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Computed tomography-assessed presarcopenia and clinical outcomes after laparoscopic surgery for rectal cancer

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Purpose: Previous studies have reported that presarcopenia negatively affects rectal cancer treatment. However, most studies have analyzed patients including majority of open surgery, and the association between presarcopenia and clinical outcomes after laparoscopic rectal cancer surgery remains unclear. This study aimed to evaluate the impact of presarcopenia on the clinical and oncological outcomes after laparoscopic rectal cancer surgery.

Methods: Three hundred and one patients undergoing laparoscopic rectal cancer surgery between December 2009 and May 2016 were enrolled. Body composition was assessed using computed tomography by measuring the muscle and fat areas at the third lumbar (L3) vertebra. The L3 skeletal muscle area was used to calculate the skeletal muscle index and evaluate presarcopenia.

Results: Presarcopenia was more common in older (\geq 70 years, P=0.008) or female patients (P=0.045). Patients with presarcopenia had decreased skeletal muscle area (P<0.001), lower hemoglobin level (P=0.034), longer time to first flatus (P<0.001), and more frequent surgical site infection (P=0.001). However, survival rates were not significantly different between those with and without presarcopenia.

Conclusion: Computed tomography-assessed presarcopenia was associated with delayed functional recovery and increased surgical site infection, although it was not revealed as a prognostic factor for oncological outcomes.

Keywords: Sarcopenia; Treatment outcome; Laparoscopy; Rectal neoplasms

INTRODUCTION

Surgical resection plays a vital role in the treatment of rectal cancers. Since Heald [1] introduced the concept of total mesorectal excision (TME) in 1980s, it has become the standard surgical procedure for rectal cancer [2]. With the development of laparoscopic techniques, performing TME using a laparoscopic approach is widely accepted for rectal cancer surgery [3]. Several multicenter randomized control trials found that laparoscopic surgery for rectal cancer had similar safety, short-term benefits, and oncologic safety as open surgery [4, 5]. However, laparoscopic TME is challenging for surgeons because it is performed in a narrow pelvic cavity and causes limited vision, particularly in patients who receive preoperative chemoradiotherapy (CRT), resulting in fibrotic

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tissue changes. Therefore, there remains debate regarding the safety of laparoscopic surgery for rectal cancer compared to open surgery. In the ACOSOG (American College of Surgeons Oncology Group) Z6051 and AlaCaRT (Australasian Laparoscopic Cancer of the Rectum) trials, the noninferiority of laparoscopic surgery to open surgery for rectal cancer was not established [6, 7]. However, laparoscopic surgery for rectal cancer is widely performed.

Sarcopenia, defined as the age-related degenerative loss of size, quality, and strength of skeletal muscle, is a predictor of poor patient prognoses [8]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) classified the stages of sarcopenia into "presarcopenia," "sarcopenia," and "severe sarcopenia," according to muscle mass, strength, and physical performance [9]. The presarcopenia is characterized by low muscle mass without affecting muscle strength or physical performance. Currently, most patients with rectal cancer routinely undergo abdominal computed tomography (CT) for cancer staging, which can be used to identify the patient's body composition [10]. The skeletal muscle index (SMI) on CT images at the third lumbar (L3) vertebra level can be used to assess presarcopenia. Several studies have shown that presarcopenia adversely affects postoperative complications and survival rates in rectal cancer patients [11-14]. However, most of these studies did not determine whether laparoscopic surgery could reduce the negative impacts of presarcopenia. In our previous study, laparoscopic surgery was shown to reduce the negative impact of presarcopenia on clinical and oncological outcomes in patients with colon cancer [15]. As mentioned above, laparoscopic surgery for rectal cancer is more challenging for surgeons than that for colon cancer. This study aimed to evaluate the impact of presarcopenia on the clinical and oncological outcomes after laparoscopic rectal cancer surgery.

METHODS

Ethics statement

This retrospective study was approved by the Institutional Review Board of Chungnam National University Hospital (No. 2018-05-003). The requirement for informed consent was waived due to the retrospective nature of the study.

