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Impact of Sarcopenia on One-year Survival in Patients Undergoing Elective Resection for Colorectal Cancer

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ABSTRACT

Purpose: Many factors, including body composition, can influence the prognosis of colorectal cancer (CRC). This study aimed to investigate the effect of sarcopenia on survival in patients subjected to elective resection of colorectal cancer.
Methods: The study included 93 patients with adenocarcinoma of the colon or rectum scheduled for elective resection. Sarcopenia was diagnosed by CT scan measurement of the total cross-sectional area of the psoas muscles (TPA).
Results: Sarcopenia was detected in 29 patients (31.2%). The only factor associated with sarcopenia was tumor size ($p < 0.001$). Sarcopenia was associated with worse overall survival (OS) (50.4% vs. 86.7% in non-sarcopenic patients, $p < 0.001$, HR: 5.58, 95%CI: 2.19-14.24). Sarcopenia was associated with worse disease free survival (47.7% vs. 77.1% in non-sarcopenic patients, $p = 0.004$, HR: 3.37, 95%CI: 1.53-7.43).
Conclusion: Sarcopenia is an independent factor negatively affecting the overall and disease-free survival of patients surgically treated for colorectal cancer.
Keywords: sarcopenia, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second cause of cancer mortalities all over the world (1,2). In Egypt, CRC ranked 8th among commonly diagnosed cancers (3). Surgical resection is the main treatment modality of non-metastatic CRC, based on resecting tumor mass and eliminating draining lymph nodes (4). The prognosis of CRC is influenced by many factors including, tumor stage, potentially curative surgery, grade, histology, and location, among many others (5). Nevertheless, the oncological outcome may also be negatively affected by surgical complications and patient-

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related factors (6), especially body composition and functional status (7).

Sarcopenia was demonstrated as a risk factor for reduced survival in many cancers (8-10) including CRC (11,12). However, other studies did not demonstrate this relationship (13). Sarcopenia is defined by diminished muscle strength, quantity or quality, and physical performance (14). Moreover, cancer is frequently associated with weight loss and reduction of muscle mass (15).

The goal of this study was to investigate the effect of sarcopenia on survival in patients subjected to elective resection of colorectal cancer.

PATIENTS AND METHODS

This study included a consecutive sample of eligible patients with adenocarcinoma of the colon or rectum scheduled for elective colorectal resection from September 2014 to April 2017. The diagnosis was confirmed upon pathological examination of biopsy specimens. As judged by the relevant clinical specialists, stage 4 cases with resectable liver and lung metastases were included. Informed consent was taken from all cases. The study protocol adheres to the ethical guidelines of the 1975 Declaration of Helsinki. The ethical committee of Cairo University Hsopitals approved the protocol (N-89-2024)

According to our institutional protocol, patients with rectal cancer received neoadjuvant chemo- and radiotherapy with postoperative adjuvant chemo- and radiotherapy as well. On the other hand, stage II, III, and IV colonic cancer received postoperative adjuvant chemotherapy, while some selected cases of stage IV colon cancer received radiotherapy. In patients with stage 0 disease, colonoscopic resection was inadequate due to inadequate surgical margins, so we proceeded to surgery.

Patients were excluded if they received neoadjuvant therapy for colon cancer, had an operation to manage a disease other than colorectal cancer, had widespread unresectable metastatic disease, or had an emergency operation.

Demographic, anthropometric, and clinical data encompassing height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) score, operative procedure, American Joint Committee on Cancer (AJCC) TNM stage (16), duration of hospital stay (days), postsurgery complications, and readmission to the hospital within 30 days were registered. All cases were followed up for a minimum of 12 months after resection.

Sarcopenia Measurement by CT Scan

The total cross-sectional area of the psoas muscles (total psoas area, TPA) was assessed employing a manual technique at the level of the L3 vertebra during the preoperative CT scan (17). To confirm standardization, the precise level of assessment was determined as the CT slice in which both L3 transverse processes were most clearly visible. The area was delineated with a free-hand drawing method on Picture Archiving and Communication System (PACS) software (*fig. 1*). The contour of each psoas muscle was delineated. The area of each was calculated and summated to provide the TPA (mm^2). The TPA was then standardized for patient height using the formula: TPA (mm^2)/height (m^2). This provided the total psoas index (TPI) for each patient.

