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Impact of Sarcopenic Obesity on Surgical Site Infection after Laparoscopic Total Gastrectomy

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ABSTRACT

Background. The critical risk factors for surgical site infection (SSI) after laparoscopic total gastrectomy (LTG) remain unclear. We analyzed the association between body composition and SSI after LTG.

Methods. We performed a retrospective study of patients with gastric cancer who underwent LTG between March 2006 and October 2014 at Kyoto University Hospital, Japan. Visceral fat area and skeletal muscle mass were assessed from preoperative computed tomography scans to define sarcopenia and obesity. Patients were classified into one of four body composition categories according to the presence or absence of sarcopenia or obesity. The incidence of SSI was compared between the four body composition categories.

Results. Of the 157 eligible patients, 45 (24 %) fulfilled the criteria for sarcopenic obesity, 28 (18 %) for nonsarcopenic obesity, 52 (33 %) for sarcopenic nonobesity, and 32 (20 %) for nonsarcopenic nonobesity. Thirty-two patients developed SSI (overall incidence rate, 20 %). The incidence of SSI in each body composition category was 33, 25, 13, and 9 %, respectively ($P = 0.03$). Multivariate logistic regression analysis showed that only sarcopenic obesity was associated with an increased incidence of SSI (odds ratio 4.59, 95 % confidence interval 1.18–17.78, $P = 0.028$).

Conclusions. Sarcopenic obesity is an independent risk factor for the development of SSI after LTG.

Laparoscopic gastrectomy offers several benefits over open surgery, including reduced pain, less scarring, faster recovery time, and improved postoperative quality of life.[1–3] Laparoscopic distal gastrectomy has already been a viable treatment option for early gastric cancer. However, complications with laparoscopic total gastrectomy (LTG) occur more frequently than laparoscopic distal gastrectomy, and LTG remains somewhat challenging.[4–6] Because of technically demanding esophagojejunal anastomosis and splenic hilar dissection, surgical site infection (SSI), which is related to anastomotic leakage and pancreatic leakage, are therefore the major postoperative complication after LTG.[4–7]

In addition, LTG is not yet widely used due to the lower incidence of upper gastric cancer. However, the incidence of gastric cardia cancer and the aging of the population continue to increase.[8–10] In the near future, the need for a less invasive surgery for elderly patients with gastric cardia cancer will continue to increase. The identification of preoperative risk factors for postoperative complications is a crucial step to overcome morbidity associated with LTG. Preoperative risk assessment facilitates appropriate decision-making and perioperative management. However, the critical risk factors for SSI after LTG remain unclear.

Recently, there is an increasing interest in the relationship between surgical outcome and body composition, as determined by the measurement of body fat and muscle mass. Accumulation of visceral fat, termed central obesity, can be associated with postoperative complications after colorectal surgery, open gastrectomy, and laparoscopic distal gastrectomy, whereas the loss of skeletal muscle mass, called sarcopenia, is reportedly also a significant predictor of complications after surgery for esophageal, colorectal, and pancreatic cancers.[11–16] Moreover, sarcopenic obesity, i.e., the combined state of obesity and

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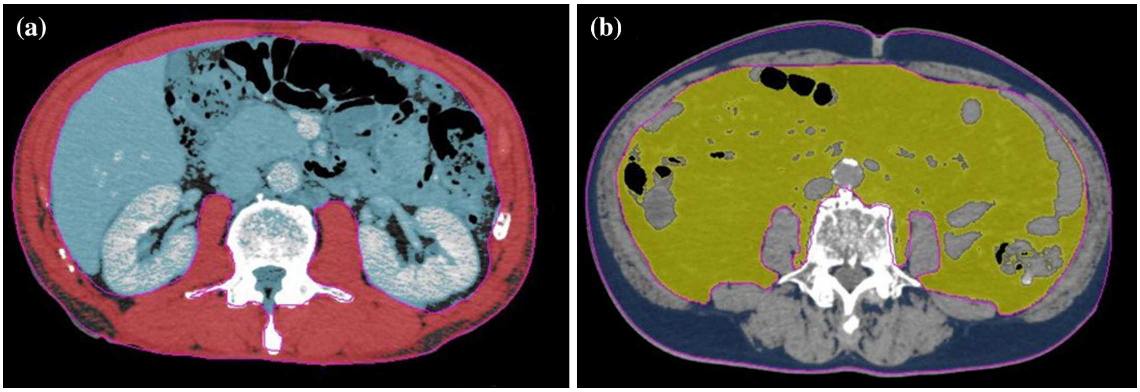

