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博　士　論　文

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（食道切除術を受ける食道がん患者において術前のサルコペニアは術後呼吸器合併症の予測因子である：後ろ向きコホート研究）

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牧浦　大祐

Preoperative Sarcopenia is a Predictor of Postoperative Pulmonary Complications in Esophageal Cancer Following Esophagectomy; A Retrospective Cohort Study

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Abstract

Objectives

The number of geriatric patients with esophageal cancer has been increasing. Geriatric syndromes such as sarcopenia might adversely affect postoperative recovery. The aim of this study was to evaluate the relationships between sarcopenia and postoperative complications, and the associations between sarcopenia and perioperative functional changes in esophageal cancer patients following esophagectomy.

Materials and Methods

Participants comprised 104 patients who underwent esophagectomy from July 2011 to April 2015. Preoperative sarcopenia was diagnosed by the presence of low muscle mass and low physical functions according to Asian Working Group for Sarcopenia criteria. Low physical function was defined by loss of grip strength and/or slow walking speed. Postoperative pulmonary, cardiac, infection, and surgical complications were extracted. Perioperative functional changes were calculated (value at postoperative day 30 – value before surgery). For statistical analyses, both uni- and multivariate logistic regression analyses were performed.

Results

Twenty-nine patients (27.9 %) were diagnosed with sarcopenia. The incidence of postoperative pulmonary complications was significantly higher in the sarcopenia group (37.9 %) than in the non-sarcopenia group (17.3 %; *P*=0.04). There was no relationship between sarcopenia and other complications or perioperative functional changes. Multivariate analysis identified sarcopenia (odds ratio (OR), 3.13; 95% confidence interval (CI), 1.12-8.93) and high Brinkman index (OR, 3.46; 95% CI, 1.20-11.77) as independent risk factors for the development of pulmonary complications.

Conclusion

The assessment of sarcopenia may be useful to predict the postoperative pulmonary complications following esophagectomy. On the other hand, sarcopenia does not predict cardiac, infection, and surgical complications or perioperative function.

Keywords

sarcopenia; postoperative pulmonary complications; esophagectomy; esophageal cancer; rehabilitation; functional status

Introduction

Esophageal cancer is a highly aggressive malignant tumor, and esophagectomy is associated with high morbidity and mortality rates [1,2]. The proportion of older patients with esophageal cancer has been increasing in the United States, Europe, and Japan [3-5]. The impact of geriatric syndrome on esophagectomy is of considerable importance.

Sarcopenia, characterized by progressive generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, loss of independence and death [6,7], is a common geriatric syndrome. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function to diagnose sarcopenia [8]. In the previous studies, sarcopenia has been identified as an independent predictor of postoperative pulmonary complications following esophagectomy [9,10], but the diagnosis of sarcopenia in those studies was made based on the presence of low muscle mass alone. Furthermore, no published reports have described the effects of preoperative sarcopenia on perioperative functional change. We hypothesized that sarcopenia defined by both low muscle mass and low muscle function predicted postoperative complications and perioperative functional changes in esophageal cancer patients following esophagectomy.

The aim of this study was to assess preoperative sarcopenia using both muscle mass and function and to evaluate the relationship between sarcopenia and postoperative outcomes such as postoperative complications and perioperative functional change in patients with esophageal cancer who underwent esophagectomy.

Materials and methods

Participants

The present study was a retrospective cohort study. This study was conducted between July 2011 and April 2015 at the single university hospital located in the urban area. Patients with esophageal cancer were eligible if they were scheduled to undergo definitive esophagectomy. Patients were excluded if they had a recurrent cancer or declined to consent. The study was approved by the ethics committee of Kobe University Graduate School Health Science (approval number 112) and registered with the University Hospital Medical Information Network. This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and later amendments.

Measurements

Preoperative laboratory data and treatment information were collected from the medical records of patients. Laboratory data included predicted vital capacity (VC), forced expiratory volume in 1 s (FEV1.0) as a percentage of forced VC, C-reactive protein (CRP) and serum albumin. Treatment information was as follows: preoperative clinical stage, comorbidity, smoking history, performance status, weight loss over the past 6 months, preoperative treatment, operative time, blood loss, duration of inhibited oral intake, and duration of hospitalization after surgery. Clinical staging was based on the TNM classification (6th edition) [11] defined by the Union for International Cancer Control. Smoking history was assessed using the Brinkman index defined as numbers of cigarette smoked per day times smoking years. Performance status was defined based on the Eastern Cooperative Oncology Group Performance Status. Neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil was provided as preoperative treatment. We calculated the Geriatric Nutritional Risk Index (GNRI) [12] using preoperative serum albumin and body weight.

