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## Retrospective Cohort Study

**Sex-based differences in histology, staging, and prognosis among 2983 gastric cancer surgery patients**

Yonghoon Choi, Nayoung Kim, Ki Wook Kim, Hyeong Ho Jo, Jaehyung Park, Hyuk Yoon, Cheol Min Shin, Young Soo Park, Dong Ho Lee, Hyeon Jeong Oh, Hye Seung Lee, Young Suk Park, Sang-Hoon Ahn, Yun-Suhk Suh, Do Joong Park, Hyung-Ho Kim, Ji-Won Kim, Jin Won Kim, Keun-Wook Lee, Won Chang, Ji Hoon Park, Yoon Jin Lee, Kyoung Ho Lee, Young Hoon Kim

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**Abstract****BACKGROUND**

Few studies have been conducted on sex differences in the incidence, pathophysiology, and prognosis of gastric cancer (GC).

### AIM

To analyze the differences in GC characteristics according to sex in patients who underwent surgical treatment for GC.

### METHODS

A total of 2983 patients diagnosed with gastric adenocarcinoma who received surgical treatment at the Seoul National University Bundang Hospital between 2003 and 2017 were included. Baseline clinicopathological characteristics, histologic type of GC, overall and GC-specific survival rates, and associated risk factors were analyzed.

### RESULTS

Among the 2983 patients, 2005 (67.2%) and 978 (32.8%) were males and females, respectively. The average age of the female group (59.36 years) was significantly younger than that of the male group (61.66 years;  $P < 0.001$ ). Cancer of the gastric body ( $P < 0.001$ ) and diffuse-type histology ( $P < 0.001$ ) were more common in females than in males. This trend was more prominent in females younger than 60 years of age, with a significantly higher proportion of diffuse-type cancer than in the male group. Regardless of sex, diffuse-type GC was more common in younger patients, and the proportion of intestinal-type GC increased with age. The overall survival rate was significantly higher in females ( $P < 0.001$ ). However, this difference disappeared for GC-specific survival ( $P = 0.168$ ), except for the poor GC-specific survival rate in advanced-stage cancer (stage III or above) in females ( $P = 0.045$ ). The risk factors for GC-related mortality were older age, upper location of GC, and diffuse- or mixed-type histology. In terms of comorbidities, more males died from diseases other than GC, including other malignancies such as lung cancer, hepatocellular carcinoma, and pancreatic cancer, and respiratory diseases such as interstitial lung disease and chronic obstructive pulmonary disease, while there were relatively more cardiovascular or cerebrovascular deaths in females.

### CONCLUSION

Sex-based differences in GC were observed in clinicopathological features, including age at diagnosis, tumor location, histologic type, survival rate, and comorbidities.

**Key Words:** Gastric cancer; Histology; Prognosis; Sex difference; Survival

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**Core Tip:** In the analyses of sex differences in gastric cancer (GC), the sex ratio between males and females was 2:1, but the incidence of diffuse-type cancer was higher in females until the age of 60 years. The average age of the female group was significantly younger, and cancer of the gastric body and diffuse-type histology were more common than those in the males. In addition, there was poor GC-specific survival rate in advanced-stage cancer in females, while comorbidities including cancers of other organs and respiratory diseases were more common in males.

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## INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer-related deaths worldwide[1]. Age-standardized incidence rates are approximately twice as high in males than in females[2]. Major risk factors for developing GC include *Helicobacter pylori* (*H. pylori*) infection, family history of GC, dietary habits, ionizing radiation, smoking, alcohol, and pernicious anemia, and the difference in incidence between males and females is likely due to the difference in exposure to these risk factors[3-5]. However, these factors alone do not fully explain the different characteristics of GC between the sexes. Recent research has revealed the role of sex hormones in various diseases and the resulting sex differences. It is well known that sex differences exist in the location and prognosis of

various cancers, including colorectal cancer[6,7], renal cell carcinoma[8], and bladder cancer[9]. In addition, sex differences are also known in central nervous system diseases such as cognitive disorders, Alzheimer's disease[10], Parkinson's disease[11], and autoimmune diseases[12]. However, the role of sex hormones such as testosterone and estrogen in the etiology, response to therapy, and survival of patients with GC, and the involved mechanisms and pathways remain unclear. Also, few studies to date have detailed the epidemiological and prognostic differences in GC between males and females.

Lauren classification is an independent prognostic factor in patients with GC[13]. That is, intestinal-type GC shows better clinicopathological characteristics and prognosis than diffuse-type GC. Diffuse-type cancer exhibits a higher recurrence rate than intestinal-type cancer, and the clinical appearance and survival of mixed-type cancers are known to be similar to those of diffuse-type GC[14]. Environmental factors reportedly play an important role in the development of intestinal-type versus diffuse-type GC [15]. There is also a sex-based difference in the histologic type of GC. That is, there is a marked predominance of older age and male sex in intestinal-type GC and a younger female predominance in diffuse-type GC. Younger female patients seem to exhibit a higher percentage of diffuse-type GC, resulting in more aggressive tumor behavior[14]; therefore, treatment methods may vary according to the Lauren type[16]. From this point of view, we hypothesized that an accurate analysis of sex-based differences in GC is possible in a well-designed surgical cohort with regular follow-up observations, clear histologic results, accurate information on family history, and social history such as smoking and alcohol consumption. Based on this background, the aim of this study was to analyze the sex-based differences in clinicopathological features and staging in GC, and to investigate prognostic factors including survival and death.

