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Impact of preoperative muscle quality on postoperative severe complications after radical gastrectomy for gastric cancer patients

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Abstract

Background: Preoperative sarcopenia is an important risk factor for postoperative complications in patients with gastric cancer. However, the relationship between muscle quality and postoperative complications in patients with gastric cancer is inadequately studied. Therefore, we investigated the impact of preoperative muscle quality on severe postoperative complications after radical gastrectomy.

Methods: A total of 840 patients who underwent radical gastrectomy for p-stages I–III primary gastric cancer between April 2008 and June 2018 with preoperative computed tomography (CT) scans and body composition analysis were included. We measured intramuscular adipose tissue content (IMAC) as an indicator of muscle quality. A higher IMAC signified a poorer quality. All statistical analyses were performed with EZR, and a P-value < 0.05 was considered statistically significant.

Results: The low-IMAC and high-IMAC groups had 422 (50.2%) and 418 (49.8%) patients, respectively. The latter were older (P < 0.001), had higher body mass index (BMI) (P < 0.001), and higher rates of chronic kidney disease (CKD) (P = 0.002) and diabetes (P < 0.001). They had lower skeletal muscle indexes (SMI) (P = 0.011) and higher visceral fat areas (VFA) (P < 0.001). They also experienced more intraoperative blood loss (P < 0.001) and greater complications (P = 0.016). Multivariate analysis showed that high-IMAC was an independent risk factor for severe complications (odds ratio: 2.260, 95% confidence interval: 1.220-4.190, P = 0.010).

Conclusions: Poor preoperative muscle quality is an independent risk factor for severe postoperative complications after radical gastrectomy in patients with gastric cancer.

KEYWORDS
gastric cancer, intramuscular adipose tissue content, muscle quality, postoperative severe complication

1 | INTRODUCTION

In 2010 the European Working Group on Sarcopenia in Older People announced a consensus on the definition of sarcopenia as a syndrome characterized by the loss of skeletal muscle mass.[1] Use of preoperative body composition analysis has increased and many studies report that loss of skeletal muscle mass appears to increase postoperative complications in patients with gastric cancer.[2-11] Systematic reviews have also found reduced preoperative skeletal muscle mass to be an independent risk factor for postoperative complications in patients with gastric cancer.[12-14] Although the reported prevalence of preoperative sarcopenia in patients with gastric cancer varies widely from 7% to 70%,[13] body composition analysis is considered an important tool for predicting postoperative complications.

The European Working Group on Sarcopenia in Older People revised its guidelines in 2018 and included reduced skeletal muscle quality in addition to reduced quantity to confirm the diagnosis of sarcopenia.[15] Recently, studies have been published linking poor skeletal muscle quality to postoperative complications in patients with gynecologic cancer,[16] colorectal cancer,[17] and hepatocellular carcinoma.[18,19] The relationship between muscle quality and postoperative complications in patients with gastric cancer is inadequately studied. As muscle quality is thought to decrease in correlation with age,[20-22] with the increasing number of elderly patients, there is a need to develop and refine tools to assess muscle quality.

Our objective was to study the impact of preoperative muscle quality on severe postoperative complications after radical gastrectomy in patients with gastric cancer. This is important as severe postoperative complications are known predictors of poor prognosis.[23-25] Our hypothesis was that poor preoperative muscle quality increases severe postoperative complications in patients with gastric cancer.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a retrospective study conducted at the Ishikawa Prefectural Central Hospital. Patients who underwent radical gastrectomy for p-stages I–III primary gastric cancer between April 2008 and June 2018 with preoperative computed tomography (CT) scans that allowed body composition analysis were included. We excluded patients with residual gastric cancer, cancers of other organs, performance status ≥2, preoperative gastrointestinal obstruction, patients who underwent different surgical procedures, patients who received neoadjuvant chemotherapy, and those with insufficient data.