For the purpose of this work, the threshold numbers defined for the diagnosis of sarcopenia are the same as those described by Prado et al. in their widely cited research (18); 524 mm^2/m^2 for males and 385 mm^2/m^2 for females. All subjects with a TPI below this value were considered sarcopenic. Sixteen scans were randomly chosen and assessed for TPI by blindly competent physicians to ensure technique reliability to estimate inter- and intra-class correlation coefficients (ICCC). The ICCC thresholds for inter and intra-class reliability were 0.93 and 0.98, respectively.

Statistical Methods

Statistical analysis was done using IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY, USA). Chi-square test was employed to define the relation between qualitative data. For quantitative data,

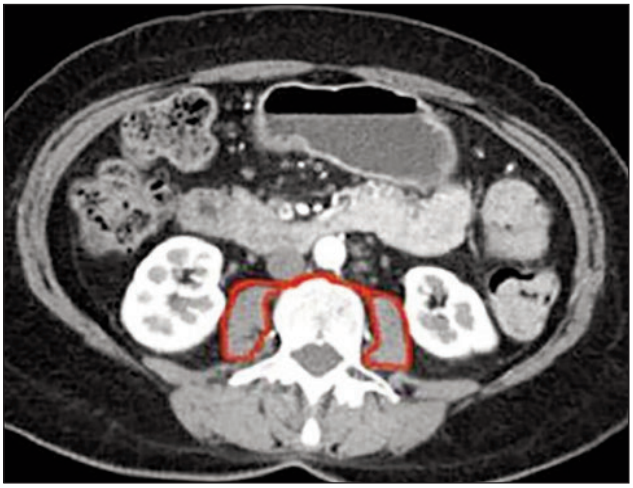

Figure 1 - Total psoas area (TPA) at the level of L3 with both vertebral spines visible

comparison between two arms was made using independent sample t-test or Mann-Whitney test. Survival analysis was done employing Kaplan-Meier method, and contrast between two survival curves was done using log-rank analysis. Multivariate analysis was done using Cox proportional-hazards model for factors affecting survival on univariate analysis. Hazard ratio (HR) with its 95% confidence interval (CI) was used for hazard estimation. A p-value < 0.05 was viewed as significant.

RESULTS

Throughout the research time, 132 patients underwent elective colorectal surgery; 93 (70.4%) were eligible for inclusion in the study (*fig. 2*).

Table 1 shows the baseline characteristics of the studied group. Eight patients had stage 4 tumors; however, they had resectable lung/liver metastases, so they were operated upon with curative intent. Mucinous adenocarcinoma was the most encountered pathological type, followed by Signet ring cell adenocarcinoma. Most patients (78.5%) present with stage II or II disease. Surgical resection succeeded in achieving an R0 resection margin in 88.2% of cases. Neoadjuvant chemoradiotherapy and adjuvant radiotherapy were used for patients with rectal cancer only. A single patient with stage IV colon cancer did not receive adjuvant chemotherapy. *Table 2* shows the clinical and laboratory characteristics of the studied group.

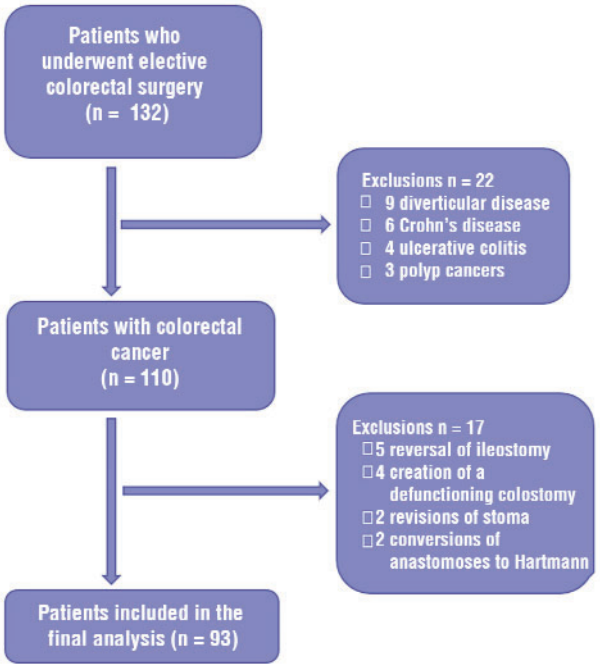

Figure 2

Table 1 - Baseline characteristics of the studied group (n=93)