FIG. 1 Area of skeletal muscle at level of third lumbar vertebra (**a**) and of visceral fat at level of umbilicus (**b**) was measured on preoperative computed tomography scans in HU by AquariusNET Server

sarcopenia, increased the risk of postoperative infections in patients who underwent cardiac surgery.[17]

The body composition of preoperative patients is a factor that can be altered by future preoperative intervention, whereas tumor and surgical factors are generally difficult to change. In this study, we focused on preoperative body composition of patients who underwent LTG to investigate whether postoperative SSI was predictable.

PATIENTS AND METHODS

Eligible Patients and Data Collection

This retrospective cohort study was conducted at the Department of Surgery, Kyoto University Hospital, Kyoto, Japan. The study protocol was approved by the ethics committee at Kyoto University. Consecutive patients diagnosed with histologically proven primary gastric cancer who underwent LTG between March 2006 and October 2014 were enrolled onto this study from a prospectively maintained database. The exclusion criteria included concomitant primary cancers and unavailability of a preoperative computed tomographic (CT) scan. Tumors were staged according to the Japanese Classification of Gastric Carcinoma, 3rd English edition.[18] With the agreement of the patients, neoadjuvant chemotherapy (S-1 plus cisplatin with or without docetaxel) was administered to those diagnosed with marginally resectable advanced gastric cancer. Information on the patients was extracted from the database, and detailed information was obtained from original medical records.

Measurement of Visceral Fat and Skeletal Muscle Mass

We calculated patients' visceral fat area and skeletal muscle mass from the latest preoperative CT scans. We measured the cross-sectional skeletal muscle mass at the level of the third lumbar vertebra (L3) and the cross-sectional visceral fat mass at the level of the umbilicus.[19–21] The distinction among muscle, fat, and different tissues was based on Hounsfield units (HU) using AquariusNET Server (TeraRecon, Foster City, CA, USA). A threshold range of −29 to 150 HU was used to define muscle and that of −190 to −30 HU was used to define fat.[19] Hand adjustment of the selected area was performed (Fig. 1). The observer was blinded to patients' postoperative status during the assessment of skeletal muscle mass and visceral fat area.

Definition of Sarcopenia and Obesity

Skeletal muscle mass was normalized for patients' heights to calculate the skeletal muscle mass index (cm^2/m^2). Sarcopenia was defined in skeletal muscle mass index was $\leq$52.4 cm^2/m^2 for men and $\leq$38.5 cm^2/m^2 for women, based on a study by Prado et al.[22] These cutoff values are accepted by an international consensus group on the diagnostic criteria for cachexia associated with cancer.[23]

Obesity was defined if a visceral fat area was $\geq$100 cm^2 in both sexes. This value is widely used as a cutoff value to define sarcopenic obesity for Asian population and is equivalent to that used for the diagnosis of metabolic syndrome in Japan.[24–26]

Body Composition Categories

Subjects were classified into one of four body composition categories according to the presence or absence of sarcopenia or obesity: the sarcopenic obesity, nonsarcopenic obesity, sarcopenic nonobesity, and nonsarcopenic nonobesity.

Definition of SSI

SSI was defined in accordance with the 1999 *Guideline for Prevention of Surgical Site Infection* by the Centers for Disease Control and Prevention Hospital Infection Control

Practices Advisory Committee as superficial incisional, deep, and organ/space SSI.[27] The severity of SSI was defined in accordance with the Clavien-Dindo classification criteria.[28]

Specifically, intra-abdominal abscess was defined as purulent drainage or another sign of deep infection observed by direct or radiologic examination. Pancreatic fistula was defined as a drain output of any measurable volume of fluid on or after postoperative day 3 with amylase levels of drainage fluid greater than three times the serum amylase activity according to the definition of the International Study Group on Pancreatic Fistulas.[29] Without detection of high amylase content, a deep infection was classified as an intra-abdominal abscess.

End Points

The primary end point was a comparison of the incidence of SSI in the four body composition categories. The secondary end points were the effect of body composition on operating time, amount of blood loss, and open conversion rate.