## MATERIALS AND METHODS

### Study population

Initially, 3074 patients aged > 18 years were selected from a prospective surgical cohort of patients who were diagnosed with gastric adenocarcinoma and underwent surgical treatment at Seoul National University Bundang Hospital (SNUBH) between 2003 and 2017 (Figure 1). Analyses of the effects of *H. pylori* eradication treatment, P53 overexpression and the incidence of metachronous GC in this cohort were previously published by our team[17-19]. The following patients were excluded: those with incomplete medical records or unclassified histology, who were lost to follow-up, had a prior history of other cancers at the time of diagnosis, or those who had other diseases with inoperable severity were excluded from the study. Finally, 2983 patients were included in the analysis (Figure 1). The medical records of these patients, including sex, age, death (including cause), histologic type of cancer, and social history such as alcohol consumption, smoking, and family history of GC were collected from surgical and medical cohorts, and reviewed using the Clinical Data Warehouse. The dates and causes of death of the enrolled patients were cross-reviewed with data from the National Statistical Office for verification.

### Statistical analysis

The outcomes were overall survival and GC-specific survival. Univariate and multivariate Cox proportional hazards analyses were used to identify risk factors, and variables with a *P* value < 0.2 in the univariate analyses, were used as covariates for the multivariate analysis. The Kaplan-Meier estimator method and log-rank tests were used to compare survival. Analyses were performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, United States). Statistical significance was set at *P* < 0.05. All data are available upon request from the corresponding author.

### Ethical considerations

The study was reviewed and approved by the Institutional Review Board of SNUBH (IRB No. B-1902-523-107) and registered at clinicaltrials.gov (NCT03978481). All authors have access to the study data and have approved the final manuscript.

## RESULTS

### Baseline clinicopathological characteristics

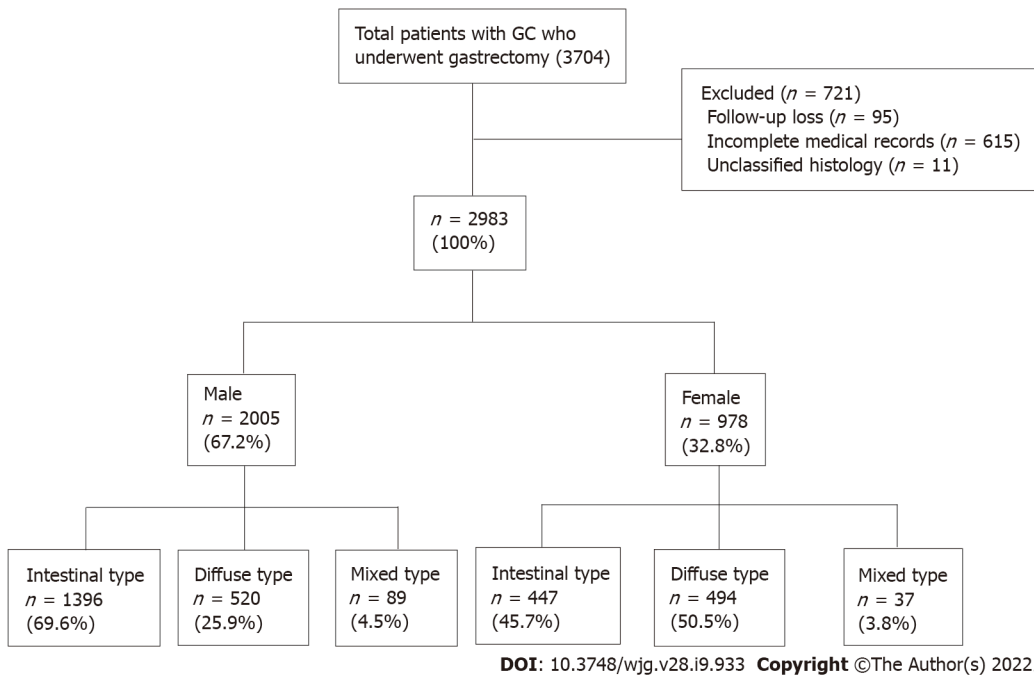
The baseline clinicopathological features of the subjects are shown in Table 1. Of the 2983 patients, 2005 were males and 978 were females, indicating a 2:1 sex ratio, with an average age of 61.66 for males and 59.36 for females, indicating a significantly younger onset age in females (*P* < 0.001). A higher proportion of males had a history of alcohol consumption and smoking (drinking history, *P* < 0.001; smoking history, *P* < 0.001). Cancer of the gastric body and diffuse-type cancer were more common in females (tumor location, *P* < 0.001; histologic type, *P* < 0.001, respectively). Overexpression of P53 was more common in males than in females (*P* < 0.001). There were no differences in family history, cancer

