The Journal of Nutrition, Health and Aging 28 (2024) 100243

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Original Article

Varying clinical relevance of sarcopenia and myosteatosis according to age among patients with postoperative colorectal cancer

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ARTICLE INFO

Keywords:
Aging
Colorectal cancer
Older persons
Sarcopenia
Myosteatosis

ABSTRACT

Objectives: The present retrospective study reviewed the association among sarcopenia, myosteatosis, and overall survival (OS) in patients with postoperative colorectal cancer (CRC) with regard to age.
Design: A retrospective study was conducted with a five-year follow-up.
Setting: Data from all patients with CRC, who underwent surgery between February 2005 and April 2014, were reviewed.
Participants: Data from 1053 patients (622 male [59.1%], 431 female [40.9%]; mean [± SD] age, 62.8 ± 11.8 years) were analyzed.
Measurements: Patients were divided into three groups according to age: ≤50, 51–74, and ≥75 years. Data, including perioperative parameters, and the presence of sarcopenia and myosteatosis according to skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD), respectively, were collected. Sarcopenia was evaluated using CT by calculating the SMI at the L3 level by dividing the area of the skeletal muscle by height squared (cm^2/m^2). SMD was also calculated using CT at the L3 level, but by evaluating fat attenuation according to Hounsfield units (HU).
Results: Patient allocation according to age group was as follows: ≤50 years, n = 147 (14.0%); 51–74 years, n = 742 (70.5%); and ≥75 years, n = 164 (15.5%). The presence of sarcopenia and myosteatosis were statistically significant with increasing age ($P = 0.004$ and $P < 0.001$, respectively). The 51–74 years age group exhibited a significant association in OS for myosteatosis ($P < 0.001$) while the ≥75 years group was significantly associated with sarcopenia ($P = 0.04$) with regard to OS. Multivariable analysis also revealed a statistically significant association between myosteatosis in the 51–74 years age group ($P = 0.033$) and sarcopenia in the ≥75 years age group ($P = 0.005$) even when adjusted for recurrence status.
Conclusion: Different age groups exhibited significantly variable skeletal muscle indices. Although an abundance of irrefutable results demonstrated a correlation between CT-defined sarcopenia, myosteatosis, and clinical prognosis, data regarding age-dependent correlations are scarce. Results of this study demonstrated that sarcopenia and myosteatosis did not influence the prognosis of young patients with postoperative CRC (≤50 years of age), inferring the existence of significantly different skeletal muscle-related parameters according to age. Patients over 75 years of age showed significant association with sarcopenia while those in the 51–74 age group displayed significant link to myosteatosis. Clinicians should consider the impact of sarcopenia and myosteatosis on patient prognosis and should also be aware that the effect may differ according to patient age.

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with an estimated projection of 2.2 million new cases and 1.1 million deaths by 2030 [1]. The number of newly diagnosed CRC cases is increasing, and the trend toward an increase in patients with early CRC (ECRC) is ever more threatening [2]. The pathogenesis of conventional CRC is often the case in the older persons, while that for ECRC is believed to be different. Conventional CRC often follows a well-characterized sequence known as adenoma-carcinoma sequence where an adenomatous polyp gradually develops into CRC over a long period of time [3]. Although similar pathogenesis may apply to ECRC, higher proportion of cases are genetic causes, such as Lynch syndrome and familial adenomatous polyposis (FAP) [4]. A different molecular profile with

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http://doi.org/10.1016/j.jnha.2024.100243
Received 18 January 2024; Received in revised form 3 April 2024; Accepted 14 April 2024
Available online 20 April 2024

higher proportion of poor histologic features are more prevalent in ECRC leading to worse patient outcome. Studies on sarcopenia and myosteatosis in individuals diagnosed with CRC have predominantly focused on the elderly, potentially diminishing the importance of age-related differences. However, considering the diverse age range of cancer patients, the impact of these conditions on prognosis may vary with age. While the influence of sarcopenia and myosteatosis on patient outcomes is somewhat recognized, we hypothesized that there might be clinical differences associated with age, especially in the context of the rising incidence of colorectal cancer in young patients.

