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Prognostic significance of surgery-induced sarcopenia in the survival of gastric cancer patients: a sex-specific analysis

Ja Kyung Lee[1], Young Suk Park[1,2]*, Kanghaeng Lee[1], Sang Il Youn[1], Yongjoon Won[1], Sa-Hong Min[1], Sang-Hoon Ahn[1,2], Do Joong Park[1,2] & Hyung-Ho Kim[1,2]

[1]*Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, South Korea;* [2]*Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea*

Abstract

Background Preoperative sarcopenia is associated with a poor long-term prognosis in patients with gastric cancer (GC). Most GC patients rapidly lose muscle mass after gastrectomy. This retrospective cohort study analysed the effect of postoperative muscle loss and surgery-induced sarcopenia on the long-term outcomes of patients with GC.

Methods Preoperative and postoperative 1 year abdominal computed tomography scans were available for 1801 GC patients who underwent curative gastrectomy between January 2009 and December 2013 at Seoul National University Bundang Hospital. The patients were categorized into normal, presarcopenia, and sarcopenia groups according to the skeletal muscle index (SMI) measured on computed tomography scans. Patients who were not sarcopenic prior to gastrectomy but became sarcopenic after surgery were defined as the surgery-induced sarcopenia group.

Results There were 1227 men and 574 women included in the study. The mean age of the patients was 59.5 ± 12.3 years. Multivariable Cox-regression analyses showed that preoperative SMI was not associated with overall survival (OS). However, postoperative sarcopenia was associated with significantly worse OS only in men [hazard ratio (HR), 1.75; 95% confidence interval (CI), 1.08–2.85]. SMI loss was an independent risk factor for OS in the entire cohort and in men (HR, 1.01; 95% CI, 1.00–1.02, for the entire cohort; HR, 1.02; 95% CI, 1.01–1.04, for men). The surgery-induced sarcopenia group was associated with significantly higher mortality (HR, 1.84; 95% CI, 1.16–2.90, for the cohort; HR, 2.73; 95% CI, 1.54–4.82, for men), although SMI loss and surgery-induced sarcopenia were not risk factors in women. Similar results were obtained for relapse-free survival.

Conclusions Postoperative muscle mass loss and surgery-induced sarcopenia are prognostic factors for survival in patients with GC. Impact of postoperative muscle mass loss and surgery-induced sarcopenia on survival outcomes is dependent on the sex.

Keywords Stomach neoplasm; Sarcopenia; Skeletal muscle; Survival

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**Correspondence to: Young Suk Park, MD., Department of Surgery, Seoul National University Bundang Hospital, 166 Gumi-ro, Bundang-gu, Seongnam-si, Kyeonggi-do, South Korea 13620. Phone: +82-31-787-7099, Fax: +82-31-787-4055, Email: youngsukmd@gmail.com*

Introduction

Gastric cancer (GC) is the third leading cause of cancer-related death in men and the fifth in women worldwide.[1] Although the incidence and mortality of GC have decreased, the prognosis of GC remains poor.[1,2] Studies investigating the prognosis of GC have mainly focused on treatment-related factors such as neoadjuvant or adjuvant chemo (radio)therapy, the extent of gastric resection and lymphadenectomy, and surgical approach methods.[3–7] However, patient-related

correctable factors such as underweight and sarcopenia have not been investigated extensively, and strategies aimed at correcting these factors are lacking.

Sarcopenia is an independent negative prognostic factor in patients with various malignancies including GC.[8–12] The literature mostly addresses preoperative sarcopenia as a prognostic factor; however, most patients who undergo gastrectomy suffer skeletal muscle loss because of difficulty with food consumption and reduced physical activity.[13] Hence, both preoperative and postoperative muscle mass should be considered when evaluating long-term survival especially in GC patients undergoing gastrectomy. Indeed, few studies demonstrated that marked postoperative weight loss is a risk factor for poor prognosis in gastrointestinal and pancreatic cancers,[14–16] and excessive skeletal muscle loss after surgery is also a prognostic factor,[17] suggesting that surgery-induced sarcopenia and postoperative muscle loss may be more harmful than preoperative sarcopenia in GC patients who undergo gastrectomy.

There are considerable sex-based differences in human skeletal muscle gene expression, as well as skeletal muscle mass, fibre composition, contractile function, and hormone regulation.[18,19] The amount and rate of muscle mass loss during ageing also differ between men and women.[20,21] These findings suggest that postoperative skeletal muscle loss patterns and the effect of sarcopenia or muscle loss on prognosis could differ according to sex.

In this study, we hypothesized that surgery-induced sarcopenia and surgery-related muscle loss are associated with worse long-term outcomes in GC patients and evaluated potential sex differences in the relationship between sarcopenia and long-term survival.

Methods

Patients

Between January 2009 and December 2013, consecutive 2136 patients with gastric adenocarcinoma who underwent curative primary gastrectomy at Seoul National University Bundang Hospital were analysed. Patients with double primary cancer, insufficient pathologic data, distant metastasis, and a history of previous gastrectomy, or in-hospital mortality were excluded. Patients who received neoadjuvant chemotherapy or adjuvant chemoradiotherapy were excluded as these are not standard practice in East Asia.[22,23] Another 208 patients with missing preoperative or postoperative computed tomography (CT) scans were also excluded. Because CT scans performed 1 year after surgery were considered 'postoperative' CT, patients who showed GC recurrence but who did not die within 1 year postoperatively could have introduced bias in the evaluation of the relationship between muscle changes and long-term survival outcomes; therefore, additional 54 patients were excluded. Finally, 1801 patients were included in the final analysis (*Figure* 1). This study was performed following 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-1909/565-105). 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 the results were only reported as aggregate data.

