Published OnlineFirst May 21, 2018; DOI: 10.1158/1055-9965.EPI-18-0122

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prognostic Roles of Perioperative Body Mass Index and Weight Loss in the Long-Term Survival of Gastric Cancer Patients

Young Suk Park[1], Do Joong Park[1,2], Yoontaek Lee[1], Ki Bum Park[1], Sa-Hong Min[1], Sang-Hoon Ahn[1], and Hyung-Ho Kim[1,2]

Abstract

Background: Most patients with gastric cancer rapidly lose weight after gastrectomy. Therefore, analysis of the effect of body mass index (BMI) on patients with gastric cancer survival should include postoperative BMI and BMI loss and preoperative BMI. This retrospective cohort study analyzed the effect of three BMI variables and their interaction on long-term outcomes.

Methods: Preoperative BMI analysis included 2,063 patients with gastric cancer who underwent curative gastrectomy between January 2009 and December 2013 at Seoul National University Bundang Hospital. BMI at postoperative 6 to 12 months was available in 1,845 of these cases.

Results: Patients with preoperative BMI 23.0 to <27.5 [HR, 0.63; 95% confidence interval (CI), 0.48–0.82 for BMI 23.0 to <25.0 and HR, 0.57; 95% CI, 0.42–0.78 for BMI 25.0 to <27.5] and postoperative BMI 23.0 to <25.0 (HR, 0.67; 95% CI, 0.46–0.98) showed significantly better overall survival (OS) than pre- and postoperative patients with BMI 18.5 to <23.0, respectively. Postoperative underweight (BMI <18.5; HR, 1.74; 95% CI, 1.27–2.37) and postoperative severe BMI loss (>4.5; HR, 1.79; 95% CI, 1.29–2.50) were associated with higher mortality. Severe BMI loss and preoperative BMI <23.0 had an adverse synergistic effect; patients with BMI <23.0 were more vulnerable to severe BMI loss than those with BMI $\geq$23.0. Associations with cancer-specific survival were similar.

Conclusions: All three BMI variables were prognostic factors for survival of patients with gastric cancer. Preoperative BMI and severe BMI loss had an interaction.

Impact: Perioperative BMI and weight loss should be analyzed collectively in patients with gastric cancer undergoing gastrectomy. *Cancer Epidemiol Biomarkers Prev; 27(8); 955–62. ©2018 AACR.*

Introduction

Overweight and mildly obese people have paradoxically better survival outcomes than those with normal body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) in the general population and in patients with coronary heart disease or heart failure, although the underlying mechanisms remain inconclusive (1–3). This "obesity paradox" applies to the 30-day mortality of patients undergoing general surgery and the long-term survival of patients undergoing colorectal and lung cancer surgery (4–6). In gastric cancer, the effects of BMI on long-term survival remain inconclusive (7–9). However, large retrospective cohort studies show that the survival outcomes of patients with BMI $\geq$25 are superior to those of patients with BMI <25 after gastrectomy (10, 11).

Most patients who undergo gastrectomy experience body weight loss because of decreased food intake after surgery, and the postoperative body weight is maintained throughout the entire life after surgery (12). Therefore, both postoperative BMI and preoperative BMI need to be considered when evaluating long-term survival. The postoperative BMI range associated with superior outcomes may be different from the preoperative range.

Large weight loss in cancer patients is a risk factor for long-term survival. Excessive postoperative or postdiagnostic weight loss in gastric, esophageal, colorectal, and breast cancer is associated with worse long-term outcomes (13–16). Consequently, these three factors, pre- and postoperative (perioperative) BMI, and the extent of BMI loss, are inter-related and need to be analyzed collectively.

In this study, we hypothesized that postoperative and preoperative high BMI are related to better survival, and severe BMI loss is associated with worse long-term outcomes, in patients with gastric cancer. In addition, the adverse effects of excess BMI loss could differ according to the preoperative BMI levels.

Materials and Methods

Patients

This retrospective cohort study was conducted using data from Korea Statistics Promotion Institute (KSPI) and hospital electronic medical records (EMR) from a consecutive series of 2,136 patients who underwent gastrectomy for gastric cancer without any other cancer history between January 2009 and December 2013 at Seoul National University Bundang Hospital (SNUBH). Patients with pathologically proven gastric adenocarcinoma who underwent curative primary gastrectomy with standard lymphadenectomy (D1+ or D2 dissection as described in the Japanese gastric cancer treatment guidelines; ref. 17) were included.

[1]Department of Surgery, Seoul National University Bundang Hospital, Korea. [2]Department of Surgery, Seoul National University College of Medicine, Korea.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Do Joong Park, Seoul National University Bundang Hospital, 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea, Seongnam-si 13620, Republic of Korea. Phone: 821051675371; E-mail: dojoongpark@gmail.com

doi: 10.1158/1055-9965.EPI-18-0122

Patients with double primary cancer in other organs, distant metastasis, or a history of palliative chemotherapy were excluded. Ten patients who died from complications after surgery were excluded. Two patients who underwent adjuvant chemoradiotherapy were also excluded because adjuvant radiotherapy is not a routine procedure in East Asia. Finally, 2,063 cases were included in the analysis of the association with preoperative BMI. In 218 (10.6%) patients, data of postoperative body weight were missing. Consequently, 1,845 cases were included in the analysis of the effect of postoperative BMI and BMI loss on long-term survival (Fig. 1). This study was performed in accordance with the Helsinki Declaration of the World Medical Association, and the study protocol was approved by the institutional review board (IRB) of SNUBH (IRB No. B-1708/415-107). Patient written informed consent to review the medical records was not required by the IRB as no personally identifiable patient information was collected. Only anonymous patient data were collected and results were only reported in aggregate.