Sarcopenia is a well-established concept often used in discussions about the natural aging process to discuss the progressive loss of skeletal muscle mass and function [5]. The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as "loss of skeletal muscle mass with either one of low muscle strength or low physical performance" [6]. In its diagnostic criterion, 3 factors were relevant to the diagnostic criteria: muscle mass, muscle strength, and physical performance. After a decade of research investigating sarcopenia, a revised definition emerged in which muscle strength and physical performance remained unchanged while muscle mass was amended to muscle quantity and quality. Moreover, traditionally a disease of the older persons, the development of sarcopenia is now recognized to begin earlier in life with multifactorial contributing factors other than age [7,8]. Consequently, its effect in CRC has been rigorously studied [9–12]. CT-defined sarcopenia in cancer patients have been researched laboriously and a crucial meta-analysis evaluating the association between SMI and clinical outcomes was published by Shachar et al. in 2016 [13]. Reviewing 37 studies, sarcopenia measured as skeletal muscle index (SMI) was a significant prognostic value in predicting poor overall survival (OS) in all cancer types (Hazard Ratio, HR 1.437; 95% Confidence Internal, CI 1.32–1.56; $P <$ 0.001). He et al. focused on colorectal cancer [14]. Reviewing 20 studies, sarcopenia measured as SMI was present in 34% of CRC patients, and presence of sarcopenia led to poor OS, DFS, and cancer-specific survival. The interest in the relationship between sarcopenia and CRC is ever more growing.

Within the definition of sarcopenia, low muscle quality has been added to the revised definition [15]. Myosteatosis, also known as infiltration of fat into skeletal muscle, is often used clinically to evaluate skeletal muscle quality. Similar to sarcopenia, according to the study carried out by our group, a systematic review and meta-analysis on CT-defined myosteatosis in CRC patients also revealed a significant increase in overall mortality in patients with myosteatosis in both univariable (HR 1.38; 95% CI 1.21–1.58; $P < 0.00001$) and multivariable (HR 1.55; 95% CI 1.23–1.96; $P <$ 0.00001) analyses [16]. Although myosteatosis is less researched, evaluating muscle quality can relate to muscle function and may more accurately reflect patient condition.

Although prevention is key, promoting health and prolonging life are also among the 3 pillars of global health. With an expected patient population of 2 billion individuals ≥60 years of age by 2050, the projected prevalence of CRC will be overwhelming [2]. Numerous studies have confirmed the prognostic value of sarcopenia and myosteatosis in patients with cancer, the mechanism by which these factors influence patient prognosis remains to be determined [13,16–20]. Is it merely a process of aging or does it activate cancer aggressiveness? There is currently an overwhelming consensus that sarcopenia and myosteatosis no longer applies only to the older patients. As such, the present study aimed to investigate the prognostic impact(s) of sarcopenia and myosteatosis in different age groups.

2. Materials and methods

2.1. Patient selection and stratification

Data from patients, who underwent colorectal surgery and were diagnosed with stage I–III postoperative CRC between February 2005 and April 2014 at the Gangnam Severance Hospital, Yonsei University College of Medicine (Seoul, Korea), were reviewed. We excluded patients who did not undergo surgical resection for CRC, and all patients included underwent computed tomography (CT) prior to surgery and were reviewed postoperatively. Of the 1629 patients considered, patients with histologically confirmed neuroendocrine tumors, gastrointestinal stromal tumors, or other non-adenocarcinoma histopathologies were excluded. Patients in whom the primary location of the tumor was in the appendix or anus were also excluded, as were those whose prognosis could be impacted or biased, such as a family history of CRC, concomitant Crohn's or ulcerative colitis, double primary cancer, and non-elective procedures (n = 466). Only patients in whom CT was performed within 2 months before surgery (n = 14 excluded) and had available data to calculate skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) (n = 96 excluded) were included.

After applying these criteria, data from 1053 patients were retrospectively reviewed. Patients were categorized into three age groups: ≤50, 51–74, and ≥75 years.

2.2. Measurement of sarcopenia and myosteatosis

Sarcopenia was evaluated using CT by calculating the SMI at the L3 level by dividing the area of the skeletal muscle by height squared (cm^2/m^2). SMD was also calculated using CT at the L3 level, but by evaluating fat attenuation according to Hounsfield units (HU). There are numerous cut-off values for sarcopenia. Many different thresholds for defining low SMI and SMD in patients with cancer have been investigated [21]. Among the various cut-off values, the value suggested by Martin et al. [22], in which patients were divided according to body mass index (BMI [kg/m^2]) and sex for both SMI and SMD, were selected. For patients with BMI < 25 kg/m^2, SMI < 43 for males and <41 for females were defined as sarcopenic. For SMD, a value <41 for both males and females was defined as myosteatosis. Similarly, in patients with a BMI > 25 kg/m^2, cut-offs for sarcopenia were <53 and <41 for males and females, respectively, and <33 for both sexes in myosteatosis.

2.3. Statistical analysis

Categorical variables were analyzed using Pearson's chi-squared test and continuous variables were analyzed using the analysis of variance (i.e., "ANOVA") test. The primary endpoint was OS, which was defined as the interval from the initial day of surgery to death from any cause or the last date of follow-up, with a limit of 5 years. Patients with OS periods >5 years were censored.