Table 1 Clinicopathological features of patients with gastric cancer

Characteristics	Total (N = 2983)	Female (n = 978)	Male (n = 2005)	P value
Age (yr, mean ± SD)	60.91 ± 12.31	59.36 ± 13.47	61.66 ± 11.63	< 0.001 <sup>a</sup>
Drinking history, n (%)				
No	1631 (54.7)	790 (80.8)	841 (41.9)	< 0.001 <sup>a</sup>
Yes	1352 (45.3)	188 (19.2)	1164 (58.1)	
Smoking history, n (%)				
No	1645 (55.1)	902 (92.2)	743 (37.1)	< 0.001 <sup>a</sup>
Yes	1338 (44.9)	76 (7.8)	1262 (62.9)	
Family history, n (%)				
No	2467 (82.7)	803 (82.1)	1664 (83.0)	0.548
Yes	516 (17.3)	175 (17.9)	341 (17.0)	
Tumor location, n (%)				
Upper	77 (2.6)	19 (2.0)	58 (2.9)	< 0.001 <sup>a</sup>
Middle	1332 (44.6)	497 (50.8)	835 (41.6)	
Lower	1574 (52.8)	462 (47.2)	1112 (55.5)	
Atrophic gastritis, n (%)				
No	2162 (72.5)	751 (76.8)	1411 (70.4)	< 0.001 <sup>a</sup>
Yes	821 (27.5)	227 (23.2)	594 (29.6)	
Intestinal metaplasia, n (%)				
No	1680 (56.3)	560 (57.3)	1120 (55.9)	0.469
Yes	1303 (43.7)	418 (42.7)	885 (44.1)	
T stage, n (%)				
T1	2134 (71.5)	696 (71.2)	1438 (71.7)	0.669
T2	330 (11.1)	102 (10.4)	228 (11.4)	
T3	420 (14.1)	144 (14.7)	276 (13.8)	
T4	99 (3.3)	36 (3.7)	63 (3.1)	
N stage, n (%)				
N0	2215 (74.3)	696 (71.2)	1519 (75.7)	0.014 <sup>a</sup>
N1	423 (14.2)	163 (16.7)	260 (13.0)	
N2	174 (5.8)	66 (6.7)	108 (5.4)	
N3	171 (5.7)	53 (5.4)	118 (5.9)	
Stage, n (%)				
I	2312 (77.5)	743 (76.0)	1569 (78.3)	0.189
II	405 (13.6)	151 (15.4)	254 (12.7)	
III	212 (7.1)	69 (7.1)	143 (7.1)	
IV	54 (1.8)	15 (1.5)	39 (1.9)	
Cancer type, n (%)				
EGC	2133 (71.5)	696 (71.2)	1437 (71.7)	0.774
AGC	850 (28.5)	282 (28.8)	568 (28.3)	
Histologic type, n (%) (Lauren classification)				
Intestinal	1843 (61.8)	447 (45.7)	1396 (69.6)	< 0.001 <sup>a</sup>
Diffuse	1014 (34.0)	494 (50.5)	520 (25.9)	

Mixed	126 (4.2)	37 (3.8)	89 (4.5)	
<i>H. pylori</i> status, n (%)				
Negative	1267 (42.5)	379 (38.8)	888 (44.3)	0.004 <sup>a</sup>
Positive	1716 (57.5)	599 (61.2)	1117 (55.7)	
P53, n (%)				
Negative	1917 (64.3)	706 (72.2)	1211 (60.4)	< 0.001 <sup>a</sup>
Positive	1066 (35.7)	272 (27.8)	794 (39.6)	

<sup>a</sup> $P < 0.05$  indicates statistical significance. SD: Standard deviation; EGC: Early gastric cancer; AGC: Advanced gastric cancer; *H. pylori*: *Helicobacter pylori*.



**Figure 1** Study flow chart of patient enrollment and exclusion process. GC: Gastric cancer.

staging, or *H. pylori* infection at the time of diagnosis between males and females (family history,  $P = 0.548$ ; cancer stage,  $P = 0.189$ ; and *H. pylori* status,  $P = 0.062$ , respectively).

### Differences in cancer histology by sex and age

To identify the histological changes in GC by age, the entire group of patients was divided into groups of under 40, 40-49, 50-59, 60-69, and 70+ years, and the trend of an increasing percentage of intestinal-type cancers with age, in both males and females, was noted (Supplementary Table 1). Considering the number of patients and histological ratios, there were more female patients under the age of 40 years and older male patients (Supplementary Figure 1). A higher number of female GC patients were under 40 years of age, while diffuse-type cancer was more common in both males and females than the other histological types (Figure 2). Among the male patients, the proportion of intestinal-type cancer increased steeply from age 50 years, whereas in female patients, the proportion of diffuse-type cancer remained high at 50-59 years of age (Figure 2). The ratio of intestinal- and diffuse-type GC in females approximately 20 years after menopause was similar to that of male patients aged  $\geq 70$  years (Figure 2).

Meanwhile, a significant correlation was observed between histological type and GC location, with a high ratio of diffuse-type cancer and stomach body cancer in females and a high ratio of intestinal-type cancer and stomach antral cancer in males (Pearson correlation analysis,  $P < 0.001$ ).

### Overall and cancer-specific survival

A statistically significant female predominance was identified in overall survival ( $P < 0.001$ ), while a non-significant male predominance was identified in GC-specific survival (Figure 3). Increasing age, proximal tumor location, and diffuse- or mixed-type histology were identified as risk factors for GC-related morbidity (Table 2). In terms of cancer stage, there were no significant differences in patients



Table 2 Univariate and multivariate analyses for gastric cancer related morbidity