Definition of variables

The primary endpoint, overall survival (OS) was calculated from the date of operation until the date of death from any cause or the last follow-up date for live patients. The secondary endpoint, relapse-free survival (RFS), was calculated from the date of surgery to the date of GC relapse, death, or the last follow-up.

Cross-sectional abdominal CT images were analysed at the level of the third lumbar vertebra using AsanJ-Morphometry software™ (Asan Image Metrics, Seoul, Korea) to determine skeletal muscle within a range of −29 to +150 Hounsfield units.[24] Skeletal muscles evaluated included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. The skeletal muscle area was normalized for height (m^2) to determine the skeletal muscle index (SMI: cm^2/m^2). Preoperative abdominal CT scans were checked within 6 weeks before surgery. Postoperative skeletal muscle was analysed using the CT scan performed at 11–13 months after surgery because postoperative body weight remained stable after 1 year postoperatively, and the most pronounced loss of muscle mass occurred within 1 year after surgery.[25,26]

To examine the difference in OS, sex-specific cut-off values for SMI were calculated, and patients were classified into three groups as follows: normal, presarcopenia, and sarcopenia groups. Because body composition varies according to ethnicity, and there is no consensus on the cut-off values for sarcopenia using SMI measured on CT scans, cut-off values in this study were calculated based on sex-specific tertiles. Cut-off values of sarcopenia were set at the lowest tertile of SMI, and those for presarcopenia were set at the middle tertile. The cut-off values were as follows: $\geq$50.8, 44.4– $<$ 50.8, $<$44.4 cm^2/m^2 for men, and $\geq$38.8, 34.1– $<$ 38.8, $<$34.1 cm^2/m^2 for women. Patients with the highest tertile of SMI per cent loss (%SMI-loss) were designated as severe loss group and the others as non-severe loss group to compare survivals according to SMI change. The %SMI-loss was calculated as (preoperative SMI − postoperative SMI) / preoperative SMI × 100. For subgroup analysis, patients who were sarcopenic before and after

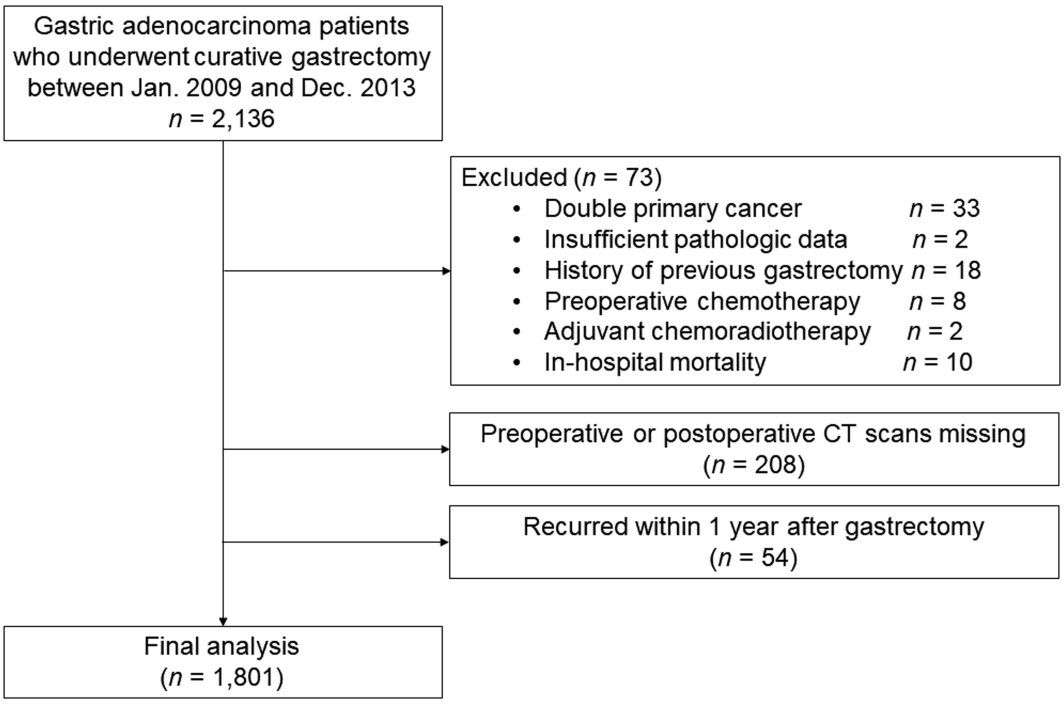

Figure 1 Flow diagram. CT, computed tomography.

gastrectomy were defined as the non-surgical sarcopenia group, and patients who were not sarcopenic prior to gastrectomy but became sarcopenic after surgery were defined as the surgery-induced sarcopenia group.

Survival and recurrence data collection

Patients' survival status was obtained from the microdata integrated service database of the Korea Statistics Promotion Institute. Recurrence status was evaluated by the postoperative regular check-ups in outpatient clinics. Follow-up was performed every 3 months for 1 year, and then every 6 months from 1 to 5 years. Abdominal ultrasonography and CT were checked alternatively every 6 months in early GC patients, and abdomen-pelvis CT scans were evaluated at least every 6 months in advanced cancer patients. Endoscopy was performed annually until 5 years after surgery. In patients who were lost to follow-up, telephone interviews with patients or their families were carried out. The survival and recurrence status of the patients were determined in April 2020.

Gastrectomy and adjuvant chemotherapy

Distal or total gastrectomy was performed as the standard procedure. In clinically early GC patients (T1N0 stage), proximal or pylorus-preserving gastrectomy was performed selectively according to patient preference. D1+ or D2 lymphadenectomy was performed according to the Korean GC treatment guidelines.[22] Adjuvant chemotherapy was recommended in patients with Stage II or higher according to the American Joint Committee on Cancer 7th edition. Some patients with old age or poor functional status did not receive chemotherapy under informed consent of patients and their family.

