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Original Article

Impact of Body Mass Index on Survival Depending on Sex in 14,688 Patients with Gastric Cancer in a Tertiary Hospital in South Korea

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Background/Aims: The incidence and prognosis of gastric cancer (GC) shows sex difference. This study aimed to evaluate the effect of body mass index (BMI) on GC survival depending on sex.

Methods: The sex, age, location, histology, TNM stages, BMI, and survival were analyzed in GC patients from May 2003 to February 2020 at the Seoul National University Bundang Hospital.

Results: Among 14,688 patients, there were twice as many males (66.6%) as females (33.4%). However, under age 40 years, females (8.6%) were more prevalent than males (3.1%). Cardia GC in males showed a U-shaped distribution for underweight (9.6%), normal (6.4%), overweight (6.1%), obesity (5.6%), and severe obesity (9.3%) but not in females (p=0.003). Females showed decreased proportion of diffuse-type GC regarding BMI (underweight [59.9%], normal [56.8%], overweight [49.5%], obesity [44.8%], and severe obesity [41.7%]), but males did not (p<0.001). Both sexes had the worst prognosis in the underweight group (p<0.001), and the higher BMI, the better prognosis in males, but not females. Sex differences in prognosis according to BMI tended to be more prominent in males than in females in subgroup analysis of TNM stages I, II, and III and the operative treatment group.

Conclusions: GC-specific survival was affected by BMI in a sex-dependent manner. These differences may be related to genetic, and environmental, hormonal factors; body composition; and muscle mass (Trial registration number: NCT04973631). **(Gut Liver 2023;17:243-258)**

Key Words: Stomach neoplasms; Body mass index; Sex; Aging; Survival

INTRODUCTION

Gastric cancer (GC) incidence rates are high,[1] mainly in developing countries, especially in Eastern Europe, Eastern Asia, and South America.[2,3] In particular, 75% of patients with GC are Asian, with South Korea having the highest incidence of GC.[4,5] Therefore, there were several studies on biomarkers and epigenetic changes related to gastric carcinogenesis in Asia.[6-8] In Korea, the proportion of elderly patients with GC is increasing, and GC is more common

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in males than in females, with a 2:1 ratio,[9] which is similar with the worldwide ratio.[10] However, in the young age group, there are many female GC patients often associated with diffuse- and undifferentiated-type GC, as well as advanced GC. In contrast, older patients have a male predominance with intestinal-type GC.[11,12] Recently, there was a study that serum pepsinogen II levels and *Helicobacter pylori* infection status suggest a risk of early-stage diffuse-type GC in young adult females.[13] In fact, the effect of sex on the prognosis of patients with GC was reported to vary by race.[14]

The obesity pandemic has become a major public health problem and has resulted in increase of metabolic syndrome, type 2 diabetes, hyperlipidemia, hypertension, and nonalcoholic fatty liver disease.[15] In addition, obesity is known to increase the incidence of cancer such as colorectal, prostate, bladder, pancreas, ovary and breast. However, the effect of obesity on the GC is controversial. Our team reported that obesity increased the risk of early and differentiated adenocarcinoma in males, but not in females showing sex difference.[16] Excess adiposity is commonly approximated by body mass index (BMI), has been supposed to poor cancer survival similar to cancer incidence. However, after obesity paradox was first reported in patients with coronary artery disease.[17] Several reports showed that the survival of cancer patients was longer in the obese population.[18-21] As fat and muscle secrete various hormones and cytokines,[22,23] they are assumed to affect the survival of cancer patients depending on body composition. However, as no clear conclusion has been reached regarding obesity paradox,[24] this inconsistency might be related with sex difference. From this background, we hypothesized that the effect of BMI reflecting excess adiposity affects survival of GC in sex-specific manners. Thus, this study aimed to evaluate the impact of BMI on survival depending on sex among 14,688 patients with GC in a tertiary hospital in South Korea.

MATERIALS AND METHODS

1. Study population

A total of 14,688 patients diagnosed with GC between May 2003 and February 2020 at the Seoul National University Bundang Hospital (SNUBH) were analyzed. Data were collected from a prospective surgical cohort and medical GC cohort of SNUBH from 2003. In addition, clinical data warehouses and electronic medical records were reviewed as needed. The medical records, including sex, age, death (including cause), cancer location, histological classification (the Lauren and the World Health Organization [WHO] classifications), TNM stage, initial treatment modality, death, and survival were collected from surgical and medical cohorts, and from the clinical data warehouses. Cardia GC or non-cardia GC was classified by a pathologist after surgery or endoscopic treatment. Body weight and height were measured at the time of the GC diagnosis. The dates and causes of death of the enrolled patients were cross-reviewed with data from the National Statistical Office for verification. Random information that guarantees patient anonymity was compiled and submitted by a third party to the National Statistical Office, and received data related to patient death. In accordance with Institutional Review Board guidelines for anonymous surveys, the need for written informed consent among participants was waived. This study was reviewed and approved by the Institutional Review Board of SNUBH (IRB number: B-2006-618-004) and registered at clinicaltrials.gov (trial registration number: NCT04973631). This study was performed in accordance with the protocols approved by the Ethics Committee.

2. Data variable and assessment

The analysis of the effect of age on GC was performed in six age groups (<40, 40–49, 50–59, 60–69, 70–79, and ≥80 years). The location of GC was divided into upper, middle, and lower,[25] and into cardia and non-cardia. The histological classification was divided according to the Lauren type: intestinal, diffuse, mixed, and indeterminate. Additionally, the patients were divided according to the WHO classification. The treatment modality was divided into four groups: curative endoscopic treatment, surgery, chemotherapy, and conservative treatment. BMI was calculated as weight divided by height squared (kg/m^2) and was categorized according to the Asia-Pacific WHO criteria: <18.5 for underweight, 18.5–22.9 for normal weight, 23.0–24.9 for overweight, 25.0–29.9 for obesity, and ≥30.0 for severe obesity.[26] Smoking and alcohol consumption were divided into two groups: never or current/past. GC-specific survival was defined as death due to GC.

3. Statistical analysis

Survival differences were assessed by the log-rank test and the univariable and multivariable analyses using a Cox proportional hazard regression model. Variables with $p<0.2$ in the univariable analysis were included in the multivariable model hazard ratios (HRs). Prespecified subgroup analyses were conducted in the intestinal and diffuse-type GC and cardia and non-cardia GC groups. All statistical analyses were performed using SPSS statistical software version 25.0 (IBM Corp., Armonk, NY, USA) and STATA version 17 (StataCorp, College Station, TX, USA).

Statistical significance was set at p<0.05.

RESULTS

1. Baseline characteristics

In GC patients, the overall rates were twice as high in males than in females (males: 9,781 [66.6%] and females: 4,907 [33.4%]), and the mean age in males (62.5 years) was 2 years older than in females (60.7 years) (Table 1). However, females were more prevalent than males in the <40 years' age group, which reversed as the older group up to 2.5 times in the 60 to 69 years age group (Table 1).