Definition of variables

The primary endpoint was the association between three BMI variables (pre- and postoperative BMI, and BMI loss) and the 5-year overall survival (OS), which was calculated from the date of operation until the date of death from any cause. The secondary endpoint was the association between each BMI parameter and the 5-year cancer-specific survival (CSS). CSS was calculated as the number of months from gastrectomy to the date of death from gastric cancer or the last follow-up date for patients still alive.

Preoperative height and weight were routinely measured 1 or 2 days before surgery, and preoperative BMI was calculated using these data. Weight loss had to occur at a maximum of 6 to 12 months postoperatively, and body weight should remain stable for 1 year postoperatively according to previous studies (18, 19). Nutritional data from SNUBH showed a similar pattern (12). In this study, postoperative BMI was calculated using the body weight measured in the outpatient clinic at 12 months after surgery for most patients (83.4%), and 9 (9.8%) or 6 (6.8%) months for the others. Perioperative BMI was classified according to Asian-specific criteria as follows (20): underweight, BMI < 18.5; normal weight, BMI 18.5 to <23.0; overweight, BMI 23.0 to <25.0; and obese, BMI $\geq$ 25.0. The obese group was subdivided into two groups as follows: BMI 25.0 to <27.5 and BMI $\geq$ 27.5. BMI loss was defined as preoperative BMI minus postoperative BMI.

Data collection

Patients' death information was obtained from the microdata integrated service (MDSI) database of KSPI, therefore, the exact death dates could be collected. Recurrence information was obtained from EMR data. Recurrence status was evaluated by postoperative regular check-ups in outpatient clinics. Follow-up was performed every 3 months for 2 years, and then every 6 months from 2 to 5 years. At each follow-up, a physical examination and laboratory tests were performed. Chest radiography, abdominal ultrasonography or computed tomography, and endoscopy were performed once or twice a year until 2 years after surgery and annually thereafter. In patients who were lost to follow-up, telephone interviews with patients or their family were carried out. The survival and recurrence status of the patients was determined in August 2017.

EMR data were also reviewed for information on demographics, smoking status, surgical procedures, pathologic data, and adjuvant chemotherapy. The preoperative American Society of Anesthesiologists (ASA) classification was used to measure comorbidity.

Gastrectomy and adjuvant chemotherapy

Distal or total gastrectomy was performed using standard procedures. In patients with early gastric cancer (clinical T1 stage), proximal or pylorus-preserving gastrectomy was performed selectively when patients desired. Adjuvant chemotherapy was

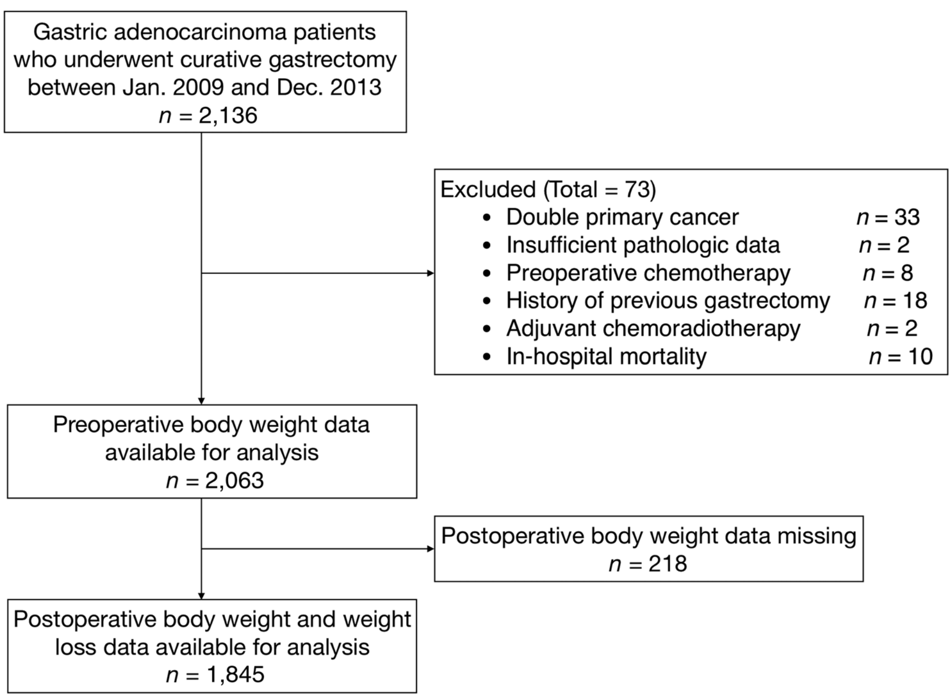

Figure 1.
Flow diagram.

Published OnlineFirst May 21, 2018; DOI: 10.1158/1055-9965.EPI-18-0122

recommended to patients with stage II or higher according to the American Joint Committee on Cancer 7th edition (21). Some patients with advanced age or poor functional status did not receive chemotherapy under informed consent of patients and their family.

Statistical analysis

Cox proportional hazards regression models were used to examine the association between BMI variables and survival, after confirmation of the proportional hazards assumption. Optimal cut-off values for the BMI loss variable used to predict mortality were determined using maximally selected rank statistics as described by Lausen (22).

Causal interaction between preoperative BMI and BMI loss was analyzed to evaluate whether the effect of severe BMI loss was dependent on preoperative BMI levels (23). For the interaction analysis, patients were divided into two groups according to preoperative BMI [underweight or normal − weight group (BMI < 23.0) vs. overweight or obese group (BMI ≥ 23.0)]. The BMI loss variable was also dichotomized according to the cut-off value. The multivariable-adjusted Cox proportional hazards model was applied using dummy variables for the combinations of two factors. The relative excess risk due to interaction (RERI) was calculated as the difference between the observed hazard ratio (HR) after exposure to both risk factors [HR(+,+)] and the expected HR [HR when no exposure to any risk factor (HR (−,−), 1) + increased HRs purely due to exposure to each risk factor (HR(+,−) − 1 and HR(−,+) − 1)]: RERI = HR(+,+) − HR (+,−) − HR(−,+) + 1 (23).