	Value
Age (years)	61.4±11.3
< 65	47 (50.5%)
≥ 65	46 (49.5%)
Sex (male/female)	57/36
Smoking	24 (25.8%)
Body mass index (kg/m^2)	23.1±5.1
Underweight	30 (32.3%)
Normal	34 (36.6%)
Overweight	20 (21.5%)
Obese	9 (9.7%)
Diabetes mellitus	22 (23.7%)
Hypertension	62 (66.7%)
Coronary artery disease	8 (8.6%)
ASA grade (I/II/II)	10/40/43

Data are expressed as mean±SD, or Number (%)

Table 2 - Clinical and Laboratory characteristics of the studied group (n=93)

		Value
Site of cancer	Colon/Rectum	47/46
Pathological type	Mucinous adenocarcinoma	21 (22.60%)
	Signet ring cell adenocarcinoma	17 (18.30%)
	Medullary carcinoma	12 (12.90%)
	Serrated	11 (11.80%)
	Micropapillary	9 (9.70%)
	Undifferentiated	9 (9.70%)
	Spindle cell	7 (7.50%)
	Adenosquamous	7 (7.50%)
Tumor stage	Stage 0	4 (4.3%)
	Stage I	8 (8.6%)
	Stage II	37 (39.8%)
	Stage III	36 (38.7%)
	Stage IV	8 (8.6%)
Mass size	< 2 cm	37 (39.8%)
	2-4 cm	31 (33.3%)
	> 4 cm	25 (26.9%)
Grade	1	13 (14.0%)
	2	29 (31.2%)
	3	28 (30.1%)
	4	23 (24.7%)
Resection margin	R0	82 (88.2%)
	R1	11 (11.8%)
Neoadjuvant treatment		46 (49.5%)
Adjuvant chemotherapy		92 (98.9%)
Adjuvant radiotherapy		49 (52.7%)
Length of hospital stay (days)		8.9±2.4
In-hospital Complications		31 (33.3%)
Readmission within 30 days		14 (15.1%)
Hemoglobin concentration (gm/dL)		11.0±1.0
International normalized ratio		1.1±0.1
Serum creatinine (mg/dL)		1.1±0.2
Alanine aminotransferase (U/L)		36.5±8.1

Data are expressed as Number (%), mean±SD

Sarcopenia was detected in 29 patients (31.2%). *Table 3* shows the relationship between sarcopenia diagnosis and patients' and disease factors. Sarcopenia was not related to the type of cancer, stage, grade, or treatment modalities (*table 4*). The only factor associated with sarcopenia was tumor size; larger tumors were associated with sarcopenia ($p < 0.001$). One quarter of the patients developed in-hospital complications in the form of anastomotic leak (n=6), dehydration (n=4), peritoneal infections (n=4), pulmonary embolism (n=3), surgical site infection (n=3), ileus (n=2), chest infection (n=1), and bleeding (n=1). There was no relationship between sarcopenia and in-hospital complications ($p = 0.792$).

The cumulative overall survival (OS) proportion of the whole group at one year was 76.5%. *Table 4* shows factors affecting OS. Sarcopenia was associated with worse survival (50.4% vs. 86.7% in non-sarcopenic patients, $p < 0.001$). Other factors affecting OS were coronary artery disease ($p = 0.015$), disease stage ($p = 0.033$), tumor size ($p = 0.001$), grade ($p = 0.043$), and resection margin status ($p = 0.020$).

On multivariate analysis, sarcopenia, coronary artery disease, high grade, and positive resection margin were independent factors associated with worse OS (*table 5*). Sarcopenia carried a nearly 6-fold higher hazard of death in the first year.

During the follow-up period, seven patients developed local recurrences. Therefore, the disease-free survival (DFS) was 68.6% at one year. *Table 6* shows the factors affecting DFS. Almost the same factors worsened DFS as OS. Sarcopenia was associated with worse DFS (47.7% vs. 77.1% in non-sarcopenic patients, $p = 0.004$). DFS was worsened by advanced stage ($p = 0.016$), larger tumors ($p = 0.031$), higher grade ($p = 0.0.31$), positive resection margin ($p = 0.018$), and in-hospital complications ($p = 0.001$).