Body composition, muscle strength, mobility, fatigue and health-related quality of life (HRQoL) were assessed before esophagectomy and on postoperative day (POD) 30. We prepared the assessment manual to reduce potential measurement bias. Body composition was assessed using multifrequency bioelectrical impedance with eight electrodes (DF-860; Yamato, Hyogo, Japan). With this method, body weight, lean body mass and skeletal muscle mass were measured. Grip strength was measured using a handheld dynamometer (GRIP-D; Takei Ltd., Niigata, Japan) in accordance with the reliable methods reported previously [13]. Mobility was measured using the Short Physical Performance

Battery (SPPB) [14], assessing standing balance, walking speed, and ability to rise from a chair (total score, 0-12; higher score suggesting better mobility). Fatigue and HRQoL were measured using the Functional Assessment of Chronic Illness Therapy: Fatigue (FACIT-F) [15] and the Functional Assessment of Cancer Therapy - General (FACT-G) [16], respectively. The FACT-G total score for the Physical, Social/Family, Emotional, and Functional subscales was used. Higher scores on the FACIT-F and FACT-G represent less fatigue and better quality of life, respectively.

Definition of Sarcopenia

Sarcopenia was defined as low muscle mass plus low muscle strength and/or low physical performance according to the Asian consensus definition [17]. Low muscle mass was defined by appendicular skeletal muscle mass divided by squared height of <7.0 kg/m^2 for men and <5.7 kg/m^2 for women. Low muscle strength was defined by handgrip strength of <26 kg for men and <18 kg for women. Low physical performance was defined by gait speed of <0.8 m/s. In the non-sarcopenia group, patients with low muscle mass were described as showing presarcopenia. In the sarcopenia group, patients were described as showing severe sarcopenia when all three criteria were met.

Evaluation of Outcomes

Data on postoperative complications were collected from the medical records of patients. Postoperative complications were defined according to the Society of Thoracic Surgeons General Thoracic Surgery Database guidelines [18] and the Clavien-Dindo classification [19]. Pulmonary complication was defined as the presence of any of the following postoperative conditions within 30 days after surgery: initial ventilatory support for >48 h, reintubation for respiratory failure or pneumonia. Any cardiac disease defined as Clavien-Dindo grade ＞Ⅱ was chosen as cardiovascular complications. Infection complication was defined as the presence of wound infection, abscess, sepsis or other infections requiring antibiotics within 30 days after surgery. Surgical complication was defined as the presence of rebleeding, anastomotic leakage or chylothorax within 30 days after surgery.

Statistical Analysis

Test of normality was conducted using Shapiro-Wilk test. Relationships between patient/treatment characteristics and the presence of sarcopenia were compared using Student's t-test for normalized variables, Mann Whitney U test for non-normalized values, and Fisher's exact test for categorical values. Univariate logistic regression analyses were performed to assess the association between various prognostic predictors that have been reported previously [20,21] and postoperative pulmonary complications. Factors in univariate analysis showing values of a $P < 0.10$ were entered simultaneously into a multivariate logistic regression model. Changes in measurement values were calculated (value at POD30 – value before surgery) and group differences in measurement change were analyzed using multiple linear regression analysis. The following patients were excluded from the statistical analysis due to the missing postoperative values: 30 patients for lean body mass, 29 for grip strength, 35 for SPPB, 39 for fatigue, and 40 for HRQoL. To control for confounding factors, the baseline value, age, gender, and GNRI were entered simultaneously into the regression model. GNRI was selected because preoperative nutritional status could affect recovery after elective surgery [22]. Sensitivity analysis was performed to evaluate the effect of missing sarcopenia diagnosis on the association between sarcopenia and postoperative complications. Multivariate logistic regression analyses were performed when patients without sarcopenia diagnosis were included in either sarcopenia or non-sarcopenia group. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the JMP 8.0.1 software (SAS Institute Japan, Tokyo, Japan).

