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Original article

Phase angle as a marker for muscle abnormalities and function in patients with colorectal cancer

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SUMMARY

Background and aims: Considering the applicability of phase angle (PhA) as a marker of muscle mass and function, we aimed to investigate whether PhA is a predictor of muscle abnormalities and function in patients with cancer.

Methods: In a sample of patients with colorectal cancer (CRC), PhA was obtained from measurements of resistance and reactance from bioelectrical impedance analysis. Computerized tomography imaging at the third lumbar vertebra was used to evaluate muscle abnormalities by quantifying skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD). Muscle function was assessed by handgrip strength (HGS) and gait speed (GS).

Results: This cross-sectional study included 190 participants (X±SD), mean age 60.5 ± 11.3 years; 57% men; 78% had cancer stages III to IV. PhA was highly correlated with SMI ($r = 0.70$) and moderately correlated with HGS ($r = 0.54$). PhA explained 48% of the SMI variability ($R^2 = 0.485$), 21% of the SMD variability ($R^2 = 0.214$), 26% of HGS ($R^2 = 0.261$) and 9.8% of GS ($R^2 = 0.098$). In the multivariate model adjusted for age, sex, body mass index, performance status, comorbidities and cancer stage, 1-degree decrease in PhA was associated with low SMI (Odds Ratio (OR) = 6.56, 95% CI: 2.90–14.86) and with low SMI and HGS combined (OR = 11.10, 95% CI: 2.61–47.25). In addition, Receiving Operating Characteristics curve analysis showed that PhA had a good diagnostic accuracy for detecting low SMI, low SMI and SMD combined, low SMD and HGS and low SMI and HGS combined (AUC = 0.81, 95% CI: 0.74–0.88; AUC = 0.88, 95% CI: 0.81–0.95; AUC = 0.80, 95% CI: 0.70–0.91; AUC = 0.82, 95% CI: 0.74–0.89; respectively).

Conclusions: PhA was a predictor of muscle abnormalities and function and had a good diagnostic accuracy for detecting low muscle mass, low muscle mass and radiodensity, low muscle radiodensity and strength, and low muscle mass and strength in patients with CRC.

1. Introduction

Bioelectrical impedance analysis (BIA)-derived phase angle (PhA) has been used as a prognostic marker in cancer [1–5]. Phase angle, which is a direct derivative of reactance and resistance measurements, has been interpreted as an indicator of the amount and quality of soft tissue cells, cell membrane integrity, and water distribution between

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the intra- and extracellular spaces [6,7]. Additionally, PhA has recently emerged as a marker of muscle mass and function in several scenarios and clinical conditions [1,2,8–16].

Emerging evidence suggests that muscle composition in older adults is associated with lower strength and mobility, independently of muscle size [17–20]. As such, the European Working Group on Sarcopenia in Older People in 2018 extended measures from solely muscle mass to muscle quality evaluations, where PhA was included as a possible marker [21]. Although muscle quality is originally defined as muscle strength or power per unit of muscle mass [22], evidence suggests that other factors including muscle composition, intramuscular fat infiltration and fibrosis are implicated in its assessment, which impact muscle radiodensity [23].

Gold-standard body composition methods such as computerized tomography (CT) have been used to assess muscle abnormalities by determining skeletal muscle mass and radiodensity at the level of the third lumbar vertebra (L3) in oncology research settings [24]. These images are opportunistically obtained from abdominal CT scan of patients with colorectal cancer (CRC) as part of diagnosis and follow up [25]. Unfortunately, however, this method cannot be implemented as routine clinical practice of muscle abnormalities due to its high cost and the exposure to radiation dose. In addition, routine serial analysis for assessing the response to nutritional interventions is currently not feasible.

Phase angle incorporates both quantity and quality of muscle mass into a fast-noninvasive marker that is potentially useful in assessing patients with cancer [26,27]. Previous studies reported that patients with cancer with a lower PhA had decreased muscle mass and function [1,2,28], although conflicting results exist [29,30]. Two recent studies have shown a moderate correlation between PhA and CT-derived skeletal muscle mass and radiodensity in critically ill patients [14] and in patients with cirrhosis [15], the latter showing a good diagnostic accuracy for detection of low muscle mass [15]. However, the relationship between PhA and CT-derived muscle abnormalities has not been studied in patients with cancer.