Regarding BMI, the proportion of underweight GC

Table 1. Baseline Characteristics of Patients with Gastric Cancer (n=14,688)

Characteristics	Male	Female	Total	p-value*
Number	9,781 (66.6)	4,907 (33.4)	14,688 (100)	
Age, yr	62.5±11.9	60.7±14.3	61.9±12.8	<0.001
Age group, yr				<0.001
<40	307 (3.1)	424 (8.6)	731 (5.0)	
40–49	1,181 (12.1)	776 (15.8)	1,957 (13.3)	
50–59	2,306 (23.6)	985 (20.1)	3,291 (22.4)	
60–69	2,992 (30.6)	1,191 (24.3)	4,183 (28.5)	
70–79	2,363 (24.2)	1,113 (22.7)	3,476 (23.7)	
≥80	632 (6.5)	418 (8.5)	1,050 (7.1)	
Location§				<0.001
Upper	1,790 (19.4)	832 (18.2)	2,622 (19.0)	
Middle	2,234 (24.2)	1,369 (30.0)	3,603 (26.1)	
Lower	5,196 (56.4)	2,364 (51.8)	7,560 (54.8)	
Location§				<0.001
Cardia	581 (6.3)	205 (4.5)	786 (5.7)	
Non-cardia	8,639 (93.7)	4,360 (95.5)	12,999 (94.3)	
Lauren type§				<0.001
Intestinal	5,935 (68.1)	1,945 (45.3)	7,880 (60.6)	
Diffuse	2,514 (28.8)	2,222 (51.7)	4,736 (36.4)	
Mixed	224 (2.6)	119 (2.8)	343 (2.6)	
Indeterminate	44 (0.5)	8 (0.2)	52 (0.4)	
WHO classification§				<0.001
Tubular ADC, WD	2,066 (21.9)	632 (13.5)	2,698 (19.1)	
Tubular ADC, MD	3,282 (34.8)	1,083 (23.2)	4,365 (31.0)	
Tubular ADC, PD	1,650 (17.5)	947 (20.3)	2,597 (18.4)	
PCC, SRC	1,501 (15.9)	1,508 (32.3)	3,009 (21.4)	
Mixed carcinoma	419 (4.4)	340 (7.3)	759 (5.4)	
Mucinous ADC	82 (0.9)	25 (0.5)	107 (0.8)	
Papillary ADC	119 (1.3)	46 (1.0)	165 (1.2)	
Others	299 (3.2)	91 (1.9)	390 (2.8)	
Treatment				<0.001
Endoscopic	1,683 (17.2)	611 (12.5)	2,294 (15.6)	
Operative	5,979 (61.1)	3,173 (64.7)	9,152 (62.3)	
Chemotherapy	1,015 (10.4)	449 (9.2)	1,464 (10.0)	
Conservative	1,104 (11.3)	674 (13.7)	1,778 (12.1)	
T stage§				0.281
1	5,203 (62.4)	2,537 (62.1)	7,740 (62.3)	
2	806 (9.7)	364 (8.9)	1,170 (9.4)	
3	1,252 (15.0)	614 (15.0)	1,866 (15.0)	
4	1,075 (12.9)	568 (13.9)	1,643 (13.2)	
N stage§				0.007
0	5,706 (69.0)	2,705 (66.8)	8,411 (68.3)	
1	988 (12.0)	566 (14.0)	1,554 (12.6)	
2	614 (7.4)	287 (7.1)	901 (7.3)	
3	956 (11.6)	492 (12.1)	1,448 (11.8)	

Table 1. Continued

Characteristics	Male	Female	Total	p-value*
TNM stage[†,§]				0.074
I	5,458 (60.0)	2,598 (58.0)	8,056 (59.3)	
II	1,169 (12.8)	639 (14.3)	1,808 (13.3)	
III	1,201 (13.2)	605 (13.5)	1,806 (13.3)	
IV	1,274 (14.0)	641 (14.3)	1,915 (14.1)	
BMI[‡,§]				<0.001
Underweight	635 (6.5)	424 (8.8)	1,059 (7.3)	
Normal	3,495 (36.0)	2,017 (41.7)	5,512 (37.9)	
Overweight	2,422 (25.0)	1,035 (21.4)	3,457 (23.8)	
Obesity	2,888 (29.8)	1,189 (24.6)	4,077 (28.0)	
Severe obesity	267 (2.8)	176 (3.6)	443 (3.0)	
Smoking				<0.001
Never	2,931 (30.0)	3,816 (77.8)	6,747 (45.9)	
Current/past	5,533 (56.6)	350 (7.1)	5,883 (40.1)	
Unknown	1,317 (13.5)	741 (15.1)	2,058 (14.0)	
Alcohol				<0.001
Never	2,184 (22.3)	1,868 (38.1)	4,052 (27.6)	
Current/past	2,969 (30.4)	469 (9.6)	3,438 (23.4)	
Unknown	4,628 (47.3)	2,570 (52.4)	7,198 (49.0)	

Data are presented as number (%) or mean±SD.
WHO, World Health Organization; ADC, adenocarcinoma; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; PCC, poorly cohesive carcinoma; SRC signet ring cell carcinoma; BMI, body mass index.
*The p-value was calculated by Student t-test for continuous variable and chi-square test for categorical variables; [†]Clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer; [‡]Predefined BMI categories according to the Asia-Pacific WHO criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2; [§]Unknown or missing values were excluded from the calculation of percentages.

patients was higher in females (8.8%) than in males (6.5%) (p<0.001), and that of obesity and severe obesity was higher in males (32.6%) than in females (28.2%) (p<0.001) (Table 1). When the proportion of GC patients depending on BMI were affected by age with sex-specific manners (Table 2). That is, under the age of 40 years, males (29.6%) had a larger proportion of obesity and severe obesity than females (13.0%), while females (14.9%) had a larger proportion of underweight than males (8.2%) (p<0.001). Similarly, in the 40 to 49 years age group, the proportion of male obesity and severe obesity (38.1%) was larger than that of females (19.2%) (p<0.001), but female underweight (10.3%) was larger than that of males (4.8%) (p<0.001) (Table 2). However, in the elderly aged over 80 years the proportion of underweight patients were significantly higher in both males (16.0%) and females (16.7%).

2. Location of GC according to BMI

Location of GC also showed sex-specific manners. That is, lower third GC was more common in males (56.4%) than in females (51.8%), but middle third GC occurred more frequently in females (30.0%) than in males (24.2%) (p<0.001) (Table 1). In contrast, cardia GC occurred more frequently in males (6.3%) than in females (4.5%) (p<0.001) (Table 1).

BMI affected GC location. That is, upper and middle third GC were more common in underweight patients, which was also more prominent in females (55.7%) than males (49.9%) (Table 2). In detail there were many upper (23.9%) and middle (31.8%) third GC in underweight females, and lower (61.5%) third GC in severely obese females (p<0.001) (Table 2). Sex-specific manners showed at the cardia GC. That is, underweight (8.6%) and severe obesity (7.0%) were larger than that of normal weight (5.8%), overweight (5.3%), and obesity (5.1%), respectively, in overall GC patients (p=0.001), but this was mainly derived from males (Supplementary Table 1). In males, a higher proportion of cardia GC was found in underweight (9.6%) and severely obese (9.3%) patients (p=0.003) than normal weight showing U shape (Fig. 1A). However, in females, only the underweight group (7.0%) had a higher proportion of cardia GC (p=0.052) (Fig. 1B).