Sensitivity analyses were performed using the multiple imputation method for handling missing postoperative BMI and BMI loss data. Variables used in the imputation model were as follows: age at diagnosis in years, sex, preoperative BMI, smoking status, ASA classification, pT and pN stages, approach methods (open or laparoscopy), extent of stomach resection, reconstruction methods, perioperative cholesterol levels, and adjuvant chemotherapy. A total of 20 multiple imputed sets of missing data were produced using Amelia II.21. Analyses of the imputed datasets, and combination of the results, were performed using R statistical software with the Zeilig software. Tests of statistical significance were two-sided. A *P*-value of ≤0.05 indicated significant results.

Results

Patient demographics and surgical outcomes according to preoperative BMI

The distribution of gender and ASA classification were not associated with preoperative BMI. The mean number of retrieved lymph nodes did not differ according to BMI levels. However, mean age at diagnosis tended to decrease with increasing BMI, and mean operation time was likely to be longer in patients with a high BMI. Tumor size tended to be larger in patients with lower BMI. The proportion of patients with higher pathologic T, N, and TNM stage increased as BMI decreased. Adjuvant chemotherapy was administered at a similar rate in all BMI groups (Table 1).

Patterns of BMI changes

After surgery, most patients (97.7%) changed to lower BMI groups or remained in the corresponding preoperative BMI group. The mean BMI change (±SD) was 2.2 ± 1.9 in all patients. Higher preoperative BMI values were associated with a greater risk of weight loss after gastrectomy (Table 1). Postoperative BMI loss was greater in women and patients with a high TNM stage (2.0 ± 1.8 in men vs. 2.5 ± 1.9 in women, and 2.0 ± 1.8 in stage I vs. 2.5 ± 1.8 in stage II vs. 2.6 ± 2.1 in stage III). BMI loss was associated with the extent of stomach resection in the following order: total gastrectomy (3.1 ± 1.9) > proximal gastrectomy (2.7 ± 1.8) > distal gastrectomy (2.0 ± 1.8) and pylorus-preserving gastrectomy (2.0 ± 2.0).

Perioperative BMI levels as prognostic factors for OS

Of the 2,063 patients, 347 died (170 from gastric cancer) during a median (range) follow-up period of 68.4 (0.5–104.4) months.

The unadjusted Cox proportional hazard model for preoperative BMI and OS showed that patients with BMI ≥23.0 had better survival outcomes than normal-weight patients. Multivariable analysis indicated that patients with BMI 23.0 to <27.5 had significantly better survival outcomes than normal-weight patients [HR: 0.62; 95% confidence interval (CI), 0.47–0.81 for patients with BMI 23.0 to <25.0; and HR: 0.59; 95% CI, 0.43–0.80 for BMI 25.0 to <27.5], although the association of patients with BMI ≥27.5 with OS was not significant (HR, 0.72; 95% CI, 0.48–1.06). Preoperative underweight patients did not show an increased mortality risk (HR, 0.82; 95% CI, 0.51–1.30; Table 2).

In the multivariable analysis of postoperative BMI, postoperative underweight patients were associated with higher mortality (HR, 1.71; 95% CI, 1.25–2.35), and patients with BMI 23.0 to <25.0 showed better survival outcomes (HR, 0.65; 95% CI, 0.44–0.96), than postoperative normal-weight patients (Table 2).

Effect of the association between BMI loss and preoperative BMI levels on OS

BMI loss as a continuous variable was an independent risk factor for OS in the multivariable-adjusted Cox proportional hazard model (HR, 1.12; 95% CI, 1.05–1.20). A BMI loss of 4.5 was established as the optimal cut-off value to distinguish patients with poor prognosis, and patients with BMI loss >4.5 had an increased mortality risk (HR, 1.79; 95% CI, 1.28–2.49) in the multivariable analysis (Table 2).

To prove the hypothesis that the effect of BMI loss on survival is dependent on preoperative BMI, patients were divided into two groups according to preoperative BMI and subgroup analysis was performed first. In the subgroup analysis, the HR for BMI loss >4.5 was higher in patients with a preoperative BMI < 23.0 (HR, 2.86; 95% CI, 1.49–5.49) than in those with a preoperative BMI ≥ 23.0 (HR, 2.01; 95% CI, 1.31–3.07; Table 3). Based on this result, causal interaction analysis was performed using two risk factors for OS, BMI loss >4.5 and preoperative BMI < 23.0. When the two risk factors were acting independently, HRs were 2.06 (95% CI, 1.38–3.07) and 1.67 (95% CI, 1.28–2.18), respectively. When two risk factors acted simultaneously, HR was 4.20 (95% CI, 2.24–7.86); RERI for OS = 4.20 − 2.06 − 1.67 + 1 = 1.47 (Fig. 2A).

When we categorized BMI loss into three groups using maximally selected rank statistics twice, the cut-off values were 0.9 and 4.5 [BMI loss ≤0.9 (mild loss group), 0.9 < BMI loss ≤ 4.5 (moderate loss group), BMI loss >4.5 (severe loss group)]. The patients with moderate loss tended to have a worse survival outcome (HR, 1.37; 95% CI, 0.98–1.91; Supplementary Table S1).