Considering the applicability of PhA as a marker of muscle mass and function, this cross-sectional study aimed to investigate the clinical relevance of PhA in predicting muscle abnormalities and function in patients with CRC. Specifically, we explored the diagnostic performance of PhA and its association with skeletal muscle mass and radiodensity from CT, handgrip strength and gait speed.

2. Materials and methods

2.1. Participants and study design

Adult patients with CRC (≥18 years) scheduled to undergo a routine abdominal CT scan which included the L3 region between April 2015 and June 2016 were recruited from an outpatient clinic at the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva (INCA, Rio de Janeiro, Brazil). These included patients at any point in disease trajectory. Participants with physical deformity who were unable to carry out tests for muscle strength or physical performance, with a pacemaker, or who had congestive heart failure, chronic kidney disease and liver cirrhosis were excluded. The study was approved by the Research Ethical Committee from National Cancer Institute José Alencar Gomes da Silva (protocol number 38992014.5.0000.5274) and all participants signed an informed consent prior to participation.

2.2. Study protocol

Participants enrolled in the study received instructions to fast for 6 h before the CT scan (water-soluble oral contrast and medication were allowed). All study measurements were collected in the same day. Before the scan, participants had the anthropometric measurements, patient-generated subjective global assessment (PG-SGA), BIA and muscle function assessed by the same trained dietitian. Clinical data were collected from medical records such as age, sex, previous and current treatment, comorbidities, performance status, tumor site and stage. The same trained dietitian did the CT readings over 3 months after the CT measurements of all participants.

2.3. Nutritional status

Body weight (kg) was assessed using a platform-type mechanical scale (Filizola, Sao 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, according to the standardized protocols [31]. Body mass index (BMI) was calculated as body weight in kilograms divided by squared height and was classified using World Health Organization criteria [32]. In addition, each patient is classified as well nourished (PG-SGA A) and malnourished (PG-SGA B and C) [33].

2.4. Computerized tomography

Contrast-enhanced CT images were acquired for medical diagnosis/follow-up purposes and were digitally stored in the patient's medical record. The transverse image at the L3 level most clearly displaying both vertebral transverse processes with clear differentiation between the muscle and surrounding tissue without artifacts and no muscle cut-points was selected. Twenty CT images were randomly selected and blindly re-measured by an experienced evaluator. The inter-observer coefficient of variation was 0.52% for skeletal muscle mass. Computerized tomography images were analyzed for muscle cross sectional area (cm^2) at L3 (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus) using the Slice-O-Matic software, version 5.0 (Tomovision, Montreal, Quebec, Canada). Computerized tomography Hounsfield unit (HU) thresholds for skeletal muscle were −29HU to +150HU [25]. Skeletal muscle area was normalized by height square (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2). Skeletal muscle radiodensity (SMD) was also evaluated based on averaging the Hounsfield unit of skeletal muscle cross-sectional area. Low SMI was classified according to Derstine et al.: <45.4 cm^2/m^2 for male and <34.4 cm^2/m^2 for female [34]. Low SMD was classified as < 30 HU [35].

2.5. Bioelectrical impedance analysis

Bioelectrical impedance analysis was performed with a tetrapolar device model Quantum II (RJL Systems, Detroit, MI, USA). Participants were asked not to eat or drink anything during 6 h preceding the evaluation. Four electrodes were placed on the dorsal surface of the right hand, wrist, foot and ankle and participants rested for 5 min in a lying position with legs apart and arms not touching the torso. During the measurement, a current of low intensity (800 μA) was emitted at a frequency of 50 kHz. Resistance and reactance in Ohms (Ω) provided by the analyzer were used for the estimation of PhA (PhA (°) = arc tangent (reactance Ω/resistance Ω) x (180/π)). Individuals in the first quartile were considered of having low PhA: < 5.10° for males and <4.73° for females.

