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Original Research Article

# Risk Factors for Postoperative Paralytic Ileus in Advanced-age Patients after Laparoscopic Colorectal Surgery: A Retrospective Study of 124 Consecutive Patients

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**Abstract**

**Objectives:** Postoperative paralytic ileus (POI) is one of the most common and troublesome complications following colorectal surgery. However, to date, the risk factors for POI remain unclear. This study aimed to identify the risk factors for POI following laparoscopic colorectal surgery in advanced-age patients.

**Methods:** The clinical data of 124 patients aged ≥75 years who underwent curative colorectal surgery from January 2018 to December 2020 were retrospectively reviewed. The relationship between POI and clinicopathological data including sarcopenia and visceral fat obesity was then assessed. Sarcopenia was defined as a low skeletal muscle mass index; visceral obesity, visceral fat with an area ≥100 $cm^2$ on computed tomography at the level of the third lumbar vertebra; and sarcobesity, sarcopenia with visceral obesity.

**Results:** The rate of POI was 9% (12/124 patients), and all the affected patients improved with conservative treatment. In the univariate and multivariate analyses, sarcopenia and sarcobesity were significant predictive factors for POI.

**Conclusions:** Sarcopenia and sarcobesity may be risk factors for POI in patients aged ≥75 years after laparoscopic colorectal surgery.

**Keywords**

colorectal surgery, laparoscopic, postoperative paralytic ileus, sarcopenia, advanced-age

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## Introduction

Postoperative paralytic ileus (POI), which is characterized by failure to restore adequate peristaltic movements of the gastrointestinal tract in the absence of mechanical obstruction following surgery, is one of the most common complications after colorectal surgery[1-3]. POI manifests as abdominal distension, nausea, vomiting, and delayed oral intake, and a decompression tube is sometimes needed to relieve the symptoms. Moreover, prolonged POI can cause a series of complications such as malnutrition, muscle atrophy, delayed surgical wound healing, and pneumonia, resulting in a longer hospital stay and higher hospitalization costs[4,5]. The methods of preventing POI, such as thoracic epidural anesthesia, gum chewing, and avoidance of water overload, have shown little success[1,6,7].

For the last two decades, laparoscopic surgery has been the mainstay of colorectal cancer surgery owing to its better cosmesis, better view of the surgical field, better short-term outcome, and comparable long-term outcome than conventional open surgery. Laparoscopic colorectal surgery involves less blood loss, a smaller surgical wound, less pain, and less

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bowel manipulation[8,9]; consequently, it has been believed that the incidence of POI must be lower after laparoscopic surgery than after open surgery. Indeed, some retrospective studies have demonstrated a reduction of POI in association with the laparoscopic approach[10-12]. However, a systematic review and a prospective study showed that the laparoscopic approach for colorectal surgery does not entirely decrease the incidence of POI[13,14]. Therefore, the effect of the laparoscopic approach on the incidence of POI continues to be debated, and attention should be given to the risk of POI even in the era of laparoscopic surgery.

POI following colorectal surgery is common among advanced-age patients while very rare among younger patients[15-18]. However, several studies have suggested that laparoscopic colorectal cancer surgery in older patients is as safe and feasible as that in younger patients[19,20]. Unlike younger patients, older ones generally have progressive frailty represented by sarcopenia[21]. Therefore, it is important to understand the risk factors for POI in older patients after laparoscopic colorectal surgery considering the aging-associated features of these patients. This study was conducted to elucidate the risk factors for POI in advanced-age patients after laparoscopic colorectal cancer surgery.

## Methods

### *Patients*

This study was approved by the Ethics Committee of Saga University (Number: 2019-504). Because the study design was retrospective, written informed consent was not obtained. However, the protocol is published on our website according to the Declaration of Helsinki.

From January 2018 to December 2020, 318 patients with colorectal cancer underwent surgical treatments in our institution, and laparoscopic procedures were performed in 308 of them. Of these 308 patients, 124 who were aged ≥75 years and underwent laparoscopic curative surgery for colorectal cancer were enrolled in this study (Figure 1). Patients with unmanaged preoperative ileus and patients who received preoperative chemotherapy, chemoradiotherapy, colostomy, or ileostomy were excluded from the study. The patients' clinicopathological data were collected from their medical records. The tumor stage was defined according to the classification established by the Union for International Cancer Control[22]. The patients' physical status was graded according to the Eastern Cooperative Oncology Group performance status and American Society of Anesthesiologists physical status. Data are expressed as median and range. The following information was also obtained: age, sex, body weight, body height, body mass index (BMI), surgical history, preoperative serum levels of albumin and C-reactive protein, preoperative differential leukocyte count, prognostic nutritional index, C-reactive protein-to-albumin ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, skeletal muscle mass, visceral fat mass at the level of the third lumbar vertebra, tumor location, level of lymph node dissection, operative time, blood loss volume, performance of blood transfusion, and method of anesthesia.

