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Adverse Effects of Preoperative Sarcopenia on Postoperative Complications of Patients With Gastric Cancer

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Abstract. *Background: Sarcopenia is known to have an important influence on postoperative complications in several diseases, and on the prognosis of patients with cancer. However, whether sarcopenia is associated with complications and prognosis after gastrectomy in patients with gastric cancer remains controversial. This study evaluated the impact of the preoperative muscle mass on postoperative complications of gastric cancer surgery. Materials and Methods: The muscle mass of 153 patients who underwent gastrectomy for gastric cancer from January 2014 to August 2016 was assessed before surgery by a multifrequency bioelectrical impedance analysis (In Body 3.0; Biospace, Tokyo, Japan) and was expressed as the muscle mass index (MMI). Sarcopenia was defined as an MMI value of one standard deviation or more below the gender-specific mean MMI. Complications of Clavien–Dindo grade 2 or more were defined as significant postoperative complications. The impact of preoperative sarcopenia on postoperative infectious complications was analyzed by univariate and multivariate analyses. Results: A total of 153 patients were analyzed, sarcopenia was present in 24 out of 153 patients (15.7%). Thirty (19.6%) patients developed postoperative complications, 20 (13.1%) of which were infectious complications. Sarcopenia was significantly associated with age, body mass index, serum albumin, pulmonary disease in comorbidities, operative time, surgical approach, and postoperative complications. The univariate analyses revealed that male sex, sarcopenia, total gastrectomy, laparotomy, and intraoperative blood loss were associated with postoperative infectious complications. In the multivariate analyses, sarcopenia and intraoperative blood loss ≥400 ml were independently associated with postoperative infectious complications. Conclusion: Preoperative sarcopenia was found to be an independent risk factor for postoperative infectious complications in gastric cancer patients.*

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Despite recent advances in surgical procedures and perioperative management techniques, postoperative complications sometimes occur after gastrectomy in patients with gastric cancer. Several factors, such as older age and a low nutrition status, have been identified as risk factors for postoperative complications of gastric cancer surgery.

Sarcopenia, a newly identified marker of frailty, is characterized by decreased muscle mass and a low muscle strength and function by the European Working Group on Sarcopenia in Older People (EWGSOP) (1). Sarcopenia is known to have an important influence on postoperative complications in several diseases (2-9) and on the prognosis of patients with cancer (2, 10-12).

Bioelectrical impedance analysis (BIA) is a safe, easy and non-invasive method for evaluating body composition (13, 14). The measurement of body composition by BIA is reported to be useful for evaluating the preoperative nutritional status of patients and in predicting outcomes (5, 15). However, few studies have evaluated the association between the preoperative muscle mass, as measured by a BIA, and the perioperative outcomes of patients with gastric cancer.

The aim of this study was to examine the utility of determination of sarcopenia, as evaluated by BIA, in predicting postoperative complications among patients undergoing gastrectomy for gastric cancer.

Materials and Methods

Patients. A total of 202 consecutive patients underwent gastrectomy for gastric cancer at the Department of Gastroenterological Surgery, Osaka City University between April 2014 and August 2016. Five patients with remnant gastric cancer, nine patients who underwent R2 resection, and 35 patients for whom there were no muscle mass

data were excluded from the analysis. Finally, 153 patients were enrolled in this study (Figure 1). Tumors were histologically diagnosed based on the Japanese Classification of Gastric Carcinoma, 14th edition (16).

Assessment of sarcopenia. The body composition was assessed before gastrectomy by multifrequency BIA (InBody 3.0; Biospace, Tokyo, Japan). The muscle mass was converted to the muscle mass index (MMI) by dividing the patient's muscle mass by their height squared (kg/m^2). Sarcopenia was defined as an MMI value of one standard deviation below the gender-specific mean MMI based on previously published studies (17).

Treatment strategy. All patients were managed routinely according to the Japanese Gastric Cancer Treatment Guidelines, 2010 (version 3) (18). Laparoscopic gastrectomy was performed in patients who fulfilled the two following criteria: ≤cT2, and ≤cN1. Other patients underwent gastrectomy by laparotomy.

Evaluation of outcome. Postoperative complications that developed within 30 days after gastrectomy were evaluated. In this study, postoperative complications were classified as infectious or non-infectious complications, and were evaluated according to the Clavien–Dindo (CD) classification (19). We defined postoperative complications as CD grade 2 or more. Pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula definition (20): output *via* an operatively placed drain of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content more than three times higher than the upper normal serum value.