2.6. Muscle strength and performance

Handgrip strength (HGS) was measured using a hydraulic dynamometer (Jamar®, Sammons Preston, Chicago, IL).

Participants sat in a chair, placed their elbow at a 90° angle, and were asked 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. Handgrip strength was considered low when <30 kg for male and <16 kg for female (2.5 SD below the mean of a reference Brazilian population) [36].

Gait speed test (GS) was applied to assess muscle performance. Participants were instructed to walk as fast as possible without 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 for use. Gait speed was considered low when ≤0.8 m/s [21].

2.7. Statistical analyses

Clinical data, anthropometric, CT and BIA results are presented as means and standard deviations or median and interquartile range stratified by sex, depending on its normality distribution (assessed by Shapiro–Wilk test). We first examined the Pearson correlation coefficients for PhA, SMI, SMD, HGS, GS, age and clinic parameters. The correlation coefficient was interpreted as follows: 0.00–0.30 negligible, 0.30–0.50 low, 0.50–0.70 moderate, 070–0.90 high and 0.90–1.00 very high [37]. Next, linear regression models among SMI, SMD, HGS, GS and clinical variables (such as sex, age, BMI, performance status, cancer stage, comorbidities and cancer treatment in the 3 months prior to enrollment) were evaluated. Variables with $p < 0.05$ will be used in multivariate regression models, in addition to age and sex (variables well known to influence muscle mass and function). Subsequently, liner regression analyses were conducted to verify the association of PhA (independent variable) with SMI, SMD, HGS and GS (dependent variable) using simple and multiple linear regression model (adjusted for sex, age, BMI, performance status, comorbidities and cancer stage). SMI, HGS and GS, were 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}. 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. Logistic regression analyses were done to verify the association between PhA (independent variable) and muscle abnormalities and function categories (low SMI, low SMD, low HGS, low GS, low SMI and SMD combined, low SMD and HGS combined, low SMI and HGS combined and low SMI, HGS and GS combined) using simple and multiple regression model. When PhA was analyzed as a continuous variable, odds ratio (OR) was expressed for every 1-degree decrease in PhA to show increased risk. Multiple linear and logistic regression models were assessed within 188 participants because performance status of two participants were missing.

Lastly, receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of PhA for detection muscle abnormalities and function. Diagnostic accuracy was considered excellent for area under the receiver operating characteristic curve (AUC) values between 0.90 and 1.00, good for 0.80–0.90; fair for 0.7–0.8, poor for 0.60–0.70, and failed for values between 0.50 and 0.60 [38]. Statistical significance was defined as $p < 0.05$. STATA software version 16 (StataCorp, College Station, TX, USA) was used for statistical analyses.

3. Results

From 194 participants initially included in the study, 190 were eligible to participate. Four participants were excluded due to lack of CT scans (n = 2), due lack of BIA (n = 1) and lack of GS test (n = 1). A total of 190 participants were enrolled in the study, mostly males (n = 109; 57%) with a mean age of 60.5 ± 11.3 years, and mean BMI of 27.3 ± 5.4 kg/m^2; 62% (n = 118) presented with overweight or obesity. In addition, most participants (68%; n = 130) were well-nourished according to PG-SGA, had cancer stage III (n = 52; 27%) and IV (n = 96; 51%) and performance status 1–2 (n = 109; 58%). Most participants (n = 119; 63%) were not receiving cancer treatment (chemotherapy, radiotherapy, or surgery) in the 3 months before enrollment in the study, whereas 71 participants (37%) were receiving treatment, either chemotherapy or radiotherapy. The PhA, SMI, SMD, HGS and GS were significantly higher in male when compared to female participants (Table 1). Out of 190 participants, 47 (25%) had low SMI, 64 (34%) had low SMD, 28 (15%) low HGS, 16 (8%) low GS, 18 (9%) low SMI and SMD combined, 13 (7%) low SMD

Table 1
Main characteristics of the patients according to sex (n = 190).

