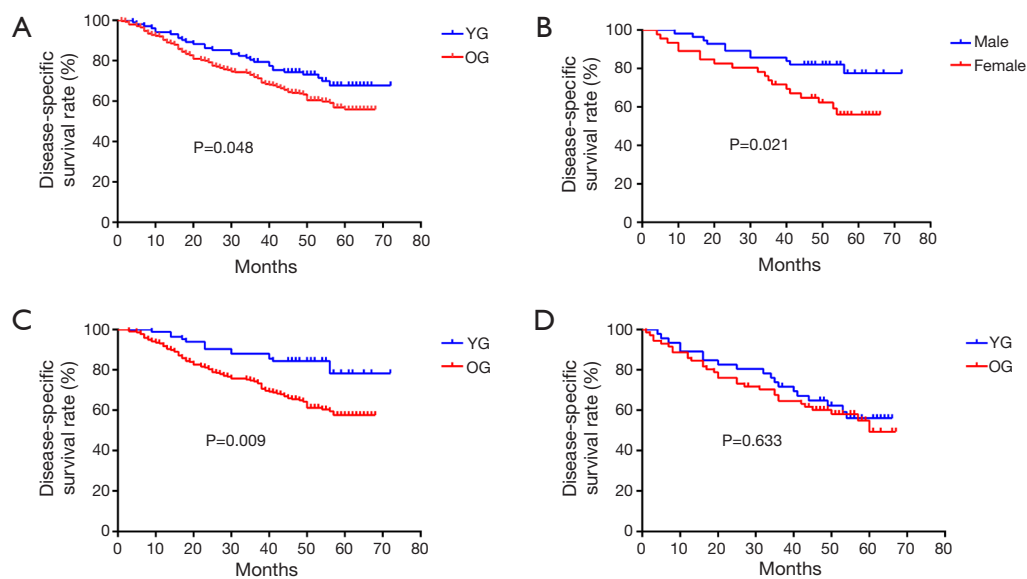


Figure 2 Analysis of disease-specific survival curves of each group. (A) Disease-specific survival curves for patients with GC in the YG and OG (P=0.048); (B) disease-specific survival curves for male and female patients with GC in the YG (P=0.021); (C) disease-specific survival curves for male patients with GC in the YG and OG (P=0.009); (D) disease-specific survival curves for female patients with GC in the YG and OG (P=0.633).

Table 3 Univariate and multivariate survival analysis in 102 younger GC patients

Variable	Univariate analysis (P-value)	Multivariate analysis (P-value)	HR	95% CI
Tumour size (≥5 cm)	<0.001*	0.043*	2.446	1.028–5.822
T classification (T3/4)	<0.001*	0.082	2.961	0.872–10.05
N classification (N2/3)	<0.001*	0.001*	5.603	1.944–16.148
Distant metastasis (M1)	<0.001*	0.659	0.665	0.109–4.059
Lymphatic infiltration (yes)	0.038*	0.945	0.945	0–5.339E79
Borrmann type (III/IV)	0.067	—	—	—
Venous invasion (yes)	0.029*	0.952	0.952	0–1.467E85
Differentiation (poorly)	0.445	—	—	—
Serum CEA (Elevated)	0.565	—	—	—
Serum CA19-9 (Elevated)	0.002*	0.037*	7.035	1.122–44.122
Sex (Female)	0.021*	0.009*	3.538	1.372–9.123

*, significant difference. GC, gastric carcinoma; HR, hazard ratio; CI, confidence interval.

The TNM stage distribution was compared between the YG and OG, males and females in the YG, males in the YG and OG, and females in the YG and OG (Figure 3). More patients were in the I-stage and fewer patients were in the III-stage in the YG than the OG, but this finding was not significant (39.2% and 37.3% vs. 25.2% and 44.8%, respectively; Figure 3A, P=0.062). In the YG, males showed

a higher proportion of I-stage disease than females, but this finding also was not significant (44.6% vs. 32.6%, respectively; Figure 3B, P=0.289). In addition, no significant difference was found between the TNM stage distribution of the YG and OG in females (Figure 3D, P=0.826). Figure 3C shows that there was a significant difference between the YG and OG among males; in particular, males in the