Surgical Procedure

In the earlier period, the indication for laparoscopic surgery was T1/2 N0 gastric cancer. In July 2009, a prospective study of laparoscopic gastrectomy for more advanced gastric cancer was initiated (trial registration UMIN000002085). Since then, LTG has been a standard treatment option for patients who require total gastrectomy.

Details of the procedures of LTG have been reported elsewhere.[30–33] In brief, the patient was placed in a modified lithotomy position. Five abdominal ports, including those for an umbilical laparoscope and a Nathanson liver retractor, were used under a carbon dioxide pneumoperitoneum of 8 mm Hg. D1 + or D2 lymph node dissection was performed.[34,35] Splenectomy was performed for patients with T2–4 tumors located in the greater curvature, and concomitant resection of adjacent organ was added if oncologically necessary. Intracorporeal reconstruction was performed using the Roux-en-Y method. All procedures were performed or supervised by surgeons who are qualified by the Japan Society for Endoscopic Surgery or board-certified with equivalent qualifications.[36]

Statistical Analysis

Continuous variables were expressed as means and standard deviations or as medians and interquartile ranges. Categorical data were expressed as numbers and proportions. The characteristics of the study population in the four body composition categories were analyzed by one-way analysis of variance, the Kruskal–Wallis test, or the Chi square test. The incidence of SSI was compared among the body composition categories by the Chi square test. The association between SSI and the categories was analyzed by multivariate logistic regression models. The nonsarcopenic nonobesity group was used as a reference group. In addition to the four body composition categories, preoperative factors with P values of <0.2 in a univariate analysis were included in the multivariate analysis. To assess the learning curve, the incidence of SSI in the former group was compared with that in the latter. One third of the cases were assigned to the former group, while the rest were assigned to the latter. P values of <0.05 were considered to indicate statistical significance. All analyses were performed by Stata 12.1 statistical software (StataCorp, College Station, TX, USA).

RESULTS

Patient Characteristics

A flowchart to illustrate patient selection is shown in Fig. 2. Although 48 patients (22 %) who underwent open total gastrectomy were excluded, only three patients were excluded after July 2009. Thus, a total of 157 eligible patients were divided into four body composition groups as follows: 45 with sarcopenic obesity (24 %), 28 with nonsarcopenic obesity (18 %), 52 with sarcopenic nonobesity (33 %), and 32 with nonsarcopenic nonobesity (20 %).

The clinical characteristics of the patients in each group are summarized in Table 1. There were significant differences in body mass index, sex, and the prevalence of diabetes mellitus between the four body composition categories.

Body Composition Categories and Surgical Outcomes

Table 2 shows the relationship between the body composition categories and surgical outcomes. There was no