On multivariate analysis, sarcopenia, advanced stage, high grade, and positive resection margin were independent factors associated with worse DFS (*table 7*). Sarcopenia carried over a 3-fold higher hazard of recurrence or death at one year.

Table 3 - Comparison between patients with and without sarcopenia regarding patients' and disease characteristics and in-hospital complications

		Sarcopenic Group n=29	Non-Sarcopenic Group n=64	p-value
Age (years)	< 65	15 (31.9%)	32 (68.1%)	0.878
	≥ 65	14 (30.4%)	32 (69.6%)	
Sex	Male	19 (33.3%)	38 (66.7%)	0.573
	Female	10 (27.8%)	26 (72.2%)	
Smoking	Yes	9 (37.5%)	15 (62.5%)	0.438
	No	20 (29.0%)	49 (71.0%)	
Diabetes mellitus	Yes	9 (40.9%)	13 (59.1%)	0.260
	No	20 (28.2%)	51 (71.8%)	
Hypertension	Yes	9 (29.0%)	22 (71.0%)	0.752
	No	20 (32.3%)	42 (67.7%)	
Coronary artery disease	Yes	3 (37.5%)	5 (62.5%)	0.687
	No	26 (30.6%)	59 (69.4%)	
Site of cancer	Colon	15 (31.9%)	32 (68.1%)	0.878
	Rectum	14 (30.4%)	32 (69.6%)	
Tumor stage	0, I, II	14 (28.6%)	35 (71.4%)	0.566
	III, IV	15 (34.1%)	29 (65.9%)	
Grade	1	5 (38.5%)	8 (61.5%)	0.894
	2	9 (31.0%)	20 (69.0%)	
	3	9 (32.1%)	19 (67.9%)	
	4	6 (26.1%)	17 (73.9%)	
Mass size	< 2 cm	8 (21.6%)	29 (78.4%)	< 0.001
	2-4 cm	5 (16.1%)	26 (83.9%)	
	> 4 cm	16 (64.0%)	9 (36.0%)	
Neoadjuvant chemotherapy	Yes	14 (30.4%)	32 (69.6%)	0.878
	No	15 (31.9%)	32 (68.1%)	
Adjuvant radiotherapy	Yes	14 (28.6%)	35 (71.4%)	0.566
	No	15 (34.1%)	29 (65.9%)	
In-hospital complications	Yes	21 (72.4%)	48 (75.0%)	0.792
	No	8 (27.6%)	16 (25.0%)	

Data are expressed as Number (%)

Table 4 - Factors associated with overall survival at one year in the studied group

		n	Events	Cumulative Survival Proportion (%)	p-value
Sarcopenia	Yes	29	12	50.4	0.001
	No	64	8	86.7	
Site	Colon	47	9	79.5	0.651
	Rectum	46	11	74.1	
Age (years)	≥ 65	46	12	72.0	0.309
	< 65	47	8	80.4	
Sex	Male	57	11	78.0	0.523
	Female	36	9	73.8	
Hypertension	Yes	31	6	80.4	0.693
	No	62	14	74.4	
Diabetes Mellitus	Yes	22	6	72.1	0.386
	No	71	14	78.2	
Coronary artery disease	Yes	8	4	31.3	0.015
	No	85	16	80.1	
Stage	0, I, II	49	6	87.7	0.033
	III, IV	44	14	65.3	
Mass Size	≤ 4 cm	68	9	86.4	0.001
	> 4 cm	25	11	49.0	
Grade	I, II	42	5	88.0	0.043
	III, IV	51	15	67.3	
Neoadjuvant Therapy	Yes	46	11	74.1	0.561
	No	47	9	79.5	
Adjuvant Radiotherapy	Yes	49	12	72.6	0.456
	No	44	8	81.3	
Resection margin	R0	82	15	79.4	0.020
	R1	11	5	54.5	
In-hospital complications	Yes	31	9	70.7	0.148
	No	62	11	79.9	

Table 5 - Multivariate Cox Proportional Hazard Model for factors affecting overall survival

	B	p-value	HR	95% CI for HR	
				Lower	Upper
Sarcopenia	1.719	< 0.001	5.58	2.19	14.24
Coronary artery disease	1.873	0.005	6.51	1.77	23.92
Grade	1.040	0.048	2.83	1.01	7.93
Resection margin	1.132	0.033	3.10	1.09	8.80