Statistical analysis

Continuous variables are presented as the mean with standard deviation, and categorical variables are presented as the number of patients with proportion. Student's *t* test and χ^2 test were used to compare continuous and categorical variables, where appropriate. The Kaplan–Meier analyses were performed for OS and RFS for the preoperative and postoperative SMI groups and for the severe and non-severe loss groups.

The impact of perioperative skeletal muscle mass status on survival was examined using the Cox proportional hazard model after confirmation of the proportional hazard assumption. Cox regression models adjusted for age at diagnosis in years, sex, American Society of Anesthesiologists (ASA) classification, T-stage, N-stage, venous invasion, perineural invasion, adjuvant chemotherapy, extent of gastric resection, preoperative prognostic nutritional index (PNI), severe

(Clavien–Dindo Classification III or more) complication, and preoperative body mass index (BMI). Same variables except for preoperative or postoperative SMI groups [normal (reference), presarcopenia, sarcopenia] were used for each preoperative and postoperative regression model, as well as for comparison of severe and non-severe loss groups. Continuous preoperative SMI, postoperative SMI, and %SMI-loss variables were also analysed using separate Cox regression models for each, with other variables being identical. When conducting multivariable analysis in a male or female group, the model was adjusted for the same variables except for sex. Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 21.0 (SPSS, Inc., Chicago, IL). A *P* value of <0.05 indicated significant results.

Results

Patient demographics and surgical outcomes according to preoperative skeletal muscle index

There were 1227 men and 574 women included in the study. The mean age of the patients was 59.5 ± 12.3 years. The preoperative sarcopenia group had significantly older patients and lower preoperative and postoperative BMI and SMI than preoperative non-sarcopenia group (preoperative normal and presarcopenia). The absolute BMI and %SMI-losses were significantly lower in the preoperative sarcopenia group. The distribution of ASA classification indicated that the preoperative sarcopenia group had worse functional capacity. The PNI values were significantly lower in the sarcopenia group before and after surgery. The pathologic stages were not different between the groups (*Table* 1).

Postoperative complications according to preoperative skeletal muscle index

The complication rates were higher in the preoperative sarcopenia group, with greater percentage of systemic complications. Among the systemic complications, pulmonary complications were more frequent in the preoperative sarcopenia group. The distributions of the Clavien–Dindo classification did not differ between the preoperative non-sarcopenia and sarcopenia groups (*Table* 2).

Patterns of skeletal muscle index changes according to sex

Pathologic stage, extent of gastric resection, preoperative BMI, adjuvant chemotherapy, postoperative complications, and preoperative PNI may be important factors affecting postoperative muscle loss in terms of tumour, surgery, patient, and postoperative care. In men, the %SMI-loss differed according to pathologic stage, the extent of resection, and preoperative BMI. However, these differences were not observed in women. Patients who received adjuvant chemotherapy had significantly higher %SMI-loss, in both men and women. Postoperative complications did not affect %SMI-loss (*Table* 3). In addition, higher preoperative PNI was correlated with greater %SMI-loss in both men ($P < 0.001$) and women ($P = 0.005$).

Perioperative skeletal muscle index levels as prognostic factors for overall survival

Of the 1801 patients, 273 (200 men and 73 women) died during a median follow-up period of 99.5 months (range, 13.7–137.7 months).

The 5 year OS rates of preoperative normal, presarcopenia, and sarcopenia groups were 93.7%, 90.3%, and 86.0%, respectively ($P < 0.001$; *Figure* 2A). However, preoperative SMI, both as continuous and categorical variables, did not have a significant effect on the OS on the multivariable Cox proportional hazard model (*Table* 4).

In terms of postoperative SMI, the normal, presarcopenia, and sarcopenia groups had 5 year OS rates of 94.7%, 90.8%, and 85.7%, respectively ($P < 0.001$; *Figure* 2D). In the multivariable analysis, postoperative SMI as continuous variable showed a significant association between less SMI and poor OS (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.95–0.99). The presarcopenia and sarcopenia groups tended to have higher mortalities, with marginal statistical significance (HR, 1.36; 95% CI, 0.92–1.99, for presarcopenia; and HR, 1.42; 95% CI, 0.97–2.08, for sarcopenia; Table 4).

Men had similar trend of survival curves as the entire cohort, with significantly worse survivals in the sarcopenic patients according to the preoperative and postoperative SMI levels (both <0.001; Figure 2B, E). The multivariable analysis showed that only postoperative SMI had significant effect on OS, both as continuous and categorical variables (continuous, HR, 0.97; 95% CI, 0.94–0.99; categorical, HR, 1.75; 95% CI, 1.08–2.85, for sarcopenia; Table 4). In contrast, both preoperative and postoperative SMI statuses were not associated with survival in women (*Figure* 2C and 2F; *Table* 4).

Effects of skeletal muscle loss and surgery-induced sarcopenia on overall survival

The patients with severe %SMI-loss had significantly worse OS outcomes on Kaplan–Meier analysis ($P = 0.02$; *Figure* 2G). On the multivariable analysis, the %SMI-loss as a continuous variable was an independent risk factor for OS in the entire patient cohort (HR, 1.01; 95% CI, 1.00–1.02; Table 4).