Associations between OS and clinicopathological values were analyzed using both univariable and multivariable analyses. In univariable and multivariable cox regression analyses, hazard ratio (HR) with corresponding 95% confidence interval (CI) were calculated using Cox proportional hazards modeling. Variables with $P < 0.05$ in univariable analysis were included in the multivariable analysis with backward selection of variables. Kaplan–Meier curves for OS in the 3 groups were generated. For correlation analysis of SMI and SMD by gender, Pearson correlation was used.

All analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/). Differences with $P < 0.05$ were considered to be statistically significant in all analyses.

3. Results

3.1. Patients

Data from 1053 patients (622 male [59.1%], 431 female [40.9%]; mean [± SD] age, 62.8 ± 11.8 years) were analyzed. Patient allocation in each age group was as follows: ≤ 50 years, n = 147 (14.0%); 51–74 years, n = 742 (70.5%); and ≥ 75 years, n = 164 (15.5%).

3.2. Correlation between SMI and SMD

The correlation between SMI and SMD was analyzed, and the scatter plot demonstrated a correlation coefficient (R) of 0.15 with a corresponding significant *P* value (< 0.0001) (Figure S1). On further examination, stratified according to sex, a significant correlation between the two variables was observed in both males ($P < 0.0001$) and females ($P = 0.011$). However, an interesting finding was the inverse relationship between sarcopenia and myosteatosis in females (R = -0.12).

3.3. Clinical and pathological characteristics

According to the demographic comparison of the 3 age groups, females were younger than males ($P < 0.027$), and older patients had a BMI < 25 kg/m^2 ($P < 0.001$). Carcinoembryonic antigen (CEA) levels (ng/mL), tumor size (cm), and postoperative complications were also significantly different among the 3 age groups ($P < 0.003$, $P = 0.003$, and $P < 0.001$, respectively). The proportion of patients who underwent adjuvant chemotherapy were significantly higher in the youngest (i.e., ≤50 years) age group ($P < 0.001$). Recurrence was uniformly similar between all three age groups ($P = 0.620$). Sarcopenia was more prevalent in older patients ($P = 0.004$), and a similar trend was observed for myosteatosis ($P < 0.001$). The results are shown in Table 1.

3.4. Kaplan–Meier survival curves for sarcopenia and myosteatosis according to age group

Applying the Kaplan-Meier survival curve in the ≤ 50 years age group, sarcopenia status did not impact 5-year OS (90.0% versus [vs.] 91.5%, $P = 0.97$). Similarly, myosteatosis status did not exhibit a statistically significant survival difference (5-year OS, 86.7% vs. 91.7%, $P = 0.28$) (Fig. 1A and B).

Plotting the Kaplan-Meier survival curve for 5-year OS in the 51-74 years age group, patients with sarcopenia and myosteatosis exhibited significantly worse survival than those without sarcopenia and myosteatosis (5-year OS, 82.1% vs. 88.8%, $P = 0.047$; 80.2% vs. 89.6%, $P = 0.003$, respectively) (Fig. 1C and D).

Finally, applying the Kaplan-Meier survival curve in the ≥ 75 years age group, patients with sarcopenia exhibited a significantly worse 5-year OS than those without (55.2% vs. 69.8%, $P = 0.038$). However, this did not apply to patients with myosteatosis (61.2% vs. 70.5%, $P = 0.2$) (Fig. 1E and F).

3.5. Univariable analysis

Univariable analysis of factors associated with OS was performed for each age group. The stage was divided into 2 categories: stages I and II in 1 group and stage III in the other. In the univariable analysis, stage was significant in all 3 age groups (HR 4.4 [95%CI 1.1–17], $P = 0.031$; HR 2.8 [95%CI 1.8–4.3], $P < 0.001$; and HR 2.4 [95%CI 1.4–4], $P = 0.002$, respectively). In addition, recurrence was also significantly associated with overall survival in all 3 age groups (HR 66.56 [95% CI 8.41-526.3], $P < 0.001$; HR 16.17 [95% CI 10.61−24.65], $P < 0.001$; HR 5.55 [95% CI 3.04−10.12], $P < 0.001$, respectively).

In the 51–74 years age group, BMI ≥ 25 kg/m^2 significantly reduced the risk (HR 0.58 [95%CI 0.36–0.94]; $P = 0.028$), and CEA ≥ 5 ng/mL significantly increased the risk (HR 1.75 [95%CI 1.13–2.7]; $P = 0.012$). Tumor size ≥ 5 cm was also significantly associated with OS (HR 1.9 [95% CI 1.2–2.8]; $P = 0.003$). Histological factors, such as poor histological grade (grade 3, mucinous, or signet ring cell histology, HR 2.9 [95%CI 1.7–5]; $P < 0.001$) and presence of lymphovascular invasion (HR 2.5 [95%CI 1.58–3.9], $P < 0.001$) were also a statistically significant variable in predicting OS. Non-sarcopenic and non-myosteatotic patients exhibited lower risk in this age group (HR 0.64 [95%CI 0.41–1], $P = 0.048$; HR 0.48 [95%CI 0.31–0.72], $P < 0.001$).

