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Original article

Frailty is associated with myosteatosis in obese patients with colorectal cancer

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SUMMARY

Background & aims: We aimed to explore the determinants of muscle fat infiltration and to investigate whether myosteatosis, assessed as muscle fat infiltration percentage (%MFI) and muscle attenuation from computed tomography (CT), is associated with frailty in a group of patients with colorectal cancer (CRC).
Methods: Cross sectional study including CRC patients. CT scan of the third lumbar vertebra was used to quantify body composition and the degree of %MFI (reported as percentage of fat within muscle area). Frailty was defined by Fried et al. (2001) as the presence of more than 3 criteria: unintentional weight loss, self-reported exhaustion, weakness (low handgrip strength), slow walking speed (gait speed) and low physical activity. Obesity was defined according to sex-and-age-specific body fat percentage (%BF) cutoff.
Results: A sample of 184 patients (age 60 ± 11 years; 58% men; 29% of patients with frailty) was studied. The sample was divided according to tertiles of MFI% (1st tertile 0 to 2.89%, n = 60; 2nd tertile ≥ 3.9 −8.19%, n = 64; 3rd tertile ≥ 8.2−26%, n = 60). Age, females, body mass index, %BF, subcutaneous and visceral adipose tissue and the proportion of patients with frailty were significantly higher in the 3rd % MFI tertile. Phase angle and muscle attenuation were significantly lower in the 3rd %MFI tertile. The determinants of %MFI ($r^2 = 0.49$), which was log transformed due to its normal distribution, were %BF ($\beta = 0.54$; $e^{\beta} = 1.72$; 95% CI: 0.032 to 0.051; $P < 0.01$), age ($\beta = 0.34$; $e^{\beta} = 1.40$; 95% CI: 0.016 to 0.032; $P < 0.01$) and gait speed ($\beta = -0.12$; $e^{\beta} = 0.87$; 95% CI: −0.84 to −0.001; $P = 0.049$). In addition, in obese patients (n = 74) presenting 4 or 5 frailty criteria increased the chance of having higher %MFI and lower muscle attenuation, after adjustment for sex, age and comorbidities when compared to none or 1 criteria.
Conclusions: In a sample of CRC patients, %BF and gait speed were the determinants of %MFI. In addition, markers of myostetatosis were associated with frailty in the obese patients.

1. Introduction

With an increasingly aging population, the prevalence of age-related cancers such as colorectal cancer (CRC) is rising, especially in the less developed regions [1]. CRC is amongst the types of cancer with the highest incidence rates and in fact, CRC is the third in world incidence and fourth in the mortality rates [2]. In the context where cancer and aging are present, other comorbidities might occur. Frailty is defined as an age-associated syndrome of decreased physiologic reserves and function, leading to increased vulnerability for adverse events. In oncology, frailty is highly prevalent in young and older cancer patients [3,4] and has been associated with

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increased chemotherapy toxicity, surgical complications and mortality [3–5].

In general, the decline in function is commonly attributable to a decrease in muscle size, but emerging evidence suggests that intramuscular fat infiltration, known as myosteatosis, is associated with lower muscle strength and mobility independently of muscle size [6–9]. Increased intramuscular fat infiltration is present in aging, in conditions of physical inactivity [7,8,10,11] and in multiple disease states including diabetes, obesity, chronic obstructive pulmonary disease (COPD), cirrhosis and cancer [12–17]. The importance of such condition lies on its association with poor outcomes, including increased postoperative complications and higher mortality rates [14–16,18,19].

However, the assessment of myosteatosis requires the use of images techniques not available for daily clinical use, such as computed tomography (CT) and magnetic resonance imaging (MRI) [20]. CT and MRI are considered gold-standard imaging methods for evaluating body composition, especially muscle mass, and have been used to assess intramuscular adipose tissue and muscle attenuation, markers of myosteatosis. In the setting of oncology, TC and MRI are applied for medical diagnosis and for follow-up purposes and could also be opportunistically used to assess body composition. The CT scan of the abdomen normally used for CRC diagnosis include the level of the third lumbar vertebra (L3). This set has recently been validated as the standard landmark for muscle mass analysis and can be also used to assess myosteatosis in cancer patients [21].

As frailty and muscle mass abnormalities are prevalent in patients with cancer and are associated with adverse outcomes, we sought to better understand their relationship. Therefore, our goal is to explore the determinants of muscle fat infiltration and to investigate whether skeletal muscle measurements, especially myosteatosis, is associated with frailty in patients with CRC.