2.2 | Data collection

Skeletal muscle quality, visceral fat mass, and skeletal muscle mass were measured on preoperative CT images using the graphic analysis software Ziostation (ZIOSOFT). For muscle quality, CT values (Hounsfield units: HUs) of the regions of interest were measured at the umbilical level, and the intramuscular adipose tissue content (IMAC) was calculated by dividing the CT value of the multifidus muscles by that of subcutaneous fat, as in previous studies.[18-22] Visceral fat area (VFA), defined as HUs of −150 to −50, was measured at the umbilical level and skeletal muscle, defined as HUs of −29 to 150, at the level of the third lumbar vertebra. Skeletal muscle mass index (SMI) was calculated by dividing the cross-sectional muscle mass area by height in meters squared.[26]

2.3 | Cut-off values of IMAC and SMI to define sarcopenia

Cut-off values for IMAC and SMI were estimated separately for men and women from the median. The cut-off value for IMAC was −0.430 for men, and −0.310 for women. Patients below the cut-off were categorized as low-IMAC, and patients above as high-IMAC. A higher IMAC indicated poorer muscle quality. The cut-off value for SMI was calculated as 43.08 cm^2/m^2 for men and 33.73 cm^2/m^2 for women. Similar to IMAC, patients below the cut-off were categorized as low-SMI, and patients above as high-SMI. In addition, we also evaluated previously reported cut-off values for SMI and IMAC to diagnose sarcopenia in patients with gastric cancer.[22,27]

2.4 | Outcome

The primary outcome was Clavien-Dindo classification (CD) grade 3a or higher severe postoperative complications, and the secondary outcomes were operating time, intraoperative blood loss, length of postoperative hospital stay, total postoperative complications, and infectious complications. Postoperative complications were defined as CD grade 2 or higher complications that occurred within 30 postoperative days. The high- and low-IMAC groups were compared with regard to postoperative outcomes, and a multivariate analysis of risk factors was carried out for severe complications.

2.5 | Clinicopathological variables

The variables analyzed were sex, age, body mass index (BMI), surgical procedure, surgical approach, pathological stage, lymph node dissection, comorbidities, SMI, and VFA. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2, diabetes as either having a history of treatment or preoperative HbA1c ≥6.5%, chronic obstructive pulmonary disease as FEV1.0% <70% on spirometry, congestive heart failure as either having a history of treatment or ejection fraction <50% on the echocardiogram.

2.6 | Statistical analyses

Patient characteristics and postoperative outcomes between the high- and low-IMAC groups were compared using the Mann-Whitney U-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Logistic regression analysis was used for univariate analyses to identify the factors with *P*-values <0.05, on which multivariate analysis was performed and odds ratios (OR) were calculated. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is based on R (The R Foundation for Statistical Computing) and R commander,[28] and a *P*-value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 840 eligible patients were enrolled. The cut-off values for diagnosing sarcopenia and prevalence are shown in Table 1. With our cut-off values, of the 840 patients, 418 patients (49.8%) were allocated to the low-IMAC group and 422 patients (50.2%) were allocated to the high-IMAC group. Patient characteristics are shown in Table 2. The high-IMAC group was older (*P* < 0.001) and had a higher BMI (*P* < 0.001). As for comorbidities, more patients in the high-IMAC group had CKD (*P* = 0.002) and diabetes (*P* < 0.001). In terms of body composition, the high-IMAC group had a lower SMI (*P* = 0.011) and higher VFA (*P* < 0.001).

3.2 | Comparison of postoperative outcomes after radical gastrectomy

Comparisons between the high- and low-IMAC groups for postoperative outcomes are shown in Table 3. There was no difference in operating time and length of postoperative hospital stay. Intraoperative blood loss was higher in the high-IMAC group (*P* < 0.001).

The high-IMAC group not only had more severe postoperative complications (*P* = 0.002), but also had a larger number of total complications (*P* = 0.016) and more infectious complications (*P* = 0.024). As for the breakdown of complications, there were more intra-abdominal abscesses and anastomotic leakages in the high-IMAC group (*P* = 0.052 and *P* = 0.034, respectively).