Table 4 Univariate and multivariate survival analysis in 290 old GC patients

Variable	Univariate analysis (P-value)	Multivariate analysis (P-value)	HR	95% CI
Tumour size (≥ 5 cm)	<0.001*	0.432	1.214	0.748–1.971
T classification (T3/4)	<0.001*	0.023*	2.678	1.145–6.261
N classification (N2/3)	<0.001*	0.001*	2.312	1.434–3.728
Distant metastasis (M1)	<0.001*	0.825	1.132	0.378–3.394
Lymphatic infiltration (yes)	<0.001*	0.095	3.241	0.815–12.886
Borrmann type (III/IV)	<0.001*	0.957	0.983	0.527–1.835
Venous invasion (yes)	<0.001*	0.685	0.755	0.195–2.925
Differentiation (poorly)	0.020*	0.181	0.670	0.373–1.204
Serum CEA (Elevated)	<0.001*	0.381	1.257	0.754–2.097
Serum CA19-9 (Elevated)	0.001*	0.078	1.63	0.947–2.806
Sex (Female)	0.370	—	—	—

*, significant difference; GC, gastric carcinoma; HR, hazard ratio; CI, confidence interval.

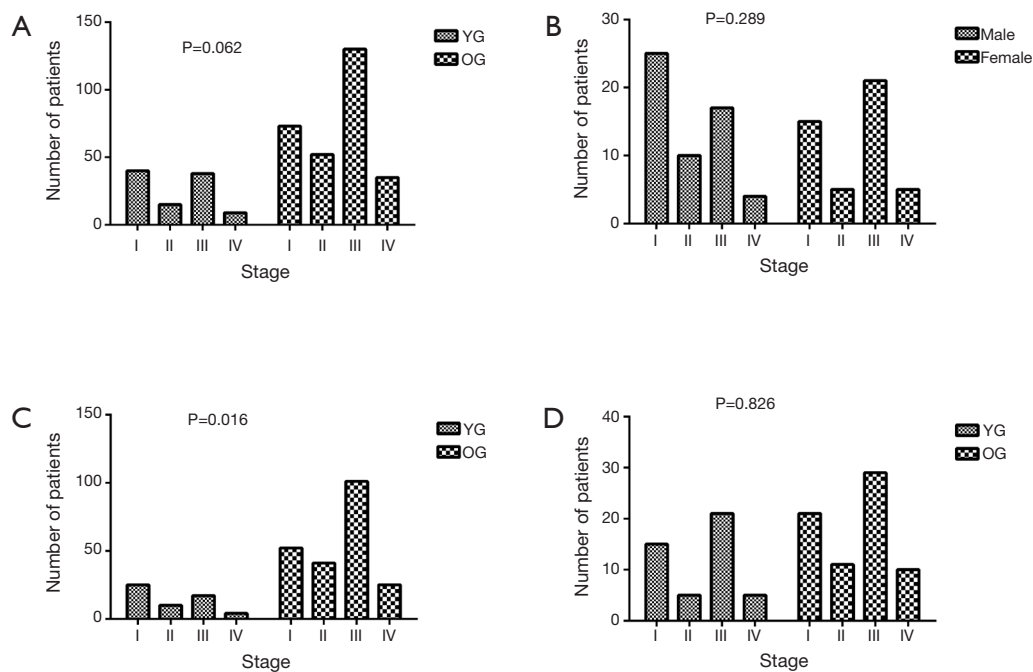


Figure 3 Analysis of the TNM stage distribution in different groups. (A) The TNM stage distribution of the YG and OG ($P=0.062$); (B) the TNM stage distribution of male and female patients with GC ($P=0.629$); (C) the TNM stage distribution of male patients with GC in the YG and OG ($P=0.016$); (D) the TNM stage distribution of female patients with GC in the YG and OG ($P=0.826$). TNM, tumor-node-metastasis; GC, gastric carcinoma.

YG showed a higher percentage of I-stage and a lower percentage of III-stage compared to males in the OG (44.6% and 30.4% vs. 23.7% and 46.1%, respectively; $P=0.016$).

Discussion

GC is generally considered a disease of the elderly, and patients have a mean age of over 60 years at diagnosis (10,11). GC occurs most frequently in the 50–70 year age group (2-5). However, the rate of GC in young patients has increased in recent decades despite a reduction in the overall prevalence of the disease (12-14). Due to incomplete data regarding whether GC in younger patients differs from that in older patients, we focused on patients ≤ 50 years old. In particular, we retrospectively analysed 392 patients with GC who underwent a stomach resection operation performed by the same surgeon, including 102 (26.0%) patients in the YG and 290 (74.0%) in the OG.