2. Materials and methods

2.1. Subjects and study design

This study included patients with CRC recruited between April 2015 and June 2016 at the outpatient clinic of the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva (INCA, Rio de Janeiro, Brazil). Those that were scheduled for abdominal CT scan at the L3 region as part of routine care and that met study eligibility criteria were invited to participate. Inclusion criteria comprised age higher than 18 years old and Eastern Cooperative Oncology Group (ECOG) performance score below 3. In addition, those with physical deformity unable to carry out tests for muscle strength or physical performance, with pacemaker, congestive heart failure, chronic kidney disease and liver cirrhosis were not included in the study. From 194 patients initially included in the study, 10 were excluded due to lack of CT scans (n = 1), lack of bioelectrical impedance analysis (BIA) (n = 1), CT scan with no images from the third lumbar vertebra (n = 1) and not having data on the frailty phenotype (n = 7). Therefore, 184 patients were included as depicted in Fig. 1. The local Research Ethical Committee from National Cancer Institute José Alencar Gomes da Silva approved the study (protocol number 38992014.5.0000.5274) and informed consent was obtained from each subject before their inclusion.

2.2. Study protocol

After consenting to participate, patients received instructions to keep normal hydration and to fast for 6 h before the CT scan (water-soluble oral contrast and medication were allowed). After CT scan, all participants had the nutritional status, body composition, and muscle function assessed. Blood samples were then scheduled to be collected under fasting conditions not later than 30 days after the CT scan. Clinical data were collected from medical records such as age, sex, previous and current treatment, ECOG performance score, tumor site, stage and pre-existing comorbidities (hypertension, diabetes, dyslipidemia, coronary heart disease, hypothyroidism, renal disease, congestive heart failure and COPD).

2.3. Nutritional assessment

Body weight (kg) was assessed using a platform-type mechanical scale (Filizola, São Paulo, Brazil) with a maximum capacity of 150 kg and variation 0.1 kg and height (cm) by a vertical stadiometer 200 cm long and with a 0.1 cm precision. Body mass index (BMI) was calculated as body weight in kilograms divided by squared height. The scored Patient-generated Subjective Global Assessment (PG-SGA) was carried out by a trained dietitian. The scored PG-SGA includes two sections 1): history of weight loss over the previous six months, dietary intake, gastro-intestinal symptoms and functional capacity 2): clinical condition, metabolic stress, and physical examination assessing muscle wasting, loss of subcutaneous fat mass and presence of edema/ascites. Each patient was classified as well nourished (PG-SGA A), mild to moderately malnourished (PG-SGA B), or severely malnourished (PG-SGA C) [22].

2.4. Body composition

Body composition was assessed by BIA and CT. BIA was performed with a tetrapolar device model Quantum II (RJL Systems, Detroit, MI, USA), with one electrical current of 800 A at 50 kHz. The BIA device provides resistance and reactance values in Ohms (Ω). Phase angle (PA) was calculated with the following equation: PA (°) = arc tangent (reactance Ω/resistance Ω) x (180/π). The resistance was used to calculate skeletal muscle mass (SMM) obtained through the equation proposed by Janssen et al. [23] and SMM was normalized by height square (m^2) and reported as skeletal muscle index (SMI) (kg/m^2). The SMM (kg) equation follows: [((height centimeter)^2/resistance × 0.401) + (sex (0 for female and 1 for male) × 3.825) + (age years × (−0.071))] + 5.102. The percentage of total body fat (% BF) was assessed by BIA based on the predictive equation provided from the manufacturer's software. Obesity was defined according to sex-and-age-specific % BF cutoff points for the healthy population [24].

The CT images were acquired for medical diagnosis/follow-up purposes and were digitally stored in the patient's medical record, which are useful for the assessment of body composition as well. CT images were analyzed for tissue cross sectional area (cm^2) at L3 using the Slice-O-Matic software, version 5.0 (Tomovision, Montreal, Quebec, Canada). One image extending from the L3 was assessed for skeletal muscle (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus), and adipose tissue (visceral, subcutaneous, and intramuscular). CT Hounsfield unit (HU) thresholds for each tissue were −29HU to +150HU for skeletal muscle, −190HU to −30HU for subcutaneous and intramuscular adipose tissue and −150HU to −50HU for visceral adipose tissue [21]. The same trained dietitian read all the CT images. Skeletal muscle area was normalized by height square (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2). Muscle attenuation was also evaluated from CT and was derived by averaging the Hounsfield unit of skeletal muscle. The attenuation of skeletal