3.3 | Independent risk factors of severe complications

There were 55 (6.5%) severe postoperative complications. The results of the analyses of risk factors for severe complications are shown in Table 4. In the univariate analysis, being male (*P* = 0.006), age >70 years (*P* = 0.007), open surgery (*P* = 0.005), p-stage ≥III (*P* = 0.039), CKD (*P* = 0.046), and high-IMAC (*P* = 0.002) were significant. Multivariate analysis revealed that being male (OR: 2.890, 95% CI: 1.330-6.290, *P* = 0.008), open surgery (OR: 1.960, 95% CI: 1.050-3.640, *P* = 0.033), and high-IMAC (OR: 2.260, 95% CI: 1.220-4.190, *P* = 0.010) were significant independent risk factors.

4 | DISCUSSION

Our study has shown that poor muscle quality determined on preoperative CT images can predict an increase in postoperative complications such as infectious complications and anastomotic leakages, and is an independent risk factor for severe complications after radical gastrectomy. There are a few points that require further discussion. First is why poor muscle quality leads to severe postoperative complications, second, the relationship between poor muscle quality

TABLE 1 Cut off values for diagnosing sarcopenia and prevalence for each

	Cut off values		Prevalence of sarcopenia in this study
	For men	For women	
SMI:			
Prado et al	52.4	38.5	84.6% (711/840)
Martin et al	53.0 for BMI ≥ 25	41	70.4% (591/840)
	43.0 for BMI ≤ 25		
Sakurai et al	43.2	34.6	52.9% (444/840)
Zhuang et al	40.8	34.9	43.2% (363/840)
Iritani et al	36	29	16.1% (135/840)
This study	43.08	33.73	50.0% (420/840)
IMAC:			
Waki et al	−0.2541	−0.1095	12.3% (103/840)
This study	−0.43	−0.31	50.2% (422/840)

Abbreviations: SMI, skeletal muscle mass index (cm^2/m^2); BMI, body mass index (kg/m^2); IMAC, intramuscular adipose tissue content.

TABLE 2 Patient characteristics

	Low-IMAC (N = 418)	High-IMAC (N = 422)	P value
Gender			
Male	287 (68.7%)	286 (67.8%)	0.824
Female	131 (31.3%)	136 (32.2%)	
Age, mean ± SD	63.09 ± 11.68	69.91 ± 9.24	<0.001
Body Mass Index, mean ± SD	22.13 ± 3.06	23.76 ± 3.28	<0.001
Surgical approach			
Laparoscopic surgery	328 (78.5%)	323 (76.5%)	0.51
Open surgery	90 (21.5%)	99 (23.5%)	
Surgical procedure			
Distal gastrectomy	281 (67.2%)	290 (68.7%)	0.758
Proximal gastrectomy	40 (9.6%)	37 (8.8%)	
Total gastrectomy	97 (23.2%)	95 (22.5%)	
Pathological stage			
I	287 (68.7%)	278 (65.9%)	0.678
II	64 (15.3%)	68 (16.1%)	
III	67 (16.0%)	76 (18.0%)	
Lymph node dissection			
D1+	248 (59.3%)	271 (64.4%)	0.136
D2	170 (40.7%)	150 (35.6%)	
Comorbidity			
CKD	50 (12.0%)	83 (19.7%)	0.002
COPD	81 (19.4%)	93 (22.0%)	0.35
Diabetes	47 (11.2%)	91 (21.6%)	<0.001
CHF	20 (4.8%)	19 (4.5%)	0.871
SMI (cm^2/m^2), median (range)	41.35 (5.17-83.96)	39.25 (4.42-68.43)	0.011
Low SMI	187 (44.7%)	233 (55.2%)	0.003
VFA (cm^2/m^2), median (range)	60.45 (1.52-289.79)	103.92 (7.89-351.34)	<0.001

Abbreviations: CHF, chronic heart failure; SMI, skeletal muscle mass index; VFA, visceral fat area; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IMAC, intramuscular adipose tissue content; SD, standard deviation.

and intra-abdominal infections and anastomotic leakages, and finally, why low SMI was not a risk factor for complications.