Statistical analysis. All statistical analyses were performed using JMP program (SAS Institute, Cary, NC, USA). Fisher's exact test and the chi-squared test were used to compare categorical variables, and the Wilcoxon test was used to compare continuous variables. Postoperative complications were examined by univariate and multivariate logistic regression analysis. *p*-Values of less than 0.05 were considered to indicate statistically significant differences.

Results

The distribution of MMI is shown in Figure 2. In men and women, the mean values (one standard deviation) are 17.15 (1.71), and 14.56 (1.23), respectively. Thus, the cut-off points were 15.44 kg/m^2 (men) and 13.33 kg/m^2. Patients with low and high MMI values were classified into groups with and without sarcopenia, respectively. Twenty-four patients were classified into the sarcopenic group (17 males; seven females).

A summary of patient characteristics is shown in Table I. The group with sarcopenia was significantly older than the group without (74 *vs*. 68 years, respectively; p=0.023). The body composition analysis revealed that the BMI and MMI values of the group with sarcopenia were significantly lower than those without (17.9 *vs*. 22.6 kg/m^2 and 14.5 *vs*. 16.8 kg/m^2, respectively; both p<0.001). Regarding the nutritional status, the serum albumin level of the group without sarcopenia was significantly higher than that of sarcopenic group (3.8 *vs*. 4 g/dl; p=0.037). The levels of C-reactive protein (a marker of systemic inflammation) of the two groups were similar (sarcopenia *vs*. non-sarcopenia: 0.05 *vs*. 0.08 mg/dl; p=0.446). The American Society of Anesthesiologists physical status (ASA-PS) of the two groups did not differ to a statistically significant extent (p=0.312). Regarding comorbidities, the incidence of pulmonary disease was significantly higher in the group with sarcopenia (p=0.028), while the incidence of other comorbidities did not differ statistically significantly. The clinical TNM stage, which reflects clinical cancer progression, did not differ to a statistically significant extent (p=0.556).

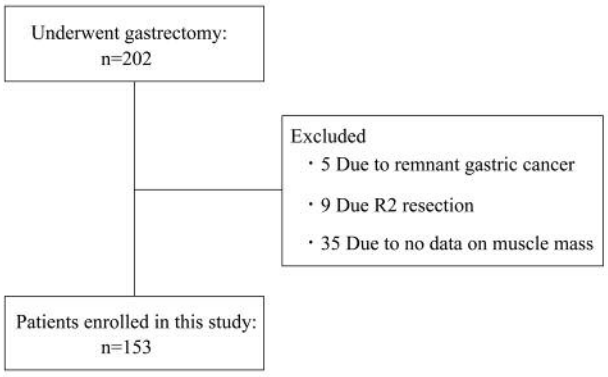

Figure 1. *The patient selection process followed in this study.*

As shown in Table II, there was no significant difference in the type of surgery; however, the rate of laparotomy in the group with sarcopenia was significantly higher than that in the group without (70.8 *vs*. 44.2%; p=0.015). The higher number of cT3 or 4 cases in the group with sarcopenia may have accounted for this difference. The operative times and blood loss of the two groups did not differ to a statistically significant extent. Grade 2 or more postoperative complications occurred significantly more frequently in the group with sarcopenia (37.5 *vs*. 16.3%, respectively; p=0.024). When postoperative complications were classified as infectious or non-infectious, infectious complications occurred significantly more frequently in the group with sarcopenia (29.2 *vs*. 10%, respectively; p=0.021), while the incidence of non-infectious complications did not differ to a statistically significant extent (8.4 *vs*. 6.2%, respectively; p=0.707). To further analyze the association between sarcopenia and postoperative complications, we investigated risk factors for postoperative infectious complications. The results of the univariate and multivariate analyses of factors associated with postoperative infectious complications (grade 2 or more) are shown in Table III. In the univariate analysis, male sex [odds ratio (OR)=5.421, p=0.008)], sarcopenia (OR=3.674, p=0.021), total gastrectomy (OR=3.586, p=0.011), laparotomy (OR=2.839, p=0.036), and intraoperative blood loss (OR=7.552, p<0.001) were associated