Results

A total of 104 of the 131 eligible patients were enrolled in the study. Postoperative follow-up was performed until discharge. The reasons for exclusion and the number of patients available for analyses are shown in Figure 1. Sixteen patients excluded from analysis due to the missing preoperative assessment were devoid of the opportunities to be assessed sarcopenia before esophagectomy. Of the analysis population, 29 patients (27.9%) were classified into the sarcopenia group and 75 patients (72.1%) into the non-sarcopenia group. All patients in the non-sarcopenia group showed presarcopenia. Nine patients in the sarcopenia group showed severe sarcopenia.

Clinical characteristics of analysis population are summarized in Table 1. Patients in the sarcopenia group were significantly older and diagnosed with more advanced clinical stage compared to the non-sarcopenia group. In addition, sarcopenia patients had significantly higher CRP levels, lower serum albumin levels, and greater weight loss over the past 6 months than non-sarcopenia patients. Both preoperative respiratory function and nutritional status were poorer in the sarcopenia group than in the non-sarcopenia group, but presence of comorbidities, performance status, and preoperative treatment were comparable. Although the rate of received neoadjuvant chemotherapy (43.8 %) was significantly lower in the 16 patients excluded from analysis due to the missing preoperative assessment than the others, the other characteristics including operative variables and surgical outcomes had no significant difference.

Pulmonary complications occurred in 24 patients (23.1 %, pneumonia = 24, reintubation = 9). Postoperative pulmonary complications occurred significantly more frequently in the sarcopenia group

(37.9 %) than in the non-sarcopenia group (17.3 %) (Table 2). Rates of postoperative cardiac, infection, and surgical complications did not differ significantly between the groups.

Univariate logistic regression analysis revealed sarcopenia and high Brinkman index as factors significantly associated with postoperative pulmonary complications (Table 3). Moreover, multivariate logistic regression analysis showed sarcopenia and high Brinkman index were independent risk factors for pulmonary complications (Table 3). The rate of postoperative pulmonary complications was 18.8 % in patients without sarcopenia diagnosis. In sensitivity analysis, sarcopenia was an independent risk factor for pulmonary complications (ORs, 3.04; 95% CI, 1.12 – 8.23) when all of the patients without sarcopenia diagnosis were included in the non-sarcopenia group. On the other hand, sarcopenia was not an independent risk factor (ORs, 2.15; 95% CI, 0.87 – 5.38) when all of the patients without sarcopenia diagnosis were included in the sarcopenia group.

The relationship between sarcopenia and perioperative functional change are shown in Table 4. In the baseline comparison, body weight, lean body mass, grip strength, and SPPB were significantly lower in the sarcopenia group than in the non-sarcopenia group ($p < 0.001$). In comparison of change at POD30, perioperative decrease in body weight was significantly less in the sarcopenia group ($p = 0.004$), but sarcopenia patients were significantly more likely to experience increased fatigue ($p = 0.002$). In multiple linear regression analysis adjusted for baseline value, age, gender, and GNRI (shown in Table 4), no significant difference in measurement change was evident between groups.

Discussion

The aim of this study was to assess sarcopenia using both muscle mass and function, and to evaluate relationships between sarcopenia and postoperative complications and between sarcopenia and perioperative functional changes in patients with esophageal cancer who underwent esophagectomy. The prevalence of sarcopenia at the baseline was 27.9 %. Sarcopenia was associated with the development of postoperative pulmonary complications. There was no relationship between sarcopenia and other complications or perioperative functional changes.

The prevalence of sarcopenia (27.9 %) was lower than that shown in previous reports (44.2 - 74.9 %) [9,10], of which sarcopenia was diagnosed by the presence of low muscle mass alone based on their own cut-off values. All patients in the non-sarcopenia group in the present study had presarcopenia, although all these patients were diagnosed as sarcopenia based on the presence of low muscle mass alone. Patients with esophageal cancer frequently experience dysphagia, and the weight loss results in decreased muscle mass [23]. Assessing sarcopenia using the presence of low muscle mass alone may overestimate sarcopenia and decrease sensitivity in esophageal cancer. The most common definition of sarcopenia is defined by both low muscle mass and low muscle function based on consensus values. Our findings may be more realistic and give the strong support to the relationship between sarcopenia and postoperative pulmonary complications. A previous study showed that grip strength offered an effective predictor of complications and mortality after elective esophagectomy [24], and that walking speed predicted risk of mortality [25]. Because tests for grip strength and walking speed are inexpensive and predictive of high-risk patients, not only muscle mass but also muscle function may be worth assessing before esophagectomy.