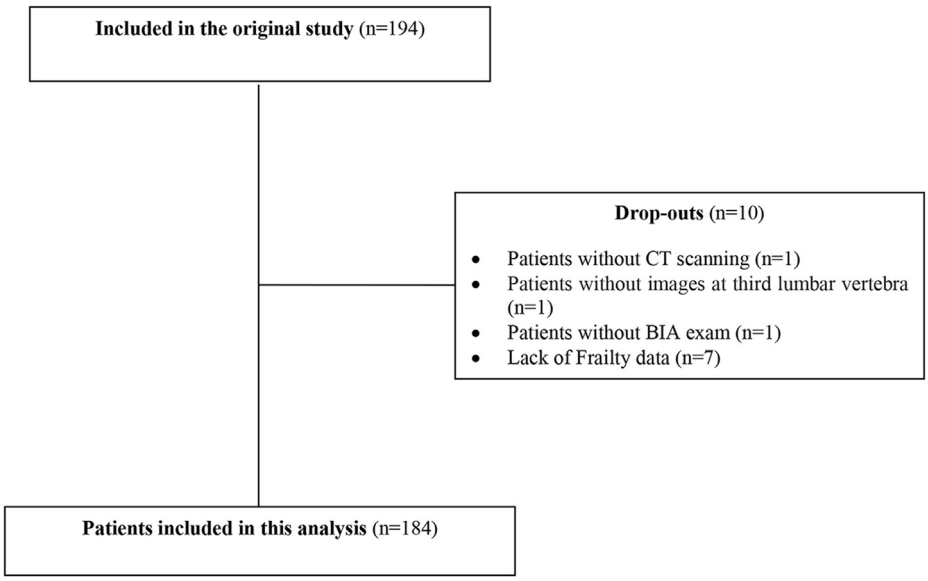

Fig. 1. Flow chart of study inclusion and exclusion. CT: Computed tomography; BIA: Bioelectrical impedance analysis.

muscle is inversely related to muscle fat content [15,20]. In addition, the percentage of muscle fat infiltration (% MFI) in relation to the skeletal muscle mass in the slice L3 was calculated using the following formula [17]:

% MFI = IAT (cm^2)/[IAT (cm^2) + SMM(cm^2)] x 100. Where, MFI: muscle fat infiltration; IAT: intramuscular adipose tissue; SMM: skeletal muscle mass.

2.5. Measurement of muscle strength and physical performance

Muscle strength was measured using a Jamar® hydraulic hand dynamometer (Sammons Preston, Chicago, IL). Each individual sat in a chair with armrests, without rings, watches, or other objects on their hands or wrists. The upper limb to be evaluated was placed alongside the body with the elbow at a 90° angle; the contralateral limb was relaxed on the thigh. During the exam, the patient was instructed to use the maximum strength in each measurement. Three measurements were determined for each hand in an alternating manner, and the maximum strength was defined as the greatest of the six measurements.

Physical performance was assessed by 4.6 m gait speed test. The subject was instructed to walk as fast as possible, but not running, through a predetermined 4.6 m straight path with no obstacles while the time to complete the course was measured. The test was applied twice, with an interval of approximately 30 s between applications and the lower of the two measurements was considered.

2.6. Definition of sarcopenia

Sarcopenia was defined as low skeletal muscle mass plus low muscle strength and/or low physical performance according to the European Working Group on Sarcopenia in Older People (EWGSOP) [25]. Individuals who did not meet these criteria were considered normal for the outcome studied. Low SMI assessed by CT were classified according to Martin et al. cutoff points [15] (men: <43 cm^2/m^2 for BMI <25 kg/m^2 and <53 cm^2/m^2 for BMI ≥25 kg/m^2; women: <41 cm^2/m^2). Low handgrip strength were defined as less than 30 kg for men and less than 20 kg for women and for gait speed was less than 0.8 m/s [25].

2.7. Frailty phenotype

Frailty phenotype was defined by Fried et al. [26] as the presence of at least 3 of the following criteria: 1. unintentional weight loss (>3 kg in past year); 2. low handgrip strength (the lowest 20% of the population adjusted for sex and body mass index); 3. slow walking speed (the slowest 20% of the population based on time to walk 4.6 m, adjusting for sex and height); 4. low physical activity level (defined as the lowest quintile of physical activity according to sex. Physical activity was evaluated by the International Physical Activity Questionnaire Short Form) [27]; 5. self-reported of exhaustion (identified by two questions from the Center for Epidemiological Studies Depression scale) [28].

2.8. Laboratorial measurements

Serum dosages of albumin (bromocresol-green method) and high sensitivity C-reactive protein (hsCRP) (turbidimetric method) was quantified by specific kits from Roche® using a COBAS 311 analyzer (Roche Diagnostics®, Mannheim, German), according to laboratory routine of the National Cancer Institute José Alencar Gomes da Silva Hospital.