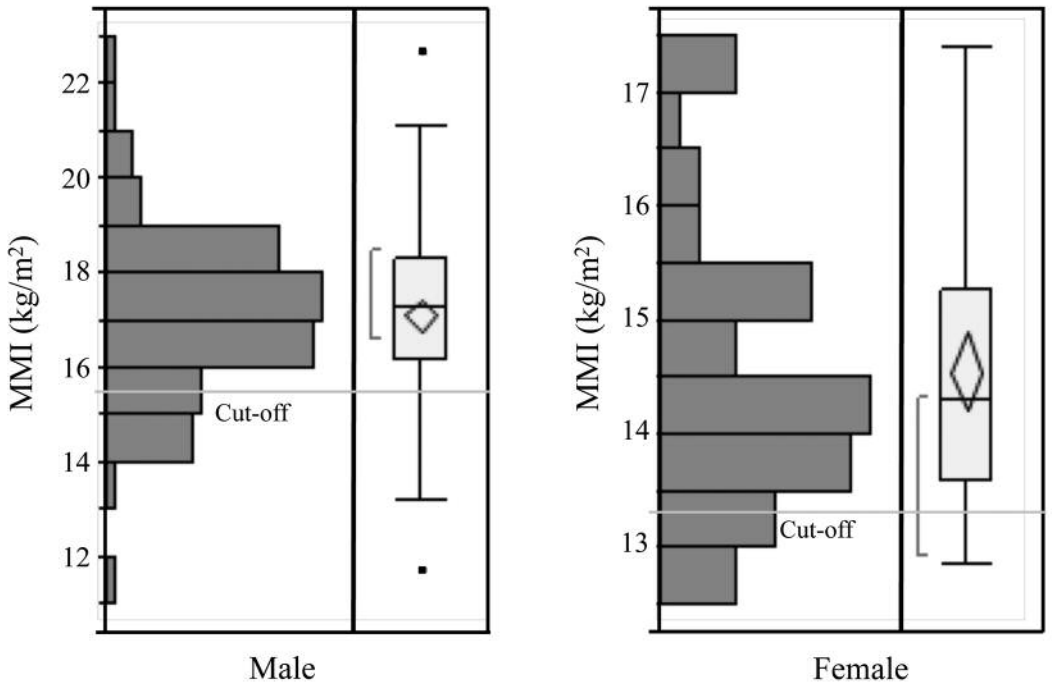

Figure 2. *The distribution of muscle mass index (MMI) values and box plot according to gender. Each horizontal line shows the cut-off for sarcopenia.*

with postoperative infectious complications. In the multivariate analysis, sarcopenia (OR=4.358, p=0.024) and intraoperative blood loss (OR=6.151, p=0.006) were independently associated with postoperative infectious complications.

Discussion

Surgery is the most important curative treatment for gastric cancer other than early-stage gastric cancer, for which endoscopic treatment is indicated. Despite recent advances in surgical procedures and perioperative management techniques, postoperative complications sometimes occur after gastrectomy in patients with gastric cancer. Postoperative complications impair healthy lifestyles, increase healthcare costs, and may diminish adherence to postoperative treatment, which results in poorer oncological outcomes (21). Several factors, such as comorbidities, older age, poor activities of daily living, and obesity are generally identified as risk factors for postoperative complications after gastric cancer surgery. However, there is no reliable evidence to support that any of these are risk factors for postoperative complications, and no definite consensus has been achieved. Sarcopenia is characterized by decreased muscle mass, and low muscle strength and function (1). It was found to be associated with postoperative complications after surgery for esophageal (5, 6), colorectal (3), pancreatic (4, 7), hepatocellular (2, 8), and metastatic liver cancer (9). In this study, we demonstrated that muscle mass, one of the elements of sarcopenia, is a risk factor for postoperative infectious complications after surgery for gastric cancer.

Various methods have been used to analyze muscle, including BIA, dual-energy X-ray absorptiometry, and cross-sectional computed tomography (CT)-based muscle assessment. Mourtzakis *et al*. reported that the cross-sectional area of the psoas muscle at the level of the third lumbar vertebra was directly correlated with the whole-body skeletal muscle mass in patients with cancer (22). CT is regularly conducted before surgery for the clinical staging of gastric cancer; thus, the psoas muscle may be assessed by this method without an undue burden on patients. For this reason, CT imaging has been the modality most frequently used to predict preoperative sarcopenia and investigate the relationship between sarcopenia and postoperative outcomes. However, it is controversial whether the cross-sectional area of the intestinal psoas muscle at the third lumbar level truly reflects the whole-body muscle mass. On the other hand, BIA is not routinely performed as a preoperative examination; however, it is free from radiation exposure and is inexpensive and convenient to perform. In addition, BIA is a safe, non-invasive method that can be performed repeatedly to evaluate body composition. Furthermore, Kaido *et al*. who demonstrated that BIA enables the accurate