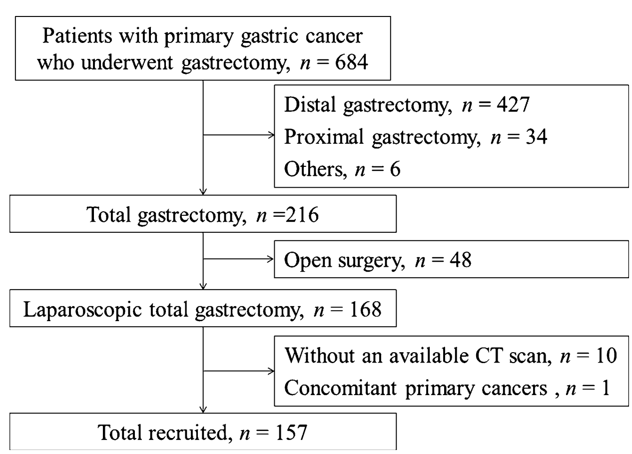

FIG. 2 Flow diagram of patient selection

TABLE 1 Clinical and surgical characteristics

Variable	Category	SO ($n = 45$)	NO ($n = 28$)	SN ($n = 52$)	NN ($n = 32$)	*P*
Age (y)		68.3 ± 8.9	65.8 ± 9.2	65.9 ± 13.1	65.5 ± 9.2	0.60
Sex	Male	37 (82 %)	21 (75 %)	34 (65 %)	11 (34 %)	0.00
	Female	8 (18 %)	7 (25 %)	18 (35 %)	22(64 %)	
BMI (kg/m^2)	<18.5	0	0	10 (19 %)	3 (9 %)	0.00
	≤18.5, <25.0	29 (64 %)	11 (40 %)	41 (79 %)	29 (91 %)	
	25≤	16 (36 %)	17 (61 %)	1 (2 %)	0	
Diabetes mellitus		9 (20 %)	9 (32 %)	3 (6 %)	5 (16 %)	0.02
ASA score	I	8 (18 %)	3 (11 %)	13 (25 %)	14 (44 %)	0.07
	II	33 (73 %)	22 (79 %)	37 (71 %)	16 (50 %)	
	III	4 (9 %)	3 (11 %)	2 (4 %)	2 (6 %)	
FEV1.0 % (%)		76.7 ± 8.1	78.0 ± 10.8	76.9 ± 10.7	76.8 ± 18.0	0.97
Serum albumin (g/dl)		4.0 ± 0.3	4.0 ± 0.6	4.0 ± 0.3	3.9 ± 0.5	0.71
cT	1	20 (44 %)	13 (46 %)	23 (44 %)	17 (53 %)	0.51
	2	5 (11 %)	4 (14 %)	4 (7 %)	5 (16 %)	
	3	11(24 %)	6 (21 %)	11 (21 %)	1 (3 %)	
	4	9 (20 %)	5 (18 %)	14 (27 %)	9 (28 %)	
cN	0	32 (71 %)	20 (71 %)	37 (71 %)	24 (75 %)	0.87
	1	6 (13 %)	3 (11 %)	4 (7 %)	2 (6 %)	
	2	6 (13 %)	4 (14 %)	9 (17 %)	3 (9 %)	
	3	1 (2%)	1 (4 %)	2 (4 %)	3 (9 %)	
cM	0	42 (93 %)	28 (100 %)	47 (90 %)	29 (91 %)	0.40
	1	3 (7 %)	0	5 (10 %)	3 (9 %)	
cStage	I	26 (58 %)	18 (64 %)	27 (52 %)	22 (69 %)	0.67
	II	9 (20 %)	5 (18 %)	10 (19 %)	2 (6 %)	
	III	7 (16 %)	5 (18 %)	10 (19 %)	5 (16 %)	
	IV	3 (7 %)	0	5 (10 %)	3 (9 %)	
History of NAC		9 (20 %)	4 (14 %)	15 (29 %)	8 (25 %)	0.47
Lymph node dissection	D1+	36 (80 %)	23 (82 %)	36 (69 %)	33 (72 %)	0.48
	D2	9 (20 %)	5 (18 %)	16 (31 %)	9 (28 %)	
Splenectomy		4 (9 %)	2 (7 %)	9 (17 %)	6 (19 %)	0.36

ASA American Society of Anesthesiologists, *BMI* body mass index, *FEV1.0 %* forced expiratory volume in 1 s as a percentage of forced vital capacity, *NAC* neoadjuvant chemotherapy, *NN* nonsarcopenic nonobesity group, *NO* nonsarcopenic obesity group, *SN* sarcopenic nonobesity group, *SO* sarcopenic obesity group

difference between the four categories in the duration of surgery, blood loss, and open conversion rate.

Body Composition Categories and SSI

The details of the SSIs are shown in Table 3. Thirty-two patients developed SSIs (overall rate, 20 %). There were two superficial incisional, one deep, and 30 organ-space SSIs. According to the Clavien-Dindo classification, 31 patients were classified as having grade II or higher events. Of 15 patients with intra-abdominal abscess, 14 were treated by intravenous antibiotics alone (grade II). Of the patients with anastomosis leakage or pancreatic fistula, seven (4 %) underwent postoperative intervention (grade III or higher).

The incidence of SSI was 33 % in the sarcopenic obesity group, 25 % in the nonsarcopenic obesity group, 13 % in the sarcopenic nonobesity group, and 9 % in the nonsarcopenic nonobesity group. There was a significant difference between the categories ($P = 0.03$).