3. Pathologic classification according to age and BMI

Tubular adenocarcinoma and poorly cohesive carcinoma accounted for almost all of the WHO classifications and mixed carcinoma (5.4%), while mucinous adenocarcinoma and papillary adenocarcinoma accounted for

Table 2. Distribution of Patients with Gastric Cancer According to BMI and Sex

Variable	Male						Female					
	Underweight	Normal	Overweight	Obesity	Severe obesity	p-value*	Underweight	Normal	Overweight	Obesity	Severe obesity	p-value*
Number	635 (6.5)	3,495 (36.0)	2,422 (25.0)	2,888 (29.8)	267 (2.8)		424 (8.8)	2,017 (41.7)	1,035 (21.4)	1,189 (24.6)	176 (3.6)	
Age, yr	66.0±13.4	63.5±12.2	62.3±11.7	61.0±11.1	58.8±11.8	<0.001	60.3±17.4	58.4±14.8	61.3±13.1	63.7±12.3	63.7±12.6	<0.001
Age group, yr						<0.001						<0.001
<40	25 (8.2)	116 (38.2)	73 (24.0)	73 (24.0)	17 (5.6)		62 (14.9)	244 (58.8)	55 (13.3)	44 (10.6)	10 (2.4)	
40–49	56 (4.8)	379 (32.4)	289 (24.7)	402 (34.4)	44 (3.8)		79 (10.3)	377 (49.2)	164 (21.4)	132 (17.2)	15 (2.0)	
50–59	107 (4.7)	751 (32.9)	567 (24.8)	787 (34.5)	71 (3.1)		63 (6.5)	429 (44.1)	222 (22.8)	226 (23.3)	32 (3.3)	
60–69	167 (5.6)	1,026 (34.5)	784 (26.3)	922 (31.0)	77 (2.6)		61 (5.2)	424 (36.0)	281 (23.9)	354 (30.1)	57 (4.8)	
70–79	180 (7.7)	947 (40.3)	570 (24.3)	598 (25.4)	55 (2.3)		91 (8.2)	389 (35.2)	241 (21.8)	333 (30.2)	50 (4.5)	
≥80	100 (16.0)	276 (44.2)	139 (22.3)	106 (17.0)	3 (0.5)		68 (16.7)	154 (37.9)	72 (17.7)	100 (24.6)	12 (3.0)	
Location[§]						0.003						<0.001
Upper	106 (19.9)	665 (20.6)	449 (19.3)	512 (18.2)	53 (20.5)		85 (23.9)	363 (19.4)	171 (17.3)	180 (15.9)	27 (16.0)	
Middle	160 (30.0)	796 (24.6)	544 (23.4)	647 (23.0)	58 (22.4)		113 (31.8)	597 (31.8)	280 (28.3)	317 (28.1)	38 (22.5)	
Lower	267 (50.1)	1,770 (54.8)	1,334 (57.3)	1,654 (58.8)	148 (57.1)		157 (44.2)	915 (48.8)	537 (54.4)	633 (56.0)	104 (61.5)	
Location[§]						0.003						0.052
Cardia	51 (9.6)	206 (6.4)	142 (6.1)	157 (5.6)	24 (9.3)		25 (7.0)	92 (4.9)	34 (3.4)	46 (4.1)	6 (3.6)	
Non-cardia	482 (90.4)	3,025 (93.6)	2,185 (93.9)	2,656 (94.4)	235 (90.7)		330 (93.0)	1,783 (95.1)	954 (96.6)	1,084 (95.9)	163 (96.4)	
TNM stage[†,§]						<0.001						<0.001
I	171 (32.1)	1,675 (52.1)	1,481 (64.4)	1,930 (69.9)	184 (72.2)		120 (32.5)	993 (54.6)	619 (64.9)	737 (65.2)	113 (65.7)	
II	79 (14.8)	449 (14.0)	287 (12.5)	321 (11.6)	29 (11.4)		67 (18.2)	274 (15.1)	126 (13.2)	145 (12.8)	19 (11.0)	
III	97 (18.2)	518 (16.1)	280 (12.2)	285 (10.3)	19 (7.5)		70 (19.0)	254 (14.0)	123 (12.9)	135 (11.9)	20 (11.6)	
IV	186 (34.9)	575 (17.9)	252 (11.0)	224 (8.1)	23 (9.0)		112 (30.4)	298 (16.4)	86 (9.0)	114 (10.1)	20 (11.6)	
Lauren type[§]						<0.001						0.003
Intestinal	306 (66.2)	1,973 (65.6)	1,526 (68.4)	1,931 (71.0)	171 (68.4)		120 (36.7)	701 (40.3)	454 (47.8)	560 (51.9)	92 (56.4)	
Diffuse	145 (31.4)	945 (31.4)	628 (28.1)	712 (26.2)	67 (26.8)		196 (59.9)	989 (56.8)	470 (49.5)	483 (44.8)	68 (41.7)	
Mixed	10 (2.2)	72 (2.4)	69 (3.1)	64 (2.4)	9 (3.6)		11 (3.4)	49 (2.8)	25 (2.6)	31 (2.9)	3 (1.8)	
Indeterminate	1 (0.2)	17 (0.6)	9 (0.4)	14 (0.5)	3 (1.2)		0	2 (0.1)	1 (0.1)	5 (0.5)	0	

Data are presented as number (%) or mean±SD. Predefined body mass index (BMI) categories according to Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2.

*The p-value was calculated Student t-test for continuous variable and chi-square test for categorical variables; [†]Clinical stage was established according to the guidelines of the 8th American Joint Committee on Cancer; [§] The total number was different because unknown or missing values were excluded from the percentage calculation.