Table I. *Summary of patient characteristics (n=153).*

Variable	Sarcopenia (n=24)	Non sarcopenia (n=129)	*p*-Value
Age, years			
Median (range)	74 (38-83)	68 (32-83)	0.023
Gender, n (%)			
Male	17 (70.8)	84 (65.1)	0.583
Female	7 (29.2)	45 (34.9)	
Body mass index, kg/m^2			
Median (range)	17.9 (13.4-23)	22.6 (15.7-33.4)	<0.001
Muscle mass index, kg/m^2			
Median (range)	14.5 (11.7-15.4)	16.8 (13.3-22.7)	<0.001
Serum albumin, g/dl			
Median (range)	3.8 (2.9-4.5)	4 (1.8-5)	0.037
CRP, mg/dl			
Median (range)	0.045 (0.01-2.21)	0.08 (0.01-3.96)	0.446
ASA-PS, n (%)			
1	2 (8.3)	17 (13.2)	0.312
2	18 (75)	103 (79.8)	
3	4 (16.7)	9 (7)	
Comorbidity, n (%)			
Pulmonary disease	7 (29.2)	14 (10.9)	0.028
Cardiovascular disease	3 (12.5)	6 (4.7)	0.175
Liver disease	1 (4.2)	10 (7.7)	0.433
Renal disease	0	4 (3.1)	0.239
Cerebrovascular disease	4 (16.7)	14 (10.9)	0.436
Diabetes melitus	2 (8.3)	22 (17)	0.249
Histology, n (%)			
Differentiated	12 (50)	75 (58.1)	0.461
Undifferentiated	12 (50)	54 (41.9)	
cT, n (%)			
cT1	9 (37.5)	63 (48.8)	0.41
cT2	3 (12.5)	21 (16.2)	
cT3	9 (37.5)	27 (20.1)	
cT4	3 (12.5)	18 (13.9)	
cN, n (%)			
cN0	12 (50)	78 (60.5)	0.809
cN1	4 (16.7)	16 (12.4)	
cN2	4 (16.7)	16 (12.4)	
cN3	4 (16.7)	19 (14.7)	
cStage, n (%)			
I	10 (41.7)	74 (57.4)	0.556
II	6 (25)	22 (17.1)	
III	7 (29.2)	28 (21.7)	
IV	1 (4.1)	5 (3.8)	

ASA-PS: American Society of Anesthesiologists physical status; CRP: C-reactive protein.

Table II. *Perioperative data for 153 patients with gastric cancer according to sarcopenia status.*

Variable	Sarcopenia (n=24)	Non sarcopenia (n=129)	*p*-Value
Type of surgery			
TG, n (%)	7 (29.2)	32 (24.8)	0.77
DG, n (%)	17 (70.8)	96 (74.4)	
PG, n (%)	0	1 (0.8)	
Approach of surgery			
Laparotomy, n (%)	17 (70.8)	57 (44.2)	0.015
Laparoscopy, n (%)	7 (29.2)	72 (55.8)	
Operative times, min			
Median (range)	236 (138-385)	251 (85-483)	0.056
Intraoperative blood loss, ml			
Median (range)	100 (5-2390)	100 (0-1880)	0.735
Postoperative complications, n (%)			
Grade 2 or more	9 (37.5)	21 (16.3)	0.024
Infectious complications			
Total	7 (29.2)	13 (10)	0.021
Anastomotic leakage	1 (4.2)	6 (4.6)	
Pancreatic fistula	4 (16.6)	3 (2.3)	
Intraabdominal infection	0	2 (1.5)	
Pneumoia	1 (4.2)	0	
Colitis	1 (4.2)	1 (0.8)	
Incisional surgical site infection	0	1 (0.8)	
Non-infectious complications			
Total	2 (8.4)	8 (6.2)	0.707
Lymphorrhea	0	1 (0.8)	
Delayed gastric emptying	1 (4.2)	2 (1.5)	
Ileus	1 (4.2)	3 (2.3)	
Pleural effusion	0	1 (0.8)	
Abdminal effusion	0	1 (0.8)	
Hospital stay after operation, days			
Median (range)	12 (8-46)	11 (6-57)	0.23

TG: Total gastrectomy, DG: distal gastrctomy, PG: proximal gastrectomy.

measurement of the skeletal muscle mass without being influenced by edema or ascites in patients with chronic hepatitis, considered BIA to be the gold standard for assessing sarcopenia (23). However, there have been few studies on the use of BIA methods in the evaluation of patients with gastric cancer for sarcopenia. Thus, we selected a BIA method for the present study.