Patients

A total of 301 patients diagnosed with rectal cancer who underwent laparoscopic surgery between December 2009 and May 2016 at Department of Surgery, Chungnam National University Hospital (Daejeon, Korea), were enrolled. The exclusion criteria were as follows: (1) distant metastases at the initial diagnosis; (2) conversion to open surgery; and (3) emergency surgery due to complications such as obstruction or perforation. Clinical data such as age, sex, weight, height, and comorbidities were used based on the contents of the medical records. The variables known to affect patient prognosis were reviewed, such as type of operation, histological grade, TNM stage, and preoperative carcinoembryonic antigen (CEA) level. The TNM stage was classified by the 8th edition of the American Joint Committee on Cancer [16].

Body composition evaluation

Body composition analysis methods have been described in our previous study [15]. Contrast-enhanced CT scans were routinely performed before surgery for rectal cancer staging. CT images were accessed through the hospital picture archiving and communication system, and those at the L3 spinal level in the axial view of the portal phase were selected. In the cases of preoperative chemoradiotherapy, post-treatment CT scans were used for evaluation. For the selected images, total body fat area, visceral fat area, subcutaneous fat area, and abdominal circumference were automatically measured using the TeraRecon Aquarius Workstation program (TeraRecon). The total area, visceral fat area, and skeletal muscle area were measured using adipose tissue (-190 to -30 Hounsfield unit [HU]) and skeletal muscle (-29 to 150 HU) [17]. Presarcopenia was defined using points for the SMI at the L3 level. At the L3 level, it was calculated as the area of the skeletal muscle (cm^2) divided by the height squared (m^2) . For men, the cutoff points were 43 cm^2/m^2 for those with a body mass index $(BMI) < 25 \text{ kg/m}^2$ and 53 cm^2/m^2 for those with BMI > 25 kg/m^2 , and $41 \text{ cm}^2/\text{m}^2$ for women [8].

Outcome parameters

The patients were divided into 2 groups according to the presence or absence of presarcopenia. Functional recovery parameters, postoperative complications, and survival data were also recorded. Overall survival was defined as the time from surgery to death from any other cause or from surgery to last follow-up, and disease-free survival was defined as the time to recurrence after surgery.

Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 26 (IBM Corp). The chi-square test and Fisher exact test were used for categorical parameters, and the t-test was used to compare between-group differences in continuous parameters. Univariate logistic regression analysis was performed to determine the clinical parameters affecting postoperative complications. Multivariate logistic regression analysis was performed, including variables with P < 0.2. Univariate analyses of overall and disease-free survival

were performed using the Kaplan-Meier method. Multivariate analyses of overall and disease-free survival, including variables with P < 0.2 as covariants, were calculated using Cox regression analysis. Statistical significance was set at P < 0.05.

Table 1. Demographic analysis of patients according to presarcopenia
(n=301)

Chamataristia	Р	resarcopenia	
Characteristic	No (n = 244)	Yes (n = 57)	P-value
Age (yr)			0.008
<70	169 (69.3)	29 (50.9)	
≥70	75 (30.7)	28 (49.1)	
Sex			0.045
Male	163 (66.8)	30 (52.6)	
Female	81 (33.2)	27 (47.4)	
Body mass index (kg/m ²)			0.866
<25	157 (64.3)	36 (63.2)	
≥25	87 (35.7)	21 (36.8)	
Comorbidity			0.226
No	133 (54.5)	26 (45.6)	
Yes	111 (45.5)	31 (54.4)	
Tumor location			0.568
Upper (>8 cm)	29 (11.9)	4 (7.0)	
Middle (4–8 cm)	116 (47.5)	29 (50.9)	
Lower (<4 cm)	99 (40.6)	24 (42.1)	
Preop chemoradiotherapy			0.637
No	181 (74.2)	44 (77.2)	
Yes	63 (25.8)	13 (22.8)	
ASA physical status			0.130
I, II	222 (91.0)	48 (84.2)	
III, IV	22 (9.0)	9 (15.8)	
Type of operation			0.786
Abdominoperineal resection	11 (4.5)	1 (1.8)	
Low anterior resection	212 (86.9)	51 (89.5)	
Coloanal anastomosis	21 (8.6)	5 (8.8)	
Histology	· · ·	()	0.515
WD or MD	232 (95.1)	53 (93.0)	
PD or mucinous	12 (4.9)	4 (7.0)	
Pathologic T			0.865
T0-T2	140 (57.4)	32 (56.1)	
T3-T4	104 (42.6)	25 (43.9)	
Pathologic N			0.950
N0	168 (68.9)	39 (68.4)	
N+	76 (31.1)	18 (31.6)	
Adjuvant chemotherapy		. (0.324
No	115 (47.1)	31 (54.4)	
Yes	129 (52.9)	26 (45.6)	

Values are presented as number (%).