Two methods are used to evaluate muscle quality using CT images. The first is to measure muscle attenuation directly with CT values (HUs). The second method is to calculate the IMAC as we have done. In a study of patients with gynecologic cancer, Silva et al found that having more muscle with reduced attenuation was an independent predictor for surgical complications.[16] Hamaguchi et al reported that high preoperative IMAC was an independent risk factor for increased major postoperative complications in patients with

hepatocellular carcinoma.[19] These studies show that with either method, poor skeletal muscle quality is a risk factor for postoperative complications, and we came to the same conclusion using IMAC as a measure of muscle quality in patients with gastric cancer. In a study of patients with gastric cancer, Zhang et al termed low mean muscle attenuation as "myosteatosis," and reported that patients with this condition had higher rates of total postoperative complications.[26] Furthermore, Waki et al showed that there are higher rates of total postoperative complications in the high-IMAC group than the low-IMAC group,[22] which is similar to our results. Thus, body composition assessment is an important part of preoperative patient evaluation. To the best of our knowledge, this is the first study to show that poor skeletal muscle quality is an independent predictive factor for severe complications after gastrectomy. A summary of the relationship between the muscle quality and postoperative complications is shown in Table 5.[18-22,26,29-33]

The causative pathophysiology behind postoperative complications in patients with poor muscle quality is not clear. Accumulation of lipids in the skeletal muscle, known as muscle steatosis, is associated with insulin resistance and the development of type-2 diabetes.[34] It has been reported that postoperative blood glucose levels >200 mg/dL after gastrectomy in nondiabetic patients with gastric cancer are related to increased postoperative complications[35]; thus, hyperglycemia may play a role. In our study, there were more diabetic patients in the high-IMAC group, which may have affected the result of increased postoperative complications. Hamaguchi et al pointed out that measuring skeletal muscle area on CT imaging may not always be accurate because the measured area also includes intramuscular adipose tissue content, and that since IMAC is calculated as the ratio of CT values between skeletal muscle and subcutaneous fat, it reflects not only intramuscular adipose tissue but also muscle mass.[19] It could be that IMAC accurately assesses the difference between muscle and fat and may be an even more effective tool than SMI to measure decrease in muscle mass, although we calculated the cut-off values of IMAC and SMI using the same method. The cytokine interleukin-15 (IL-15), which is required for the development and survival of natural killer lymphocytes, is highly expressed in skeletal muscle tissue.[36] As natural killer lymphocyte-mediated cytotoxicity and cytokine secretion controls infections and cancers,[37] decreased muscle mass could lead to increased susceptibility to infections and affect cancer prognosis. Since IMAC is also reported to be a significant predictor of both muscle strength and mobility,[18] high-IMAC probably leads to increased complications because it reflects not only a decrease in muscle quality, but also a decrease in muscle mass.

In a meta-analysis, Kamarajah et al reported that reduced skeletal muscle mass leads to increase in major complications and mortality.[13] In another meta-analysis, Yang et al found that preoperative loss of skeletal muscle mass increases postoperative pneumonia and paralytic ileus, but not intra-abdominal infections and anastomotic leakages.[38] In the previously mentioned studies by Waki et al[22] and Zhang et al[26], reduced muscle quality predicted postoperative complications after gastrectomy, but the breakdown was not specified.