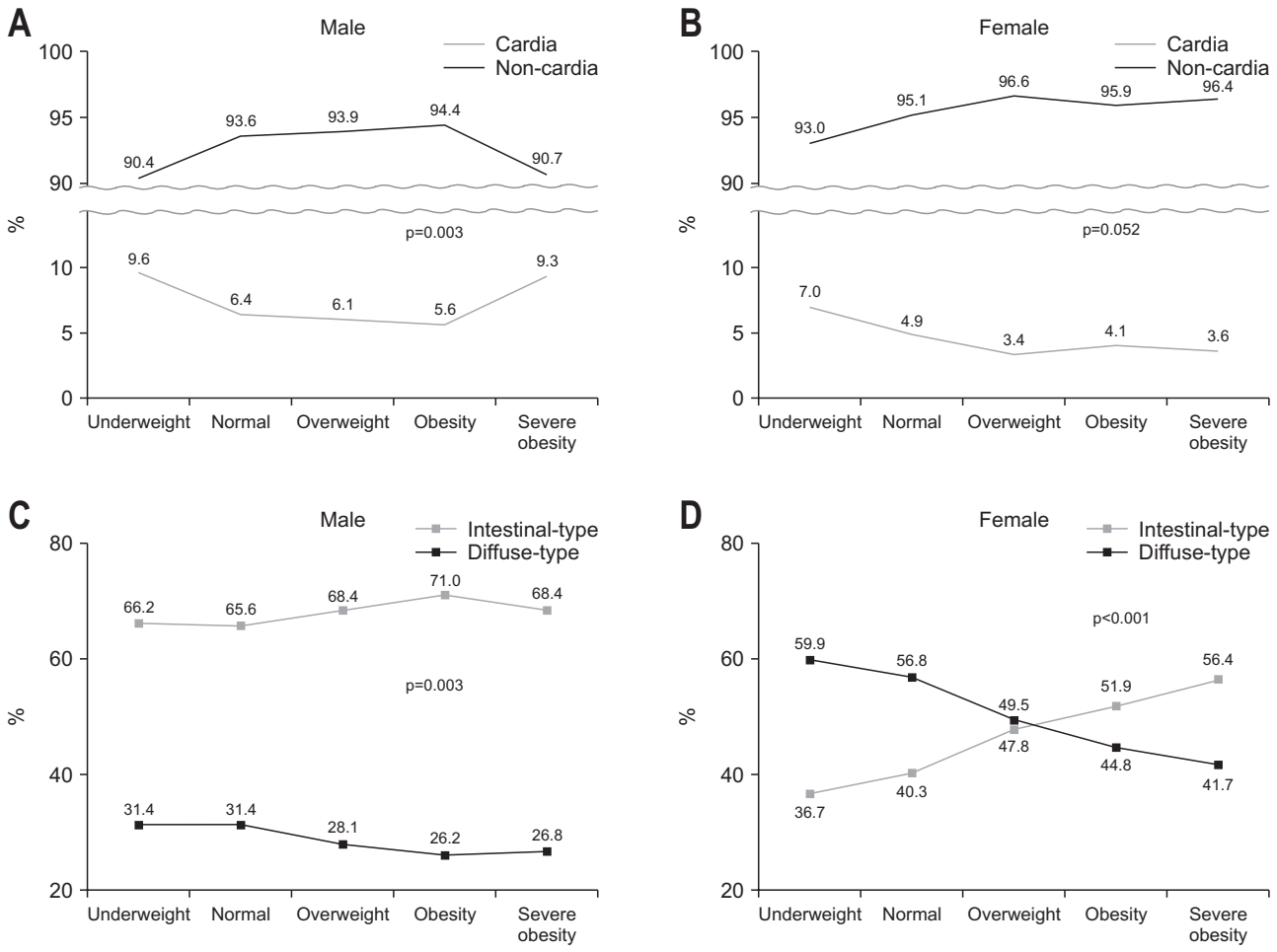


Fig. 1. Sex differences in the proportion of cardia, non-cardia, and Lauren classification of gastric cancer (GC) according to body mass index (BMI). (A) A higher proportion of cardia GC was found in underweight and severely obese patients, with a U-shaped distribution in males. (B) In females, only the underweight group had a higher proportion of cardia GC. (C) In males, the distribution showed an almost uniform plateau regardless of BMI. (D) In underweight females, the proportions of intestinal and diffuse-type were 36.7% and 59.9%, respectively. These proportions became inverted in severe obesity, at 56.4% and 41.7%, respectively. Predefined BMI categories according to Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2.

approximately 1% of cases, respectively (Table 1). There was a sex difference in the pathology, that is, well (21.9%) and moderately differentiated (34.8%) adenocarcinoma accounted for a higher proportion of males (p<0.001), in contrast to poorly differentiated adenocarcinoma (20.3%), poorly cohesive carcinoma (32.3%), and mixed carcinoma (7.3%) in females (p<0.001) (Table 1). According to the Lauren classification, intestinal-type was more common in males (68.1%) than in females (45.3%), and diffuse type was dominant in females (51.7%) compared to males (28.8%) (p<0.001) (Table 1).

The proportion of Lauren classification was affected by BMI. That is, intestinal and diffuse types accounted for 426 (54.0%) and 341 (43.2%) underweight patients, respectively (Supplementary Table 1). As the BMI increased, intestinal-type increased and diffuse-type decreased overall, reaching 65.6% for the intestinal type in the obesity group (p<0.001) (Supplementary Table 1). However, this pattern became very different depending on sex (Fig. 1). That is, in males, it was almost uniformly plateau regardless of BMI (Fig. 1C) but X-shape in females (Fig. 1D). In underweight females, the proportion of intestinal and diffuse-type was 36.7% and 59.9%, respectively but this became reverse in severe obesity females, 56.4% and 41.7%, respectively (p<0.001) (Table 2, Fig. 1D).

4. TNM stage according to BMI

In general, sex differences in TNM stage were not statistically significant (p=0.074), including the T stage (p=0.281). However, the proportion of patients with N0 stage disease was higher in males (69.0%) than in females (66.8%) (p=0.007) (Table 1). Regarding BMI, the advanced

Table 3. Univariable and Multivariable Cox Proportional Hazard Regression for Gastric Cancer-Specific Survival Stratified by Sex

Variable	Total		Male				Female			
	Events	Person-years	Univariable		Multivariable		Univariable		Multivariable	
			HR (95% CI)*	p-value	HR (95% CI)*	p-value	HR (95% CI)*	p-value	HR (95% CI)*	p-value
Age group, yr										
<40	201	3,902	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
40–49	391	10,750	0.59 (0.46–0.76)	<0.001	0.93 (0.67–1.30)	0.678	0.86 (0.68–1.09)	0.220	1.02 (0.75–1.39)	0.899
50–59	530	17,573	0.55 (0.43–0.69)	<0.001	0.90 (0.66–1.23)	0.500	0.57 (0.45–0.73)	<0.001	0.84 (0.60–1.18)	0.308
60–69	701	22,290	0.62 (0.49–0.78)	<0.001	1.04 (0.76–1.41)	0.815	0.49 (0.39–0.63)	<0.001	0.94 (0.67–1.32)	0.726
70–79	853	14,393	0.92 (0.74–1.16)	0.489	1.45 (1.07–1.97)	0.017	1.02 (0.82–1.26)	0.876	1.80 (1.31–2.46)	<0.001
≥80	403	2,586	2.03 (1.59–2.59)	<0.001	2.15 (1.52–3.03)	<0.001	1.97 (1.55–2.51)	<0.001	2.40 (1.62–3.57)	<0.001
Location										
Cardia	263	3,069	2.10 (1.81–2.44)	<0.001	1.23 (1.01–1.51)	0.041	2.23 (1.76–2.84)	<0.001	1.21 (0.85–1.70)	0.287
Non-cardia	2,357	65,130	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Lauren type										
Intestinal	1,004	40,579	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Diffuse	1,055	23,767	1.82 (1.63–2.02)	<0.001	1.37 (1.20–1.56)	<0.001	1.92 (1.64–2.25)	<0.001	1.68 (1.35–2.09)	<0.001
Mixed	51	2,123	1.15 (0.83–1.60)	0.395	0.98 (0.69–1.38)	0.904	0.92 (0.53–1.57)	0.753	0.96 (0.54–1.70)	0.878
Indeterminate	21	192	3.64 (2.28–5.81)	<0.001	1.67 (1.01–2.75)	0.044	4.32 (1.38–13.48)	0.012	2.58 (0.82–8.17)	0.107
Treatment										
Endoscopic	21	12,472	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Operative	1,174	52,482	14.14 (8.48–23.56)	<0.001	2.62 (1.52–4.53)	0.001	13.54 (6.05–30.32)	<0.001	1.87 (0.75–4.69)	0.180
Chemotherapy	955	2,220	156.99 (94.04–262.08)	<0.001	4.88 (2.78–8.59)	<0.001	142.33 (63.36–319.73)	<0.001	2.53 (0.99–6.46)	0.053
Conservative	929	4,319	117.08 (70.12–195.49)	<0.001	9.75 (5.46–17.4)	<0.001	103.89 (46.34–232.92)	<0.001	6.07 (2.35–15.67)	<0.001
BMI†										
Underweight	504	3,698	2.24 (1.97–2.55)	<0.001	1.35 (1.11–1.65)	0.003	2.68 (2.27–3.16)	<0.001	1.39 (1.07–1.79)	0.013
Normal	1,368	25,931	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Overweight	562	18,020	0.57 (0.51–0.65)	<0.001	0.78 (0.66–0.91)	0.001	0.68 (0.57–0.82)	<0.001	1.02 (0.80–1.30)	0.904
Obesity	544	21,065	0.43 (0.38–0.48)	<0.001	0.72 (0.61–0.84)	<0.001	0.67 (0.57–0.80)	<0.001	0.93 (0.73–1.18)	0.554
Severe obesity	49	2,230	0.33 (0.23–0.49)	<0.001	0.38 (0.22–0.66)	0.001	0.55 (0.36–0.84)	0.006	1.11 (0.65–1.89)	0.691
Smoking	975	29,577	0.65 (0.59–0.71)	<0.001	0.83 (0.73–0.94)	0.002	1.02 (0.80–1.30)	0.853	0.91 (0.68–1.22)	0.549