### *Perioperative period*

All 124 patients received clinical care and underwent standard laparoscopic colorectal surgery. Sodium picosulfate solution and magnesium citrate for mechanical bowel preparation as well as kanamycin and metronidazole for chemical bowel preparation were received the day before surgery. A silicone tube was inserted through the anus, and another was placed near the anastomosis line through the abdominal wall in patients with rectal cancer. A drain tube was not inserted after surgery for colon cancer. All tubes were removed within 7 days. According to the numerical rating scale of the patient, acetaminophen was administered for analgesia via the oral route or intravenous injection a few days after surgery. In addition, early mobilization and rehabilitation were performed the day after surgery.

### *Definition of POI*

According to previous studies[23,24], POI was defined as the presence of two or more of the following findings observed on and after postoperative day 4 without improvement: (i) nausea or vomiting, (ii) prolonged resumption of oral intake, (iii) absence of flatus for 24 h, and (iv) abdominal distention and small intestinal distention by gas or the presence of an air/fluid level in a radiologic image.

### *Image analysis and definition of sarcopenia*

Plain or enhanced computed tomography images obtained within 1 month before radical surgery were used to determine the presence of sarcopenia. Computed tomography images were transferred to an automated image analysis system (SYNAPSE VINCENT; Fujifilm Medical, Tokyo, Japan), and the areas of the skeletal muscle and visceral fat were calculated using the cross-sectional computed tomography image at the level of the third lumbar vertebra. Tissue Hounsfield units were used as follows: −150 to −50 for visceral fat and −29 to 150 for the skeletal muscle (Figure 2a, b)[25,26]. The skeletal muscle index (SMI) was calculated by the area of the skeletal muscle divided by the height of the patient squared ($cm^2/m^2$). In this study, sarcopenia was defined as a low SMI, the cut-off values of which were <30 and <40 $cm^2/m^2$ for female and male patients, respectively, according to a previous report[26]. Visceral obesity was also defined as visceral fat with an area of ≥100 $cm^2$, which is widely used as a cut-off value in Japan[27,28]. Sarcobesity was defined as sarcopenia with visceral obesity.