ASA, American Society of Anesthesiologists; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated.

RESULTS

Table 1 shows the demographic analysis of the patients with and without presarcopenia. Fifty-seven patients (18.9%) had presarcopenia, and 244 (81.1%) did not. Presarcopenia was more common in old age (\geq 70 years, P=0.008) or female sex (P=0.045). There was no significant between-group difference regarding other characteristics. Table 2 summarizes the differences in clinical variables between the patients with and without presarcopenia. The skeletal muscle area was smaller in patients with presarcopenia (P < 0.001), whereas the visceral and subcutaneous fat areas did not differ between the 2 groups. Preoperative hemoglobin level was lower in patients with presarcopenia (P = 0.034), however there was no significant between-group difference in preoperative albumin and initial CEA levels. Although the time to first flatus was shorter in nonpresarcopenic patients (P < 0.001), the time to tolerable soft diet and length of hospital stay were not significantly different between the 2 groups. The overall rate of postoperative complications and Clavien-Dindo classification grade III or IV were not significantly different between the 2 groups. The types of complications, according to the presence or absence of presarcopenia, are described in Table 3. Surgical site infection (SSI) was more common in patients with presarcopenia (P=0.001), however other types of complications did not differ between the 2 groups.

Clinical parameters affecting postoperative complications

The clinical parameters affecting postoperative complications are presented in Table 4. Univariate logistic regression analysis

Table 2. Clinical characteristics according to presarcopenia (n = 301)

Characteristic	Presarcopenia				
Characteristic	No (n=244)	Yes (n = 57)	P-value		
Area of skeletal muscle (cm ²)	134.97 ± 25.69	108.24 ± 24.28	< 0.001		
Area of visceral fat (cm ²)	129.80 ± 70.0	135.68 ± 80.06	0.579		
Area of subcutaneous fat (cm ²)	104.79 ± 57.55	114.85 ± 55.26	0.232		
Preoperative hemoglobin (g/dL)	13.07 ± 1.81	12.52 ± 1.63	0.034		
Preoperative albumin (g/dL)	4.06 ± 0.44	4.01 ± 0.40	0.461		
Initial CEA (ng/mL) $(n=293)^a$	7.40 ± 23.58	5.55 ± 8.56	0.560		
Time to first flatus (day)	1.94 ± 1.01	3.09 ± 1.80	< 0.001		
Time to tolerable soft diet (day)	4.39 ± 3.25	4.30 ± 3.46	0.857		
Length of hospital stay (day)	11.55 ± 11.37	9.84 ± 6.48	0.277		
Postoperative complication	69 (28.3)	21 (36.8)	0.204		
Clavien-Dindo classification (grade III or IV)	36 (14.8)	5 (8.8)	0.236		

Values are presented as mean±standard deviation or number (%). ^aExcluding 8 patients without initial carcinoembryonic antigen (CEA) data.

showed that old age (\geq 70 years, P=0.003), preoperative CRT (P=0.003), American Society of Anesthesiologists (ASA) physical status (PS) classification grade \geq III (P=0.007), abdominoperineal resection (APR; P=0.038) were significant parameters related to postoperative complications. Old age (\geq 70 years, P=0.020), preoperative CRT (P=0.008), and ASA PS grade \geq III (P=0.049) were independent parameters affecting postoperative complications in multivariate logistic regression analysis.