Table 1. Demographics and surgical outcomes according to preoperative BMI

	Preoperative BMI (kg/m^2)					
Characteristic	**<18.5 (*n* = 82)**	**18.5 to <23.0 (*n* = 761)**	**23.0 to <25.0 (*n* = 539)**	**25.0 to <27.5 (*n* = 456)**	**≥27.5 (*n* = 225)**	**Total (*n* = 2,063)**
Age, year	60.8 ± 16.2	60.2 ± 13.1	60.4 ± 12.0	59.9 ± 11.3	59.5 ± 12.3	60.1 ± 12.5
Sex, *n* (%)						
Male	55 (67.1)	485 (63.7)	385 (71.4)	340 (74.6)	143 (63.6)	1,408 (68.3)
Female	27 (32.9)	276 (36.3)	154 (28.6)	116 (25.4)	82 (36.4)	655 (31.7)
ASA classification						
I	44 (53.7)	389 (51.1)	269 (49.9)	198 (43.4)	81 (36.0)	981 (47.6)
II	35 (42.7)	331 (43.5)	247 (45.8)	245 (53.7)	134 (59.6)	992 (48.1)
≥III	3 (3.7)	41 (5.4)	23 (4.3)	13 (2.9)	10 (4.4)	90 (4.4)
Smoking status, *n* (%)						
Never	44 (53.7)	468 (61.5)	308 (57.1)	267 (58.6)	138 (61.3)	1,225 (59.4)
Past	16 (19.5)	132 (17.3)	103 (19.1)	70 (15.4)	33 (14.7)	354 (17.2)
Current	22 (26.8)	161 (21.2)	128 (23.7)	119 (26.1)	54 (24.0)	484 (23.5)
Postoperative BMI (kg/m^2), *n* (%)						
<18.5	50 (74.6)	147 (22.4)	9 (1.8)	2 (0.5)	0	208 (11.3)
18.5 to <23.0	17 (25.4)	493 (75.3)	372 (76.2)	179 (41.7)	20 (9.7)	1,081 (58.6)
23.0 to <25.0	0	13 (2.0)	99 (20.3)	173 (40.3)	79 (38.3)	364 (19.7)
25.0 to <27.5	0	2 (0.3)	8 (1.6)	73 (17.0)	62 (30.1)	145 (7.9)
≥27.5	0	0	0	2 (0.5)	45 (21.8)	47 (2.5)
BMI loss (kg/m^2)	−0.3 ± 1.7	1.5 ± 1.5	2.2 ± 1.5	2.8 ± 1.8	3.8 ± 1.9	2.2 ± 1.9
Extent of resection, *n* (%)						
Distal gastrectomy	65 (79.3)	567 (74.5)	432 (80.1)	363 (79.6)	176 (78.2)	1,603 (77.7)
Total gastrectomy	13 (15.9)	146 (19.2)	80 (14.8)	65 (14.3)	30 (13.3)	334 (16.2)
Proximal gastrectomy	4 (4.9)	39 (5.1)	23 (4.3)	22 (4.8)	17 (7.6)	105 (5.1)
Pylorus-preserving gastrectomy	0	9 (1.2)	4 (0.7)	6 (1.3)	2 (0.9)	21 (1.0)
No. of retrieved lymph nodes	54.2 ± 22.7	51.6 ± 19.6	52.8 ± 20.0	51.4 ± 20.3	53.8 ± 24.4	52.2 ± 20.6
Extent of lymphadenectomy, *n* (%)						
D1+	30 (36.6)	354 (46.5)	273 (50.6)	225 (49.3)	111 (49.3)	993 (48.1)
≥D2	52 (63.4)	407 (53.5)	266 (49.4)	231 (50.7)	114 (50.7)	1,070 (51.9)
Operation time, minutes	164.3 ± 51.3	170.9 ± 58.9	179.0 ± 58.2	178.4 ± 56.7	183.5 ± 56.4	175.8 ± 57.8
Estimated blood loss, mL	136.9 ± 146.3	126.5 ± 109.4	135.1 ± 116.0	138.5 ± 123.6	138.3 ± 142.3	133.1 ± 119.8
Tumor size, cm	4.3 ± 2.8	3.8 ± 2.6	3.4 ± 2.1	3.4 ± 2.3	3.3 ± 2.2	3.6 ± 2.4
Histologic type, *n* (%)						
Differentiated	58 (70.7)	532 (69.9)	393 (72.9)	336 (73.7)	153 (68.0)	1472 (71.4)
Undifferentiated	20 (24.4)	209 (27.5)	130 (24.1)	103 (22.6)	60 (26.7)	522 (25.3)
Others	4 (4.9)	20 (2.6)	16 (3.0)	17 (3.7)	12 (5.3)	69 (3.3)
pT-stage, *n* (%)						
T1	45 (54.9)	460 (60.4)	349 (64.7)	297 (65.1)	158 (70.2)	1,309 (63.5)
≥T2	37 (45.1)	301 (39.6)	190 (35.3)	159 (34.9)	67 (29.8)	754 (36.5)
pN-stage, *n* (%)						
N0	48 (58.5)	495 (65.0)	364 (67.5)	314 (68.9)	162 (72.0)	1383 (67.0)
≥N1	34 (41.5)	266 (35.0)	175 (32.5)	142 (31.1)	63 (28.0)	680 (33.0)
pStage[a], *n* (%)						
I	47 (57.3)	489 (64.3)	373 (69.2)	311 (68.2)	165 (73.3)	1385 (67.1)
II	11 (13.4)	119 (15.6)	82 (15.2)	71 (15.6)	30 (13.3)	313 (15.2)
III	24 (29.3)	153 (20.1)	84 (15.6)	74 (16.2)	30 (13.3)	365 (17.7)
Adjuvant chemotherapy, *n* (%)						
No	65 (79.3)	584 (76.7)	414 (76.8)	347 (76.1)	179 (79.6)	1589 (77.0)
Yes	17 (20.7)	177 (23.3)	125 (23.2)	109 (23.9)	46 (20.4)	474 (23.0)

Abbreviation: p, pathologic.

[a]The TNM stage was determined according to the seventh edition of the American Joint Committee on Cancer staging manual.[21]

Subgroup analyses of perioperative BMI and OS

To confirm the result that postoperative underweight and not preoperative underweight was a risk factor for long-term survival, the postoperative underweight group was subdivided into two groups: underweight patients before and after surgery (weight maintenance group), and postoperative underweight patients who were not underweight before surgery (weight loss group). In the multivariable analysis, only the weight loss group showed a significantly elevated mortality risk (HR, 1.90; 95% CI, 1.34–2.69) compared with the postoperative normal-weight group (Table 4).