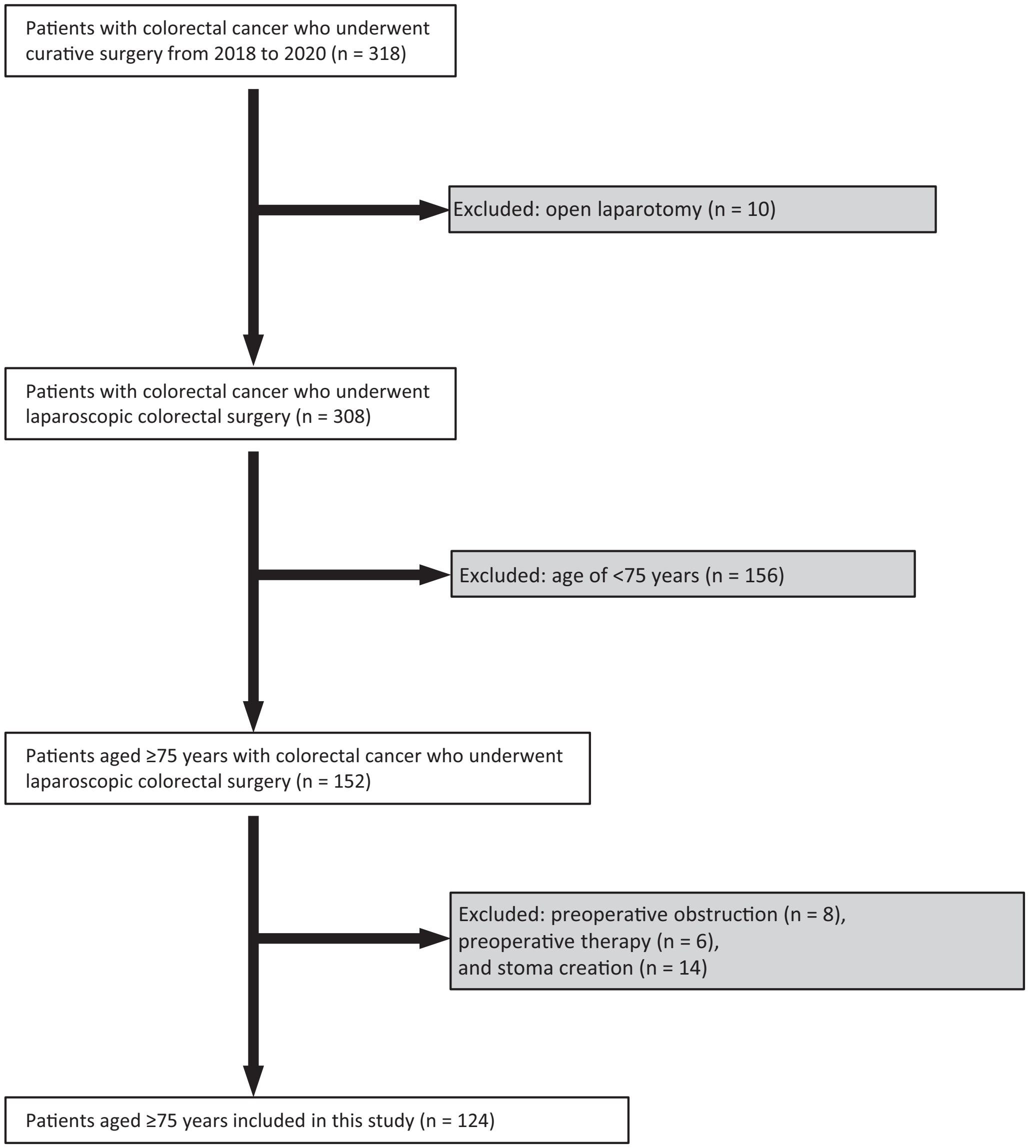


**Figure 1.** Flow diagram of older patients undergoing colorectal surgery in the present study.

### *Statistical analysis*

The statistical analysis was conducted using the JMP® statistical software, version 15.2.1 (SAS Institute Inc., Cary, NC, USA). For the descriptive analysis, continuous variables were compared between the groups using the Mann-Whitney U test, whereas categorical variables were compared using the chi-squared test. For the univariate analysis, simple logistic regression analysis was employed. Among the aforementioned clinicopathological factors that could influence outcome, those with a probability of approximately 0.1 in the univariate analysis were applied for multivariate analysis using a stepwise logistic regression to identify factors that were independently associated with POI. A $p$ value of <0.05 was considered statistically significant.

## Results

The patient and clinical characteristics are summarized in Table 1. Among the 124 patients, POI was observed in 12 (9%), all of whom had no intra-abdominal septic complications. Among the 12 patients with POI, 4 were treated with a decompression tube, and 1 developed aspiration pneumonia. The length of postoperative hospital stay was significantly longer in patients with than without POI. The univariate analysis revealed that age, sarcopenia, and sarcobesity were significantly associated with the incidence of POI (Table 2). A multivariate analysis with stepwise logistic regression including sarcopenia, sarcobesity, age, platelet-to-lymphocyte ratio, pathological stage, operating time, and blood loss was conducted to identify independent factors associated with the incidence of POI. POI was independently associated with sarcopenia (odds ratio, 19.0710; 95% confi-