Table 3.	Types	of com	plications	according to	presarco	penia ($n = 301$)
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	Presarcopenia				
Complication	No (n=244)	Yes (n = 57)	P-value		
Surgical site infection	2 (0.8)	6 (10.5)	0.001		
Postoperative ileus	9 (3.7)	1 (1.8)	0.694		
Postoperative bleeding	5 (2.0)	0 (0)	0.588		
Bladder dysfunction	8 (3.3)	5 (8.8)	0.077		
Intraabdominal abscess	10 (4.1)	1 (1.8)	0.696		
Anastomotic leakage	12 (4.9)	2 (3.5)	> 0.999		
Intestinal obstruction	3 (1.2)	0 (0)	> 0.999		
Rectovaginal fistula	3 (1.2)	1 (1.8)	0.570		
Urinary tract infection	1 (0.4)	1 (1.8)	0.343		
Cardiovascular	3 (1.2)	0 (0)	> 0.999		
Renal	1 (0.4)	0 (0)	> 0.999		
Pulmonary	1 (0.4)	0 (0)	> 0.999		
Chyle	2 (0.8)	1 (1.8)	0.469		
Ischemic colitis	7 (2.9)	1 (1.8)	> 0.999		
High output stoma	2 (0.8)	2 (3.5)	0.164		
Total	69 (28.3)	21 (36.8)	0.204		

Values are presented as number (%).

Survival analysis

In univariate analysis (Table 5), the 5-year overall survival was better in the <70 years old (P<0.001), initial CEA <5 (P=0.050), ASA PS grade I or II (P=0.029), no APR (P=0.002), pathologic T0 to T2 (P<0.001), and pathologic N0 groups (P=0.001). Among them, the pathologic T0 to T2 (P<0.001) and pathologic N0 groups (P=0.004) also showed better disease-free survival. There was no significant difference in overall survival in the group that did not receive preoperative CRT, but disease-free survival was better (P=0.010). In multivariate analysis (Table 6), the 5-year overall survival was better in patients aged <70 years (P=0.008), female sex (P=0.013), no APR (P=0.021), and pathologic T0 to T2 (P=0.004). Disease-free survival was better in the group that did not receive preoperative CRT (P=0.009) and the pathologic T0 to T2 group (P=0.026).

DISCUSSION

Sarcopenia is defined as the age-related degenerative loss of size, quality, and strength of skeletal muscle. The EWGSOP recommended the use of both low muscle mass and function for the diagnosis of sarcopenia, and classified the stages according to muscle mass, strength and physical performance [9]. Presarcopenia was identified by low muscle mass without affecting muscle strength or physical performance. Among several methods of measuring muscle quantity, CT scan is considered to be an accurate method and widely used in research setting [18]. We also used CT images at the L3 level to measure the muscle area and SMI.

Table 4. Logistic regression analysis of clinical parameters affecting postoperative complications

Demonster	Univariate		Multivariat	Multivariate		
Parameter	OR (95% CI) P-value		OR (95% CI)	P-value		
Old age (≥70 yr)	2.152 (1.292-3.583)	0.003	1.928 (1.107–3.357)	0.020		
Male sex	1.565 (0.918–2.667)	0.100	1.644 (0.932-2.900)	0.086		
Low body mass index ($< 25 \text{ kg/m}^2$)	1.173 (0.697–1.973)	0.548	-	-		
Comorbidity	1.617 (0.984–2.657)	0.058	1.356 (0.796-2.310)	0.262		
Presarcopenia	1.479 (0.907–2.712)	0.205	-	-		
Level of hemoglobin (g/dL)	0.993 (0.865–1.141)	0.926	-	-		
Level of albumin (g/dL)	0.725 (0.411-1.279)	0.267	-	-		
Level of carcinoembryonic antigen (ng/mL)	1.005 (0.994–1.016)	0.392	-	-		
Preoperative chemoradiotherapy	2.262 (1.313-3.897)	0.003	2.193 (1.222-3.935)	0.008		
ASA physical status (\geq III)	2.825 (1.330-6.002)	0.007	2.270 (1.003-5.137)	0.049		
Abdominoperineal resection	3.475 (1.072-11.258)	0.038	2.168 (0.612-7.678)	0.231		
Histology (PD or mucinous)	1.893 (0.682-5.251)	0.220	-	-		
Pathologic T (T3-T4)	0.846 (0.512-1.397)	0.513	-	-		
Pathologic N (N+)	1.148 (0.678-1.946)	0.607	-	-		

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; PD, poorly differentiated.