Similarly, when patients were subdivided according to the combination of preoperative and postoperative BMI, those with preoperative BMI 25.0 to <27.5 and postoperative BMI 23.0 to <25.0 showed significantly better OS (HR, 0.37; 95% CI, 0.18–0.73), and only the patients with preoperative normal weight and postoperative underweight showed significantly worse outcomes (HR, 1.71; 95% CI, 1.15–2.56) than pre- and postoperative normal-weight patients (Supplementary Table S2).

Stratified analyses and sensitivity analyses for OS

The results that preoperative BMI 23.0 to <27.5 was a good prognostic factor and postoperative underweight and excess BMI loss was a bad prognostic factor were more apparent in men and TNM stage I patients than in women and stage II or III patients

Published OnlineFirst May 21, 2018; DOI: 10.1158/1055-9965.EPI-18-0122

Table 2. Hazard ratios of perioperative BMI and BMI loss

	No. at risk	No. of events	Unadjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[a]
Overall survival				
Preoperative BMI (n = 2,063)				
<18.5	82	21	1.23 (0.78–1.94)	0.82 (0.51–1.30)
18.5 to <23.0	761	168	1 [Reference]	1 [Reference]
23.0 to <25.0	539	76	0.60 (0.46–0.79)	0.62 (0.47–0.81)
25.0 to <27.5	456	52	0.48 (0.35–0.66)	0.59 (0.43–0.80)
≥27.5	225	30	0.59 (0.40–0.87)	0.72 (0.48–1.06)
Postoperative BMI (n = 1,845)				
<18.5	208	55	1.82 (1.34–2.46)	1.71 (1.25–2.35)
18.5 to <23.0	1,081	175	1 [Reference]	1 [Reference]
23.0 to <25.0	364	32	0.51 (0.35–0.75)	0.65 (0.44–0.96)
25.0 to <27.5	145	12	0.49 (0.27–0.88)	0.64 (0.35–1.16)
≥27.5	47	3	0.39 (0.12–1.22)	0.82 (0.26–2.60)
BMI loss[b] (n = 1,845)				
≤4.5	1,657	226	1 [Reference]	1 [Reference]
>4.5	188	51	2.27 (1.68–3.08)	1.79 (1.28–2.49)
Cancer-specific survival				
Preoperative BMI				
<18.5	82	9	1.08 (0.54–2.15)	0.57 (0.28–1.16)
18.5 to <23.0	761	81	1 [Reference]	1 [Reference]
23.0 to <25.0	539	36	0.60 (0.40–0.89)	0.67 (0.45–1.01)
25.0 to <27.5	456	29	0.56 (0.37–0.86)	0.79 (0.51–1.22)
≥27.5	225	15	0.60 (0.35–1.05)	0.86 (0.49–1.51)
Postoperative BMI				
<18.5	208	30	1.65 (1.10–2.47)	1.47 (0.96–2.25)
18.5 to <23.0	1,081	103	1 [Reference]	1 [Reference]
23.0 to <25.0	364	14	0.39 (0.22–0.67)	0.53 (0.30–0.94)
25.0 to <27.5	145	6	0.42 (0.18–0.95)	0.90 (0.37–2.20)
≥27.5	47	1	0.22 (0.03–1.56)	1.08 (0.15–7.95)
BMI loss[b]				
≤4.5	1657	119	1 [Reference]	1 [Reference]
>4.5	188	35	2.89 (1.98–4.22)	1.99 (1.30–3.04)

[a]Cox regression models adjusted for age at diagnosis in years, sex (male [reference] or female), ASAs classification (I [reference], II, or ≥III), smoking status (never [reference], past, or current), T-stage (1 [reference], 2, 3, or 4), N-stage (0 [reference], 1, 2, or 3), venous invasion (no [reference], yes), perineural invasion (no [reference], yes), histology (differentiated [reference], undifferentiated, or mixed), chemotherapy (no [reference], yes), and extent of gastric resection (distal gastrectomy [reference], total gastrectomy, proximal gastrectomy, or pylorus-preserving gastrectomy).
[b]BMI loss was calculated as preoperative BMI minus postoperative BMI.

(Supplementary Table S3). In sensitivity analyses using multiple imputation, the associations between postoperative BMI or BMI loss and OS were similar to those of our initial findings (Supplementary Table S4).

Effects of BMI variables on CSS

Preoperative BMI was not a significant prognostic factor for CSS. However, patients with postoperative BMI 23.0 to <25.0 exhibited reduced cancer-specific mortality risks, and the association of severe BMI loss with CSS was clearer than that with OS (Table 2). The causal interaction between BMI loss and preoperative BMI on CSS was similar to that on OS, and RERI for CSS was 1.78 ($=4.14 - 1.99 - 1.37 + 1$; Fig. 2B). When we divided BMI loss into three groups, the patients with moderate loss had a lower CSS than the mild loss group (HR, 1.88; 95% CI, 1.13–3.13; Supplementary Table S1).

Discussion

To analyze the relationship between the BMI of cancer patients and surgical outcomes, the primary interest (postoperative

Table 3. Subgroup analysis of severe BMI loss according to preoperative BMI levels

		Overall survival		Cancer-specific survival	
	No. at risk	No. of events	Multivariable adjusted HR (95% CI)[a]	No. of events	Multivariable adjusted HR (95% CI)[a]
Patients with preoperative BMI < 23.0					
BMI loss[b] ≤4.5	698	129	1 [Reference]	67	1 [Reference]
BMI loss >4.5	24	13	2.86 (1.49–5.49)	11	3.98 (1.86–8.51)
Patients with preoperative BMI ≥ 23.0					
BMI loss ≤4.5	959	97	1 [Reference]	52	1 [Reference]
BMI loss >4.5	164	38	2.01 (1.31–3.07)	24	1.80 (1.02–3.19)

[a]Cox regression models adjusted for age at diagnosis in years, sex (male [reference], female), ASAs classification (I [reference], II, or ≥III), smoking status (never [reference], past, or current), T-stage (1 [reference], 2, 3, or 4), N-stage (0 [reference], 1, 2, or 3), venous invasion (no [reference], yes), perineural invasion (no [reference], yes), histology (differentiated [reference], undifferentiated, or mixed), chemotherapy (no [reference], yes), and extent of gastric resection (distal gastrectomy [reference], total gastrectomy, proximal gastrectomy, or pylorus-preserving gastrectomy).
[b]BMI loss was calculated as preoperative BMI minus postoperative BMI.