Sarcopenia was originally considered to be decreased muscle mass which occurs in association with aging, chronic disease, and cancer. As a result, sarcopenia exerts various adverse effects, including malnutrition and immune depression. Several studies have reported sarcopenia to be associated with postoperative complications (2-9). However, the pathophysiological mechanisms underlying the association between preoperative sarcopenia and the risk of postoperative complications have not been elucidated. Luts *et al*. demonstrated that as skeletal muscle mass decreases and adipose tissue mass increases, the production of anti-inflammatory cytokines and adiponectin decreases and the production of pro-inflammatory molecules, such as leptin, chemerin, resistin, tumor necrosis factor-α, interleukin-1 and -6 increases (24). Based on this mechanism, patients with sarcopenia are considered to be in a pro-inflammatory state. The pro-inflammatory state leads to a weakening of the immune system and poor wound healing after surgery,

Table III. *The risk factors for postoperative infectious complications for 153 patients after surgery for gastric cancer.*

		Univariate analysis		Multivariate analysis	
Variables	Comparison	Odds ratio (95.0% CI)	*p*-Value	Odds ratio (95.0% CI)	*p*-Value
Age	≥75 *vs*. <75 Years	1.796 (0.656-4.709)	0.246		
Gender	Male *vs*. female	5.421 (1.48-35.007)	0.008	3.783 (0.93-25.663)	0.065
ASA PS	3 *vs*. 1/2	0.53 (0.065-4.319)	0.521		
BMI	≥25 *vs*. <25 kg/m^2	0.758 (0.161-3.561)	0.718		
Serum albumin	<3.5 *vs*. ≥3.5 g/dl	2.275 (0.733-7.062)	0.175		
Sarcopenia	Present *vs*. absent	3.674 (1.285-10.503)	0.021	4.358 (1.224-15.721)	0.024
Surgical procedure	TG *vs*. DG, PG	3.586 (1.362-9.445)	0.011	1.642 (0.495-5.177)	0.407
Surgical approach	Laparotomy *vs*. laparoscopy	2.839 (1.028-7.838)	0.036	1.217 (0.355-4.217)	0.752
Operative time	≥240 *vs*. <240 min	1.233 (0.473-3.212)	0.667		
Intraoperative blood loss	≥400 *vs*. <400 ml	7.552 (2.641-21.593)	<0.001	6.151 (1.688-23.767)	0.006
pStage	III/IV *vs*. I/II	1.941 (0.732-5.15)	0.191		

TG: Total gastrectomy, DG: distal gastrectomy, PG: proximal gastrectomy.

thereby exerting an impact on the risk of postoperative complications (4). In our study, preoperative sarcopenia had an adverse effect on postoperative infectious complications (CD grade 2 or more) in patients with gastric cancer. In detail, in the group with sarcopenia, seven patients had infectious complications, four of them had pancreatic fistula. In addition, three out of the four patients with pancreatic fistula had bulky lymph node metastasis around the pancreas; in such patients in particular, tissue vulnerability tends to cause pancreatic damage, and it is thought that the weakening of the immune system and poor wound-healing may lead to pancreatic fistula.

Amino acids are essential elements for muscle synthesis. Muscle is a reservoir of amino acids, and when the body is subjected to invasion by surgery, muscle plays a role in distributing amino acids to each organ as a biological defense reaction (25). In patients with sarcopenia, however, the amount of amino acids available for tissue repair is insufficient. This mechanism is thought to cause delayed wound healing and further lead to infectious complications. Kim *et al*. demonstrated that the combination of low-intensity exercise and essential amino acid supplementation improved skeletal muscle mass, strength, and walking speed in sarcopenic women (26). However, the preoperative effects of nutrition therapy and resistance exercise on patients with gastric cancer have not been investigated to our knowledge. Preoperative nutritional intervention using amino acids and low-intensity exercise may contribute to reducing the incidence of postoperative complications. Further prospective intervention studies are needed to address this.

The present study is associated with several limitations. Firstly, the number of patients who were evaluated was small because the study was performed in a single institution. A large-scale, multi-institutional study is needed to validate our findings. Secondly, the EWGSOP evaluated sarcopenia based on skeletal muscle mass, while we evaluated sarcopenia based on whole-body muscle mass. Thirdly, according to the EWGSOP, sarcopenia is defined as the presence of low muscle mass, low muscle strength, and low muscle function. However, the definition of sarcopenia in our study was only based on muscle mass. A validation study with large sample size and an analysis of muscle strength and function is necessary to draw any definitive conclusions. Based on the results of retrospective studies, including our own, prospective studies including those that analyze the impact of intervention based on nutrition and resistance exercise should be performed.

Conclusion

Preoperative sarcopenia was found to be an independent risk factor for postoperative infectious complications in patients with gastric cancer. We, therefore, demonstrated that preoperative sarcopenia can be a predictor of postoperative infectious complications after the surgical treatment of gastric cancer.

Conflicts of Interest

The Authors declare no conflict of interest in regard to this study.

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