In our study, patients with sarcopenia showed more advanced clinical stage, higher CRP levels, more weight loss in the past 6 months and the worse preoperative nutritional status. The etiology of sarcopenia is considered multi-factorial, involving issues such as the physiological aging process, physical inactivity, inadequate nutrition, and comorbid diseases [8]. Our results suggest that sarcopenia in esophageal cancer reflects tumor-related symptoms such as chronic inflammation, weight loss, and malnutrition and that sarcopenia may be an indicator of general condition in patients who undergo definitive esophagectomy.

It may be clinically plausible that sarcopenia affects the risk of developing postoperative pulmonary complications. Sarcopenia patients showed that the impairment of pulmonary function as the result of weakened respiratory muscles could lead to insufficient cough, atelectasis, and pneumonia [26,27].

A previous study reported that preoperative inspiratory muscle training was effective in reducing the development of postoperative pulmonary complications [28]. Preoperative interventions, such as exercise and nutritional support, might improve muscle function in sarcopenia patients.

Associations between sarcopenia and cardiac, infection, or surgical complications are unclear because few findings have been reported. Our findings are in agreement with those of the previous report [10] and suggest that sarcopenia may not predict other complications unlike pulmonary complications. Further research is needed to determine the associations between sarcopenia and cardiac, infection, or surgical complications.

We expected that sarcopenia patients would lack the physiological reserve to compensate for surgical stress, but our results showed that sarcopenia was not associated with short-term functional change. In fact, it has been reported that sarcopenia was associated with an increased inflammatory response to surgery [29]. However, that may not result in short-term functional change after esophagectomy.

Several limitations of this study should be acknowledged. First, a large-scale, multi-institutional study is needed to validate our findings, because our study was the small number of patients included and the single institutional study. Second, the results of this study may not be applicable to those who are not Asian people because of the difference in definition of sarcopenia. Third, as shown in sensitivity analysis, the missing data likely inflated the observed association between sarcopenia and pulmonary complications.

In conclusion, sarcopenia as defined by muscle mass and function may offer a predictor of postoperative pulmonary complications after esophagectomy. Sarcopenia should be defined according to not only the presence of low muscle mass, but also low muscle strength and physical performance. Further analysis is needed to clarify whether preoperative exercise intervention can improve sarcopenia and reduce postoperative pulmonary complications.