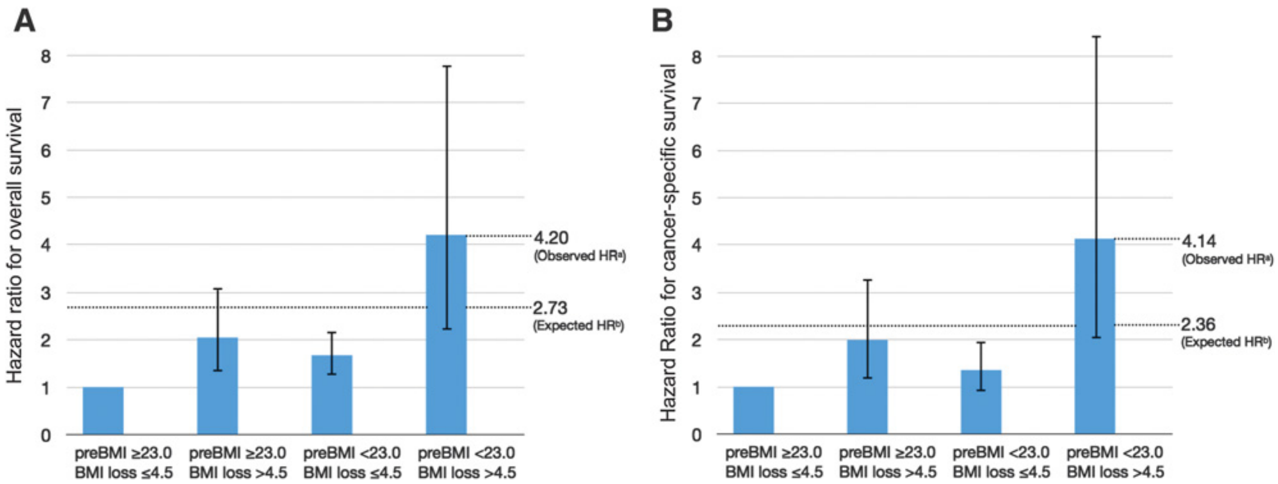

Figure 2.

Causal interaction between preoperative BMI and BMI loss. **A,** Overall survival. **B,** Cancer-specific survival. preBMI, preoperative body mass index. a, The observed HR was HR after exposure to both risk factors [HR(+,+)]. b, The expected HR was calculated as HR when no exposure to any risk factor [HR(−,−), reference = 1] plus increased HRs due to exposure to each risk factor [(HR(+,−) − 1) plus (HR(−,+) − 1)].

complications, in-hospital death, or long-term survival) and the timing of BMI measurement (preoperative or postoperative BMI) need to be determined. Postoperative complications after gastrectomy are more common in preoperative overweight or obese (BMI ≥ 25–30) patients with gastric cancer in most studies (10, 24–26), but not all studies (27, 28). Preoperative underweight (BMI <18.5) may also be associated with the prevalence and severity of morbidity and in-hospital mortality (10, 25). We previously reported that obesity (BMI ≥ 27.5) is an independent risk factor for surgical complications from laparoscopic gastrectomy (29). In this study, we focused on the relationship between long-term outcomes and BMI loss as well as perioperative BMI in patients who underwent open and laparoscopic curative gastrectomy.

Consistent with the proposed hypotheses, patients with gastric cancer with perioperative BMI higher than the normal weight (preoperative BMI 23.0 to <27.5 and postoperative BMI 23.0 to <25.0) showed significantly better OS after adjusting for several factors including comorbidity and cancer stage. Regarding preoperative BMI, studies show conflicting results about its relationship with long-term survival (10, 11, 26, 28, 30, 31). The reported association between high BMI and poor prognosis could be related to difficulties with lymph node dissection (7, 28). Large amounts of abdominal fat can lead to incomplete lymph node dissection, resulting in worse survival. In this study, however, the number of retrieved lymph nodes did not differ between patients with different preoperative BMI values, and high BMI patients showed better survival outcomes. This result could be explained using a different approach, namely, the analysis of body weight loss after gastrectomy. Although body weight loss after gastrectomy occurs in almost all patients, severe weight loss is a poor prognostic factor for OS (15, 32). The present results also showed that severe BMI loss (>4.5) was an independent risk factor for worse survival outcomes. The finding that the HRs of severe BMI

Table 4. Subgroup analysis of postoperative underweight patients

	No. at risk	No. of events	Unadjusted HR (95% CI)	Multivariate adjusted HR (95% CI)[a]
Postoperative BMI (n = 1,845)				
Overall survival				
<18.5 and preoperative BMI <18.5	50	10	1.32 (0.70–2.50)	1.23 (0.64–2.36)
<18.5 and preoperative BMI ≥18.5	158	45	1.98 (1.43–2.75)	1.90 (1.34–2.69)
18.5 to <23.0	1,081	175	1 [Reference]	
23.0 to <25.0	364	32	0.51 (0.35–0.75)	0.65 (0.44–0.95)
25.0 to <27.5	145	12	0.49 (0.27–0.88)	0.64 (0.35–1.16)
≥27.5	47	3	0.39 (0.12–1.22)	0.82 (0.26–2.60)
Cancer-specific survival				
<18.5 and preoperative BMI <18.5	50	6	1.32 (0.58–3.01)	1.00 (0.43–2.34)
<18.5 and preoperative BMI ≥18.5	158	24	1.76 (1.13–2.74)	1.69 (1.05–2.73)
18.5 to <23.0	1,081	103	1 [Reference]	
23.0 to <25.0	364	14	0.39 (0.22–0.67)	0.53 (0.30–0.93)
25.0 to <27.5	145	6	0.42 (0.18–0.95)	0.91 (0.37–2.21)
≥27.5	47	1	0.22 (0.03–1.56)	1.08 (0.15–7.93)