B: Regression coefficient, HR: Hazard ratio, CI: Confidence interval

DISCUSSION

This study demonstrated a negative impact of sarcopenia on short-term outcomes in patients surgically treated for colorectal cancer. Sarcopenic patients had reduced 1-year overall and disease-free survival. On multivariate analysis, sarcopenia was an independent factor associated with worse OS (HR: 5.6, 95%CI: 2.2-14.2), in addition to coronary artery disease, higher grade, and positive resection margin. Sarcopenia was also an independent predictor of worse DFS (HR: 3.4, 95%CI: 1.5-7.4) combined with advanced stage, high grade, and positive resection margin.

We detected sarcopenia 31.2% of the current series with no significant difference between the colon and rectal cases (p = 0.878). The prevalence of sarcopenia in surgically treated CRC patients varied from 12% to 60% (19–22). Huang et al. (19) reported the lowest prevalence of 11.9% in a cohort of 142 patients with CRC stages I to III. In a group of 259 patients with stage IV CRC, 16% of the patients had sarcopenia (23). Reisinger et al. (24) reported a high prevalence of 47.7% in 310 patients with CRC over 70 years old. In a large cohort of 3262 patients with stage I-III CRC, sarcopenia was highly common (42.4%) (25). In a recent systematic review, the

Table 6 - Factors associated with recurrence-free survival at two years in the studied group

		n	Events	Cumulative Survival Proportion (%)	p-value
Sarcopenia	Yes	29	13	47.7	0.004
	No	64	13	77.1	
Site	Colon	47	13	71.0	0.937
	Rectum	46	13	67.3	
Age (years)	≥ 65	46	14	65.8	0.597
	< 65	47	12	71.2	
Sex	Male	57	14	72.9	0.405
	Female	36	12	61.9	
Hypertension	Yes	31	7	77.4	0.413
	No	62	19	63.8	
Diabetes Mellitus	Yes	22	6	72.1	0.896
	No	71	20	68.1	
Coronary artery disease	Yes	8	4	31.3	0.065
	No	85	22	71.5	
Stage	0, I, II	49	8	82.6	0.016
	III, IV	44	18	55.1	
Mass Size	≤ 4 cm	68	15	75.6	0.031
	> 4 cm	25	11	49.0	
Grade	I, II	42	7	81.6	0.031
	III, IV	51	19	58.2	
Neoadjuvant CTH	Yes	46	13	67.3	0.937
	No	47	13	71.0	
Adjuvant RTH	Yes	49	15	64.3	0.557
	No	44	11	74.3	
Resection margin	R0	82	20	72.1	0.018
	R1	11	6	43.6	
In-hospital complications	Yes	31	15	45.1	0.001
	No	62	11	79.9	

Table 7 - Multivariate Cox Proportional Hazard Model for factors affecting disease-free survival

	B	p-value	HR	95% CI for HR	
				Lower	Upper
Sarcopenia	1.214	0.003	3.37	1.53	7.43
Stage	1.423	0.003	4.15	1.64	10.49
Grade	1.338	0.005	3.81	1.51	9.62
Resection margin	1.695	0.001	5.45	1.96	15.16

B: Regression coefficient, HR: Hazard ratio, CI: Confidence interval

pooled prevalence of sarcopenia was 37% in 18,891 with CRC (26).

In the current series, the only factor associated with sarcopenia was tumor size; larger tumors were more commonly associated with sarcopenia ($p < 0.001$). No significant relationship was found between sarcopenia and age. In the literature, the results are controversial about this association. Kroenke et al. (25) found that sarcopenia was more common in older patients (>70-80 years) than those < 50 years. Nakanishi et al. (20) reported a higher prevalence of sarcopenia in males and those with low body mass index, but not with old age.

In the present study, sarcopenia did not show a significant association with postoperative complications. This finding differs from what is reported in the most recent systematic review (26). The authors reported a pooled association from 23 studies between sarcopenia and a higher risk of postoperative complications (OR: 1.84; 95%CI: 1.35–2.49). In a recent study, sarcopenia was noticed as a predictor of a higher probability of major complications ($p = 0.003$) (27). Aro et al. (28) showed an association between sarcopenia and higher rates of pneumonia and cardiorespiratory complication, while there was no difference in other complications.