	Low-IMAC (N = 418)	High-IMAC (N = 422)	P value
Operating time (min), median (range)	250.0 (90.0-525.0)	252.5 (60.0-630.0)	0.509
Intraoperative blood loss (g), median (range)	15.0 (1.0-1480.0)	20.0 (2.0-2920.0)	0.001
Postoperative hospital stay (days), median (range)	14.0 (5.0-141.0)	15.0 (4.0-143.0)	0.438
Postoperative complications			
Pneumonia	7 (1.7%)	13 (3.1%)	0.258
Incisional SSI	12 (2.9%)	12 (2.8%)	1
Intra-abdominal abscess	29 (6.9%)	46 (10.9%)	0.052
Pancreatic fistula	17 (4.1%)	20 (4.7%)	0.737
Anastomotic leakage	13 (3.1%)	27 (6.4%)	0.034
Infectious complications	49 (11.7%)	73 (17.3%)	0.024
Severe complications	16 (3.8%)	39 (9.2%)	0.002
Total complications	63 (15.1%)	91 (21.6%)	0.016

TABLE 3 Comparison of postoperative outcomes after radical gastrectomy

Note: Abbreviations: IMAC, intramuscular adipose tissue content; SSI, surgical site infection.

Herrod et al reported that poor muscle quality was associated with an increased risk of anastomotic leakage,[33] which was also seen in our study. The mechanisms by which reduced muscle quality causes anastomotic leakage may be different than those by which reduced muscle mass causes them and further research is needed.

Finally, we would like to consider our method for evaluating muscle quality and suggest ideas for further research. IMAC is reported to be an effective way of assessing muscle quality.[18-22,39,40] It is thought to be a predictor of postoperative complications, but there is no consensus on cut-off values. Most previous studies have drawn receiver-operating characteristics curves to determine cut-off values,[18-21,39] and cut-off values in males were always higher than in females; however, the reported values vary widely. Although we defined it by the median, cut-off values may differ according to the situation, and further research is needed to clarify the appropriate values for patients with gastric cancer. Our study has indicated that high-IMAC is a predictor of major postoperative complications. Thus, an interventional trial on the impact of preoperative physical therapy to improve muscle quality would be interesting. High-IMAC reflects not only a decrease in skeletal muscle mass, but also an increase in fat mass. Preoperative exercise and increased protein intake for the former, and preoperative exercise and weight loss for the latter may be necessary. It should also be noted that the prevalence of sarcopenia based on the cut-off values of IMAC obtained in this study is extremely high, so there are potentially many patients who require preoperative intervention.

This study has some limitations. First, it was a single-institutional retrospective study. A multi-institutional study is desirable to confirm the relationship between poor muscle quality and postoperative outcomes and to examine the validity of the cut-off values used in this study. Second, the mechanisms by which poor muscle quality leads to increased postoperative complications are unknown, and more basic research is needed.

ETHICS

All experimental protocols described in this study: were approved by the Institutional Ethical Review Committee of Ishikawa Prefectural Central Hospital (authorization number: 1057); met the ethical guidelines of the Japan Ministry of Health, Labour, and Welfare for Medical and Health Research Involving Human Subjects; and conformed to the provisions of the Declaration of Helsinki. The opt-out recruitment method was applied to provide all patients an opportunity to decline to participate.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