[a]Cox regression models adjusted for age at diagnosis in years, sex (male [reference], female), ASAs classification (I [reference], II, or ≥III), smoking status (never [reference], past, or current), T-stage (1 [reference], 2, 3, or 4), N-stage (0 [reference], 1, 2, or 3), venous invasion (no [reference], yes), perineural invasion (no [reference], yes), histology (differentiated [reference], undifferentiated, or mixed), chemotherapy (no [reference], yes), and extent of gastric resection (distal gastrectomy [reference], total gastrectomy, proximal gastrectomy, or pylorus-preserving gastrectomy).

loss were not consistent with preoperative BMI values suggested an interaction between severe BMI loss and preoperative BMI. RERIs, which indicate the HR that is additional to the expected HR on the basis of the sum of the HRs under exposure to each risk factor, were 1.47 for OS and 1.78 for CSS. This may indicate that patients with preoperative BMI <23.0 are more vulnerable to severe BMI loss, and patients with preoperative BMI $\geq$ 23.0 have a lower risk of mortality than patients with BMI < 23.0 when they lose a lot of weight. This result could be a possible explanation of the "obesity paradox" in patients with gastric cancer after gastrectomy.

Postoperative BMI level was also an independent prognostic factor for OS. Patients with postoperative BMI 23.0 to <25.0 showed better survival rates than normal-weight patients. This result could be expected considering that most of these patients (74.7%) had a preoperative BMI of 23 to <27.5. However, postoperative underweight was a significant risk factor, whereas preoperative underweight was not. This is inconsistent with most previous studies showing that preoperative underweight is a predictor of worse long-term survival (9, 10, 33). The results reported by Lee and colleagues (34) were consistent with the present finding that postoperative BMI rather than preoperative BMI was an independent prognostic factor for long-term survival. In the subgroup analysis of the postoperative underweight group (weight maintenance and weight loss groups), the two groups differed significantly in mean BMI loss (0.4 $\pm$ 1.1 in the weight maintenance group vs. 3.3 $\pm$ 1.8 in the weight loss group, $P <$ 0.001), and only postoperative underweight patients with reduced weight showed significantly worse survival outcomes. This implies that postoperative underweight caused by surgery-induced weight loss, rather than preoperative underweight itself, has an adverse effect on long-term survival. Therefore, in patients who undergo gastrectomy, weight loss should be considered regardless of whether the patient is underweight or overweight to better explain the relationship between BMI and long-term survival (35).

As shown in the stratified analysis according to TNM stage, the association between BMI and survival was more obvious in stage I than in stage II or III patients. This finding may support our "reverse causality" results that higher cancer stage is associated with weight loss and higher mortality among the lower BMI group.

One strength of this study was that the loss of survival and recurrence data were minimized using national statistics database and telephone interviews. Although postoperative weight information was missing in some patients, the results were confirmed by multiple imputation of missing body weights in the survival analysis. One limitation of this study was that we were unable to collect information about peridiagnostic weight change, and severe peridiagnostic weight loss could be another prognostic factor for survival or recurrence. Another limitation was that body composition data were not included in the analyses. This information is currently being collected using computerized tomography, and data on body composition may help our understanding of the relation between BMI and the survival of cancer patients (36).

In conclusion, preoperative BMI 23.0 to <27.5 and postoperative BMI 23.0 to <25.0 were independent favorable prognostic factors for long-term survival in patients with GC who underwent curative gastrectomy. By contrast, postoperative BMI < 18.5 and severe BMI loss (>4.5) were associated with increased overall mortality. We showed that patients with preoperative BMI < 23.0 were more vulnerable to severe BMI loss, suggesting an interaction between preoperative BMI and severe BMI loss. Analysis of the relationship between BMI and survival in patients with GC who experienced gastrectomy-induced weight reduction suggested that perioperative BMI and BMI loss are organically related and should be analyzed collectively.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y.S. Park, D.J. Park, K.B. Park, S.-H. Min, H.-H. Kim
Development of methodology: D.J. Park, S.-H. Ahn, H.-H. Kim
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Lee, D.J. Park
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y.S. Park, D.J. Park
Writing, review, and/or revision of the manuscript: Y.S. Park, D.J. Park
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.J. Park
Study supervision: D.J. Park, S.-H. Ahn

Acknowledgments

This work was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HC15C1322). The authors thank the Medical Research Collaborating Center at Seoul National University Bundang Hospital.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 25, 2018; revised March 30, 2018; accepted May 15, 2018; published first May 21, 2018.

References

1. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71–82.
2. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13–22.
3. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666–78.
4. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. Ann Surg 2009;250:166–72.
5. Kroenke CH, Neugebauer R, Meyerhardt J, Prado CM, Weltzien E, Kwan ML, et al. Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol 2016;2:1137–45.
6. Li S, Wang Z, Huang J, Fan J, Du H, Liu L, et al. Systematic review of prognostic roles of body mass index for patients undergoing lung cancer surgery: does the 'obesity paradox' really exist? Eur J Cardiothorac Surg 2017;51:817–28.
7. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18–23.
8. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000;3:141–4.