2.9. Statistical analyses

Continuous variables will be summarized as mean ± SD or median and interquartile range, depending on its normality distribution (assessed by Shapiro–Wilk test). Categorical variables will be summarized as the absolute frequencies and their corresponding percentages. The % MFI was divided in tertiles. The comparisons among the groups of % MFI tertiles were performed by the χ^2 test for categorical covariates, by ANOVA test with post-hoc test of Bonferroni for continuous covariates with normal distribution and by the Kruskal–Wallis test for non-normally distributed continuous covariates. The crude association between % MFI and body fat was assessed by Spearman's correlation coefficient test. In order to evaluate the determinants of % MFI as well as to investigate the association between % MFI and frailty, multiple linear regression models were used after adjustments for sex, age and comorbidities. The % MFI, as the dependent variable, was log-transformed to

normalize its conditional distribution in the multiple linear regression analysis. Hence, the inverse function was applied to the estimated coefficients, i.e., e^{β}. The respective 95% confidence interval was obtained likewise. Under the linear regression model for the log transformed dependent variable, 100 (e^{β} - 1) is interpreted as the percent increase (if β is positive) or 100 (1 - e^{β}) as the percent decrease (if β is negative) in the expected value of the dependent variable for a unit increase in the respective covariate. As sensitivity analysis, muscle attenuation was used as proxy of muscle quality and muscle attenuation determinants was also tested in a different model, adjusted for sex, age and comorbidities. Statistical significance was defined as *P* values below 0.05. The statistical package for the social sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses.

3. Results

This study included 184 patients, mostly males (n = 107; 58%) and with a mean age of 60.4 ± 11.4 years. Hypertension was observed in 46% of the patients (n = 86), diabetes in 19% (n = 35), coronary heart disease in 3% (n = 5), hypothyroidism in 2% (n = 4) and dyslipidemia in 1,6%% (n = 3). Moreover, 23% (n = 42) had cancer stage 0 to II and 77% (n = 142) cancer stage III to IV. Table 1 describes demographic, clinical, nutritional, body composition and muscle function parameters according to the tertiles of muscle fat infiltration percentage (%MFI). Age and the proportion of females increased with the % MFI tertiles. Also of note, BMI, % BF, abdominal subcutaneous adipose tissue and visceral adipose tissue were significantly higher in the 3rd MFI% tertile, while the lumbar skeletal muscle index tended to decrease in the 3rd MFI% tertile. Moreover, phase angle and muscle attenuation, markers of muscle integrity were significantly lower in the 3rd tertile. PG-SGA, serum albumin and hsCRP were not different among the tertiles. Although there were 58 patients (31.5%) with some degree of malnutrition according to the PG-SGA, the serum albumin remained within the normal values across the %MFI tertiles. When stratified by sex, no differences were observed for HGS and gait speed among the tertiles groups. The number of patients with sarcopenia, that is, low muscle mass by lumbar skeletal muscle index and low muscle strength or gait speed, although not significant, tended to increase across the MFI% tertiles. The determinants of % MFI were assessed by multiple linear regression analysis, where log of % MFI was the dependent variable and age, sex, % BF, HGS and gait speed were listed as possible independent variables. After running a few model specification choices, the variables that remained significant in the model ($r^2 = 0.49$) were %BF (β = 0.54; $e^{\beta} = 1.72$; 95% CI: 0.032 to 0.051; $P < 0.01$), age (β = 0.34; $e^{\beta} = 1.40$; 95% CI: 0.016 to 0.032; $P < 0.01$) and gait speed (β = −0.12; $e^{\beta} = 0.87$; 95% CI: −0.84 to −0.001; $P = 0.049$).

The prevalence of frailty phenotype components according to tertiles of % MFI is shown in Table 2. Although a significantly higher proportion of patients had spontaneous weight loss in the 3rd tertile, it was also largely present in the 1st and 2nd tertiles, a finding similar to exhaustion, which was seen in about 70% of the % MFI groups. The remaining frailty components, though not significant, tended to show higher prevalence in the 3rd tertile. In fact, Fig. 2 shows that the prevalence of frailty, that it is, the concomitance of 3 or more components, was significantly higher in the 3rd tertile of % MFI (1st tertile n = 11, 18%; 2nd tertile n = 18, 28% and 3rd tertile, n = 25, 42%; P = 0.02). In the entire group, frailty was present in 29% (n = 54) of the patients.

Considering that % BF was highly correlated with % MFI in both males and females (males: r = 0.42, P < 0.001; females: r = 0.52, P < 0.001) (Fig. 3), two linear regression models were tested to investigate whether the correlation between % MFI and frailty differed in obese (n = 74) and non-obese patients (n = 110). In the multiple linear regression analysis adjusted by sex, age and comorbidities, in the obese group, but not in the non-obese group, presenting 4 or 5 criteria augments in almost 174% the expected value of % MFI as compared to the none or 1 criteria of frailty (reference group) (Table 3). Similarly, in a sensitivity analysis, muscle attenuation was used a proxy of myosteatosis and was used as dependent variable, adjusted for sex, age and comorbidities. Compared with none or 1 frailty criteria, presenting 4 or 5 criteria in the obese group, but not in the non-obese group, diminished almost 9 units of muscle attenuation in the adjusted multiple linear regression analysis (Supplementary Table 1). As lower muscle attenuation indicates higher myosteatosis, the later result indicates that presenting 4 or 5 frailty criteria was correlated with myosteatosis.