Table 1 Demographics and surgical outcomes according to preoperative SMI

	Non-sarcopenia[a] (*N* = 1208)	Sarcopenia (*N* = 593)	*P* value
Age (years)	57.0 ± 11.5	64.7 ± 12.3	<0.001
Sex			
Men	824 (68.2%)	403 (68.0%)	0.96
Women	384 (31.8%)	190 (32.0%)	
Preoperative BMI (kg/m^2)	24.6 ± 2.9	22.3 ± 2.9	<0.001
Postoperative BMI (kg/m^2)	22.4 ± 2.6	20.4 ± 2.6	<0.001
BMI loss[b] (kg/m^2)	2.3 ± 1.8	1.9 ± 1.8	<0.001
Preoperative SMI (cm^2/m^2)	47.8 ± 7.6	36.9 ± 5.2	<0.001
Postoperative SMI (cm^2/m^2)	46.4 ± 7.9	37.6 ± 6.0	<0.001
SMI per cent change[c] (%)	2.8 ± 8.1	−2.2 ± 11.0	<0.001
Postoperative sarcopenia			
Non-sarcopenia	1,024 (84.8%)	121 (20.4%)	<0.001
Sarcopenia	184 (15.2%)	472 (79.6%)	
ASA classification			
I	621 (51.4%)	247 (41.7%)	<0.001
II	549 (45.4%)	312 (52.6%)	
≥III	38 (3.1%)	34 (5.7%)	
Preoperative PNI	55.1 ± 5.4	53.1 ± 6.7	<0.001
Postoperative PNI	53.5 ± 5.1	52.5 ± 5.2	<0.001
Smoking status *n* (%)			
Never	701 (58.0%)	366 (61.7%)	0.21
Past	213 (17.6%)	104 (17.5%)	
Current	294 (24.3%)	123 (20.7%)	
Approach methods			0.65
Laparoscopy	1,014 (83.9%)	492 (83.0%)	
Open	194 (16.1%)	101 (17.0%)	
Operation time (min)	173.0 ± 56.7	178.7 ± 57.9	0.05
Estimated blood loss (mL)	127.7 ± 114.5	136.7 ± 122.3	0.15
Hospital stay (days)	7.0 ± 5.8	7.4 ± 6.4	0.11
No. of retrieved lymph nodes	52.1 ± 20.9	52.0 ± 20.1	0.95
Extent of lymphadenectomy *n* (%)			
D1+	612 (50.7%)	278 (46.9%)	0.15
≥D2	596 (49.3%)	315 (53.1%)	
Extent of resection *n* (%)			0.21
Distal gastrectomy	954 (79.0%)	456 (76.9%)	
Total gastrectomy	174 (14.4%)	103 (17.4%)	
Proximal gastrectomy	69 (5.7%)	26 (4.4%)	
Pylorus-preserving gastrectomy	11 (0.9%)	8 (1.3%)	
pT-stage *n* (%)			0.26
T1	803 (66.5%)	368 (62.1%)	
T2	142 (11.8%)	73 (12.3%)	
T3	159 (13.2%)	95 (16.0%)	
T4	104 (8.6%)	57 (9.6%)	
pN-stage *n* (%)			
N0	838 (69.4%)	399 (67.3%)	0.40
≥N1	370 (30.6%)	194 (32.7%)	
pStage[d] *n* (%)			0.54
I	843 (69.8%)	400 (67.5%)	
II	174 (14.4%)	88 (14.8%)	
III	191 (15.8%)	105 (17.7%)	
Tumour size (cm)	3.4 ± 2.3	3.6 ± 2.3	0.09
Histologic type *n* (%)			
Differentiated	829 (68.6%)	448 (75.5%)	0.002
Undifferentiated	344 (28.5%)	123 (0.7%)	
Others	35 (2.9%)	22 (3.7%)	
Adjuvant chemotherapy *n* (%)	297 (24.6%)	120 (20.2%)	0.05

Abbreviations: ASA, American Society of Anaesthesiologists; p, pathologic; PNI prognostic nutritional index; SMI, skeletal muscle index.
Student's *t* test and χ^2 test were used to compare continuous and categorical variables, respectively.
[a]Non-sarcopenia include preoperative normal and presarcopenia groups.
[b]Body mass index (BMI) loss was calculated as preoperative BMI minus postoperative BMI.
[c]SMI per cent change was calculated as preoperative SMI minus postoperative SMI divided by preoperative SMI.
[d]The TNM stage was determined according to the 8th edition of the American Joint Committee on Cancer staging manual.

Table 2 Comparisons of postoperative complications

	Number of patients (%)		*P* value
	Non-sarcopenia[a] (*N* = 1208)	Sarcopenia (*N* = 593)	
Any complications	159 (13.2%)	106 (17.9%)	0.01
Clavien–Dindo classification			0.55
I–II	101 (63.5%)	72 (67.9%)	
III–IV	58 (36.5%)	34 (32.1%)	
Any local complications[b]	114 (9.4%)	59 (9.9%)	0.79
Wound problem	14 (1.2%)	12 (2.0%)	0.22
Anastomosis bleeding	4 (0.3%)	2 (0.3%)	0.99
Anastomosis leakage	19 (1.6%)	11 (1.9%)	0.81
Stump leakage	4 (0.3%)	5 (0.8%)	0.28
Postoperative bleeding	7 (0.6%)	5 (0.8%)	0.74
Anastomosis obstruction	13 (1.1%)	6 (1.0%)	0.99
Pancreas fistula	24 (2.0%)	6 (1.0%)	0.19
Pancreatitis	5 (0.4%)	0 (0.0%)	0.28
Abdomen abscess	20 (1.7%)	5 (0.8%)	0.24
Intestinal obstruction	8 (0.7%)	2 (0.3%)	0.59
Adhesive ileus	2 (0.2%)	2 (0.3%)	0.85
Bowel stricture	6 (0.5%)	3 (0.5%)	0.99
Other local complications	9 (0.7%)	5 (0.8%)	0.99
Any systemic complications[c]	63 (5.2%)	57 (9.6%)	<0.01
Pulmonary complication	27 (2.2%)	30 (5.1%)	<0.01
Urinary complication	29 (2.4%)	20 (3.4%)	0.30
Other systemic complications	11 (0.9%)	10 (1.7%)	0.23