In the ≥ 75 years age group, additional significant factors, other than stage, were the presence of postoperative complications (HR 1.9 [95%CI

Table 1
Patient characteristics according to age group.

Variables	Categorization	≤50 (n = 147) N (%)	51–74 (n = 742) N (%)	≥75 (n = 164) N (%)	*P*
Sex	Female	75 (51.0)	292 (39.4)	64 (39.0)	0.027
	Male	72 (49.0)	450 (60.6)	100 (61.0)	
BMI (kg/m^2)	< 25	112 (76.2)	494 (66.6)	135 (82.3)	<0.001
	≥ 25	35 (23.8)	248 (33.4)	29 (17.7)	
CEA (ng/mL)	< 5	109 (74.1)	524 (70.6)	96 (58.5)	0.003
	≥ 5	31 (21.1)	182 (24.5)	63 (38.4)	
	unknown	7 (4.8)	36 (4.9)	5 (3.0)	
Tumor location	Colon	106 (72.1)	506 (68.2)	123 (75.0)	0.184
	Rectum	41 (27.9)	236 (31.8)	41 (25.0)	
Tumor size (cm)	< 5	85 (57.8)	480 (64.7)	87 (53.0)	0.011
	≥ 5	62 (42.2)	262 (35.3)	77 (47.0)	
Complications	No	133 (90.5)	576 (77.6)	107 (65.2)	<0.001
	Yes	14 (9.5)	166 (22.4)	57 (34.8)	
Histologic grade	G1 & G2	133 (90.5)	689 (92.9)	149 (90.9)	0.480
	G3 & MC & SRC	14 (9.5)	53 (7.1)	15 (9.1)	
LVI	Absent	100 (68.0)	521 (70.2)	108 (65.9)	0.361
	Present	27 (18.4)	146 (19.7)	41 (25.0)	
	unknown	20 (13.6)	75 (10.1)	15 (9.1)	
Stage	I&II	94 (63.9)	424 (57.1)	99 (60.4)	0.274
	III	53 (36.1)	318 (42.9)	65 (39.6)	
Chemotherapy	No	47 (32.0)	271 (36.5)	103 (62.8)	<0.001
	Yes	100 (68.0)	471 (63.5)	61 (37.2)	
Recurrence	No	126 (85.7)	657 (88.5)	145 (88.4)	0.620
	Yes	21 (14.3)	85 (11.5)	19 (11.6)	
Sarcopenia	Yes	30 (20.4)	179 (24.1)	58 (35.4)	0.004
	No	117 (79.6)	563 (75.9)	106 (64.6)	
Myosteatosis	Yes	15 (10.2)	192 (25.9)	103 (62.8)	<0.001
	No	132 (89.8)	550 (74.1)	61 (37.2)	

BMI: Body mass index, CEA: Carcinoembryonic antigen, MC: Mucinous adenocarcinoma, SRC: Signet-ring cell, LVI: Lymphovascular invasion.