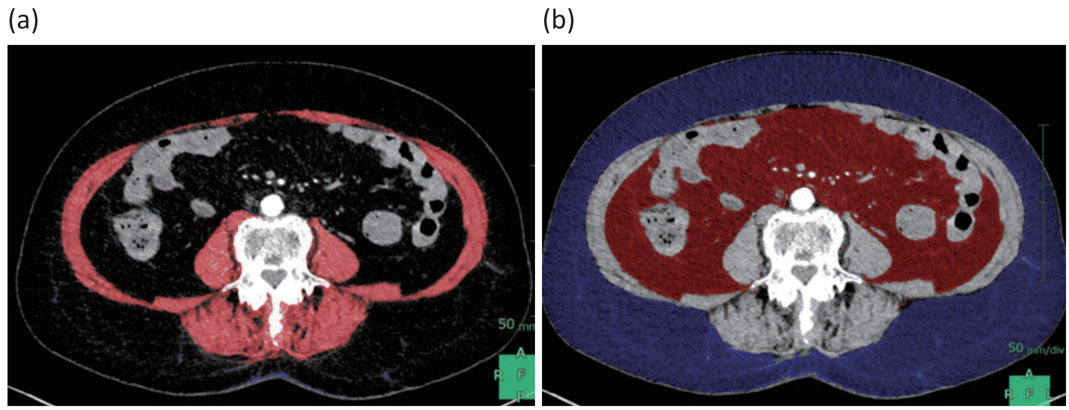


**Figure 2.** Measurement of the skeletal muscle mass index and the visceral fat area on computed tomography sectional imaging at the level of the third lumbar vertebra. (a) The areas of the total skeletal muscle were measured using tissue Hounsfield unit thresholds from −50 to 100, and the skeletal muscle mass index was calculated and normalized for height squared. (b) The areas of visceral fat and subcutaneous fat were measured using tissue Hounsfield unit thresholds from −150 to −50 for visceral fat (red) and from −190 to −30 for subcutaneous fat (blue).

dence interval, 1.9300-188.4928; $p$ = 0.0031) and sarcobesity (odds ratio, 12.3564; 95% confidence interval, 1.3359-114.2926; $p$ = 0.0152) (Table 2).

## Discussion

This is the first study to demonstrate that POI can be significantly affected by sarcopenia in patients of advanced-age after laparoscopic surgery for colorectal cancer. Among the patients without sarcopenia, POI was very rare (1.1%). Previous studies demonstrated several factors that can cause POI following colorectal surgery, such as male sex, chronic obstructive pulmonary disease, increasing age, poor performance status, high BMI, visceral obesity, intraoperative manipulation of the bowels, creation of a stoma, an open approach, mechanical bowel preparation, use of analgesics, perioperative fluid overload causing intestinal edema, nutritional delay, and postoperative complications[12,24,27,29-33]. The present study involving a cohort of older patients who underwent laparoscopic colorectal surgery showed that no clinical factors other than sarcopenia and sarcobesity were significantly associated with the incidence of POI.

According to the European Working Group on Sarcopenia in Older People, sarcopenia is a disorder of the aging process characterized by progressive loss of skeletal muscle mass, strength, and function, with increased odds of adverse outcomes[34]. In a pooled analysis of patients with and without sarcopenia, sarcopenia was significantly associated with a higher risk of severe complications, postoperative mortality, infections, cardiopulmonary complications, and prolonged length of stay following colorectal cancer surgery as well as significantly shorter overall and cancer-specific survival[35,36]. With respect to postoperative complications, several studies have shown that infectious complications are significantly associated with sarcopenia[35]. However, the correlation between sarcopenia and POI has not been thoroughly investigated. The pathogenesis of sarcopenia is multifactorial; it involves not only age-related changes in neuromuscular function, muscle protein turnover, and hormonal levels and sensitivity but also a chronic proinflammatory state, oxidative stress, poor nutritional status, and low physical activity[21]. Likewise, the pathogenesis of POI is also considered multifactorial, involving neurogenic, hormonal, and pharmacological components[37]. Considering the results of the present study, POI might be affected by the same background factors as those in sarcopenia. One possible reason for the relation between sarcopenia and POI is that POI is caused by lack of ghrelin. The expression of ghrelin, which is involved in the release of growth hormone, was repressed in POI[38]. However, ghrelin and growth hormone hyposecretion occurred with increasing years, resulting in the reduction of skeletal muscle mass and increase in somatic fat volume[39-41]. Further investigation is needed to elucidate the correlation between POI and sarcopenia.