	Total (n = 190)	Men (n = 109)	Women (n = 81)	*p*
Age (years)	60.5 ± 11.3	60.1 ± 12.1	60.9 ± 10.3	0.645[a]
PG-SGA[d]				
A	130 (68.8%)	73 (68%)	57 (70%)	0.855[b]
B and C	59 (31.2%)	35 (32%)	24 (30%)	
Tumor stage				
0-II	42 (22.1%)	21 (19%)	21 (26%)	0.274[b]
III-IV	148 (77.9%)	88 (81%)	60 (74%)	
Performance status[e]				
0	79 (42%)	49 (45%)	30 (37%)	0.280[b]
1-2	109 (58%)	59 (55%)	50 (63%)	
Body mass index (kg/m^2)	27.0 (22.9; 31.1)	27.0 (23.2; 29.3)	26.9 (22.8; 32.9)	0.208[c]
Phase angle (°)	5.59 ± 0.9	5.8 ± 0.9	5.3 ± 0.8	<0.001[a]
Skeletal muscle index (cm^2/m^2)	46.6 (41.0; 52.8)	49.1 (44.6; 56.7)	43.1 (37.4; 47.6)	<0.001[c]
Skeletal muscle radiodensity (HU)	34.4 ± 7.9	37.1 ± 7.2	30.6 ± 7.4	<0.001[a]
Handgrip strength (kg)	29.0 (23.0; 36.0)	36.0 (30.0; 41.0)	22.0 (18.0; 27.0)	<0.001[c]
Gait speed (m/s)	1.07 (0.92; 1.20)	1.12 (0.94; 1.34)	1.0 (0.87–1.11)	<0.001[c]

Results are shown as n (%), mean ± standard deviation or median (IQR Q1–Q3).
[a] t – test.
[b] Chi-square test.
[c] Mann–Whitney test.
[d] n = 189.
[e] n = 188.

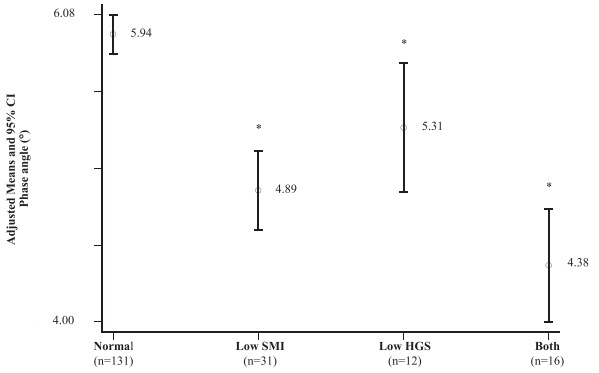

Fig. 1. Box plot of phase angle adjusted by sex according to muscle abnormalities and function categories (n = 190). Results are shown as median (IQR Q1–Q3); Normal = 5.94° (5.81°; 6.07°); Low SMI = 4.89° (4.62°; 5.16°); Low HGS = 5.31° (4.88°; 5.75°); Both = 4.38° (3.99°; 4.76°). SMI: skeletal muscle mass; HGS: handgrip strength; *$p < 0.001$ when compared to normal group.

and HGS combined, and 16 (8%) low SMI and HGS combined. Considering the low prevalence of low SMI, HGS and GS combined (n = 5), these results were not shown. According to Figs. 1 and 2, PhA was significantly lower among individuals with low SMI, low SMD or low HGS and with low SMI and SMD or with low SMI and HGS combined compared with those without muscle mass abnormalities and low strength ($p < 0.001$).

Table 2 shows correlations among PhA and age, clinic parameters, muscle abnormalities, and function; PhA was strongly correlated with SMI (r = 0.70) and moderately correlated with HGS (r = 0.54). Linear regression analysis of PhA predicting muscle abnormalities and function is shown in Table 3. In the crude model, PhA explained 48% of the SMI variability ($R^2 = 0.48$), 21% of the SMD variability ($R^2 = 0.21$), 26% of HGS ($R^2 = 0.26$) and 10%% of GS ($R^2 = 0.10$) ($p < 0.001$). In addition, 1-degree increase in PhA augmented the expected value of SMI, HGS, GS by in 6%, 8% and 3%, respectively, and increased almost 4 units of SMD. In the multivariate regression analysis adjusted for age, sex, BMI, performance status, comorbidities and cancer stage, the association remained significant for all variables, except for GS (Table 3).