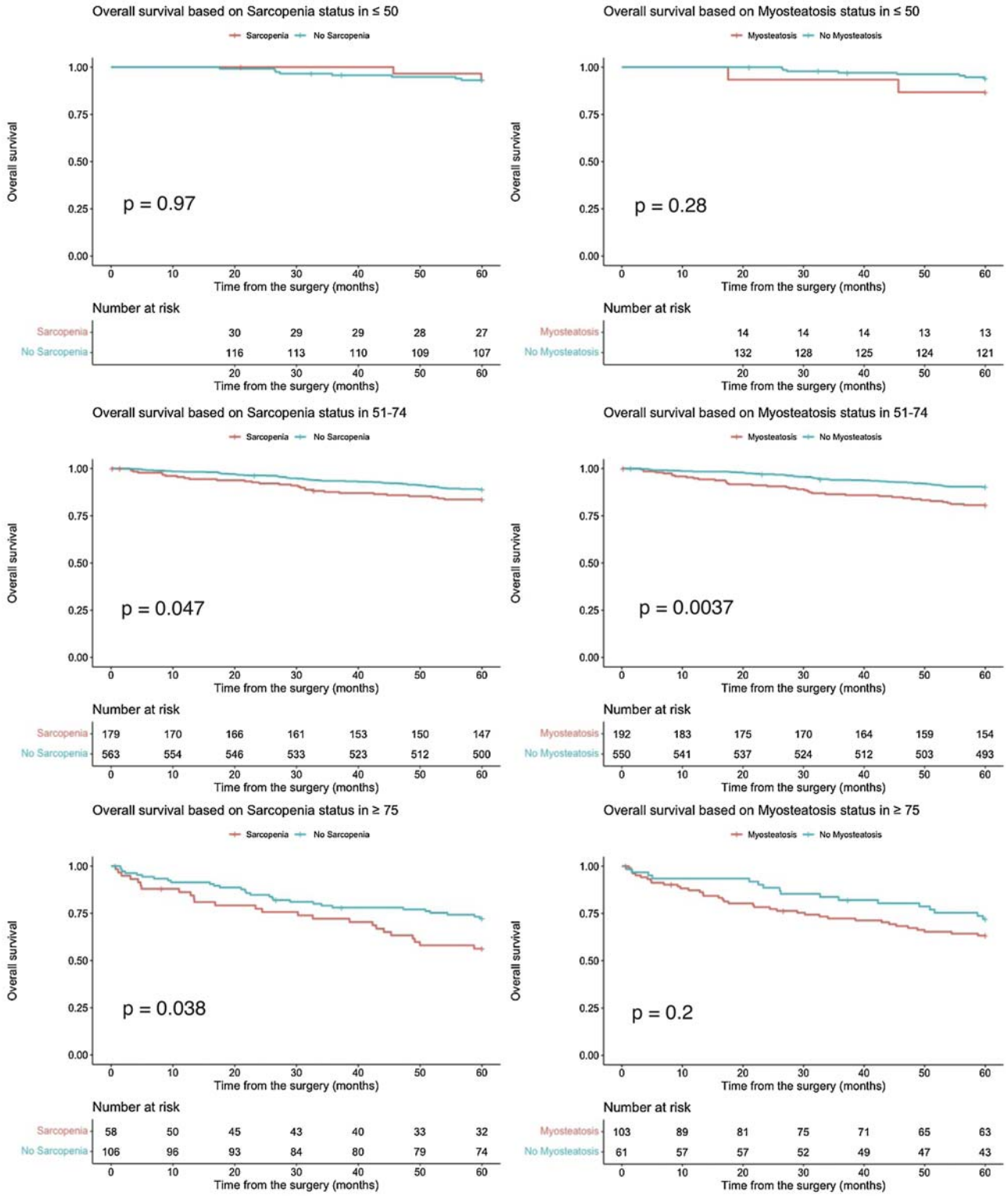

Fig. 1. Kaplan-Meier survival curve of overall survival according to sarcopenia and myosteatosis status by age group.

1.1–3.3]; $P = 0.016$) and sarcopenia (HR 0.57 [95%CI 0.33–0.98], $P = 0.04$). The results are summarized in Table 2.

3.6. Multivariable analysis

Variables that showed significance in association with overall survival in univariable cox regression analysis were considered. These variables were clinical factors, such as age, BMI, CEA, tumor size, histologic grade, postoperative complications, presence of lymphovascular invasion, recurrence, and pathologic stage. Multivariable analysis adjusted for significant variables in the univariable analysis revealed that in the 51–74 years age group, myosteatosis exhibited statistical significance in its association with OS (HR 0.63 [95%CI 0.41–0.96]; $P = 0.033$) whereas sarcopenia was strongly associated with OS in the ≥75 years age group

Table 2
Univariable analysis of factors associated with overall survival.

		≤50 (n = 147)		51–74 (n = 742)		≥75 (n = 164)	
Variables	Categorization	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	Female	1	0.552	1	0.681	1	0.288
	Male	0.68 (0.19–2.41)		1.09 (0.72–1.67)		1.36 (0.77–2.39)	
BMI (kg/m^2)	< 25	1	0.636	1	0.028	1	0.111
	≥ 25	1.39 (0.36–5.46)		0.58 (0.36–0.94)		0.50 (0.22–1.17)	
CEA (ng/mL)	< 5	1		1		1	
	≥ 5	–		1.75 (1.13–2.71)	0.012	1.31 (0.76–2.26)	0.331
	unknown	–		1.37 (0.55–3.42)	0.502	0.68 (0.09–4.95)	0.700
Tumor location	Colon	1	0.562	1	0.978	1	0.771
	Rectum	0.63 (0.13–2.98)		0.99 (0.64–1.54)		1.09 (0.59–2.01)	
Tumor size (cm)	< 5	1	0.612	1	0.003	1	0.093
	≥ 5	1.38 (0.39–4.76)		1.88 (1.25–2.83)		1.58 (0.93–2.71)	
Complications	No	1	0.998	1	0.118	1	0.016
	Yes	1.00 (0.13–7.92)		1.44 (0.91–2.26)		1.94 (1.13–3.32)	
Histologic grade	G1 & G2	1	0.230	1	<0.001	1	0.961
	G3 & MC & SRC	2.58 (0.55–12.20)		2.89 (1.66–5.03)		1.02 (0.41–2.57)	
LVI	Absent	1		1		1	
	Present	–		2.49 (1.58–3.91)	<0.001	1.42 (0.78–2.57)	0.255
	unknown	–		1.78 (0.94–3.35)	0.075	1.18 (0.46–3.04)	0.721
Stage	I&II	1	0.031	1	<0.001	1	0.002
	III	4.42 (1.14–17.10)		2.79 (1.81–4.30)		2.35 (1.37–4.04)	
Chemotherapy	No	1	0.906	1	0.170	1	0.664
	Yes	1.09 (0.28–4.20)		1.37 (0.87–2.15)		0.88 (0.51–1.54)	
Recurrence	No	1	<0.001	1	<0.001	1	<0.001
	Yes	66.56 (8.41–526.3)		16.17 (10.61–24.65)		5.55 (3.04–10.12)	
Sarcopenia	Yes	1	0.969	1	0.048	1	0.040
	No	1.03 (0.22–4.86)		0.64 (0.41–0.99)		0.57 (0.33–0.98)	
Myosteatosis	Yes	1	0.293	1	<0.001	1	0.204
	No	0.44 (0.09–2.05)		0.48 (0.31–0.72)		0.69 (0.39–1.22)	