χ^2 test was used to compare categorical variables between the groups.
[a]Non-sarcopenia include preoperative normal and presarcopenia groups.
[b]Local complications include: wound problem, anastomosis bleeding, anastomosis leakage, stump leakage, postoperative bleeding, anastomosis obstruction, pancreas fistula, pancreatitis, abdomen abscess, intestinal obstruction, adhesive ileus, bowel stricture, and other operation related complications.
[c]Systemic complications include: pulmonary, urinary, and other systemic complications.

Table 3 Sex differences in %skeletal muscle index (SMI)-loss after surgery

	%SMI-loss		
	Men	Women	Total
pStage[a]			
I	0.8 ± 8.2	0.4 ± 8.7	0.6 ± 8.4
II	3.2 ± 9.7	1.2 ± 9.5	2.5 ± 9.6
III	1.9 ± 11.3	1.7 ± 15.2	1.8 ± 12.6
P value	<0.01	0.12	<0.01
Extent of resection			
Distal gastrectomy	0.8 ± 8.8	0.6 ± 9.6	0.8 ± 9.1
Total gastrectomy	2.9 ± 9.8	2.2 ± 13.5	2.7 ± 10.9
Proximal gastrectomy	2.6 ± 9.1	0.8 ± 7.8	2.2 ± 8.8
Pylorus-preserving gastrectomy	2.5 ± 11.7	−3.3 ± 10.4	0.04 ± 11.3
P value	0.09	0.15	<0.01
Preoperative BMI (kg/m^2)			
<18.5	−2.0 ± 13.4	0.0 ± 13.8	−1.3 ± 13.5
18.5 to <23.0	−0.2 ± 9.5	0.5 ± 8.0	0.07 ± 9.0
23.0 to <25.0	1.5 ± 8.1	−0.3 ± 9.7	1.0 ± 8.6
25.0 to <27.5	2.8 ± 8.8	1.4 ± 14.2	2.4 ± 10.4
≥27.5	2.9 ± 7.9	3.0 ± 8.9	2.9 ± 8.2
P value	<0.001	0.14	<0.001
Adjuvant chemotherapy			
No	0.6 ± 8.6	−0.1 ± 10.2	0.4 ± 9.1
Yes	3.7 ± 10.0	3.5 ± 9.8	3.6 ± 9.9
P value	<0.001	<0.001	<0.001
Postoperative complication			
No	1.4 ± 8.8	0.9 ± 10.1	1.3 ± 9.3
Yes	0.7 ± 10.2	−1.1 ± 10.6	0.3 ± 10.3
P value	0.24	0.14	0.10

Abbreviations: %SMI-loss, skeletal muscle index per cent loss; BMI, body mass index; p, pathologic.
Analysis of variance or *t* test was used for comparisons of values, where appropriate.
[a]The TNM stage was determined according to the 8th edition of the American Joint Committee on Cancer staging manual.