Table 4 shows the logistic regression analysis of PhA predicting muscle abnormalities and function categories. In the multivariate model, 1-degree decrease in PhA was associated with low SMI (OR = 6.56, 95% CI: 2.90–14.86) and also with low SMI and HGS combined (OR = 11.10, 95% CI: 2.61–47.25) (Table 4 and Fig. 3). ROC analysis indicated fair to good predictive abilities of PhA for detection muscle abnormalities and function (AUC: 0.71–0.88) and improved with model adjustment (AUC: 0.87–0.95). In the crude model, PhA had a good diagnostic accuracy for detecting low SMI (AUC = 0.81, 95% CI: 0.74–0.88; adjusted AUC = 0.91, 95% CI: 0.87–0.96), low SMI and SMD combined (AUC = 0.88, 95% CI: 0.81–0.95; adjusted AUC = 0.90, 95% CI: 0.83–0.97), low SMD and HGS combined (AUC = 0.80, 95% CI: 0.70–0.91; adjusted AUC = 0.92, 95% CI: 0.87–0.98), and low SMI and HGS combined (AUC = 0.82, 95% CI: 0.74–0.89; adjusted AUC = 0.95, 95% CI: 0.92–0.98), Table 4. The association between the lower quartile of PhA and muscle abnormalities and function was also observed for SMI, SMD and HGS in the crude and adjusted models, except for GS (Supplementary Tables 1 and 2).

4. Discussion

This is the first study investigating the association between PhA with CT-derived muscle abnormalities and function in patients with cancer. This study showed that PhA was lower among patients with CRC who presented with low SMI, low SMD or low HGS and those with both low SMI and low SMD, and low SMI and low HGS adjusted by sex. Phase angle was highly correlated with SMI and

Table 2
Pearson and Spearman correlation coefficients for age, clinic parameters, muscle abnormalities, function and phase angle (n = 190).

	Skeletal muscle index (cm^2/m^2)[c]	Skeletal muscle radiodensity[b]	Handgrip strength (kg)[c]	Gait speed (m/s)[c]
Age (years)	−0.21[a]	−0.43[a]	−0.22[a]	−0.27[a]
Performance status[d]	−0.11	−0.08	−0.24[a]	−0.25[a]
Comorbidities[e]	0.04	−0.24[a]	−0.17[a]	−0.15[a]
Cancer stage[f]	−0.06	0.001	0.05	0.004
Body mass index (kg/m^2)	0.55[a]	−0.23[a]	0.08	0.09
Phase angle (°)	0.70[a]	0.47[a]	0.54[a]	0.31[a]
Skeletal muscle index (cm^2/m^2)	1.00	0.37[a]	0.50[a]	0.20[a]
Skeletal muscle radiodensity (HU)	0.37[a]	1.00	0.44[a]	0.34[a]
Handgrip strength (kg)	0.50[a]	0.44[a]	1.00	0.50[a]
Gait speed (m/s)	0.20[a]	0.34[a]	0.50[a]	1.00

[a] $p < 0.05$.
[b] Pearson's test.
[c] Spearman's test.
[d] Performance status: 0–2 (n = 188).
[e] Number of comorbidities: 0, 1 and ≥2.
[f] Cancer stage: 0–IV.

Table 3
Crude and adjusted linear regression analysis of muscle abnormalities and function (dependent variable) and phase angle (independent variable) (N = 188).

	Skeletal muscle index (log)[a]			Skeletal muscle radiodensity (HU)			Handgrip strength (log)[a]			Gait speed (log)[a]		
	β (95%CI)	*p*	Adj. R^2	β (95%CI)	*p*	Adj. R^2	β (95%CI)	*p*	Adj. R^2	β (95%CI)	*p*	Adj. R^2
Phase angle (°)												
Crude	1.06 (1.05; 1.07)	< 0.001	0.48	3.91 (2.84; 4.97)	< 0.001	0.21	1.08 (1.06; 1.10)	< 0.001	0.26	1.03 (1.02; 1.05)	< 0.001	0.10
Adjusted[b]	1.04 (1.03; 1.05)	< 0.001	0.67	3.52 (2.37; 4.66)	< 0.001	0.50	1.04 (1.02; 1.06)	< 0.001	0.64	1.02 (1.0; 1.04)	0.056	0.19

95% CI: 95% confidence interval.
[a] Skeletal muscle index, handgrip strength and gait speed were log-transformed: β (phase angle) = Exp *β* (phase angle).
[b] Model adjusted for sex, age, body mass index, performance status, comorbidities and cancer stage.