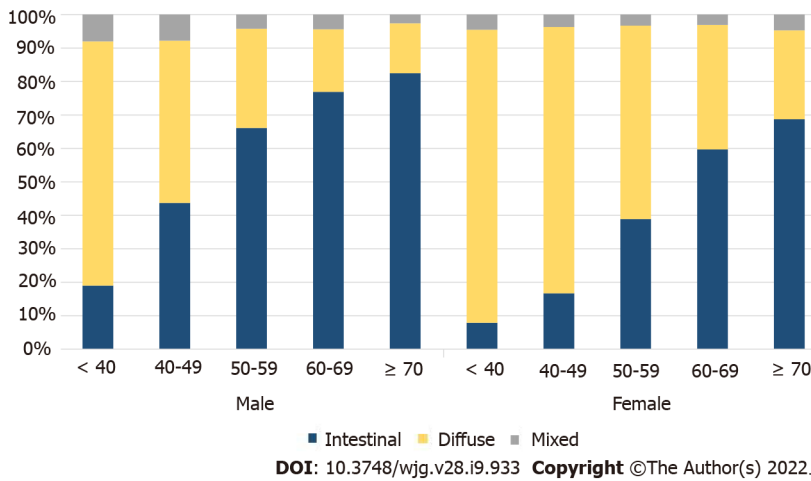
Variable	Univariate analysis	P value	Multivariate analysis	P value
Sex				
Male	Ref	0.169	Ref	0.672
Female	1.22 (0.92-1.61)		1.06 (0.80-1.42)	
Age				
< 60	Ref	0.001 <sup>a</sup>	Ref	< 0.001 <sup>a</sup>
≥ 60	1.64 (1.23-2.18)		2.02 (1.50-2.73)	
Drinking history				
No	Ref	0.996		
Yes	1.00 (0.76-1.32)			
Smoking history				
No	Ref	0.283		
Yes	1.16 (0.88-1.53)			
Family history				
No	Ref	0.189	Ref	0.165
Yes	0.77 (0.51-1.14)		0.75 (0.51-1.12)	
Tumor location				
Upper	Ref	0.003 <sup>a</sup>	Ref	< 0.001 <sup>a</sup>
Middle	1.65 (0.41-6.71)		1.40 (0.34-5.71)	
Lower	2.61 (0.65-10.54)		2.63 (0.65-10.64)	
Atrophic gastritis				
No	Ref	0.871		
Yes	0.97 (0.71-1.34)			
Intestinal metaplasia				
No	Ref	0.412		
Yes	0.89 (0.67-1.18)			
Histologic type (Lauren classification)				
Intestinal	Ref	< 0.001 <sup>a</sup>	Ref	< 0.001 <sup>a</sup>
Diffuse	2.16 (1.62-2.89)		3.07 (2.25-4.19)	
Mixed	2.25 (1.29-3.92)		2.50 (1.43-4.35)	
P53				
Negative	Ref	0.651		
Positive	1.07 (0.80-1.42)			

<sup>a</sup> $P < 0.05$  indicates statistical significance.

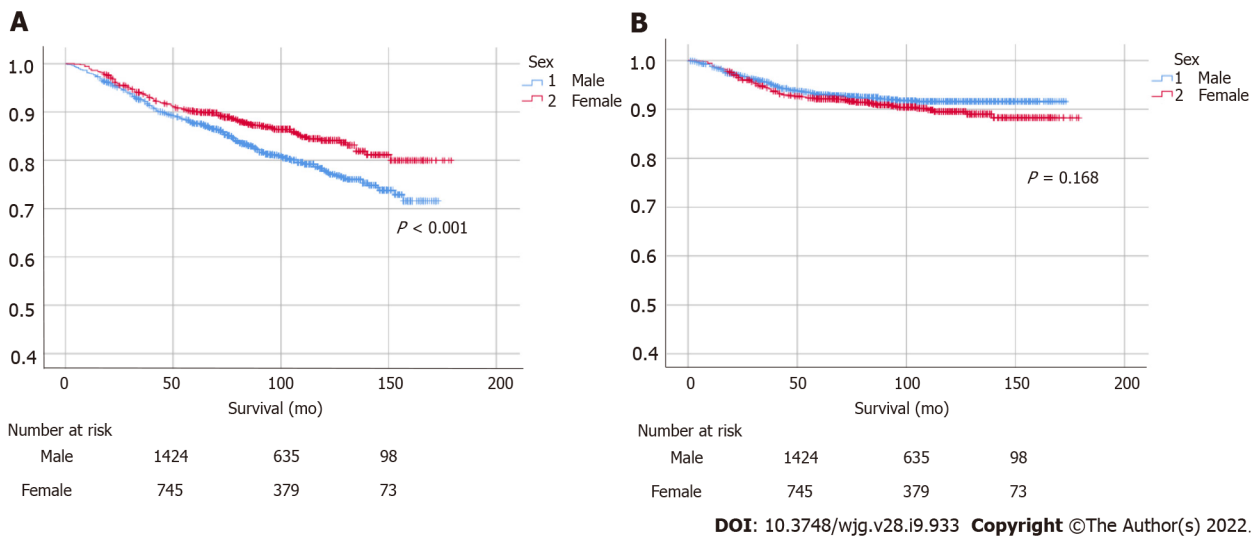
$P < 0.2$  were used for multivariable analyses.

with stage I or II GC, whereas a statistically significant male predominance was observed in patients with advanced-stage cancer (stage III or above,  $P = 0.045$ ; Figure 4). Histologically, patients with intestinal-type GC had a significantly higher survival rate than those with diffuse-type GC, and there were no statistically significant differences between males and females in intestinal- or diffuse-type GC (Supplementary Figure 2).