HR: Hazard Ratio; CI: Confidence Interval.
BMI: Body mass index, CEA: Carcinoembryonic antigen, MC: Mucinous adenocarcinoma, SRC: Signet-ring cell, LVI: Lymphovascular invasion.

Table 3
Multivariable analysis of factors associated with overall survival.

		51–74 (n = 742)		≥ 75 (n = 164)	
Variables		HR (95% CI)	*P*	HR (95% CI)	*P*
Sarcopenia	Yes			1	0.005
	No			0.46 (0.26–0.80)	
Myosteatosis	Yes	1	0.033		
	No	0.63 (0.41–0.96)			

HR: Hazard Ratio; CI: Confidence Interval.
Multivariable analysis was adjusted for age, body mass index, carcinoembryonic antigen, tumor size, histologic grade, complications, lymphovascular invasion, recurrence, and stage.

(HR 0.46 [95%CI 0.26–0.80]; $P = 0.005$) (Table 3). Predicted survival probability of results from multivariable cox regression analysis is shown in Supplementary Fig. S2.

4. Discussion

Results of the present study revealed a dramatic difference in the association between SMI, SMD, and OS in patients with postoperative CRC according to age group. Consistent with other studies, sarcopenia was significantly associated with OS in older patients with postoperative CRC [18,20]. However, patients with postoperative CRC < 75 years of age did not exhibit a significant relationship between sarcopenia and OS but rather exhibited a significant association with myosteatosis. Patients with ECRC exhibited no significant prognostic value for either SMI or SMD, indicating the need for further research. To the best of our knowledge, the present study is the first to report the prognostic impact of SMI and SMD according to different age groups in patients with postoperative CRC.

Globally, the incidence of CRC has doubled over the past 20 years, reaching 2.17 million in 2019, with a mortality up to 1.09 million [2]. In the present study, the peak age group was identified as 60–74 years, which coincides with our data of 70.5% of patients in the 51–74 years age group. Although the most profound increase in the incidence is still most apparent in older patients, patients with young-onset CRC are also an increasing segment that cannot be ignored.

Among the numerous prognostic factors for postoperative CRC, sarcopenia has attracted considerable interest over the past decade. Sarcopenia, defined as the loss of skeletal muscle mass and function, is a natural process of aging [5]. In relation to cancer prognosis, a meta-analysis including 7843 patients revealed that low SMI was associated with poor OS, worse cancer-specific survival, and worse disease-free survival in postoperative CRC [13]. In the Framingham Heart Study published in 2003, a two-fold increase in the risk for mortality was reported for every 1 kg/m^2 reduction in muscle mass [23]. The use of sarcopenia in outcome prediction extends beyond patients with cancer, as Lim et al [24] revealed that sarcopenia is associated with outcomes in liver transplant patients in terms of patient and graft survival. Our study showed significant correlation between sarcopenia and OS only in the ≥75 years age group. As we assessed sarcopenia with preoperative CT scans, we are unaware of the postoperative changes in muscle mass that may have affected the patients' prognosis, especially in the elderly group where the rapidity of muscle loss may be different from that of younger patients. Lee et al. evaluated perioperative changes in sarcopenia and have shown that those with persistent sarcopenia postoperatively showed worse OS and recurrence-free survival (RFS) (OS 96.2% vs. 90.2%, $P = 0.001$; RFS: 91.1% vs. 83.9%, $P = 0.002$) [25]. Further study on the postoperative changes in sarcopenia according to different age group may be warranted for both preoperative and postoperative intervention.

Although muscle mass peaks in the third decade of life and decreases at a rate of 0.1–0.5%/year, sarcopenia in younger patients cannot be explained by an aging process [19]. According to our data, 20.4%, 24.1%, and 35.4% of patients in the ≤50, 51–74, and ≥75 years age groups, respectively, were sarcopenic.