BMI, body mass index, HR, hazard ratio; CI, confidence interval.

*Cox proportional hazards regression was used to estimate the HR and 95% CI with adjustment for TNM stage; †Predefined BMI categories according to the Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2.

TNM stage (II, III, IV) was higher in underweight patients regardless of sex. In particular, stage IV cancer accounted for most underweight patients (33.0%), and only 8.7% and 10.1% of obese and severely obese patients, respectively (Supplementary Table 1). In particular, the proportion of patients with stage I cancer was 72.2% in males with severe obesity (p<0.001) (Table 2).

5. GC-specific survival according to BMI, location, and treatment modality

There was a significant difference in GC-specific survival according to GC location. That is, HR of GC-specific survival was higher in cardia (HR, 1.21; 95% confidence interval [CI], 1.02 to 1.44) than in non-cardia GC. This difference was mainly originated from males (HR, 1.23; 95% CI, 1.01 to 1.51; p=0.041), but no difference in females (HR, 1.21; 95% CI, 0.85 to 1.70; p=0.287) (Table 3). Furthermore, the diffuse-type group had a worse survival rate than the intestinal-type group in both males (HR, 1.37; 95% CI, 1.20 to 1.56; p<0.001) and females (HR, 1.68; 95% CI, 1.35 to 2.09; p<0.001) (Table 3).

The GC-specific survival rate regarding BMI showed definite sex-specific manners except underweight group. That is, both males (HR, 1.35; 95% CI, 1.11 to 1.65; p=0.003) and females (HR, 1.39; 95% CI, 1.07 to 1.79; p=0.013) showed higher HR in the underweight group than in the normal weight group (Table 3). However, in males, the GC-specific survival rate became clearly increased proportionally to BMI. That is, HR was lower in overweight (HR, 0.78; 95% CI, 0.66 to 0.97; p=0.001), obesity (HR, 0.72; 95% CI, 0.61 to 0.84; p<0.001), and severe obesity (HR, 0.38; 95% CI, 0.22 to 0.66; p=0.001) than in the normal weight group, which was statistically significant (Table 3, Fig 2A). In females there was a significance among five groups of BMI (p<0.001) (Fig. 2B) but there was no difference of HR in overweight (HR, 1.02; 95% CI, 0.80 to 1.03; p=0.904), obesity (HR, 0.93; 95% CI, 0.73 to 1.18; p=0.554), and severe obesity (HR, 1.11; 95% CI, 0.65 to 1.89; p=0.691) compared to the normal weight (Table 3).

We analyzed the sex difference for prognosis according to BMI by dividing it into treatment modality and TNM stage. In the group receiving endoscopic treatment, there was no significant difference prognosis according to BMI in females (Fig. 3B), and the prognosis was poor in males and underweight patients (Fig. 3A). In the group receiving operative treatment, both males and females had poor prognosis in underweight patients, and the prognosis improved as BMI increased in males (Fig. 3C). In females, there was no significant difference between the four groups except for underweight group (Fig. 3D). In the group that received chemotherapy, there was no significant difference in the prognosis according to BMI for both males (Fig. 3E) and females (Fig. 3F). In the group of conservative treatment, both males (Fig. 3G) and females (Fig. 3H) showed better prognosis due to increased BMI. In the subgroup analysis according to the TNM stage, the prognosis of

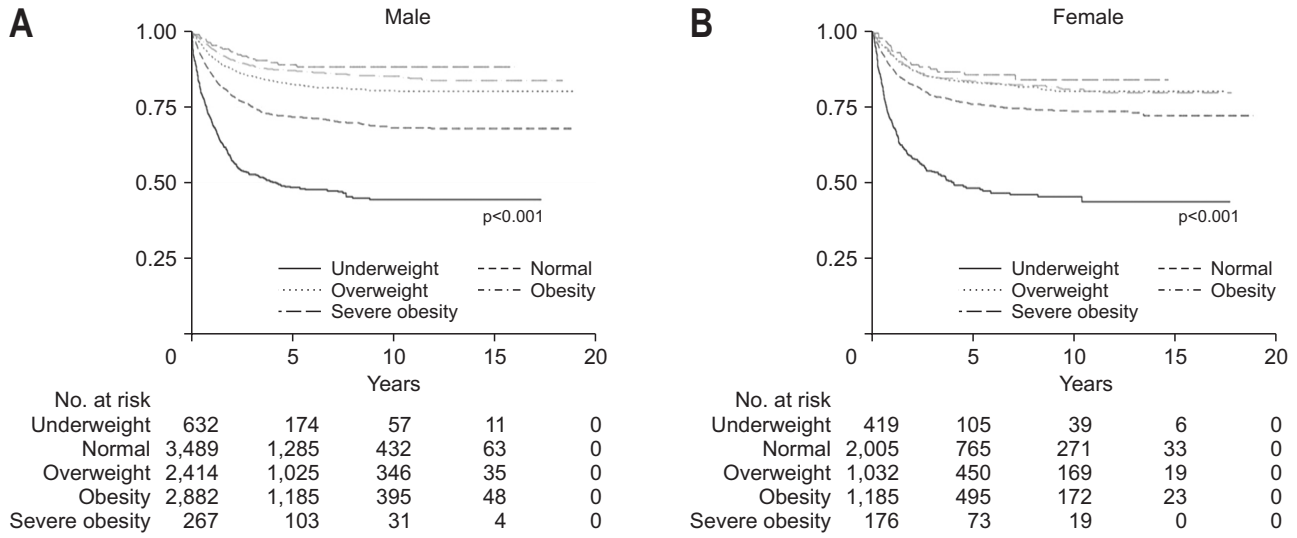


Fig. 2. Gastric cancer-specific survival distributed by sex and body mass index (BMI). Both males and females showed the worst prognosis in the underweight group. (A) Among males, overweight, obese, and severely obese patients had a better prognosis than normal weight patients. (B) Among females, there was no difference of survival according to overweight and severe obesity compared to that for normal weight. That is, in males, the higher the BMI was, the better the prognosis, but not in females. Cumulative survival was calculated using Kaplan-Meier estimates; the p-values were calculated using the log-rank test. Predefined BMI categories according to Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2.