Obesity is a well-known risk factor for various health disorders and is defined in various ways, such as high BMI, visceral obesity, and sarcobesity. A high BMI is easily defined as overweight, but it does not represent the body component due to the lack of differentiation between adiposity and muscle mass. Visceral obesity represents a high visceral fat volume as calculated via computed tomography, and sarcobesity is defined as visceral obesity with sarcopenia. He et al.[42] and Duchalais et al.[43] reported that obesity defined as a high BMI is a risk factor for POI. Contrarily, Morimoto et al.[27] reported that visceral obesity, not a high BMI, is

**Table 1.** Patient and Clinical Characteristics.

| Factors | | Total n = 124 | POI Yes n = 12 | POI No n = 112 | *p* value |
|---|---|---|---|---|---|
| Age | Median (range) | | 85.5 (77–93) | 82 (75–100) | 0.024 |
| Sex | Female | 66 | 4 | 62 | 0.223 |
| | Male | 58 | 8 | 50 | |
| BMI (kg/m2) | Median (range) | | 21.5 (13.9–24.8) | 21.2 (14.7–30.4) | 0.729 |
| PS | 0, 1 | 110 | 11 | 99 | 1 |
| | 2, 3 | 14 | 1 | 13 | |
| ASA-PS | <3 | 107 | 10 | 97 | 0.669 |
| | ≥3 | 17 | 2 | 15 | |
| Previous laparotomy | Yes | 45 | 5 | 40 | 0.76 |
| | No | 79 | 7 | 72 | |
| PNI | Median (range) | | 42.3 (31.3–53.3) | 43.8 (25.9–57.8) | 0.469 |
| CAR | Median (range) | | 0.1 (0.0–0.7) | 0.0 (0.0–6.7) | 0.283 |
| NLR | Median (range) | | 2.2 (1.0–5.1) | 2.7 (1.1–9.2) | 0.249 |
| PLR | Median (range) | | 119.3 (68.2–281.5) | 163.6 (56.1–532.8) | 0.097 |
| LMR | Median (range) | | 4.1 (2.0–7.1) | 4.1 (0.9–15.0) | 0.899 |
| Sarcopenia* | Yes | 30 | 11 | 19 | <0.001 |
| | No | 94 | 1 | 93 | |
| Visceral obesity† | Yes | 46 | 6 | 40 | 0.359 |
| | No | 78 | 6 | 72 | |
| Sarcobesity‡ | Yes | 8 | 6 | 2 | <0.001 |
| | No | 116 | 6 | 110 | |
| Tumor location§ | Right side | 75 | 8 | 67 | 0.762 |
| | Left side | 49 | 4 | 45 | |
| Lymph node dissection | With apical node | 116 | 11 | 105 | 0.568 |
| | Without apical node | 8 | 1 | 7 | |
| Operative time (min) | Median (range) | | 348 (173–408) | 262 (102–593) | 0.025 |
| Blood loss (g) | Median (range) | | 74.5 (15–355) | 27 (1–1660) | 0.009 |
| Transfusion | Yes | 16 | 2 | 14 | 0.653 |
| | No | 108 | 10 | 98 | |
| Anesthesia | With EA | 90 | 9 | 81 | 1 |
| | Without EA | 34 | 3 | 31 | |
| IN/OUT balance (mL/kg) | Median (range) | | 39.2 (21.2–74.5) | 35.6 (10.1–113.4) | 0.32 |
| Pathological stage‖ | I, II | 72 | 4 | 68 | 0.121 |
| | III, IV | 52 | 8 | 44 | |
| Postoperative hospital stay (day) | Median (range) | | 15 (10–29) | 8 (5–108) | <0.001 |

*Sarcopenia was defined as a low skeletal muscle mass index. †Visceral obesity was defined as visceral fat with an area of ≥100 $cm^2$ at the level of the third lumbar vertebra. ‡Sarcobesity was defined as sarcopenia with visceral obesity. §The right-side colon includes the cecum, ascending colon, and transverse colon, and the left-side colon includes the descending colon, sigmoid colon, and rectum. ‖According to the classification by the Union for International Cancer Control.

POI, postoperative paralytic ileus; BMI, body mass index; PS, performance status; ASA-PS, American Society of Anesthesiologists physical status; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; IN/OUT balance, intraoperative in-out balance per body weight; EA, epidural anesthesia

an independent predictor of POI. However, the body component was not examined in these studies. Recently, Pedrazzani et al.[44] reported that sarcobesity, not visceral obesity, is associated with POI. However, sarcopenia itself was not investigated in their study. Similarly, in the present study, high BMI and visceral adiposity were not associated with the incidence of POI, whereas sarcobesity and sarcopenia were independent risk factors for POI. The incidence of POI among patients with sarcobesity was 75.0%, which was higher than that among patients with sarcopenia. One possible reason is that excess adiposity exacerbates sarcopenia by increasing the infiltration of fat into the muscle and lowering physical function, especially in older people[45]. In addition, in patients with high adiposity, surgical manipulation