In the assessment of comorbidities, we investigated sex-based causes of death. Patients with a prior history of other cancers at the time of diagnosis or having severe diseases with inoperable conditions were excluded from the study, as mentioned above. Among the patients, 453 died including 135 males (6.7%) and 86 females (8.8%) died of GC. Significantly more males died from diseases other than GC (193 males and 39 females). In males, there were more deaths from malignancies such as lung cancer,



**Figure 2 Proportion of histological types of gastric cancer according to sex and age.** The trend of an increasing proportion of intestinal-type cancers with increasing age was observed in both males and females. In males, the proportion of intestinal-type cancer increased steeply from an age of 50 years. In females, the proportion of diffuse-type cancer remained high until 60 years of age. The ratio of intestinal- and diffuse-type gastric cancer in females became similar to that of male patients aged 70 years or older, about 20 years after menopause.



**Figure 3 Survival according to sex and initial cancer stage.** (A) Overall and (B) gastric cancer-specific survival. A statistically significant female predominance in overall survival was identified ( $P < 0.001$ ), while a non-significant male predominance was identified in gastric cancer-specific survival.  $P$  values were calculated using the log-rank test.

hepatocellular carcinoma, pancreatic cancer, and respiratory diseases such as interstitial lung disease and chronic obstructive pulmonary disease, while there were relatively more cardiovascular or cerebrovascular deaths in females. Details regarding these are given in [Supplementary Tables 2-4](#).

**Subgroup analyses by sex and histology**

The results of the subgroup analyses based on sex and histology are presented in [Table 3](#) and [Supplementary Table 3](#). In females, intestinal-type GC was associated with older age and a family history of GC, while diffuse-type GC was associated with younger age and P53 negativity. In males, intestinal-type GC was associated with older age, while diffuse-type GC tended to be associated with younger age and smoking history.

**DISCUSSION**

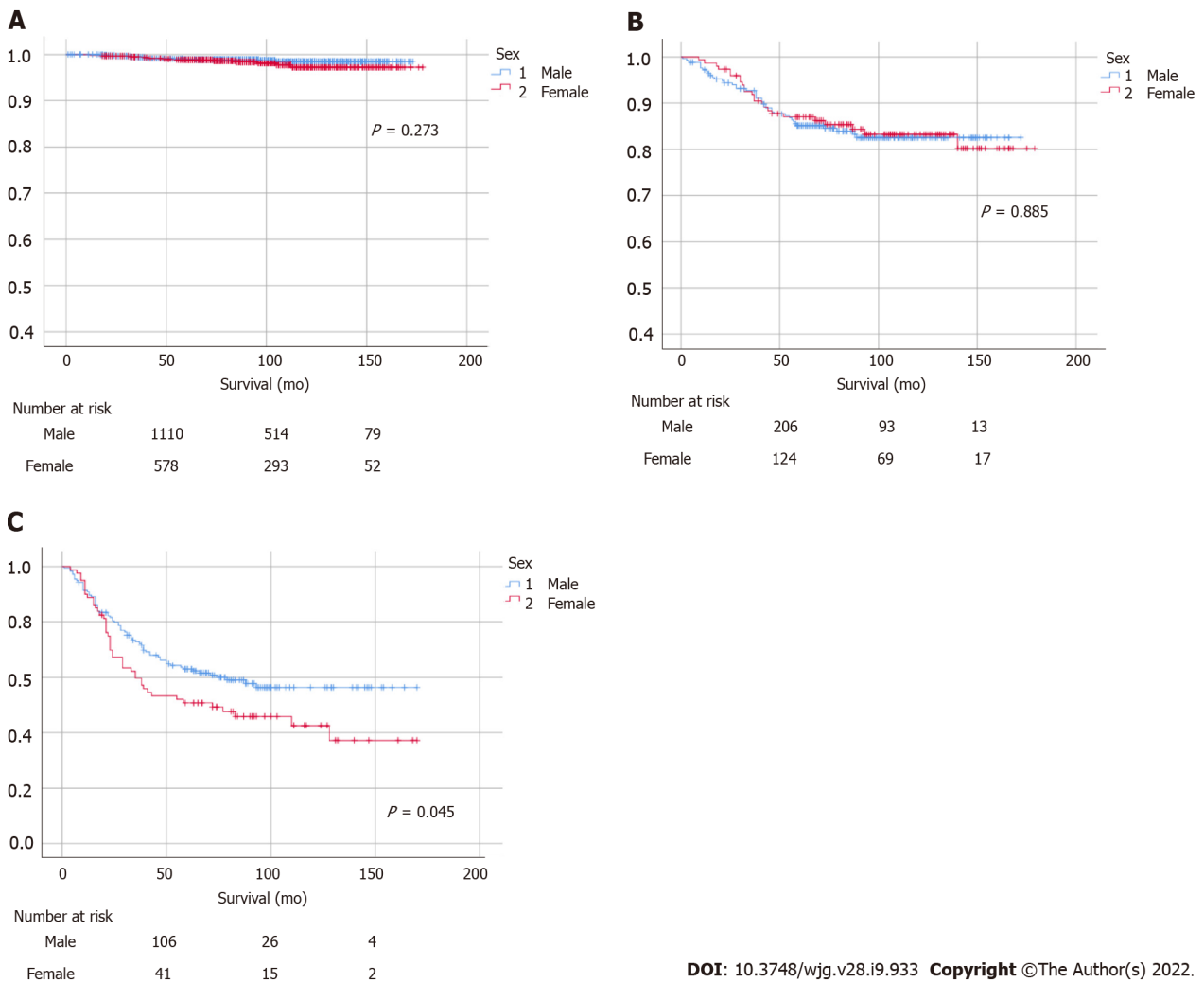
To the best of our knowledge, this study is the first to provide evidence of sex differences in GC with exact histologic diagnosis and long-term follow-up in nearly 3000 patients. In our data, a statistically significant overall survival benefit in females and a non-significant GC-specific survival in males were