Sarcopenia was associated with worse OS (50.4% vs.

86.7% in non-sarcopenic patients, p < 0.001) and DFS (47.7% vs. 77.1% in non-sarcopenic patients, p = 0.004) in the present study. In a retrospective study of 220 patients with stage I-III CRC, sarcopenia was associated with a poor outcome. Five-year OS and RFS were significantly shorter in sarcopenic patients (OS, 68 vs. 85%, p = 0.015; RFS, 56 vs. 79 %, p = 0.006;). On multivariate analysis, sarcopenia was an independent predictor of OS and RFS (29). Another study demonstrated significantly lower OS in sarcopenic patients, while the recurrence-free survival (RFS) rate was not different compared to patients with no sarcopenia (30).

A systematic review of 12 studies involving 5337 patients with CRC showed that sarcopenia predicted a decreased OS and DFS (31). A more recent systematic review of 44 studies revealed significantly shorter OS (HR: 1.83; 95% CI: 1.57-2.14) and DFS (HR: 1.55; 95% CI: 1.29-1.88) in sarcopenic as compared with non-sarcopenic patients (26).

Previous studies reported that sarcopenia and systemic inflammation are independent factors for a decreased OS and RFS. Their combination is a predictor of higher risk (32). A more recent study found that sarcopenic obesity and inflammatory status were independent factors affecting OS (30). Sarcopenia combined with inflammation almost doubled the mortality risk of OS in patients with non-metastatic CRC (33). Inflammation was shown to be stage-dependent (28,34). Decreased skeletal muscle density promotes systemic inflammation, which accelerates tumor cell proliferation leading to worse survival (35).

The mechanism of how sarcopenia affects survival of cancer patients remains undetermined. It appears to be multifactorial. Systemic inflammation is known to increase the risk of cancer (36). It was suggested that inflammation is enhanced by muscle breakdown. In CRC, markers of systemic inflammation are correlated with elevated circulating cytokines involved in activating several catabolic pathways. Tumor necrosis factor inhibits skeletal myocyte differentiation and promotes muscle atrophy, and interleukin-6 can reduce muscle protein synthesis. The tumor causes low-grade systemic inflammation that may lead to local inflammation in the muscle. This increases systemic inflammation and muscle degradation (32).

The association of sarcopenia with cancer mortality is suggested to run through its direct and indirect role in cancer management. Sarcopenia is a symbol of cachexia (37,38). It reduces tolerance to anti-cancer treatments (39,40). It was found as an independent factor of cancer treatment toxicity, including chemotherapy targeted therapy (39,41). Reduced muscle mass is shown to be associated with abnormal nutritional status, which is associated with increased mortality (42). Increased mortality may also be due to decreased immune function due to the reduced amino acid substrate required for stress response. Altered voluntary muscles and reduced function may lead to impaired physiologic homeostasis as these muscles are necessary to generate force and facilitate movement (43,44).

The study is not with out limitaions. Firstly, the participation of more male patients than females might affect the study results. Other limitations include being a non-randomized controlled trial. Also, further studies are warranted to elucidate the long-term effect (more than one year) of sarcopenia on survival after resection for colorectal cancer

Despite the above, to our knowledge, only a few studies focused on the impact of sarcopenia after elective colorectal cancer surgery. Furthermore, the reasonable sample size of the current study is one of the strengths of this study. This article adds momentum to the growing literature by suggesting that sarcopenia can considerably impact survival rates following resection of colorectal cancer. This work may provide innovative perspectives to classify patient's pre-operative risk, allowing targeted approaches such as rehabilitation to be adopted to modify sarcopenia and enhance long-term outcomes for these subjects.

CONCLUSIONS

We can conclude that in patients subjected to curative surgical treatment of colorectal cancers, sarcopenia is found in nearly one-third of cases. It had a negative impact on short-term outcomes in terms of one-year survival. Sarcopenic patients had reduced one-year overall and disease-free survival. Sarcopenia was an independent factor associated with worse OS with coronary artery disease, higher grade, and positive resection margin. It was also an independent predictor of worse disease-free survival combined with advanced stage, high grade, and positive resection margin. It is recommended to investigate the effect of sarcopenia on the long-term outcomes of these patients.

Conflict of Interest

No interests to declare

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, (Salman Ahmed), upon reasonable request.

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