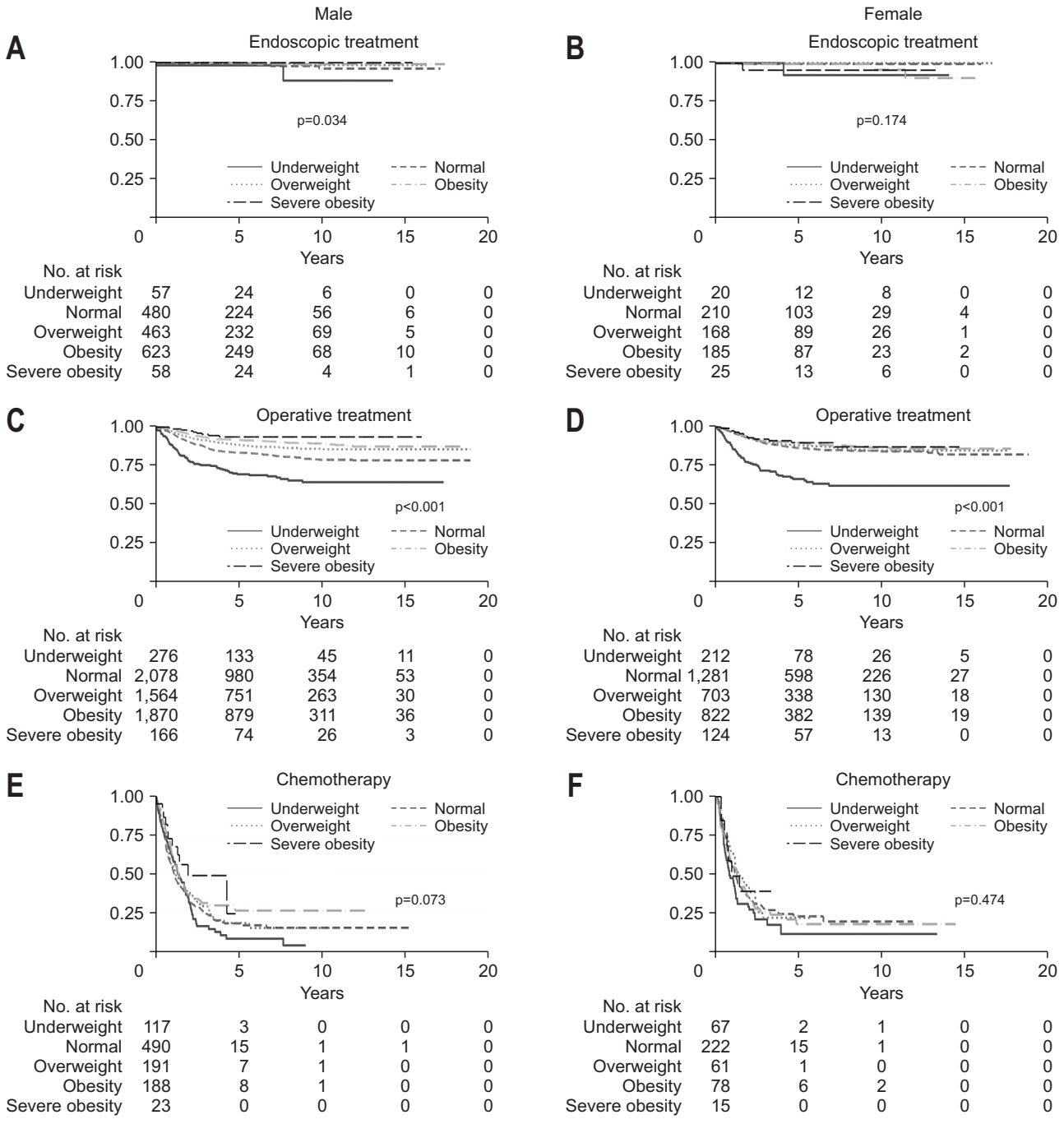
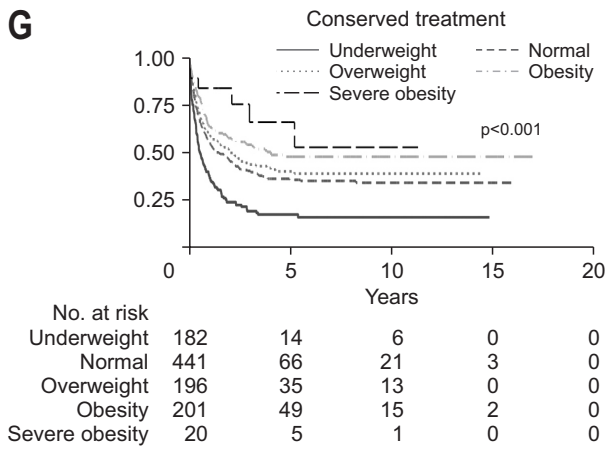


Fig. 3. Gastric cancer-specific survival distributed by sex and body mass index (BMI) according to treatment modality. Endoscopic treatment in males (A) and in females (B). Operative treatment in males (C) and in females (D). Chemotherapy in males (E) and in females (F). Conservative treatment in males (G) and in females (H). Cumulative survival was calculated using Kaplan-Meier estimates; the p-values were calculated using the log-rank test. Predefined BMI categories according to Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2.

underweight patients was poor in TNM stages I, II, III except stage IV (Supplementary Fig. 1). In addition, in TNM stages I, II, and III, the pattern to improve prognosis was noticeable in males as BMI increased (Supplementary Fig. 1).

Multivariable analyses of GC-specific survival according to sex and BMI are shown in Table 4. The subgroups with the most pronounced tendency to decrease HR as BMI increased were intestinal-type and non-cardia GC in males. In male intestinal-type GC, the HR of overweight (HR,



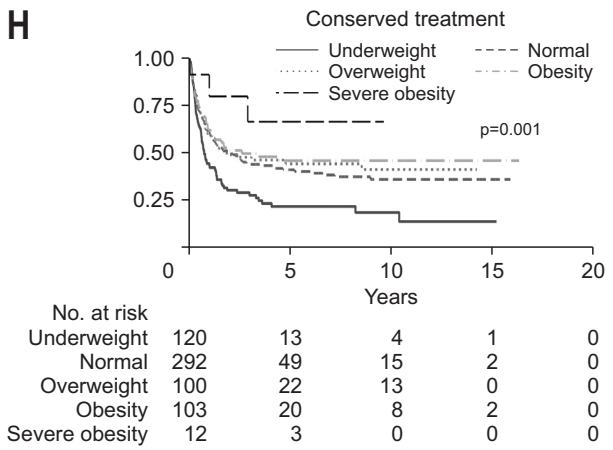


Fig. 3. Continued.

0.72; 95% CI, 0.58 to 0.90), obesity (HR, 0.69; 95% CI, 0.55 to 0.87), and severe obesity (HR, 0.45; 95% CI, 0.21 to 0.95) showed a significant decrease compared to normal weight (Table 4). In male non-cardia GC patients, the HR of overweight (HR, 0.78; 95% CI, 0.67 to 0.92), obesity (HR, 0.72; 95% CI, 0.61 to 0.86), and severe obesity (HR, 0.41; 95% CI, 0.22 to 0.77) also showed a significant decrease. In contrast, the underweight group had an HR of 1.34 (95% CI, 1.08 to 1.66) compared to the normal weight group (Table 4). Diffuse-type and cardia GC in males also showed lower HR as BMI increased; however, this difference was not statistically significant (Table 4). In contrast to males, there was no significant difference in prognosis according to BMI in a subgroup of females except non-cardia group HR of 1.42 (95% CI, 1.09 to 1.85) compared to the normal weight (Table 4).