**Table 2.** Univariate and Multivariate Analysis of the Risk Factors for POI.

| Factors | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | Odds ratio (95% CI) | *p* value | Odds ratio (95% CI) | *p* value |
| Age | | 0.0431 (0.0025–0.7542) | 0.032 | 0.8830 (0.7260–1.0738) | 0.1961 |
| Sex | Female/Male | 0.4032 (0.1148–1.4169) | 0.223 | | |
| BMI | | 1.2100 (0.0559–26.1707) | 0.903 | | |
| PS | 0, 1/2, 3 | 1.4444 (0.1721–12.1208) | 1 | | |
| ASA-PS | <3/≥3 | 0.7732 (0.1541–3.8783) | 0.669 | | |
| Previous laparotomy | Yes/No | 0.7778 (0.2317–2.6108) | 0.756 | | |
| PNI | | 2.1419 (0.1419–32.3313) | 0.585 | | |
| CAR | | 3.4624 (0.0035–3416.889) | 0.687 | | |
| NLR | | 9.6966 (0.2348–400.4109) | 0.185 | | |
| PLR | | 26.0699 (0.3496–1943.884) | 0.102 | 1.0040 (0.9916–1.0167) | 0.5149 |
| LMR | | 2.0548 (0.02062–204.7582) | 0.754 | | |
| Sarcopenia | | 53.842 (6.5555–442.2179) | <0.001 | 19.0710 (1.9300–188.4928) | 0.0031 |
| Visceral obesity | | 0.5555 (0.1680–1.8367) | 0.359 | | |
| Sarcobesity | | 55.000 (9.1012–332.3738) | <0.001 | 12.3564 (1.3359–114.2926) | 0.0152 |
| Tumor location | Right side/Left side | 0.7444 (0.2115–2.6199) | 0.762 | | |
| Lymph node dissection | With/without apical node | 1.3636 (0.1533–12.1287) | 0.568 | | |
| Operative time | | 0.1074 (0.0070–1.6392) | 0.117 | 0.9928 (0.9834–1.0022) | 0.0941 |
| Blood loss | | 0.3137 (0.0048–20.5121) | 0.615 | 1.0021 (0.9945–1.0097) | 0.5475 |
| Transfusion | | 1.4000 (0.2775–7.06137) | 0.653 | | |
| Anesthesia | With/without EA | 1.1481 (0.2916–4.5213) | 1 | | |
| IN/OUT balance (mL/kg) | | 0.3852 (0.0247–6.0041) | 0.509 | | |
| Pathological stage | I, II/III, IV | 0.3235 (0.0918–1.1391) | 0.121 | 1.2713 (0.2310–6.9969) | 0.783 |

POI, postoperative paralytic ileus; CI, confidence interval; BMI, body mass index; PS, performance status; ASA-PS, American Society of Anesthesiologists physical status; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; EA, epidural anesthesia; IN/OUT balance, intraoperative in-out balance per body weight; EA, epidural anesthesia.

can easily induce inflammation through adipokines, which induce inflammatory cytokines, leading to POI[27,44].

This study has several limitations. First, this was a retrospective small-sized study based on patients' medical records. Second, sarcopenia was defined only by the SMI calculated via computed tomography, not using actual muscle functions such as walking speed and grip strength[46]. Therefore, the sarcopenia examined in this manuscript might be different from real sarcopenia. Third, the pathophysiological mechanism of the association between sarcopenia and POI was not investigated and therefore remains unclear.

In conclusion, POI is associated with preoperative sarcopenia and sarcobesity in advanced-age patients undergoing laparoscopic colorectal surgery, and assessment of the body composition might be helpful in predicting POI in these patients.

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Conflicts of Interest
There are no conflicts of interest.

Author Contributions: Takaaki Fujimoto performed the data acquisition, analysis, and interpretation and wrote the paper. Tatsuya Manabe performed the data acquisition and revised the manuscript. Yasuhiro Tsuru, Hiroshi Kitagawa, Keiichiro Okuyama, and Shin Takesue performed the data acquisition. Kumpei Yukimoto identified and quantified the image analysis. Keita Kai checked the histopathological assessment. Hirokazu Noshiro revised and finally approved the manuscript.

Approval by Institutional Review Board (IRB): This retrospective study was conducted in a single institution. The study was approved by the Ethics Committee of Saga University (Number: 2019-504).

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