4. Discussion

This study aimed to explore the determinants of % MFI and to investigate whether muscle fat content, known as myosteatosis, was associated with frailty in a representative group of 184 well characterized CRC patients with measurements of body composition. By using CT images available for diagnostic purposes, we assessed body composition with high precision and no harm for the patient. Our main finding was that body fat and gait speed were independent determinants of % MFI in a model adjusted for sex and age. Moreover, we also found that in obese CRC patients, presenting 4 or more components of frailty were positively associated with % MFI and inversely associated with muscle attenuation. This finding indicates that myosteatosis was associated with frailty in obese patients. Overall, these findings suggest that body fat and gait speed were the determinants of % MFI and highlight the importance of % MFI as a contributor of frailty in CRC obese patients.

Of note, we found positive associations between % MFI and body fat measurements, including BMI, total body fat, abdominal subcutaneous adipose tissue and visceral adipose tissue, all of which were significantly higher in the 3rd tertile of % MFI. Therefore, obesity plays an important role in % MFI and subsequently in increased myosteatosis, a finding previously shown in studies including individuals with and without cancer [12,29,30]. The alterations inherent to the increased body fat accumulation (i.e. obesity), such as the changes in mitochondrial function, the impaired fatty acid metabolism, the defect in the ability of subcutaneous fat to store excess fatty acids, insulin resistance, and the accumulation of macrophage and T-cell, which induce muscle inflammation with consequent fat accumulation in the skeletal muscle [31–33] are likely to explain the role of obesity in increasing % MFI. The consequence of myosteatosis is a worse muscle quality and diminished muscle contractile area, which has been claimed to be associated with lower muscle function in the elderly [7–9,34], due to a change in activation, proliferation and differentiation of skeletal muscle stem cells into adipocytes [31]. Aligned with this speculation, in the present study, patients in the 3rd tertile of % MFI were significantly older than that those in the 1st tertile of % MFI, reinforcing the notion that aging is related to myosteatosis, even in CRC patients. Regarding muscle mass, we found that lumbar SMI assessed by CT and total SMI assessed by BIA were not significantly different among the tertiles. We hypothesize that this result is justified by the inability of the muscle mass measurements to discriminate the amount of fat within the muscle. In fact, a previous study including oncologic patients could not find a variation in the skeletal muscle mass area, although muscle attenuation (a marker of myosteatosis) varied across the individuals [15]. Surprisingly, phase angle, considered a marker of the amount and quality of soft tissue mass [35], was able to follow the differences between the %

Table 1
Demographic, clinic, nutritional status, body composition and muscle function parameters according to tertiles of muscle fat infiltration percentage (n = 184).