The results of univariate and multivariate analyses of SSI are presented in Table 4. Sarcopenic obesity was significantly associated with SSI in the univariate analyses. In a multiple logistic regression analysis, only sarcopenic obesity was significantly associated with an increased

TABLE 2 Relationship between body composition categories and intraoperative factors

Variable	SO ($n = 45$)	NO ($n = 28$)	SN ($n = 52$)	NN ($n = 32$)	*P*
Open conversion rate	0	0	3 (6 %)	0	0.10
Duration of operation (min)	407 ± 138	402 ± 103	386 ± 93	392 ± 112	0.80
Amount of blood loss (ml), median (IQR)	110 (40–200)	88.5 (41.5–204)	73.5 (38.5–202.5)	100 (30–268.5)	0.96

NN nonsarcopenic nonobesity group, *NO* nonsarcopenic obesity group, *SN* sarcopenic nonobesity group, *SO* sarcopenic obesity group

TABLE 3 Relationship between body composition categories and SSI

Variable	All ($n = 157$)	SO ($n = 45$)	NO ($n = 28$)	SN ($n = 52$)	NN ($n = 32$)	*P*
Organ/space	30 (19 %)	14 (31 %)	6 (21 %)	7 (13 %)	3 (9 %)	
Anastomotic leakage	8 (5 %)	3 (7 %)	1 (4 %)	2 (4 %)	2 (6 %)	
Pancreatic fistula	8 (5 %)	5 (11 %)	1 (4 %)	2 (4 %)	0	
Intra-abdominal abscess	16 (10 %)	7 (16 %)	4 (14 %)	4 (8 %)	1 (3 %)	
Deep	1 (1 %)	0	1 (4 %)	0	0	
Superficial incisional	2 (1 %)	2 (4 %)	0	0	0	
Total	32 (20 %)	15 (33 %)	7 (25 %)	7 (13 %)	3 (9 %)	0.03
Clavien-Dindo classification						
I	1 (1 %)	1 (2 %)	0	0	0	
II	24 (15 %)	12 (27 %)	6 (21 %)	5 (10 %)	1 (3 %)	
III or higher	7 (4 %)	2 (4 %)	1 (4 %)	2 (4 %)	2 (6 %)	

NN nonsarcopenic nonobesity group, *NO* nonsarcopenic obesity group, *SN* sarcopenic nonobesity group, *SO* sarcopenic obesity group

relative risk of developing SSI (odds ratio 4.59, 95 % confidence interval 1.18–17.78, $P = 0.028$).

DISCUSSION

Total gastrectomy for gastric cancer is a rather complicated procedure, and its postoperative morbidity is 17.8 % after total gastrectomy alone and 39.7 % with splenectomy via the open approach.[37] To reduce the invasiveness, the laparoscopic approach has been adopted gradually, but its postoperative complication rate remains 19 % to 27 %.[4–7] SSIs, including leakage and intra-abdominal abscess, are the major causes of postoperative complications. Therefore, if SSI could be overcome, LTG would be an even less invasive procedure.

In the current study, we analyzed 157 consecutive patients who underwent LTG and showed that sarcopenic obesity, which was defined on the basis of established cutoff values, was the only independent risk factor for postoperative SSI. To our knowledge, this is the first study to demonstrate a modifiable preoperative risk factor of complications after LTG. The incidence of intra-abdominal abscess seems rather high, but most cases were treated by intravenous antibiotics alone, and only one required surgical intervention (0.6 %).

CT assessment of body composition is considered a precise method and has become the reference standard for detecting obesity and sarcopenia. For surgical candidates who routinely undergo preoperative CT scan, it is also convenient, and no extra cost and irradiation are required.

In terms of preoperative risk factors of SSI after gastrectomy, high body mass index and hypoalbuminemia were previously described in open gastrectomy era.[38,39] However, none of these factors was related to the development of SSI after LTG. We targeted a relatively large number of patients undergoing LTG and found that only body composition is a useful tool to predict SSI after LTG.

The mechanism that links sarcopenic obesity and SSI after LTG is unclear. Skeletal muscle is considered an important source of amino acids in times of stress.[40] Central obesity is known to affect inflammation, and sarcopenic obesity is strongly associated with increased insulin resistance.[41,42] These conditions might impair the right response to operative stress, resulting in an increased risk of SSI.