Similarly, myosteatosis, defined as excess infiltration of fat into muscle, is also part of the natural aging process of fat gain and is often measured as SMD [26]. Systemic reviews and meta-analyses have demonstrated that SMD acts as an independent prognostic factor for OS, not only in CRC but also in numerous cancer types [16,17].

Using CT to measure skeletal muscle area and expressing the abundance or deficiency of skeletal muscle based on this measurement might be more appropriately termed "myopenia" rather than sarcopenia. Strictly speaking, sarcopenia requires consideration of both quantity and quality of skeletal muscle, with various tests needed for accurate assessment. However, despite the need for multiple tests to precisely measure sarcopenia, the convenience of using CT to assess muscle status without conducting additional tests has led to its continued clinical significance. Moreover, this measurement method is known to effectively reflect the state of sarcopenia. While the term sarcopenia was employed in our study to encompass these aspects, there may be a need for a more precise distinction and using terms like "CT-defined sarcopenia" could be one possible way to differentiate and provide clarity in terminology.

Although the etiology of sarcopenia is not fully understood, several mechanisms of muscle wasting associated with aging have been proposed. Several studies have reported a general reduction in basal muscle protein synthesis attributed to a reduction in muscle mass [27–29]. At the cellular level, mitochondrial DNA deletion mutations have been hypothesized to reduce enzyme activity and ATP energy stores, ultimately leading to a reduction in the overall metabolic rate [30,31]. Together with the loss of muscle itself, neurological deterioration that accompanies aging affects muscle function and strength at multiple levels, from the brain to the neuromuscular junctions [32]. Our study confirmed that sarcopenia measured according to SMI was only significantly associated with OS in the ≥75 years age group. The biological processes of muscle wasting with age may become more influential, and treatment approaches should be planned accordingly.

The 2019 definition by the EWGSOP emphasized the importance of muscle quality. Interest has been growing in the assessment of muscle quality because its influence spreads not only to the survival of patients with cancer but also to their quality of life (e.g., physical performance, chemotherapy toxicity, and hospitalizations) [17]. The most commonly used measurement method is to calculate the amount of fat infiltration in muscle tissue (i.e., myosteatosis), known as SMD.

To the best of our knowledge, no study has investigated the effect of myosteatosis on OS in patients with postoperative CRC according to age group. Our study demonstrated that myosteatosis was a significant prognostic factor for OS only in the middle (i.e., 51–74 years) age group. Lifestyle changes in Korea since the 1980s have shifted toward a more Western diet, and the obesity rate has increased from 28.1% in 1998 to 37.3% in 2017 [33]. The role of adipose tissue is commonly associated with inflammation and insulin resistance. Although the in-depth pathophysiology and interactions of these molecular changes have not been delineated, we can deduce that the ultimate detrimental effects on muscle degradation, decreased physical function, and tumor growth and proliferation lead to poor survival. Not quite affected by the muscle wasting mechanisms with aging, as mentioned earlier, middle-aged patients rely heavily on not only muscle mass itself, but the quality of the muscle affected by fat infiltration.

Sex differences are another important aspect of this discussion. The correlation between SMI and SMD according to sex revealed an important finding regarding the relationship between these two factors. This may explain why not all patients with sarcopenia are myosteotic, and vice versa. When stratified according to sex, males exhibited a higher incidence and mortality rate for CRC, accounting for 57.2% and 54.9%, respectively [2]. Bae et al. [34] reported a significant difference in the prevalence of sarcopenia according to sex in different age groups. The young age group (20–39 years) exhibited a higher percentage of sarcopenia among males, whereas the opposite was apparent in the 40–64 years age group. Another explanation may be hormonal dysfunction due to adipogenesis in menopausal females. The protective effects of estrogen from adipose tissue against muscle damage in females may explain the inverse relationship between SMI and SMD [35].

Clinical factors, such as age, BMI, CEA, tumor size, histologic grade, postoperative complications, presence of lymphovascular invasion, and pathologic stage were considered when analyzing multivariable cox regression analysis. These variables initially showed statistically significance in association with overall survival in univariable cox regression analysis. The above-mentioned variables are well-known and accepted prognostic factors associated with patient outcome in numerous studies [36–38]. The variables listed can influence both sarcopenia and myosteatosis through direct and indirect mechanisms. Age is a foremost primary risk factor for sarcopenia. On the other hand, BMI is more closely associated with myosteatosis as obesity is associated with increased risk of myosteatosis. CEA and other tumor-related factors may indirectly impact muscle mass and quality through cancer-related systemic inflammation, a common thread in cancer and obesity. Nutritional status, impacted by large tumor size, postoperative complications, and cancer stage can also directly affect muscle mass and the development of sarcopenia and myosteatosis. Altogether, these variables provide insight into the complex interplay between cancer and the risk of developing sarcopenia and myosteatosis.