DISCUSSION

Our study showed sex differences in GC related to histology, location, TNM stage, and prevalence. GC patients were twice as many in males as in females, but reversed under the age of 40: that is, GC in females (8.6%) versus in males (3.1%). Furthermore, diffuse-type GC was more frequent in females (86.4%) than in males (76.6%).These results were also found in previous reports of GC patients receiving surgical treatment, with diffuse-type GC common in young females, and females had a poor prognosis than males in the advanced TNM stage group.[27] However, BMI information was not included in the report. Above all, we highlighted the sex differences in the association between BMI and GC location, treatment modality, TNM stage, and tissue type, that is, a higher proportion of patients with severe obesity (9.3%) was found only in males but not in females (3.6%). Diffuse-type GC was more prevalent in underweight females (59.9%) than in severely obese females (41.7%) which was a big contrast to males (31.4% and 26.8%, respectively). In males, the ratio of intestinal-type GC and diffuse-type GC according to BMI was maintained at almost 7:3. On contrast, it was not definite in females. There were previous reports that estrogen plays a leading role in female obesity and the association between sex hormones and BMI in menopausal females.[28,29] There was also a study that female reproductive factors could play a role in the prevention of intestinal-type GC.[30] In addition, there was a report of the association of estrogen receptor expression with tumor invasion in diffuse-type GC.[31] In this study, the difference in the composition of Lauren classification GC types according to BMI in females may be derived from difference in sex hormone levels according to BMI. Further research to elucidate the link between change in distribution of intestinal and diffused type GCs according to BMI are needed. Underweight was associated with the worst GC-specific survival regardless of sex, but a better prognosis was observed in the obese population only in males, suggesting an obesity paradox.

In a 1999–2010 study analyzing data from the Korea Central Cancer Registry and National Statistical Office, males had approximately two to three times higher incidence rate of GC in the population aged 40 to 79, but the incidence rate was slightly higher in females than in males in the 20 to 39 age group.[32] Globally, the ratio of males to females by age among GC patients increases with age, reaching a peak at age around 60 years, and decreasing thereafter,[10] which was confirmed in our study. However, they did not show a sex difference depending on BMI or GC-specific survival. As our study performed the prospective and comprehensive study regarding sex difference of GC from surgical and medical cohort several interesting

Table 4. Effect of BMI on Gastric Cancer-Specific Survival Estimated by Cox Proportional Hazards Regression

BMI*	Male			Female			Total		
	Events	Person-years	HR (95% CI)†	Events	Person-years	HR (95% CI)†	Events	Person-years	HR (95% CI)†
Intestinal-type									
Underweight	110	1,206	1.18 (0.90–1.56)	45	490	2.06 (1.23–3.45)	155	1,696	1.35 (1.06–1.70)
Normal	345	9,819	1 (reference)	91	3,570	1 (reference)	436	13,389	1 (reference)
Overweight	158	8,187	0.72 (0.58–0.90)	41	2,536	0.87 (0.53–1.44)	199	10,723	0.74 (0.61–0.91)
Obesity	143	10,174	0.69 (0.55–0.87)	40	3,103	0.84 (0.55–1.30)	183	13,278	0.71 (0.58–0.87)
Severe obesity	12	818	0.45 (0.21–0.95)	5	497	0.60 (0.22–1.67)	17	1,315	0.47 (0.25–0.85)
Diffuse-type									
Underweight	74	486	1.57 (1.15–2.13)	89	712	1.26 (0.93–1.72)	163	1,197	1.39 (1.12–1.72)
Normal	269	4,539	1 (reference)	204	5,004	1 (reference)	473	9,543	1 (reference)
Overweight	113	3,321	0.79 (0.62–1.00)	83	2,499	1.06 (0.80–1.42)	196	5,820	0.90 (0.75–1.08)
Obesity	106	3,760	0.71 (0.55–0.91)	88	2,571	1.03 (0.77–1.37)	194	6,331	0.83 (0.69–1.00)
Severe obesity	8	387	0.82 (0.39–1.75)	14	335	1.50 (0.81–2.78)	22	721	1.14 (0.71–1.83)
Cardia									
Underweight	35	126	1.76 (0.96–3.21)	15	65	2.24 (0.67–7.46)	50	191	1.93 (1.16–3.21)
Normal	84	833	1 (reference)	32	308	1 (reference)	116	1,141	1 (reference)
Overweight	32	549	0.60 (0.34–1.05)	9	168	1.14 (0.35–3.69)	41	717	0.71 (0.43–1.16)
Obesity	34	696	0.72 (0.43–1.20)	14	187	1.33 (0.55–3.19)	48	883	0.86 (0.56–1.34)
Severe obesity	5	88	0.31 (0.09–1.05)	1	47	2.04 (0.24–17.58)	6	135	0.45 (0.16–1.26)
Non-cardia									
Underweight	209	1,764	1.34 (1.08–1.66)	148	1,204	1.42 (1.09–1.85)	357	2,968	1.37 (1.16–1.61)
Normal	705	14,443	1 (reference)	344	8,829	1 (reference)	1,049	23,272	1 (reference)
Overweight	311	11,578	0.78 (0.67–0.92)	140	5,175	0.97 (0.75–1.24)	451	16,753	0.83 (0.73–0.96)
Obesity	283	13,910	0.72 (0.61–0.86)	147	5,791	0.87 (0.68–1.11)	430	19,701	0.77 (0.67–0.89)
Severe obesity	19	1,220	0.41 (0.22–0.77)	20	826	0.99 (0.57–1.70)	39	2,046	0.60 (0.40–0.90)

BMI, body mass index, HR, hazard ratio; CI, confidence interval.

*Predefined BMI categories according to the Asia-Pacific World Health Organization criteria were used: underweight, BMI <18.5 kg/m^2; normal, BMI 18.5 to 22.9 kg/m^2; overweight, BMI 23.0 to 24.9 kg/m^2; obesity, BMI 25.0 to 29.9 kg/m^2; severe obesity, BMI ≥30.0 kg/m^2; †Cox proportional hazards regression was used to estimate HR and 95% CI with adjustment for TNM stage.