Table 3 Clinicopathological features by sex and histologic type

Characteristics	Intestinal type		P value	Diffuse type		P value
	Female (n = 447)	Male (n = 1396)		Female (n = 494)	Male (n = 520)	
Age (yr, mean ± SD)	65.72 ± 10.71	64.06 ± 10.34	0.792	53.60 ± 13.06	55.82 ± 12.48	0.229
Drinking history, n (%)						
No	385 (86.1)	619 (44.3)	< 0.001 <sup>a</sup>	374 (75.7)	183 (35.2)	< 0.001 <sup>a</sup>
Yes	62 (13.9)	777 (55.7)		120 (24.3)	337 (64.8)	
Smoking history, n (%)						
No	420 (94.0)	530 (38.0)	< 0.001 <sup>a</sup>	447 (90.5)	175 (33.7)	< 0.001 <sup>a</sup>
Yes	27 (6.0)	866 (62.0)		47 (9.5)	345 (66.3)	
Family history, n (%)						
No	348 (77.9)	1138 (81.5)	0.088	419 (84.8)	447 (86.0)	0.606
Yes	99 (22.1)	258 (18.5)		75 (15.2)	73 (14.0)	
Tumor location, n (%)						
Upper	12 (2.7)	44 (3.2)	0.053	7 (1.4)	10 (1.9)	< 0.001 <sup>a</sup>
Middle	139 (31.1)	517 (37.0)		334 (67.6)	284 (54.6)	
Lower	296 (66.2)	835 (59.8)		153 (31.0)	226 (43.5)	
Atrophic gastritis, n (%)						
No	320 (71.6)	951 (68.1)	0.168	400 (81.0)	389 (74.8)	0.018 <sup>a</sup>
Yes	127 (28.4)	445 (31.9)		94 (19.0)	131 (25.2)	
Intestinal metaplasia, n (%)						
No	229 (51.2)	751 (53.8)	0.344	303 (61.3)	306 (58.8)	0.418
Yes	218 (48.8)	645 (46.2)		191 (38.7)	214 (41.2)	
T stage, n (%)						
T1	355 (79.4)	1087 (77.9)	0.529	314 (63.6)	305 (58.6)	0.445
T2	40 (9.0)	138 (9.9)		57 (11.5)	66 (12.7)	
T3	40 (9.0)	145 (10.4)		99 (20.0)	118 (22.7)	
T4	12 (2.6)	26 (1.8)		24 (4.9)	31 (6.0)	
N stage, n (%)						
N0	356 (79.6)	1140 (81.7)	0.745	319 (64.6)	335 (64.4)	0.055
N1	56 (12.5)	149 (10.7)		97 (19.6)	85 (16.4)	
N2	20 (4.5)	62 (4.4)		42 (8.5)	38 (7.3)	
N3	15 (3.4)	45 (3.2)		36 (7.3)	62 (11.9)	
Stage, n (%)						
I	375 (83.9)	1171 (83.9)	0.49	342 (69.2)	347 (66.7)	0.152
II	47 (10.5)	142 (10.2)		96 (19.5)	89 (17.1)	
III	23 (5.1)	65 (4.6)		43 (8.7)	66 (12.7)	
IV	2 (0.5)	18 (1.3)		13 (2.6)	18 (3.5)	
Cancer type, n (%)						
EGC	355 (79.4)	1086 (77.8)	0.469	314 (63.6)	305 (58.7)	0.109
AGC	92 (20.6)	310 (22.2)		180 (36.4)	215 (41.3)	
P53, n (%)						
Negative	293 (65.5)	770 (55.2)	< 0.001 <sup>a</sup>	385 (77.9)	393 (75.6)	0.374

Positive	154 (34.5)	626 (44.8)	109 (22.1)	127 (24.4)
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<sup>a</sup>*P* < 0.05 indicates statistical significance. SD: Standard deviation; EGC: Early gastric cancer; AGC: Advanced gastric cancer.



**Figure 4** Gastric cancer-specific survival in (A) stage I, (B) stage II, and (C) stage above III. There were no significant differences between males and females in stages I and II, but a statistically significant male predominance was observed in advanced-stage cancer (stage III or above, *P* = 0.045). *P* values were calculated using the log-rank test.

observed. In both males and females, a high proportion of diffuse-type cancers was observed among younger patients, while intestinal-type cancer became more prominent with increasing age. However, more females of all ages had diffuse-type cancer, while the ratio of diffuse-type to intestinal-type cancer was higher in females until the age of 60 years. In addition, the incidence of higher proportion of diffuse-type and gastric body cancers in females, compared to intestinal-type and antral cancers in males could be the reasons for higher N stage and poor GC-specific survival in females. Furthermore, there were also differences in comorbidities, including causes of death other than GC, between males and females.