Factor	No. of patients	Overa	ll survival	Disease-free survival	
	(n=301)	% P-value		%	P-value
Age (yr)			< 0.001		0.311
<70	198	90.5		89.8	
≥70	103	72.3		85.7	
Sex			0.059		0.504
Male	193	84.3		87.9	
Female	108	84.9		90.4	
Body mass index (kg/m ²)			0.222		0.306
<25	193	85.1		90.0	
≥25	108	83.5		85.6	
Comorbidity			0.240		0.586
No	159	86.6		89.2	
Yes	142	84.6		87.7	
Presarcopenia			0.460		0.603
No	244	87.7		88.9	
Yes	57	66.5		90.6	
Preoperative chemoradiotherapy			0.206		0.010
No	225	87.2		91.4	
Yes	76	68.7		79.7	
Initial CEA (ng/mL) $(n=293)^a$			0.050		0.208
<5	216	88.6		89.9	
≥5	77	68.5		84.7	
ASA physical status			0.029		0.207
I, II	270	88.5		89.0	
III, IV	31	58.7		96.0	
Abdominoperineal resection			0.002		0.055
No	289	89.1		90.8	
Yes	12	40.0		70.0	
Histology			0.459		0.808
WD or MD	285	88.8		90.6	
PD or mucinous	16	74.0		86.7	
Pathologic T			< 0.001		< 0.001
Т0-Т2	172	93.7		93.7	
Т3-Т4	129	74.8		81.3	
Pathologic N			0.001		0.004
NO	207	91.5		92.0	
N+	94	68.5		80.8	
Adjuvant chemotherapy	·		0.077		0.139
No	146	91.9		87.4	
Yes	155	85.2		83.9	

CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated.

^aExcluding 8 patients without initial CEA data.

A large-scale meta-analysis including 70 studies was conducted to examine the prevalence of CT-assessed presarcopenia [19]. Most studies have used the SMI of L3 level to evaluate presarcopenia. Seventeen of 70 studies used the cutoff introduced by Martin et al. [8] as we used. In those 17 studies, the prevalence of presarcopenia ranged from 14.7% to 69.8%. In the present study, 57 of 301 patients (18.9%) had presarcopenia, which was comparable to the results of other studies.

Presarcopenia is known to negatively affect clinical and oncological outcomes [11–14]. However, most previous studies did not determine whether laparoscopic surgery could eliminate the adverse effects of presarcopenia. Several studies have found that lap-



Table 6. Multivariate analysis factors associated with 5-year overall and disease-free survival

Factor	No. of patients	Overall survival		No. of patients	Disease-free survival	
	$(n=293)^{a}$	HR (95% CI)	P-value	(n=301)	HR (95% CI)	P-value
Age (yr)			0.008	-	-	-
<70	191	1 (Reference)				
≥70	102	2.200 (1.223-3.959)				
Sex			0.013	-	-	-
Female	105	1 (Reference)				
Male	188	2.239 (1.184–4.236)				
Initial CEA (ng/mL)			0.442	-	-	-
<5	216	1 (Reference)				
≥5	77	1.263 (0.697–2.289)				
Preoperative chemoradiotherapy	-	-	-			0.009
No				255	1 (Reference)	
Yes				76	2.709 (1.276-5.750)	
ASA physical status			0.095	-	-	-
I, II	263	1 (Reference)				
III, IV	30	1.824 (0.900-3.694)				
Abdominoperineal resection			0.021			0.306
No	281	1 (Reference)		289	1 (Reference)	
Yes	12	2.969 (1.181–7.466)		12	1.917 (0.551–6.669)	
Pathologic T			0.004			0.026
Т0-Т2	167	1 (Reference)		172	1 (Reference)	
T3-T4	126	2.624 (1.351-5.098)		129	2.539 (1.115-5.781)	
Pathologic N			0.332			0.055
N0	200	1 (Reference)		207	1 (Reference)	
N+	93	1.360 (0.731–2.531)		94	2.166 (0.985-4.764)	
Adjuvant chemotherapy			0.995			0.722
Yes	154	1 (Reference)		155	1 (Reference)	
No	139	1.002 (0.542-1.853)		146	1.155 (0.523-2.547)	

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists.