ECRC is a growing field expected to double by 2030, thereby presenting a global threat [4]. ECRC, often diagnosed before 50 years of age, is a conundrum for clinicians. Rather than the conventional pathogenesis of adenoma-carcinoma sequences and genetic factors, early exposure to environmental factors, such as obesity, carcinogens, Western diet, and the microbiota, are some of the proposed factors contributing to the increased incidence of ECRC [4]; thus, tumor characteristics and patient prognosis will differ. Sarcopenia and myosteatosis in patients with ECRC may not have the same pathological effects as those in patients with conventional CRC.

A meta-analysis by Chang et al. [39] revealed that pre-habilitation in patients with frailty undergoing CRC surgery improved the incidence of postoperative complications and length of hospital stay. The application of different treatment strategies according to age should be emphasized. While focusing on weight training and increasing physical activity may be needed in older patients, they may not be beneficial for those in their sixth to eighth decades of life. A well-balanced fat reduction and muscle gain treatment program is the key to improving survival outcomes in middle-aged patients with CRC.

Despite these promising results, our study had several limitations, the first of which was the inherent constraints of its retrospective design. The fundamental limitation of a retrospective study is selection bias, and single-center design limits the generalizability of these findings to the general population. Another limitation was the absence of data regarding other potential confounding factors that could affect the survival of patients with CRC, such as nutritional status, socioeconomic factors, and physical activity levels, and colorectal cancer patients care system, etc. In addition, the measurement of sarcopenia and myosteatosis relied solely on the SMI and SMD values obtained from CT scans. Although this is a commonly used method, there are varying definitions and thresholds for sarcopenia and myosteatosis, which may have influenced our results. Several studies have explored various thresholds for defining low SMI and SMD in patients with different types of cancers. Consequently, in clinical decision-making, the selection of the cut-off may heavily depend on the unique characteristics of each patient. As mentioned earlier, different cut-off values for sarcopenia are available, of which the most recognized and used thresholds are from studies by Martin and Prado [22,40]. Variability of these values often derived from patients in Western countries with higher BMI that may be different composition from lean Asian patients is of another challenge, and we acknowledge that additional research is necessary to address these limitations.

In addressing the challenge of variable diagnostic criteria for sarcopenia, two significant studies offer insights into optimal cut-off values for SMI evaluated by CT scans. Ohashi et al. focused on patients with chronic liver disease, comparing SMI cut-off values determined by CT against those assessed by Dual-Energy X-ray Absorptiometry (DEXA), suggesting specific thresholds for presarcopenia in this population [41]. Bahat et al. proposed cut-off values for SMI and psoas muscle index at the L3 vertebra level, identified through CT scans, to accurately assess low muscle mass in a broader patient cohort [42]. Both studies highlight the importance of refining diagnostic criteria for sarcopenia, underscoring the need for consensus on cut-off values that accommodate diverse patient groups and methodologies, thereby enhancing the precision of sarcopenia diagnosis and its prognostic relevance in clinical practice. Therefore, more suitable cut-off values for sarcopenia and myosteatosis are needed. The generalizability of these findings may be another limitation because the data were obtained from a single center, which may not precisely represent a larger population of patients with postoperative CRC. Future prospective studies addressing these limitations could provide a more concrete understanding of the different effects of sarcopenia and myosteatosis on the survival of patients with postoperative CRC.

5. Conclusion

Different age groups exhibited significantly variable skeletal muscle indices. Although an abundance of irrefutable results demonstrates a correlation between CT-defined sarcopenia, myosteatosis, and clinical prognosis, data regarding age-dependent correlations are scarce. This study demonstrated that sarcopenia and myosteatosis did not influence the prognosis of young patients with postoperative CRC $\leq$ 50 years of age, inferring the existence of different significant skeletal muscle-related parameters according to age. Clinicians should consider the impact of sarcopenia and myosteatosis on patient prognosis and should also be aware that the effect may differ according to patient age.

Funding

This study was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (No. 2022R1F1A1074811).

Statement of authors' contributions to manuscript

Hye Jung Cho (HJC) and Jeonghyun Kang (JK) have contributed to the design, data collection, methodology, analysis, as well as writing and reviewing of the manuscript. Hye Sun Lee (HSL) contributed to the analysis and review of manuscript. All authors (HJC, HSL, and JK) have read and approved the manuscript.

Ethical standards

This study was approved by Gangnam Severance Hospital Institutional Review Board (No. 3-2023-0106) and was conducted according to the principles of the Declaration of Helsinki. A written informed consent was not required for this retrospective study.

Conflict of interest

The authors declare no actual or potential conflicts of interest.

Acknowledgments

We would like to thank Editage (www.editage.co.kr) for English language editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100243.

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