findings were found regarding the effect of BMI on GC. First, the proportion of cardia GC was higher in the underweight and severe obesity groups, but it showed sex difference, making a U-shaped pattern in males and reverse J-shaped pattern in females. Obesity provokes gastroesophageal reflux, which is known to increase the risk of cardia GC, especially in Western countries where obesity is frequent.[33] And increased BMI was positively associated with risk of cardia GC but not with non-cardia GC.[34] There was a study showed that obesity was associated with the risk of GC, especially for males and among non-Asians.[35] In our study, the prevalence of cardia GC was high in obese males and low in obese females. The high prevalence of cardia GC in obese males could be related to gastroesophageal reflux. On the other hand, it could be estimated that the low prevalence of cardia GC in obese females is related to the difference in female sex hormone levels according to BMI. There was also a study that reported the results of female sex hormones prevention cardia GC.[36] The level of female sex hormones is relatively higher in overweight and obesity females than that of normal weight or underweight.[29] And for this reason, the protection effect on cardia GC is relatively high, so the prevalence of cardia GC could be low in obesity females. And a previous study reported an increased risk of non-cardia GC in low BMI.[37] Another study found that atrophic gastritis increases in underweight patients, which may reflect poor absorption from the state of severe gastritis.[38] However, in this study, the prevalence of cardia GC in underweight patients was high in both males and females. BMI was measured at the time of diagnosis in this study, and cardia GC often may be accompanied by dysphagia. Therefore, it is not clear whether underweight is the cause or result of cardia GC. Further research on this is likely to be needed. Second, the proportion of diffuse-type GC was the highest in the underweight group, decreasing as BMI increased. In contrast, intestinal GC showed the opposite trend. In case of diffuse type GC this proportion decreased in females as the BMI increased but this was not definite in males. Third, the proportion of TNM stage I in overweight and obesity was large; in contrast, the proportion of advanced stage (II, III, IV) was higher in underweight patients regardless of sex. A previous study[20] based on GC patients also reported that the proportion of advanced stage (III, IV) was twice higher in BMI <18.5 kg/m^2 than in BMI ≥25.0 kg/m^2. However, they performed the study in the GC patients undergoing gastrectomy without sex-specific analysis.[20] Furthermore, there was no difference in the TNM stage in another study divided into two groups based on BMI 25.0 kg/m^2 without sex-specific analysis.[21] This inconsistency in the difference in TNM stage by BMI could depend on how detailed the BMI is classified. In addition, most studies did not perform comprehensive sex analysis regarding BMI. It is well known that male and female have different BMI and body composition mainly due to sex hormones thus this sex factor could be confounding factor even they analyzed multivariate analysis based on sex and age.

The obesity paradox was initially revealed in cardiometabolic diseases, but has yet to be concluded in cancer.[17] There are several reasons of this inconsistency regarding the obesity paradox and cancer. BMI is a relatively crude measure of body adiposity and body composition and does not differentiate between lean mass and fat mass.[24] However, BMI is appealing as it is routinely measured in primary care and hospital settings and there are well-defined criteria for normal, overweight, and obese categories. Furthermore, it is rather difficult to measure the muscle mass in large cohort studies. Thus, instead of muscle mass, we evaluated relationship of BMI and GC depending on sex. Actually, most studies have evaluated the association between BMI and prognosis in patients with GC. The prognosis of GC patients who underwent gastrectomy in Japan and Korea was better in overweight and obesity than in normal weight.[18,19] In addition, low BMI was associated with more severe postoperative complications and poorer prognosis in GC patients in China.[20] Meanwhile, in a study of advanced GC patients who underwent curative resection, there was no difference in postoperative recurrence or survival rate according to BMI.[39] Similarly in a study of Western GC patients, being overweight was not an independent prognostic factor for long-term survival of GC.[40] Postoperatively, being overweight was rather associated with higher rates of cardiopulmonary complications and intra-abdominal abscess in the same study.[40] Most of several studies on BMI and prognosis in GC had limitation in being based on patients who received gastrectomy or analyzing BMI by dividing it into only 2 to 3 categories. In addition, most of these studies did not investigate the sex difference of BMI with GC-specific survival. In contrast, our study included all patients with GC since 2003 (the opening of SNUBH) from well-constructed medical and surgical cohorts, including clinical and histopathological information, as well as GC-specific survival rate. Furthermore, sex differences were analyzed by subdividing the BMI showing obesity paradox based on sex, which is the first report so far. Our study showed the worst prognosis in underweight patients regardless of sex. In contrast, overweight and obese patients had a better prognosis compared to normal weight in males. In particular, the larger the BMI, the better the prognosis, and this pattern was noticeable in patients with intestinal-type and non-cardia GC. However, this finding was not observed in female patients

with GC.

Several mechanisms might underlie the better prognosis in obese patients and poor prognosis in underweight patients. First, the type of cancer tends to be more aggressive in underweight patients and less aggressive in obese patients. A previous study on BMI and mortality in patients with GC showed that GC with less differentiation and with lower metastatic lymph node were more frequently observed in the high BMI group.[21] In another study regarding the correlation between visceral fat and lymph node metastasis, visceral obesity was associated with decreased lymph node metastasis.[41] Our study also showed that advanced stage cancer was common in underweight patients, and stage I cancer was more common in obese patients. This trend was prominent in males, which is thought to be related to a better prognosis in males with obesity. Second, patients with low BMI frequently have low muscle mass,[42] which can lead to poor immunity. In studies of GC patients, underweight patients had a higher risk of cancer recurrence and died from causes other than cancer, especially infection.[43,44] Third, treatment such as gastrectomy or chemotherapy is often accompanied by weight loss, which can affect survival. A study reported that weight loss may occur after gastrectomy; therefore, overweight or obese patients achieved ideal body weight after gastrectomy, which may improve their long-term prognosis.[21] In a study of patients with overall cancer who underwent chemotherapy, patients with sarcopenic obesity had the poorest prognosis. Actually, obesity predicted a higher survival rate only in the absence of sarcopenia.[45] Fourth, in this study, the prognosis was good only in overweight and obese males but not in females, and the reason can be suggested as follows. Previous studies have shown that low muscle mass stands out in females.[46,47] Despite the same BMI, females have a lot of fat and low muscle mass mainly due to hormones and partially due to different exercise. In a previous study on the sex difference between skeletal muscle mass and prognosis in GC patients, skeletal muscle mass was an important prognostic factor in males, but not in females,[48] which is similar to our results. Differences in body composition according to sex and age, andchanges in body composition during the natural course of GC or treatment could affect prognosis. However, our study did not measure muscle and fat composition, which is a limitation of our study. Another limitation is the small data on the presence or eradication of *H. pylori* infection. Even though we published beneficial effect of *H. pylori* eradication after subtotal gastrectomy on the survival rate of GC patients with follow-up for up to 15 years we performed the *H. pylori* tests mainly in early GC patients[49] because medical insurance covered the *H. pylori* eradication only in early GC from 2018. Nevertheless, our study had several strengths. In Korea, there has been a study on the composition of sex and age among GC patients; however, detailed clinical-pathological variables including tumor location, stage, and histology were not deliberated.[50] Another study reported that GC prognosis exhibits different clinical-pathological features and histology depending on age.[51,52] However, these results may not represent the entire GC group because of selection biases for treatment modality.

In conclusion, our comprehensive study revealed sex differences in GC. GC-specific survival was affected by BMI in a sex-dependent manner. These differences may be related to genetic, and environmental, hormonal factors; body composition; and muscle mass.

CONFLICTS OF INTEREST

J.W.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: N.K. Data acquisition: N.K., H.H.J. Data analysis and interpretation: H.H.J, Y.C., J.P. Drafting of the manuscript: H.H.J. Critical revision of the manuscript for important intellectual content: N.K., H.H.J., J.J. Statistical analysis: Y.M.P., S.A. Obtained funding: N.K. Administrative, technical, or material support; study supervision: H.Y., C.M.S., Y.S.P., D.H.L., H.J.O., H.S.L., Y.S.P., S.H.A., Y.S.S., D.J.P., H.H.K., Ji-Won Kim, Jin Won Kim, K.W.L., W.C., J.H.P., Y.J.L., K.H.L., Y.H.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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