TABLE 4 Univariate and multivariate analyses of SSI

Variable	Categories or units	No. of patients	Univariate analyses		Multivariate analyses	
			OR (95 % CI)	*P*	OR (95 % CI)	*P*
Body composition	SO	45	4.83 (1.26–18.47)	0.02	4.59 (1.18–17.78)	0.028
	NO	28	3.22 (0.74–13.94)	0.12	3.09 (0.70–13.61)	0.14
	SN	52	1.50 (0.36–6.29)	0.58	1.41 (0.33–6.00)	0.64
	NN	32	1.0		1.0	
Age (y)	≥75	32	1.36	0.56		
	>75 ≥65	69	0.95 (0.39–2.32)	0.91		
	<65	56	1.0			
Sex	Male	103	1.75 (0.73–4.21)	0.21		
	Female	54	1.0			
ASA score	Grade III or higher	11	2.41 (0.66–8.80)	0.18	1.86 (0.52–3.14)	0.39
	Grade I, II	146	1.0		1.0	
FEV1.0 %	<70 %	29	1.31 (0.50–3.41)	0.58		
	≥70 %	128	1.0			
Diabetes mellitus	Yes	26	1.21 (0.44–3.32)	0.71		
	No	131	1.0			
Body mass index (kg/m^2)	<18.5	13	0.69 (0.14–3.32)	0.64		
	<25, ≥18.5	110	1.0	0.97		
	≥25.0	34	0.98 (0.38–2.54)			
Serum albumin (g/dl)	<4.0	67	1.70 (0.78–3.71)	0.18	1.28 (0.52–3.14)	0.59
	≥4.0	90	1.0		1.0	
cStage	Stage II or higher	64	1.88 (0.86–4.12)	0.11	1.86 (0.73–4.20)	0.21
	Stage I	93	1.0		1.0	
NAC	Yes	36	1.42 (0.59–3.43)	0.44		
	No	121	1.0			
Lymph node dissection	D1+	118	1.01 (0.41–2.48)	0.98		
	D2	39	1.0			
Splenectomy	Yes	21	1.69 (0.60–4.78)	0.32		
	No	136	1.0			
Period[a]	Former	52	0.74 (0.32–1.76)	0.50		
	Latter	105	1.0			

ASA American Society of Anesthesiologists, *CI* confidence interval, *FEV1.0* forced expiratory volume in 1 s as a percentage of forced vital capacity, *NAC* neoadjuvant chemotherapy, *NN* nonsarcopenic nonobesity group, *NO* nonsarcopenic obesity group, *OR* odds ratio, *SN* sarcopenic nonobesity group, *SO* sarcopenic obesity group [a]One third of cases were assigned to the former group, while the rest were assigned to the latter

The current results imply that independent predictors for SSI after LTG can be obtained from preoperative CT scans. In addition, it could be hypothesized that preoperative intervention to improve patients' body composition, i.e., toward increasing skeletal muscle mass and reducing visceral fat, could lead to favorable outcomes of LTG for patients with sarcopenic obesity. Although a weight loss therapy of energy restriction alone was reported to decrease skeletal muscle mass, additional exercise training attenuated this loss.[43,44] Moreover, even in the short preoperative period, exercise training was found to improve exercise capacity [45–47] Cho et al. reported that preoperative exercise therapy without diet control reduced not only visceral fat mass but also postoperative morbidity in patients with metabolic syndrome undergoing gastrectomy for early gastric cancer.[48] Further investigation of the effects of perioperative intervention, such as rehabilitation nutrition in sarcopenic obese patients, is necessary.

Our study had several limitations. First, because of its retrospective nature, it may have been influenced by selection and information biases. However, we believe that using consecutive patients from a prospective database containing the perioperative information of all patients with gastric cancer minimized these biases. Second, this study included only Japanese patients. In a previous study, Asian populations were found to be more prone to central obesity and low skeletal muscle mass with increased insulin resistance compared to their Western counterparts.[49] Therefore, the result of the current study may not be applicable to other biogeographic ethnic groups. Third, the cutoff values for sarcopenia are still contested. However, the cutoff values proposed by Prado et al. used in this study are widely used to diagnose sarcopenic individuals among patients with colorectal, esophageal, and breast cancers as well as cirrhosis, and are accepted cutoff values for the diagnosis of cachexia associated with cancer [15,22,23,50–52] However, this cutoff was based on data obtained from Western populations. To exclude the influence of the ethnic differences from the definition of sarcopenia, we conducted additional analysis with a definition of sarcopenia of the lowest sex-specific tertile of skeletal muscle mass index, which also demonstrated that sarcopenic obesity was associated with SSI after LTG in multivariate analysis (data not shown).

In conclusion, sarcopenic obesity is an independent risk factor for the development of SSI after LTG.

DISCLOSURE The authors declare no conflict of interest.

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