There are few studies on the prognosis of GC by sex, and sex-based differences in GC are not clear, as in other cancers such as colorectal cancer[6,7]. A recent study based on the Surveillance, Epidemiology, and End Results (SEER) database in the United States reported survival advantages in females[20]. A female advantage was observed in both overall survival and GC-specific survival, and the prognosis of GC and the risk of developing GC were significantly worse in males than in females in that study, so the authors insisted on the necessity for early intervention in high-risk male patients due to their relatively poor prognosis[20]. However, this difference from our results could be due to a difference in the histologic type of GC, with a higher proportion of adenocarcinoma and a lower proportion of signet ring cell carcinoma (SRC), especially in females. In a large meta-analysis of data obtained from the Korea Central Cancer Registry and National Statistical Office reported by Song *et al*[21], the prognosis of female GC patients was also better than that of male GC patients, with differential incidence and

mortality patterns among age groups. However, females tend to have a worse prognosis when they are diagnosed later than 40 years of age. In that study, the histologic type or anatomic subsites of GC could not be identified. Since the 2000s, many early GC (EGC) patients have been identified and treated through a national endoscopic surveillance project in Korea, possibly showing different results from data prior to the 2000s[22]. Contrary to earlier results, a recent study in Korea reported poor prognosis in females[23], similar to the present study. The authors concluded that female GC patients were significantly younger, had more poorly differentiated adenocarcinomas, and were more likely to have SRC than male GC patients. In addition, females with advanced GC (AGC) and SRC had significantly poorer overall survival rates. In our data, among patients with advanced-stage disease (stage III or above), females had significantly lower GC-specific survival rates than males. In our data, the ratio of diffuse-type (undifferentiated) GC was relatively high, especially among younger females. Diffuse-type GC is known to be related to genetic factors such as E-cadherin mutations, feature a poorer prognosis due to rapid growth and poor treatment response, and is generally more common in younger patients [24,25]. Comparing the characteristics of GC in Korea and the United States, more upper-third and differentiated cancers were observed in the United States, while Korean patients showed fewer upper-third cancers with poorer cancer differentiation, deeper invasion, and poorer prognosis; hence, a difference in GC characteristics between Korean and United States populations is suspected[26].

The same results have been shown in previous studies in relation to histologic type and GC location, as more diffuse-type, gastric body location cases were noted in females versus more intestinal-type, stomach antrum location cases in males[27,28]. Based on previous reports on GC location, the distribution was reported as cardia 4%-8%, body 15%-30%, and antrum 60%-80% in a study of EGC in Korea [29]. In another Korean study of patients who underwent endoscopic resection for EGC, the most common location for EGC was the antrum (57.5%) and lesser curvature (37.8%), and body cancers were associated with younger patient age, larger tumor size, and more frequent poorly differentiated or SRC histology than cancers at other sites[30]. Our data are consistent with those of the aforementioned studies, and this relation to histologic type and GC location is believed to be due to differences in the composition of gastric mucous cells, such as the gastric body with a large distribution of parietal cells and the antrum with a large distribution of G cells[31].

The effects of sex hormones may cause this sex-based difference in GC. Epidemiological studies have reported that exogenous sex hormone exposure reduces the risk of esophageal adenocarcinoma[32,33] and esophageal squamous cell carcinoma[34], and a decrease in the risk of GC[35] and colorectal cancer [33,36] have been reported in females taking oral contraceptives or hormone replacement therapy. A large cohort study in Japan also reported that females in early menarche had a decreased risk of GC, especially differentiated-type GC, in subgroup analyses of histologic subtypes[37]. In addition, in a Chinese study of approximately 2000 surgically treated GC patients, the proportion of female GC patients showed a decreasing tendency, and the proportion of male GC patients showed an increasing tendency with age, but this trend stopped after 60 years of age[38]. Furthermore, a recent study in Korea reported that no premenopausal females had intestinal-type GC and that the ratio of intestinal-type GC increased in females after menopause and became similar to that of males about 10 years after menopause; this parity was associated with an increased risk of intestinal-type GC in females after menopause[27].

These results suggest that estrogen plays a role in curbing the development of GC in females, especially in intestinal-type GC. However, the specific mechanisms of estrogen in different histologic subtypes have not yet been established. Several studies have attempted to explain this by investigating the role of estrogen receptors (ER) in GC. First, Yi *et al*[39] showed that ER $\alpha$  expression was associated with diffuse-type GC and shorter disease-free survival. Wang *et al*[40] reported that well-differentiated gastric adenocarcinoma has a higher expression rate of ER $\beta$  and that poorly differentiated gastric adenocarcinoma is associated with a reduction or loss of ER $\beta$ . According to previous studies, diffuse-type GC may be initiated by the downregulation of E-cadherin by 17 $\beta$ -estradiol (E2), the most potent isoform of estrogen, through ER $\alpha$ [41-43].

In addition to the action of estrogen, Gan *et al*[44] reported that the four sex hormone receptors, ER $\alpha$ , ER $\beta$ , progesterone receptor, and androgen receptor (AR), were expressed independently and showed a decreased expression pattern in gastric tumors compared to adjacent normal tissues, suggesting that sex hormone receptors may be partly involved in gastric carcinogenesis. Jukic *et al*[2] reported a significantly higher frequency of cases with AR-positive cells in the stroma of intestinal-type GC in males than in females, which may be the reason for the greater invasiveness of this cancer type in males and presented the possibility of AR-targeted agents in GC treatment. Another study by Hsu *et al*[45] showed that males were more likely to develop tumor recurrence and liver metastasis than females, especially in cases of stage III GC. The authors suggested that the cause was higher programmed death ligand 1 expression in males and GC patients aged 65 years or older, and supporting data suggest that sex hormones are the basis of these differences[46,47].