^aExcluding 8 patients without initial CEA data.

aroscopic surgery for colorectal cancer is feasible and can reduce presarcopenia's adverse effects on treatment outcomes [20, 21]. Our previous study also reported that presarcopenia was not negatively associated with functional recovery, median hospital stay, and oncological outcomes after laparoscopic surgery for colon cancer [15]. We hypothesized that patients with presarcopenia did not compromise the clinical and oncological outcomes of laparoscopic surgery for rectal cancer. Bhattacharyya et al. [22] compared clinical outcomes after gastric cancer surgery between the sarcopenia and nonsarcopenia groups. They demonstrated that delayed passage of first flatus and postoperative complications are high in sarcopenic patients and concluded that sarcopenia is an independent prognostic factor for adverse short-term outcomes in patients with gastric cancer after curative intent resection. In our study, the time to first flatus was longer and SSI was higher in presarcopenic patients, although there was no significant difference in overall and disease-free survival between with and without presarcopenia. Therefore, our results suggested that presarcopenia might affect functional recovery and SSI, whereas oncologic outcomes after laparoscopic surgery for rectal cancer were not affected by presarcopenia.

Many studies have analyzed the risk factors for postoperative complications after rectal cancer surgery. Lohsiriwat et al. [23] reported that preoperative hypoalbuminemia is a significant risk factor for postoperative complications after rectal cancer surgery. Kang et al. [24] analyzed the risk factors of postoperative complications following robotic rectal cancer surgery. They found that male sex, previous abdominal surgery, and low tumor level were risk factors for postoperative complications. In the present study, we demonstrated that old age (\geq 70 years, P=0.020), preoperative CRT (P=0.008), and a high ASA PS grade (\geq III, P=0.049) were identified as clinical parameters affecting postoperative complications.

Several studies have reported that presarcopenia is a risk factor for postoperative complications [11, 15]. However, Ouchi et al. [20] found that there was no significant difference in the incidence of complications after laparoscopic colorectal cancer surgery between the presarcopenia and non-presarcopenia groups. Similarly, in our results, there were no significant differences between the presarcopenia and non-presarcopenia groups in the overall rate of postoperative complications (P = 0.204). There was also no significant between-group difference regarding complications classified as Clavien-Dindo grade III or IV (P=0.236). Moreover, presarcopenia was not an independent factor in the logistic regression analysis of postoperative complications (P=0.205). Among type of complications, SSI was more common in presarcopenic patients. There are some debates that sarcopenia was associated with SSI after colorectal surgery. Lieffers et al. [25] showed that presarcopenia was an independent predictor of SSI, whereas Olmez et al. [26] reported no relationship between presarcopenia and SSI after colorectal surgery. The relationship between presarcopenia and SSI after colorectal surgery might require further investigation in the future.

The present study had several limitations. First, it was a retrospective study based on a review of medical records. As this study only included patients who underwent laparoscopic surgery, cases in which laparoscopic surgery was impossible due to the stage IV or tumor complications were excluded, and selection bias may exist accordingly. Further studies are needed in patients with rectal cancer with distant metastases or those who have undergone emergency surgery. Second, the definition of sarcopenia changed in 2018. According to the EWGSOP2 [27], muscle strength is first evaluated before measuring the quantity and quality of muscles to assess sarcopenia. This study did not assess sarcopenia as muscle strength could not be determined. Third, rectal cancer is heterogeneous, as not all patients received CRT, which may affect clinical and oncological outcomes. Fourth, detailed descriptions of some complications were limited due to paucity of information in medical records. For example, the severity or extent of SSI is usually not described in medical records in detail. The existence of SSI could be noted, whereas detailed status of infection could not be identified in our study.

In conclusion, CT-assessed presarcopenia was associated with delayed recovery of bowel function and increased SSI, although it was not revealed as a prognostic factor for short-term and oncological outcomes. Further studies are necessary to validate whether laparoscopic surgery can eliminate the negative impact of presarcopenia on treatment outcomes in patients with rectal cancer.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: JSK; Data curation: JHS, RKO, JEL, KHL; Formal analysis: KHL, JYK; Investigation: JHS, RKO, JEL, JSK; Methodology: JHS, JEL; Project administration: JYK, JSK; Supervision: KHL, JYK; Validation: all authors; Visualization: all authors; Writing-original draft: JHS; Writing-review & editing: all authors. All authors read and approved the final manuscript.

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