Previous studies have demonstrated numerous clinical differences between younger and old patients with GC. In particular, these results showed that the percentage of females was higher among younger compared to old patients (8,15-19), and our findings are consistent with these reports ($P<0.001$). Several reports have also suggested that hormonal factors might account for the higher percentage of young females with GC. Younger females show a higher level of oestrogen and an increased proportion of oestrogen receptor-positive cells (19-21). Nevertheless, the correlation between gender hormones and GC prognosis remains controversial, and further research is needed to confirm whether gender impacts the prognosis of younger patients.

According to our data, there were higher proportions of cases with an undifferentiated histological grade and the signet ring cell type of GC in younger patients, which is consistent with previous studies showing that younger patients display poorly differentiated histology (4,6,8,22). However, there were no significant differences in the tumor size, tumor location, TNM stage, Borrmann type, lymph node metastasis, distant metastasis, angiolymphatic invasion, and anaemia between the two groups in our study. The YG had a longer latency before presenting to the hospital than the OG, indicating that younger patients lack awareness of their self-health, which may lead to delayed diagnosis. Additionally, there were no significant differences in surgical features between the groups, such as the type of gastrectomy, curative resection, lymphadenectomy, radicality, and cancer-related combined resection. Though no significant difference was found between two groups,

the comparatively shorter hospital stay after surgery for the YG might indicate that younger patients were more able to withstand stomach resection surgery.

The higher percentage of T1 depth of invasion, early stage and good physical fitness might explain the good outcome of the YG. In addition, the aggressive histology of younger GC patients may be balanced by the comparatively higher percentage of I/II TNM stage distribution. A higher percentage of patients with a normal CA19-9 level was also associated with the improved survival observed in the YG. Angiolymphatic invasion has been reported to be a negative factor associated with distant metastasis (23), and the YG showed a lower frequency of angiolymphatic invasion than the OG, but the difference lacked significance ($P=0.347$).

The 5-year disease-specific survival rate in the YG was significantly higher than that in the OG ($P=0.048$), which is consistent with the results of recent studies (6,7). In the YG, male patients showed a significantly higher survival rate than females ($P=0.021$). The 5-year disease-specific survival rate of male patients with GC in the YG was significantly higher than that of male patients in the OG ($P=0.009$), while the 5-year disease-specific survival of females was not different between age groups ($P=0.633$). These findings indicated that the better prognosis of the YG was most likely due to the higher survival rate among males than females. The lower TNM stage distribution of males in the YG and more advanced TNM stage of males in the OG may partially explain the good prognosis of males in the YG. Younger patients, especially males, diagnosed in earlier stage might be associated with their positive attitude and convenience to hospital. So, male GC patients under 50 years of age showed an improved 5-year survival rate. Additionally, the prognosis of females was poor for both the YG and OG, with no significant difference related to age. A previous study is in agreement with our findings (24); however, there is no precise explanation for these similarities. Furukawa *et al.* (25) suggested that females' analogues or sex hormones might affect carcinogenesis or stomach cancer progression. In addition, pregnancy and delivery may accelerate the growth of stomach cancer cells, although the exact molecular mechanism responsible for this effect remains unclear.

Younger patients show distinguishing features and prognostic results compared to elderly patients; therefore, exploring and evaluating the prognostic factors that influence the survival rate in younger patients is meaningful. The prognosis for females was worse than that for males in the YG. In the present study, we also found that tumor

size (≥ 5 cm), N classification (N2/3), elevated CA19-9 level and sex (Female) served as independent negative prognostic factors for younger patients with GC. Similarly, the CA19-9 level was previously reported to be a negative prognostic indicator (26), which is consistent with our findings.

It was the first time to exclude the factor of surgeon's skill and we believe our results might provide meaningful conclusions regarding younger patients with GC. However, this was a small, single-centre study which lack in-depth study of the mechanism. Further large sample study with in-depth exploration of the mechanism was needed.

In summary, GC patients ≤ 50 years of age showed distinct features, including a higher percentage of females, a higher percentage of the T1 depth of invasion, undifferentiated histological grade, normal preoperative CA19-9 level and normal preoperative CEA level in comparison to the OG (51–70 years of age). Males ≤ 50 years of age more commonly showed early staged disease with better survival, while the prognosis of females ≤ 50 years of age was as poor as that of females > 50 years of age. Thus, enhancing young people's awareness of self-health is necessary, particularly for young females.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the ethic committee of Fudan university cancer center and written informed consent was obtained from all patients.

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