	1st % MFI Tertile (n = 60)	2nd % MFI Tertile (n = 64)	3rd % MFI Tertile (n = 60)	*P*
	0–3.89%	≥3.9–8.19%	≥8.2–26%	
Age (years)[a]	55.2 ± 11.1[a]	61.9 ± 10.7[b]	64 ± 10.8[b]	**<0.001**[c]
Sex [n (%)]				
Male	51 (85%)[a]	31 (48%)[a]	25 (42%)[a]	**<0.001**[d]
Female	9 (15%)[b]	33 (52%)[a]	35 (58%)[b]	
Cancer stage [n (%)]				
0–II	9 (15%)	17 (27%)	16 (27%)	0.2[d]
III–IV	51 (85%)	47 (73%)	44 (73%)	
ECOG performance score [n (%)][d]				
0	26 (43%)	24 (38%)	28 (47%)	0.5[d]
1–2	34 (57%)	40 (62%)	31 (53%)	
BMI (Kg/m^2)[a]	25.4 ± 5.2[a]	26.9 ± 4.2[a]	29.3 ± 6.0[b]	**<0.001**[c]
PG-SGA[f] **[n (%)]**				
PG-SGA A	36 (60%)	46 (73%)	43 (72%)	0.2[d]
PG-SGA B/C	24 (40%)	17 (27%)	17 (28%)	
Albumin[g] **(g/dL)**[a]	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	0.7[c]
hsCRP[h] **(mg/dL)**[b]	0.43 (0.18; 1.38)	0.44 (0.27; 0.94)	0.39 (0.28; 0.67)	0.8[e]
Lumbar skeletal muscle index (cm^2/m^2)[a]				
Male	52.4 ± 9.9	49.6 ± 7.3	47.6 ± 8.8	0.08[c]
Female	44.5 ± 9.9	43.4 ± 5.7	42.2 ± 7.7	0.7[c]
Muscle attenuation (HU)[a]				
Male	42.2 ± 4.4[a]	35.8 ± 4.8[b]	28.5 ± 5.5[c]	**<0.001**[c]
Female	40.1 ± 8.6[a]	33.4 ± 5.6[b]	26 ± 4.8[c]	**<0.001**[c]
Subcutaneous adipose tissue (cm^2)[b]				
Male	113.8 (70.5; 184.4)[a]	161.2 (138; 196)[b]	161.6 (135.1; 226.3)[b]	**0.003**[e]
Female	108.2 (40.3; 214.1)[a]	184.5 (122.5; 274.1)[a,b]	285 (180.1; 348.5)[b]	**0.003**[e]
Visceral adipose tissue (cm^2)[b]				
Male	97 (53.4; 166)[a]	169.3 (120.5; 226.7)[b]	192.8 (132.4; 239.4)[b]	**<0.001**[e]
Female	33.7 (11.1; 75)[a]	74.7 (41.8; 143.9)[a,b]	114.9 (61.8; 168.3)[b]	**0.003**[e]
Body fat [%][b]				
Male	25.6 (19.7; 33.7)[a]	31 (26.9; 36)[a,b]	33 (29.4; 38)[b]	**0.003**[e]
Female	33.7 (19.8; 41.9)[a]	40.4 (35; 47.1)[a]	47 (39.6; 52.6)[b]	**< 0.001**[e]
Skeletal muscle index (BIA) (kg/m^2)[a]				
Male	10 ± 1.1	9.9 ± 1	10 ± 1.4	0.9[c]
Female	7.5 ± 1.1	7.4 ± 0.9	7.6 ± 1.4	0.9[c]
Phase angle (°)[a]				
Male	6.0 ± 1[a]	5.8 ± 0.9[a,b]	5.3 ± 0.9[b]	**0.005**[c]
Female	5.7 ± 0.6	5.3 ± 0.8	5.2 ± 0.9	0.4[c]
Handgrip strength (Kg)[b]				
Male	36 (31; 43)	36 (31; 40)	35 (29; 38)	0.4[e]
Female	18 (17; 27.5)	22 (20; 26.7)	22 (18; 27)	0.7[e]
Gait speed (m/s)[a]				
Male	1.20 ± 0.3	1.13 ± 0.2	1.08 ± 0.3	0.1[c]
Female	0.96 ± 0.2	1.01 ± 0.2	0.97 ± 0.2	0.6[c]
Sarcopenia [n (%)]	7 (12%)	8 (13%)	14 (23%)	0.1[d]

Eastern Cooperative Oncology Group (ECOG); BMI: Body mass index; hsCRP: high sensitivity C-reactive protein; PG-SGA: Patient-generated subjective global assessment; BIA: Bioelectrical impedance analysis; MFI: muscle fat infiltration.
Different letters [(a,b,c)] indicate statistically significant differences among the groups ($p < 0.05$).
The significance of bold is to highlight the result is $p < 0.05$.
[a] Mean and standard deviation.
[b] Median and interquartile range.
[c] ANOVA test.
[d] Chi-square test.
[e] Kruskal–Wallis test.
[f] N = 183.
[g] N = 163.
[h] N = 152.

Table 2
Prevalence of frailty phenotype components by muscle fat infiltration tertiles (n = 184).

	1st % MFI Tertile (n = 60)	2nd % MFI Tertile (n = 64)	3rd % MFI Tertile (n = 60)	*P*[a]
	0–3.89%	≥3.9–8.19%	≥8.2–26%	
Frequency of frailty components [n (%)]				
Unintentional weight loss	40 (67%)[a]	45 (70%)[a]	52 (87%)[b]	**0.03**
Exhaustion	47 (78%)	49 (77%)	46 (77%)	0.9
Low handgrip strength	15 (25%)	14 (22%)	19 (32%)	0.5
Low gait speed	9 (15%)	14 (22%)	15 (25%)	0.4
Low physical activity	7 (12%)	15 (23%)	13 (22%)	0.2

Different letters [(a,b,c)] indicate statistically significant differences between groups ($p < 0.05$).
The significance of bold is to highlight the result is $p < 0.05$.
[a] Chi-square test.

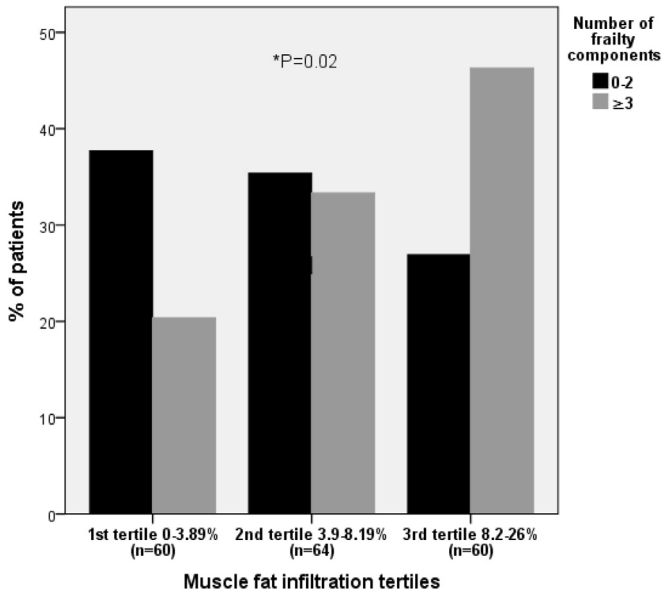

Fig. 2. Number of frailty components according to muscle fat infiltration percentage tertiles (n = 184). * Chi-square test.