The changes in the proportion of intestinal-type and diffuse-type cancers in the present study suggest that estrogen might have a protective effect on intestinal-type GC[27,28]. Thus, intestinal-type GC is much less common in young females than in males, and the prevalence of intestinal-type GC increases in females after menopause, which is likely to be similar to males about 20 years after menopause according to our data (approximately 70 years of age). Additional in-depth studies are needed to

confirm the role of sex hormones, including estrogen, in the pathogenesis and progression of GC, depending on the tissue type.

The pattern of P53 overexpression also differed by sex; P53 overexpression was more frequent in males and intestinal-type GC patients. In our previous report on P53 overexpression, the clinical and prognostic significance differed by histological type of GC; P53 overexpression was more common in intestinal-type GC, but was associated with a poor prognosis for diffuse-type GC[18]. Therefore, it is also likely to act as a factor that affects GC prognosis differently in males and females.

Our study has several limitations. First, the enrolled subjects were patients who underwent surgical treatment after receiving a diagnosis of GC; therefore, early cases treated with endoscopic resection and advanced inoperable cases were not included. Hence, in terms of GC-related survival and mortality, the data from our study are likely to be slightly different from those of all patients with GC. To compensate for this limitation, we are conducting a follow-up study of patients diagnosed with and treated for over 14000 GC in SNUBH. The results of our data analyses to this point showed no significant differences between males and females according to the treatment method. Second, there are no data on estrogen exposure such as menopause, childbirth, and breastfeeding in this study, making it difficult to provide additional evidence that estrogen has protective effects against intestinal-type cancer. Further research, including a history of sex hormone use, is required. Third, the eradication of *H. pylori* was not confirmed in all patients, although postoperative *H. pylori* eradication treatment may affect prognosis or survival [17]. In the future, additional research is needed that considers both *H. pylori* infection and sex. In contrast, our research has several strengths over existing studies. Studies involving subjects before the year 2000 reported that the prognosis of GC was relatively good in females; however, these studies did not reflect the situation in East Asia, where the prevalence of GC is high[20], or the exact histologic type of GC was not analyzed[21]. A relatively recent large-scale Korean study reflecting histological types reported that the prognosis of GC was poorer in females than in males, similar to our results[23]. In this study, the changes in the histology of GC according to age was examined, and the change in the ratio according to aging and menopause was confirmed, suggesting that female hormones would affect the development and progression of GC. However, we further analyzed the comorbidities of GC patients with respect to survival.

## CONCLUSION

In conclusion, differences in the epidemiology of GC incidence, including a higher proportion of diffuse-type histology and mortality, and poorer survival in AGC in females, were observed. The proportion of diffuse-type cancer was found to be higher in younger patients, the frequency of intestinal-type histology increased with age, and the ratio of diffuse-type cancer was higher until the age of 60 years in females. Differences in Lauren histologic type and tumor location by sex were also observed, with a high proportion of diffuse-type and gastric body location in females. Comorbidities, including other malignancies and respiratory diseases, are more common in males. These differences may originate from hormonal factors and should be considered in the diagnosis, treatment, and prediction of prognosis of GC in individuals.

## ARTICLE HIGHLIGHTS

### Research background

Despite the nationwide large-scale screening campaign, the incidence of gastric cancer (GC) in Korea is still high. The incidence is approximately twice as high in males than in females.

### Research motivation

However, studies so far have not fully explained the different characteristics of GC between the sexes. These differences might be due to the difference in exposure to the known risk factors for GC, such as frequent *Helicobacter pylori* infection, smoking, and alcohol consumption in males, but we thought that there is a possibility that sex hormones were based on this difference.

### Research objectives

This study aimed to analyze sex-based differences in clinicopathological features, staging, survival, and comorbidities in GC.

### Research methods

A total of 2983 patients diagnosed with gastric adenocarcinoma who received surgical treatment at the Seoul National University Bundang Hospital between 2003 and 2017 were included, and clinicopathological characteristics, histologic type of GC, overall and GC-specific survival rates, and associated risk

factors were analyzed.

### Research results

The male to female ratio was 2:1, and the average age of the female group was lower than that of the male group. Diffuse-type GC was more common in younger patients, especially in females younger than 60 years of age, and the proportion of intestinal-type GC increased with age. The overall survival rate was significantly higher in females, whereas GC-specific survival tended to be higher in males. Comorbidities, including other malignancies and respiratory diseases, are more common in males.

### Research conclusions

Differences in the epidemiology of GC incidence, including a higher proportion of diffuse-type histology, mortality, including poorer survival in the advanced stage in females, and comorbidities were observed. These differences may be due to hormonal factors.

### Research perspectives

We believe that a larger study including patients who received non-surgical treatment is needed. Individual sex hormone data, including menopause, childbirth, and breastfeeding, would be analyzed to prove the protective effect of estrogen against intestinal-type GC.

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## FOOTNOTES

**Author contributions:** Choi Y analyzed the data, provided statistical support, and drafted the article; Kim N designed this study, collected the data, and edited the manuscript; Kim KW, Jo HH, Park J, Yoon H, Shin CM, Park YS, and Lee DH performed endoscopies for the diagnosis of gastric cancer and edited the text; Park YS, Ahn SH, Suh YS, and Park DJ performed surgeries for gastric cancer; Kim HH kindly provided surgical cohort information, advised on the design of this study and supervised the manuscript preparation; HJO and HSL performed the histologic diagnosis of gastric cancer; Kim JW, Kim JW and Lee KW administered chemotherapy to patients with advanced gastric cancer; and Chang W, Park JH, Lee YJ, Lee KH, and Kim YH performed the radiologic studies; all authors reviewed the final manuscript and provided comments.

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