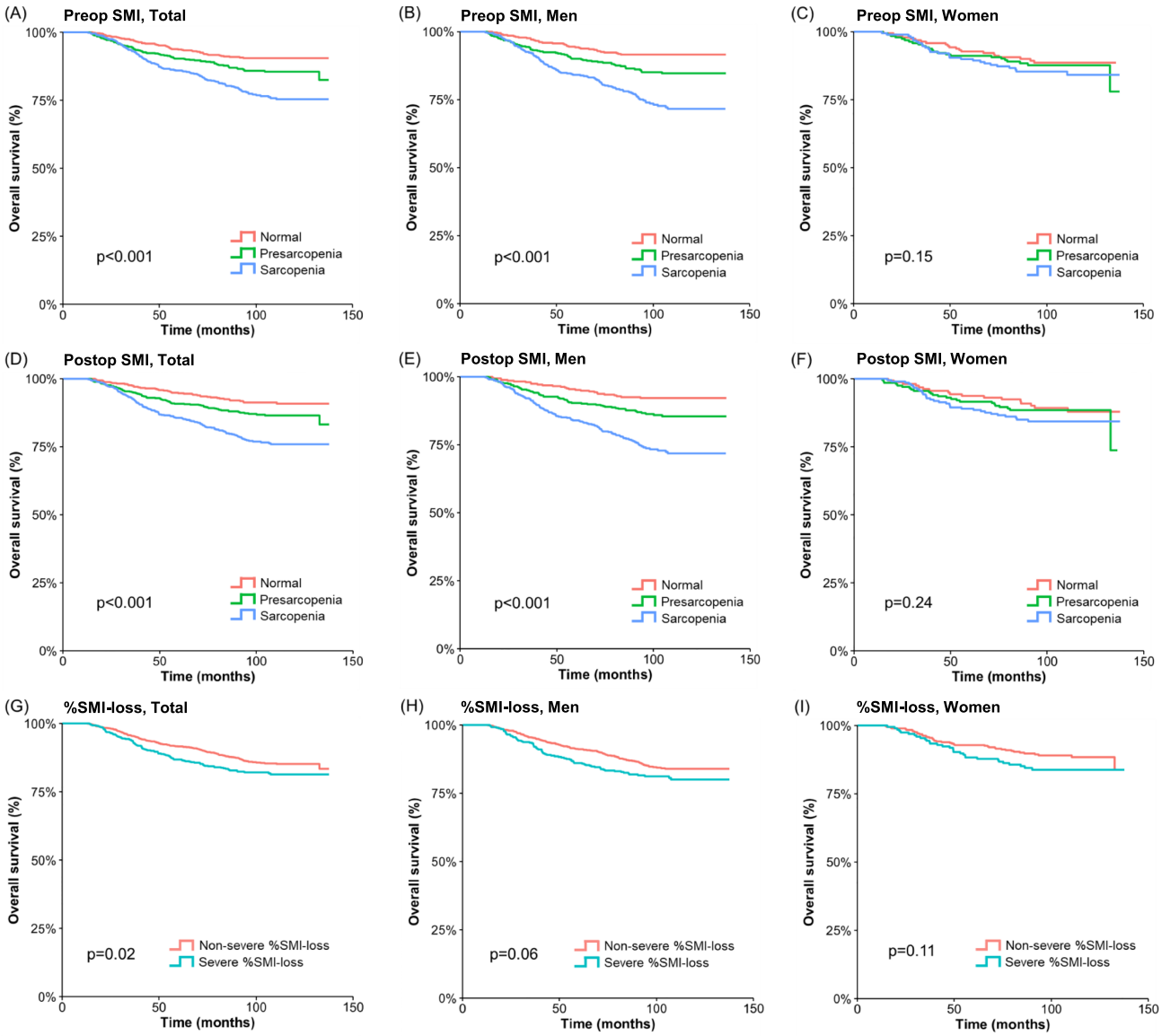

Figure 2 Kaplan–Meier curves of overall survival according to skeletal muscle index. (*A*) Preoperative SMI in total cohort; (*B*) preoperative SMI in men; (*C*) preoperative SMI in women; (*D*) postoperative SMI in total cohort; (*E*) postoperative SMI in men; (*F*) postoperative SMI in women; (*G*) %-SMI-loss in total cohort; (*H*) %-SMI-loss in men; (*I*) %-SMI-loss in women. Total: *n* = 1801, men: *n* = 1227 (68.1%), women: *n* = 574 (31.9%). Abbreviations: SMI, skeletal muscle index; %-SMI-loss, skeletal muscle index per cent loss.

However, %SMI-loss was associated with significantly higher mortality regarding OS only in men and not in women (HR, 1.02; 95% CI, 1.01–1.04, for men; and HR, 1.00; 95% CI, 0.98–1.01, for women; *Table* 4). The %SMI-loss as categorical variables also showed similar results, with the severe %SMI-loss group significantly associated with poor OS (HR, 1.38; 95% CI, 1.02–1.87; *Table* 4).

Subgroup analysis was performed to confirm the importance of skeletal muscle loss as a risk factor for OS. The postoperative sarcopenia group was subdivided into two groups: non-surgical sarcopenia and surgery-induced sarcopenia groups. In the multivariable-adjusted analysis, only the surgery-induced sarcopenia group was associated with significantly elevated mortality in the entire cohort (HR, 1.84; 95% CI, 1.16–2.90; *Table* 5). These results were reproduced in men, and the HRs became clearer (HR, 2.73; 95% CI, 1.54–4.82; *Table* 5); however, in women, surgery-induced sarcopenia was not a significant risk factor, similar to other analysis results (*Table* 5).

Effects of skeletal muscle mass on relapse-free survival

The associations between perioperative SMI and RFS were similar to those between SMI and OS. The Kaplan–Meier

Table 4 Hazard ratios of perioperative skeletal muscle index

	Multivariable-adjusted HR (95% CI)					
	Total[a]	*P* value	Men[b]	*P* value	Women[b]	*P* value
Overall survival						
Preoperative SMI (continuous)	0.99 (0.97–1.01)	0.47	0.99 (0.97–1.02)	0.51	1.01 (0.96–1.07)	0.65
Preoperative SMI (categorical)						
Normal	1 [Reference]					
Presarcopenia	1.21 (0.85–1.73)	0.29	1.21 (0.78–1.89)	0.39	1.11 (0.57–2.18)	0.75
Sarcopenia	1.16 (0.80–1.67)	0.43	1.23 (0.77–1.95)	0.39	0.99 (0.49–1.98)	0.97
Postoperative SMI (continuous)	0.97 (0.95–0.99)	0.01	0.97 (0.94–0.99)	0.01	1.02 (0.97–1.08)	0.39
Postoperative SMI (categorical)						
Normal	1 [Reference]					
Presarcopenia	1.36 (0.92–1.99)	0.12	1.46 (0.90–2.37)	0.13	1.09 (0.55–2.14)	0.81
Sarcopenia	1.42 (0.97–2.08)	0.07	1.75 (1.08–2.85)	0.02	0.70 (0.35–1.39)	0.31
%SMI-loss[c] (continuous)	1.01 (1.00–1.02)	0.04	1.02 (1.01–1.04)	0.01	1.00 (0.98–1.01)	0.63
%SMI-loss (categorical)						
Non-severe %SMI-loss	1 [Reference]					
Severe %SMI-loss	1.38 (1.08–1.78)	0.01	1.38 (1.02–1.87)	0.04	1.14 (0.70–1.87)	0.59
Relapse-free survival						
Preoperative SMI (continuous)	0.99 (0.97–1.01)	0.44	0.99 (0.97–1.02)	0.48	1.01 (0.96–1.06)	0.69
Preoperative SMI (categorical)						
Normal	1 [Reference]					
Presarcopenia	1.24 (0.88–1.75)	0.23	1.23 (0.79–1.90)	0.36	1.29 (0.68–2.45)	0.44
Sarcopenia	1.16 (0.81–1.65)	0.43	1.27 (0.80–2.00)	0.31	0.90 (0.46–1.75)	0.75
Postoperative SMI (continuous)	0.97 (0.95–0.99)	0.01	0.97 (0.94–0.99)	0.01	1.02 (0.97–1.07)	0.44
Postoperative SMI (categorical)						
Normal	1 [Reference]					
Presarcopenia	1.35 (0.93–1.97)	0.12	1.56 (0.97–2.52)	0.07	0.95 (0.49–1.82)	0.87
Sarcopenia	1.44 (0.997–2.09)	0.052	1.81 (1.12–2.93)	0.02	0.77 (0.40–1.48)	0.44
%SMI-loss[c] (continuous)	1.01 (1.001–1.02)	0.04	1.02 (1.01–1.03)	0.01	1.00 (0.98–1.01)	0.60
%SMI-loss (categorical)						
Non-severe %SMI-loss	1 [Reference]					
Severe %SMI-loss	1.35 (1.05–1.72)	0.02	1.37 (1.02–1.85)	0.04	1.03 (0.64–1.65)	0.91