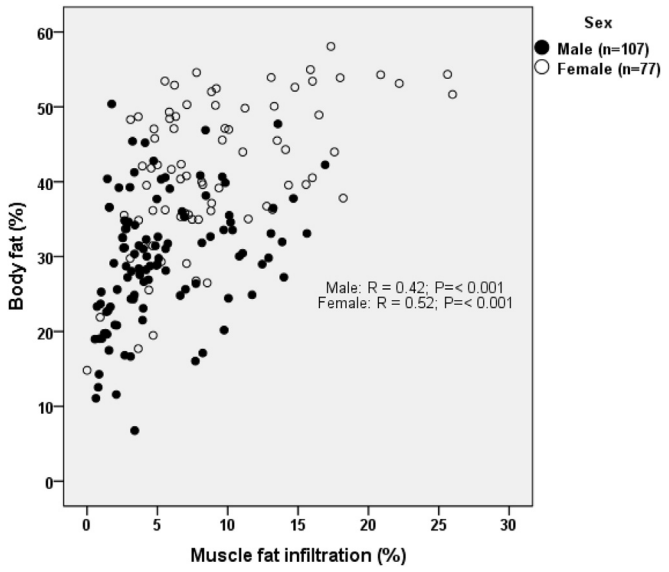

Fig. 3. Correlation between muscle fat infiltration percentage and body fat percentage (n = 184). Spearman's test-male: R = 0.42; $P < 0.001$; female: R = 0.52; $P < 0.001$.

MFI tertiles in males, signifying phase angle as a potential superior marker to discriminate for myosteatosis. Of note, serum albumin was not indicative of low values and there were no significant differences between %MFI tertiles. This finding is aligned to the fact that hsCRP was also similar among the tertiles and were not signing for an inflammatory condition. Therefore, although 31.5% (58 from 184 patients) of the patients were diagnosed with mild to severe degree of malnutrition, according to the PG-SGA, serum albumin remained within normal range, which is suggestive that serum albumin does not adequately diagnose malnutrition. Finally, although muscle function measurements were not different among the tertiles, gait speed was inversely associated with % MFI, by diminishing in 13% the expected value of % MFI, in a model adjusted for sex and age. This finding is in accordance with a previous study in oncologic patients showing that muscle attenuation was more strongly associated with physical function than with skeletal muscle mass [6]. Such finding can be explained by the fact that higher MFI diminishes the muscle contractile area and impact negatively in muscle function [9]. Overall, body fat and gait speed, representing obesity and muscle function respectively, were determinants of % MFI in a sample of CRC patients.

Frailty is an age-associated syndrome well described in the geriatric population that can also be associated with myosteatosis and therefore, higher % MFI. According to the definition conceptualized by Fried et al. [26], frailty involves the decline in many physiological domains including muscle mass, strength, loss of body weight, weakness and poor balance [36], which in turn leads to vulnerability to adverse events and worse outcome, such as increased susceptibility to falls, worse quality of life, higher mortality rate, increased risk of postoperative complications, admissions and chemotherapy intolerance [3,4,37]. More recently, frailty also became a subject of interest in oncologic patients with prevalence raging from depending on the type of cancer, the instrument and cut-point used to diagnose frailty [3]. In the present study, 29% (n = 54) of the patients fulfilled the criteria of frailty phenotype defined by Fried et al. [26] with a higher prevalence in the 3rd tertile of % MFI. Our finding agrees with those from Williams et al. [38] in which skeletal muscle density and skeletal muscle gauge, both assessed by CT and markers of myosteatosis, were related to frailty index even after adjusting by sex and age, in a sample of 162 elderly oncologic patients. Moreover, since we found that body fat was an important determinant of % MFI, we furthered our analysis, by speculating that the correlation between frailty and % MFI could be more pronounced in obese patients. In fact, we found that in obese, but not in the non-obese, presenting 4 or more criteria augmented almost 174% the expected value of % MFI as compared to the none or 1 criteria of frailty (reference group). Moreover, these findings were confirmed in a sensitivity analysis using muscle

Table 3
Association between percentage of muscle fat infiltration (log) and frailty phenotype adjusted for sex, age and presence of comorbidities in obese and non-obese patients (n = 184).[a]