TABLE 4 Results of univariate and multivariate analyses of severe complications

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Gender						
Female	1			1		
Male	2.89	1.350-6.210	0.006	2.89	1.330-6.290	0.008
Age (years)						
<70	1			1		
≥70	2.15	1.240-3.750	0.007	1.71	0.953-3.080	0.072
Surgical procedure						
Distal gastrectomy	1					
Total gastrectomy	1.71	0.949-3.080	0.074			
Surgical approach						
Laparoscopic surgery	1			1		
Open surgery	2.27	1.280-4.010	0.005	1.96	1.050-3.640	0.033
Pathological stage						
<III	1			1		
≥III	1.92	1.030-3.590	0.039	1.44	0.730-2.840	0.292
Lymph nodes dissection						
D1+	1					
D2	1.38	0.797-2.390	0.25			
Chronic kidney disease						
Absent	1			1		
Present	1.91	1.010-3.610	0.046	1.4	0.711-2.740	0.333
Diabetes						
Absent	1					
Present	1.82	0.963-3.440	0.065			
COPD						
Absent	1					
Present	1.48	0.795-2.740	0.217			
Chronic heart failure						
Absent	1					
Present	2.21	0.828-5.890	0.114			
SMI (cm^2/m^2)						
High SMI	1					
Low SMI						
This study cut-off	0.89	0.515-1.540	0.676			
Prado`s cut-off	0.804	0.394-1.640	0.549			
Martin`s cut-off	0.785	0.441-1.400	0.411			
Sakurai`s cut off	0.92	0.532-1.590	0.765			
Zhuang`s cut off	0.868	0.497-1.520	0.619			
Iritani`s cut-off	1.33	0.670-2.650	0.413			
IMAC						
Low IMAC	1			1		
High IMAC						
This study cut-off	2.56	1.410-4.650	0.002	2.26	1.220-4.190	0.01
Waki`s cut off	1.44	0.682-3.030	0.34			

Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content.

TABLE 5 Study characteristics related to low-skeletal muscle quality

Author (Year)	Country	Design	Type of patients	Sample size (male/female)	Criteria (Cut off value)	Prevalence	Postoperative short-term outcomes
Harimoto N (2018)[18]	Japan	Retrospective	Patients with hepatic resection	146 (104/40)	IMAC: Male: −0.730 Female: −0.502	26.70% (39/146)	Increased total postoperative complications Longer operation time/ hospital stays
Hamaguchi Y (2016)[19]	Japan	Retrospective	Hepatocellular carcinoma	492 (403/89)	IMAC: Male: −0.324 Female: −0.138	44.50% (219/492)	Increased infectious complications/ major postoperative complications
Hamaguchi Y (2015)[20]	Japan	Retrospective	Hepatocellular carcinoma	477 (389/88)	IMAC: Male: −0.324 Female: −0.138	43.80% (209/477)	Increased operative blood loss.
Okumura S (2015)[21]	Japan	Retrospective	Pancreatic cancer	230 (124/106)	IMAC: Male: −0.343 Female: −0.256	61.70% (142/230)	No difference in severe complications
Waki Y (2019)[22]	Japan	Retrospective	Gastric cancer	370 (256/114)	IMAC: Male: −0.2541 Female: −0.1095	25.10% (93/370)	Increased intraoperative blood loss and total postoperative complications. Longer postoperative hospital stays.
Zhang Y (2018)[26]	China	Retrospective	Gastric cancer	156 (115/41)	Muscle attenuation: Male: 44.4 HU Female: 39.3 HU	84.00% (131/156)	Increased total postoperative complications. Longer postoperative hospital stays.
Okumura S (2016)[29]	Japan	Retrospective	Extrahepatic biliary cancer	207 (111/96)	IMAC: Male: −0.341 Female: −0.096	44.00% (91/207)	Increased severe complications/ pancreatic fistula after PD
Okugawa Y (2018)[30]	Japan	Retrospective	Colorectal cancer	308 (183/125)	IMAC: Male: −0.360 Female: −0.240	49.70% (153/308)	Increased infectious complications
Horii N (2020)[31]	Japan	Retrospective	Colorectal liver metastasis	115 (79/39)	IMAC: Male: −0.335 Female: −0.258	55.70% (64/115)	Increased severe complications
Okumura S (2017)[32]	Japan	Retrospective	Intrahepatic cholangiocarcinoma	109 (67/42)	Muscle attenuation: Male: 38.3 HU Female: 31.0 HU	48.60% (53/109)	No difference in postoperative complications and operative mortality
Herrod PJJ (2019)[33]	UK	Retrospective	Colorectal cancer	169 (91/78)	Psoas density: Both: 44.5 HU	30.20% (51/169)	Increased severe complications/ anastomotic leakage

Abbreviations: HU, Hounsfield units; IMAC, intramuscular adipose tissue content; PD, pancreatoduodenectomy.

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