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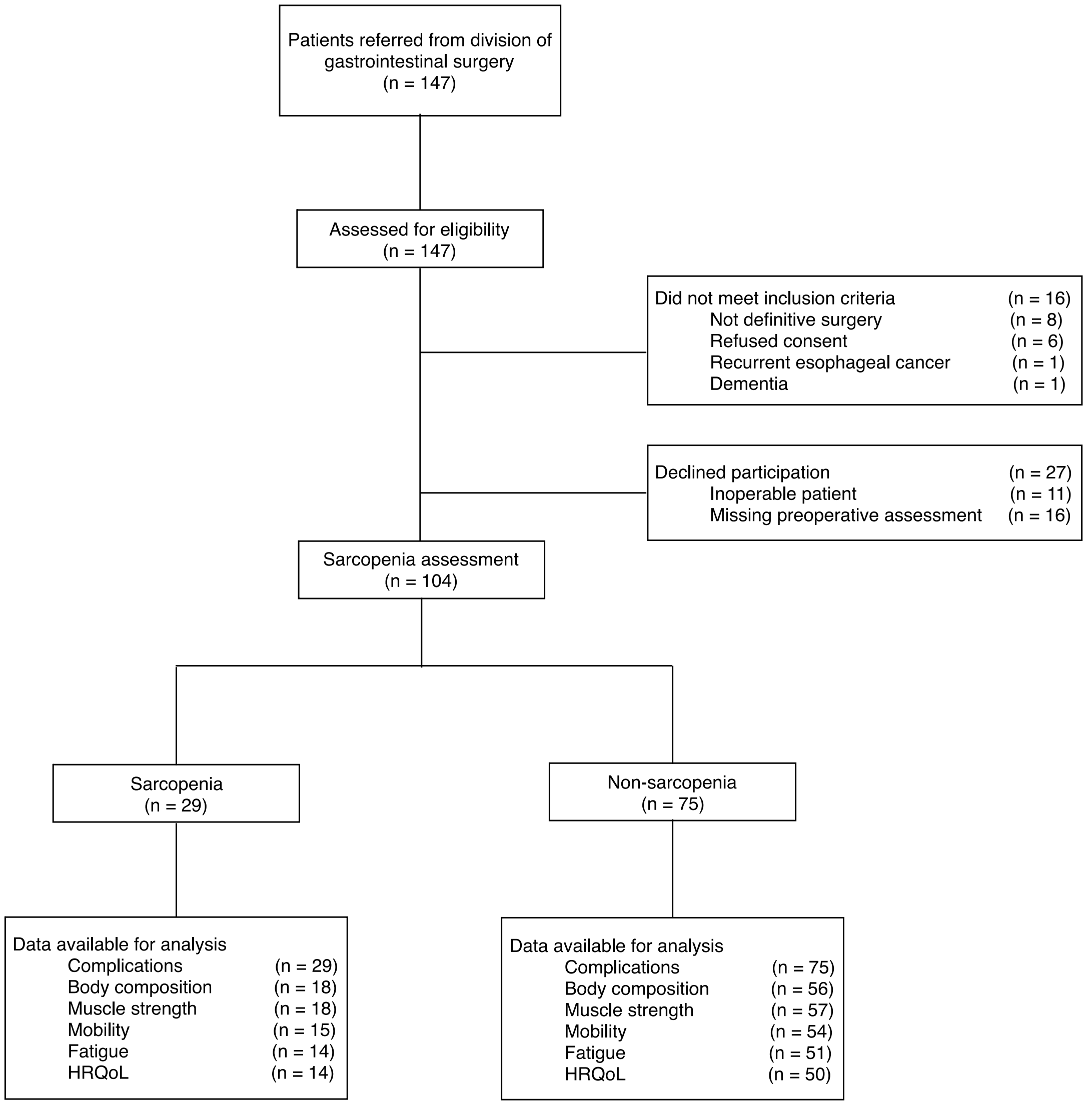

Figure 1. Flow diagram of participants

Table 1. Baseline characteristics

Variables	Sarcopenia (n = 29)	Non-sarcopenia (n = 75)	*P* value
Age (years old)	69 (66 – 76)	64 (61 – 71)	0.004
Gender (male / female)	22/7	66/9	0.14
Body mass index (kg/m^2)	19.3 ± 2.6	21.7 ± 2.8	< 0.001
Brinkman index	700 (0 – 1000)	565 (158 – 820)	0.78
CRP (mg/dl)	0.20 (0.10 – 0.44)	0.10 (0.10 – 0.18)	0.01
Serum albumin (g/dl)	3.8 (3.3 – 4.1)	4.0 (3.8 – 4.3)	0.003
Preoperative respiratory function			
Predicted VC (%)	93.2 ± 14.2	100.1 ± 12.0	0.02
FEV1.0%	70.4 ± 12.7	74.1 ± 9.5	0.12
GNRI	91.2 (82.8 – 98.8)	101.3 (95.0 – 103.9)	< 0.001
Comorbidity, n (%)			
Hypertension	8 (27.6 %)	34 (45.3 %)	0.12
Diabetes mellitus	3 (10.3 %)	7 (9.3 %)	1.00
Chronic pulmonary disease	11 (37.9 %)	20 (26.7 %)	0.34
Circulatory disease	5 (17.2 %)	4 (5.3 %)	0.11
Performance status (0/1/2)	26/2/1	70/3/2	0.69
Weight loss past 6 months (%)	8.8 ± 9.0	3.3 ± 5.9	0.001
Histology, n (%)			
AC/SCC/MM	1/28/0	4/70/1	1.00
Clinical stage (1/2/3/4)	4/6/16/3	16/32/26/1	0.02
Preoperative treatment, n (%)			
Neoadjuvant chemotherapy	24 (82.8 %)	57 (76.0 %)	0.60

Data are expressed as mean ± standard deviation or median (interquartile ranges)

CRP, C-reactive protein; VC, vital capacity; FEV, forced expiratory volume; GNRI, Geriatric Nutritional Risk Index; AC, adenocarcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma.