Abbreviation: %SMI-loss, skeletal muscle index per cent loss; CI, confidence interval; HR, hazard ratio; SMI, skeletal muscle index.
[a]Cox regression models adjusted for age at diagnosis in years, sex [male (reference) or female], American Society of Anesthesiologists classification [I (reference), II, or III], 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], chemotherapy [no (reference), yes], extent of gastric resection [distal gastrectomy (reference), total gastrectomy, proximal gastrectomy, or pylorus-preserving gastrectomy], preoperative prognostic nutritional index, severe (Clavien–Dindo Classification III or more) complication [no (reference), yes], and preoperative body mass index [<18.5, 18.5– < 23.0 (reference), 23.0– < 25.0, 25.0– < 27.5, or ≥27.5].
[b]Cox regression models adjusted for same variables as 'a' except for sex
[c]%SMI-loss was calculated as '100 × (preoperative SMI − postoperative SMI) / preoperative SMI'.

curves for RFS showed comparable results as the curves for OS (Supporting information, *Figure* S1). Postoperative sarcopenia in men was an independent risk factor for RFS (*Table* 4). SMI loss and surgery-induced sarcopenia were associated with significantly higher mortality in the entire cohort and in men (*Tables* 4 and 5).

Discussion

The definition of sarcopenia remains controversial, although it is usually explained as a syndrome characterized by the reduction of muscle mass and function.[27] Ageing is the representative cause of sarcopenia (primary sarcopenia); however, one or more other causes such as physical inactivity, malnutrition, or neurologic diseases can induce a sarcopenic condition (secondary sarcopenia).[28] Sarcopenia is associated with an increased risk of death in community-dwelling old adults,[29,30] and several recent studies demonstrated its relationship with increased mortality in various malignancies.[8–11,31] The poor prognosis of cancer patients with sarcopenia has a multi-factorial etiology. Studies have shown that cytokines secreted from muscle cells inhibit breast cancer cell proliferation, and muscle mass loss due to physical inactivity may lead to inflammatory pathways, which promote tumour growth.[32,33]

The association of preoperative sarcopenia in cancer patients with long-term outcomes has been described, whereas few studies have discussed the effects of postoperative sarcopenia or surgical muscle loss on survival.[17,34,35] Sarcopenia induced by gastrointestinal surgery, which is associated with enteral nutrition, may directly affect the survival as patients experience abrupt muscle loss, which may cause impaired immune system and disrupted body metabolism.[36] Moreover, sarcopenic patients receiving adjuvant chemotherapy would not be as tolerable as normal-weighed patients, which would additionally lead to poor oncologic outcomes. Therefore, postoperative sarcopenia or muscle loss could be

Table 5 Subgroup analysis of postoperative sarcopenia patients

	Multivariable-adjusted HR (95% CI)					
	Total[a]	*P* value	Men[b]	*P* value	Women[b]	*P* value
Overall survival						
Postoperative normal	1 [Reference]					
Postoperative presarcopenia	1.34 (0.91–1.97)	0.14	1.43 (0.87–2.32)	0.15	1.09 (0.55–2.15)	0.81
Postoperative sarcopenia and preoperative sarcopenia (non-surgical sarcopenia)	1.26 (0.84–1.88)	0.27	1.43 (0.86–2.39)	0.17	0.78 (0.36–1.67)	0.52
Postoperative sarcopenia and preoperative non-sarcopenia (Surgery-induced sarcopenia)	1.84 (1.16–2.90)	0.01	2.73 (1.54–4.82)	<0.01	0.60 (0.25–1.39)	0.60
Relapse-free survival						
Postoperative normal	1 [Reference]					
Postoperative presarcopenia	1.33 (0.92–1.94)	0.14	1.42 (0.95–2.49)	0.08	0.94 (0.49–1.81)	0.86
Postoperative sarcopenia and preoperative sarcopenia (non-surgical sarcopenia)	1.25 (0.85–1.86)	0.26	1.52 (0.92–2.51)	0.11	0.72 (0.35–1.49)	0.75
Postoperative sarcopenia and preoperative non-sarcopenia (surgery-induced sarcopenia)	1.92 (1.24–2.99)	<0.01	2.70 (1.54–4.76)	<0.01	0.85 (0.39–1.86)	0.69