9. Wada T, Kunisaki C, Ono HA, Makino H, Akiyama H, Endo I. Implications of BMI for the prognosis of gastric cancer among the japanese population. Dig Surg 2015;32:480–6.
10. Chen HN, Chen XZ, Zhang WH, Yang K, Chen XL, Zhang B, et al. The Impact of body mass index on the surgical outcomes of patients with gastric cancer: a 10-year, single-institution cohort study. Medicine 2015;94:e1769.
11. Tokunaga M, Hiki N, Fukunaga T, Ohyama S, Yamaguchi T, Nakajima T. Better 5-year survival rate following curative gastrectomy in overweight patients. Ann Surg Oncol 2009;16:3245–51.
12. Kim KH, Park DJ, Park YS, Ahn SH, Park DJ, Kim HH. Actual 5-Year nutritional outcomes of patients with gastric cancer. J Gastric Cancer 2017; 17:99–109.
13. Cespedes Feliciano EM, Kroenke CH, Bradshaw PT, Chen WY, Prado CM, Weltzien EK, et al. Postdiagnosis weight change and survival following a diagnosis of early-stage breast cancer. Cancer Epidemiol Biomarkers Prev 2017;26:44–50.
14. Meyerhardt JA, Kroenke CH, Prado CM, Kwan ML, Castillo A, Weltzien E, et al. Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California population. Cancer Epidemiol Biomarkers Prev 2017;26:30–7.
15. Aoyama T, Sato T, Maezawa Y, Kano K, Hayashi T, Yamada T, et al. Postoperative weight loss leads to poor survival through poor S-1 efficacy in patients with stage II/III gastric cancer. Int J Clin Oncol 2017;22:476–83.
16. Hynes O, Anandavadivelan P, Gossage J, Johar AM, Lagergren J, Lagergren P. The impact of pre- and post-operative weight loss and body mass index on prognosis in patients with oesophageal cancer. Eur J Surg Oncol 2017;43:1559–65.
17. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1–19.
18. Na JR, Suh YS, Kong SH, Lim JH, Ju DL, Yang HK, et al. A prospective observational study evaluating the change of nutritional status and the incidence of dumping syndrome after gastrectomy. J Clin Nutr 2014;6:59–70.
19. Davis JL, Selby LV, Chou JF, Schattner M, Ilson DH, Capanu M, et al. Patterns and predictors of weight loss after gastrectomy for cancer. Ann Surg Oncol 2016;23:1639–45.
20. World Health Organization. International association for the study of obesity, international obesity task force. Asia-Pacific Perspect 2000:15–21.
21. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077–9.
22. Lausen B, Schumacher M. Maximally selected rank statistics. Biometrics 1992:73–85.
23. de Mutsert R, Jager KJ, Zoccali C, Dekker FW. The effect of joint exposures: examining the presence of interaction. Kidney Int 2009;75:677–81.
24. Kodera Y, Sasako M, Yamamoto S, Sano T, Nashimoto A, Kurita A, et al. Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. Br J Surg 2005;92:1103–9.
25. Yasunaga H, Horiguchi H, Matsuda S, Fushimi K, Hashimoto H, Ayanian JZ. Body mass index and outcomes following gastrointestinal cancer surgery in Japan. Br J Surg 2013;100:1335–43.
26. Wu XS, Wu WG, Li ML, Yang JH, Ding QC, Zhang L, et al. Impact of being overweight on the surgical outcomes of patients with gastric cancer: a meta-analysis. World J Gastroenterol 2013;19:4596–606.
27. Ejaz A, Spolverato G, Kim Y, Poultsides GA, Fields RC, Bloomston M, et al. Impact of body mass index on perioperative outcomes and survival after resection for gastric cancer. J Surg Res 2015;195:74–82.
28. Shimada S, Sawada N, Ishiyama Y, Nakahara K, Maeda C, Mukai S, et al. Impact of obesity on short- and long-term outcomes of laparoscopy assisted distal gastrectomy for gastric cancer. Surg Endosc 2018;32:358–66.
29. Park YS, Son SY, Oo AM, Jung do H, Shin DJ, Ahn SH, et al. Eleven-year experience with 3000 cases of laparoscopic gastric cancer surgery in a single institution: analysis of postoperative morbidities and long-term oncologic outcomes. Surg Endosc 2016;30:3965–75.
30. Brown JC, Meyerhardt JA. Obesity and energy balance in GI cancer. J Clin Oncol 2016;34:4217–24.
31. Jun DH, Kim BJ, Park JH, Kim JG, Chi KC, Park JM, et al. Preoperative body mass index may determine the prognosis of advanced gastric cancer. Nutr Cancer 2016;68:1295–300.
32. Lee SE, Lee JH, Ryu KW, Nam B, Kim CG, Park SR, et al. Changing pattern of postoperative body weight and its association with recurrence and survival after curative resection for gastric cancer. Hepatogastroenterology 2012; 59:430–5.
33. Migita K, Takayama T, Matsumoto S, Wakatsuki K, Tanaka T, Ito M, et al. Impact of being underweight on the long-term outcomes of patients with gastric cancer. Gastric Cancer 2016;19:735–43.
34. Lee HH, Park JM, Song KY, Choi MG, Park CH. Survival impact of postoperative body mass index in gastric cancer patients undergoing gastrectomy. Eur J Cancer 2016;52:129–37.
35. Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. Prev Med 2014;62:96–102.
36. Caan BJ, Kroenke CH. Next steps in understanding the obesity paradox in cancer. Cancer Epidemiol Biomarkers Prev 2017;26:12.

Published OnlineFirst May 21, 2018; DOI: 10.1158/1055-9965.EPI-18-0122

Cancer Epidemiology,
Biomarkers & Prevention

American Association for Cancer Research

Prognostic Roles of Perioperative Body Mass Index and Weight Loss in the Long-Term Survival of Gastric Cancer Patients

Young Suk Park, Do Joong Park, Yoontaek Lee, et al.

Cancer Epidemiol Biomarkers Prev 2018;27:955-962. Published OnlineFirst May 21, 2018.