Table 2. Operative variables and surgical outcomes, stratified by sarcopenia status

Variables	Sarcopenia (n = 29)	Non-sarcopenia (n = 75)	*P* value
Operative time (min)	711 (628 – 773)	715 (657 – 786)	0.50
Blood loss * (ml/kg)	10.9 (8.5 – 14.9)	5.6 (3.3 – 8.3)	< 0.001
Postoperative complication, n (%)			
Pulmonary	11 (37.9 %)	13 (17.3 %)	0.04
Cardiovascular	9 (31.0 %)	17 (22.7 %)	0.45
Infection	5 (17.2 %)	10 (13.3 %)	0.76
Surgical	6 (20.7 %)	9 (12.0 %)	0.35
Duration of inhibited oral intake (days)	9 (7 – 19)	9 (7 - 14)	0.23
Hospitalization after surgery (days)	53 (32 – 80)	28 (23 – 41)	< 0.001

Data are expressed as median (interquartile ranges)

* volume of bleeding / body weight

Table 3. Risk factors for postoperative pulmonary complications

Variables		Univariate logistic regression (N=104)			Multivariate logistic regression (N=104)		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Age (years old)							
	> 70	1.76	0.69 – 4.47	0.23			
Gender							
	Male	2.33	0.59 – 15.60	0.29			
Body mass index (kg/m^2)							
	< 18.0	1.49	0.43 – 4.59	0.50			
Clinical stage							
	> 2	1.35	0.54 – 3.38	0.52			
Brinkman index							
	≥ 400	3.09	1.04 – 9.14	0.04	3.46	1.20 – 11.77	0.03
Predicted VC (%)							
	< 80	2.92	0.67 – 12.06	0.13			
FEV1.0%							
	< 70	1.61	0.61 – 4.12	0.32			
Albumin (g/dl)							
	< 3.5	2.08	0.58 – 6.78	0.23			
Chronic pulmonary disease							
	Yes	1.24	0.45 – 3.24	0.67			
Operative time (min)							
	> 540	0.14	0.01 – 1.52	0.11			
Blood loss * (ml/kg)							
	> 20	1.73	0.23 – 9.47	0.54			
Sarcopenia							
	Yes	2.91	1.12 – 7.61	0.03	3.13	1.12 – 8.93	0.03

OR, odds ratio; CI, confidence interval; VC, vital capacity; FEV1.0, forced expiratory volume in 1 s

* volume of bleeding / body weight

Table 4. Relationship between sarcopenia and perioperative functional changes

Measure	Sarcopenia (n = 29)		Non-sarcopenia (n = 75)		Adjusted group difference in mean changes * (95%CI)	Adjusted p value
	Baseline	Change at POD30	Baseline	Change at POD30		
Body weight (kg)	51.1 ± 8.9	-2.7 ± 2.3	59.7 ± 10.1	-4.2 ± 1.8	0.4 (-0.6 – 1.4)	0.41
Lean body mass (kg)	38.0 ± 7.5	-2.6 ± 2.6	45.8 ± 7.4	-3.4 ± 1.8	0.4 (-0.7 – 1.6)	0.44
Grip strength (kg)	21.7 ± 9.4	-1.5 ± 3.9	31.8 ± 5.9	-1.8 ± 2.8	0.9 (-1.1 – 2.9)	0.38
SPPB	10.5 ± 2.2	-0.5 ± 1.6	11.8 ± 0.5	-0.3 ± 0.8	-0.2 (-0.9 – 0.6)	0.68
FACIT-F	39.3 ± 6.9	-6.4 ± 13.2	35.6 ± 11.4	6.5 ± 13.3	-6.1 (-13.0 – 0.9)	0.09
FACT-G	74.9 ± 13.1	-8.1 ± 8.0	74.4 ± 14.1	-8.8 ± 12.0	0.01 (-7.0 – 7.0)	0.99

CI, confidence interval; POD, postoperative day; SPPB, short physical performance battery; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FACT-G, Functional Assessment of Cancer Therapy – General.

* Adjusted for baseline value, age, gender, and Geriatric Nutritional Risk Index.

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