[a]Cox regression models adjusted for age at diagnosis in years, sex [male (reference) or female], American Society of Anesthesiologists classification [I (reference), II, or III], 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], chemotherapy [no (reference), yes], extent of gastric resection [distal gastrectomy (reference), total gastrectomy, proximal gastrectomy, or pylorus-preserving gastrectomy], preoperative prognostic nutritional index, severe (Clavien–Dindo Classification III or more) complication [no (reference), yes], and preoperative body mass index [<18.5, 18.5– < 23.0 (reference), 23.0– < 25.0, 25.0– < 27.5, or ≥27.5].
[b]Cox regression models adjusted for same variables as 'a' except for sex

more important risk factors for worse long-term outcomes than preoperative sarcopenia. In this study, only the patients who became sarcopenic after surgery because of surgery-induced muscle loss showed poor long-term outcomes, whereas the non-surgical sarcopenia group, which had sarcopenia before surgery, did not show significant differences in survival compared with the normal group. One possible explanation for these results is that the non-surgical sarcopenia group had been slowly adjusting to the sarcopenic status for a long time before surgery, whereas the surgery-induced sarcopenia group experienced sudden negative physiological changes after gastrectomy. The surgery-induced sarcopenia group showed a greater %SMI-loss than the non-surgical sarcopenia group [11.9 ± 6.4% (12.1 ± 6.3% in men and 11.6 ± 6.8% in women; men vs. women P = 0.58) vs. 0.6 ± 9.3% (0.5 ± 9.1% in men and 1.0 ± 9.7% in women; men vs. women P = 0.59); intergroup $P < 0.001$]. The importance of postoperative sarcopenia and surgical muscle loss as prognostic factors was reported previously in other studies on GC[34,35] as well as in other malignancies.[17,37]

Skeletal muscles consist of various types of fibres, and the composition of muscle fibres differs among species and according to anatomical location and sex.[19] Sex dimorphism of skeletal muscle is presumed to be caused by different levels of hormones such as testosterone and oestrogen, as well as differences in gene expression.[18,19] Congenital differences in skeletal muscle between sexes can also lead to differences in ageing-related muscle loss. A longitudinal study showed that leg skeletal muscle loss is significantly greater in elderly men (0.7 ± 0.8 kg) than in elderly women (0.3 ± 0.8 kg) during a mean follow-up time of 4.7 ± 2.3 years.[20] The rate of loss in leg skeletal muscle mass and appendicular muscle mass is also significantly higher in elderly men than in women.[21] Because ageing-related muscle mass loss is greater and occurs at a faster rate in men than in women, its effect on health or mortality may be more severe in men than in women. Gale *et al*. revealed that poorer handgrip strength was associated with increased mortality from all-causes, cardiovascular, and cancer only in men aged ≥65 but not in women.[38] However, Batsis *et al*. showed the opposite results.[39] In their study, older women, not men, with sarcopenia had a significantly higher mortality risk than those without sarcopenia.

The difference in the effect of surgery-induced muscle mass loss between men and women has not been reported previously. Our study showed that surgery-induced sarcopenia was a risk factor for OS and RFS in men only. Analysis of the various factors that can affect muscle mass changes (e.g. tumour stage, extent of gastric resection, and body weight) showed that the %SMI-loss was affected by these variables mainly in men. Patients who received adjuvant chemotherapy showed significant decrease in SMI in both men and women, but postoperative complications did not affect the amount of SMI loss. (*Table* 3). Preoperative PNI, which would be higher in patients with greater BMI, was associated with higher %SMI-loss, in both men and women. These differences in men and women could be due to sex discrepancy in the pattern of muscle loss, as shown in previous studies on cancer mouse models and human patients.[40,41] In a previous study based on cancer mouse model, male mice had greater loss of protein and specific force; in contrast, female mice showed greater amount of muscle mass loss.[41] One reason for this difference can be due to different roles of sex hormone on skeletal muscle: Androgen has anabolic effect that promotes muscle regeneration, and oestrogen has muscle-protective effect through anti-inflammatory pathway that inhibits

proteolysis.[42] As reduction of androgen in cancer patients is a potential factor for cancer-related cachexia, especially in men,[43] these hormonal and physiologic differences could have caused sex discrepancy on the effect of muscle loss.

One limitation of this study was that we were unable to collect information about muscle strength or physical performance, which is another factor defining sarcopenia. Another limitation was that muscle quality was not included in the analyses. Muscle quality is usually evaluated through muscle attenuation in the CT scans, and the attenuation can be accurately measured in non-contrast images. However, in our centre, non-contrast images were not included in stomach CT protocols to minimize the patient's exposure to radiation. Moreover, although only marginally significant, adjuvant chemotherapy was performed more on the preoperative sarcopenia group (*Table* 1, $P = 0.05$). This could be a reflection of the clinical practice where chemotherapy is less considered in patients with old age, low BMI, and poor ASA. We, therefore, adjusted for adjuvant chemotherapy in all of our multivariable analyses to avoid its influence on our survival analyses. Lastly, as women had smaller subject number than men, there could have been insufficient statistical power to reach significance in women regarding overall survival.

In conclusion, postoperative skeletal muscle mass loss and surgery-induced sarcopenia were associated with increased mortality in patients with GC who underwent curative gastrectomy. The association between muscle mass and long-term survival was meaningful in men but not in women. Sex-specific analyses are needed to clarify the relationship between sarcopenia and survival in patients with malignancies.

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Conflict of interest

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan Meier curves of relapse-free survival according to skeletal muscle index (A) Preoperative SMI in total cohort; (B) Preoperative SMI in men; (C) Preoperative SMI in women; (D) Postoperative SMI in total cohort; (E) Postoperative SMI in men; (F) Postoperative SMI in women; (G) %-SMI-loss in total cohort; (H) %-SMI-loss in men; (I) %-SMI-loss in women Total: *n* = 1801, Men: n = 1,227 (68.1%), Women: *n* = 574 (31.9%). Abbreviations: SMI, skeletal muscle index; %-SMI-loss, skeletal muscle index percent loss.

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