	Obese (n = 74)				Non-obese (n = 110)			
	β	Exp (β)	95% CI	*P*	β	Exp (β)	95% CI	*P*
Number of frailty components								
0–1 (reference)								
2	0.299	1.349	0.840; 2.162	0.215	0.244	1.276	0.950; 1.714	0.105
3	0.407	1.502	0.908; 2.487	0.113	0.312	1.366	0.949; 1.966	0.093
4–5	1.007	2.737	1.370; 5.468	**0.004**	0.192	1.212	0.715; 2.052	0.475
Sex (male)	−0.670	0.512	0.393; 0.666	**<0.001**	−0.578	0.561	0.437; 0.720	**<0.001**
Age (y)	0.011	1.012	0.999; 1.022	0.072	0.032	1.033	1.020; 1.045	**<0.001**
Presence of comorbidities	−0.056	0.946	0.705; 1.269	0.709	0.169	1.184	0.922; 1.519	0.186

The significance of bold is to highlight the result is $p < 0.05$.
[a] Multiple linear regression analysis; Exp (β): Exponential beta; 95% CI: 95% confidence interval.

attenuation, a proxy of % MFI. In this analysis, presenting 4 or more criteria of frailty was associated with almost 9 units decrease of muscle attenuation in obese, but not in non-obese patients. Although our study design does not allow to stablish a cause–effect relation, these results clearly shows that myosteatosis is associated with frailty and therefore, should be a target of treatment.

Few studies have examined the relationship between presence of comorbidities and muscle abnormalities. Xiao et al. (2018) [29] showed an association of multiple comorbidities with low muscle attenuation in patients with non-metastatic colorectal cancer. In contrast with these findings, our data indicate that the presence of comorbidities was not associated with %MFI and muscle attenuation in regression model.

Lastly, the clinical implication of our findings deserves attentions. As far as we know, myosteatosis has not yet been a body compartment of target in interventional studies conducted in oncologic patients, since reversing wasting and cachexia were the focus of attention in nutritional interventions. With the findings from present study we instigate researchers to shift focus toward the other side of the coin that is, the adverse outcomes of obesity and sarcopenic obesity in CRC patients [39], such as myosteatosis and frailty. As obesity in the present study was present in 40.8% of the patients, targeting interventions of enhancing physical activity [40] and dietary omega-3 fatty acid supplementation [41,42] to reverse frailty and myosteatosis will likely improve quality of life, an outcome understood of high value in ill patients such as those from this study.

The limitations and strength of the present study should be addressed. As limitations, because this was a convenient sample across various time points in the cancer care continuum, we cannot draw conclusions regarding the treatment impact on skeletal muscle, %MFI and physical function. In addition, since this an observational and a cross-sectional study, a causal–effect relationship between %MFI, obesity and frailty cannot be stablished. Lastly, the slice at L3 has not been validated to assess whole body % MFI and further studies showing the best site to assess %MFI remains to be performed. However, even considering this possible drawback, the present study was able to show that %MFI evaluated at L3 was associated with frailty phenotype in obese CRC patients. The strengths include a representative and relatively large sample of CRC patients with body composition assessed by CT, which provides an accurate and precise assessment, enabling to identify muscle abnormalities, especially muscle fat infiltration, a subject not yet largely investigated in cancer patients. Also, it is one of the few studies that use CT scans to investigate the association between body composition parameters and frailty among patients with cancer.

In conclusion, body fat and gait speed were determinants of % MFI and presenting 4 or more criteria of frailty was associated with intramuscular fat infiltration and muscle attenuation in obese patients with CRC, suggesting the role of myosteatosis in frailty. Finally, clinicians should be aware of the clinical relevance of assessing body composition, particularly myosteatosis, in future studies in order to propose individualized interventions.

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Statement of authorship

Nilian Carla Souza: (1) designed research, acquisition, analysis and interpretation of data; (2) drafting the article and critical revision of important intellectual content; (3) final approval of the version to be submitted.

Maria Cristina Gonzalez: (1) designed research, analysis and interpretation of data; (2) critical revision of revision of important intellectual content; (3) final approval of the version to be submitted.

Renata Brum Marttucci: (1) designed research, acquisition of data; (2) revision of important intellectual content; (3) final approval of the version to be submitted.

Viviane Dias Rodrigues: (1) designed research; (2) critical revision of important intellectual content; (3) final approval of the version to be submitted.

Nivaldo Barroso de Pinho: (1) designed research; (2) critical revision of important intellectual content; (3) final approval of the version to be submitted.

Antonio Ponce de Leon: (1) analysis and interpretation of data, (2) critical revision of important intellectual content, (3) final approval of the version to be submitted.

Carla Maria Avesani: (1) the conception and design of the study, analysis and interpretation of data, (2) drafting the article and critical revision of important intellectual content, (3) final approval of the version to be submitted.

Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.02.026.

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