Table 4
Crude and adjusted logistic regression analysis of muscle abnormalities and function categories (dependent variable) and phase angle (independent variable) (n = 188).

	Low skeletal muscle index[b] (n = 47)		Low skeletal muscle radiodensity[c] (n = 64)		Low handgrip strength[d] (n = 28)		Low gait speed[e] (n = 16)		Low skeletal muscle index + skeletal muscle radiodensity (n = 18)		Low skeletal muscle radiodensity + handgrip strength (N = 13)		Low skeletal muscle index + handgrip strength (n = 16)	
	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)	OR (95%CI)	AUC (95%CI)
Phase angle ()[a]														
Crude	4.31 (2.52; 7.35)	0.81 (0.74; 0.88)	3.88 (2.41; 6.24)	0.79 (0.72; 0.85)	2.26 (1.38; 3.70)	0.71 (0.61; 0.81)	3.04 (1.57; 5.87)	0.75 (0.62; 0.87)	7.26 (3.06; 17.22)	0.88 (0.81; 0.95)	3.47 (1.66; 7.26)	0.80 (0.70; 0.91)	3.95 (1.93; 8.08)	0.82 (0.74; 0.89)
Adjusted[f]	6.56 (2.90; 14.86)	0.91 (0.87; 0.96)	5.63 (2.73; 11.60)	0.87 (0.82; 0.92)	3.05 (1.40; 6.68)	0.88 (0.82; 0.95)	2.18 (0.90; 5.28)	–	6.57 (2.28; 18.91)	0.90 (0.83; 0.97)	7.64 (1.99; 29.25)	0.92 (0.87; 0.98)	11.10 (2.61; 47.25)	0.95 (0.92; 0.98)

OR: Odds ratio; AUC: area under the curve; All parameters were statistically significant ($p < 0.05$) except for gait speed.

[a] Negative phase angle was used to show risk.

[b] Skeletal muscle index <45.4 cm^2/m^2 (male) and <34.4 cm^2/m^2 (female) [34].

[c] Skeletal muscle density <30 HU [35].

[d] Handgrip strength <30 kg (male) and <16 kg (female) (2.5 SD below the mean of a reference Brazilian population) [36].

[e] Gait speed ≤0.8 m/s [21].

[f] Model adjusted for sex, age, body mass index, performance status, comorbidities and cancer stage.

moderately correlated with HGS. Furthermore, PhA was an independently predictor of muscle abnormalities and function and had a good diagnostic accuracy for detecting low SMI, low SMI and SMD combined, low SMD and HGS combined, and low SMI and low HGS combined.

Previous studies have also explored the relationship among similar variables in clinical populations. Kosoku et al. reported a lower PhA in kidney-transplanted patients with low muscle mass and strength [13]. In studies in older participants, decreased PhA was also found in individuals with low muscle mass and strength [9,11,12]. In two studies, Norman et al. showed that patients with cancer who had PhA below the 5th percentile had decreased muscle strength [1,2]. In a study with breast cancer survivors, PhA was associated with strength [29]. Souza et al. also found lower PhA in patients with CRC who had low SMI, HGS and GS combined [28].

Phase angle has also been considered an indicator of muscle abnormalities and function in some clinical conditions. Looijaard et al. found a moderate correlation between CT-derived muscle mass ($r = 0.54$, $p < 0.001$) with PhA in critically ill patients [14]. Similarly, Ruiz-Margáin et al. found a moderate and significant correlation between SMI and PhA in patients with cirrhosis irrespective of the presence of ascites ($r = 0.58$ for all, $r = 0.55$ without ascites, $r = 0.60$ with ascites, $p < 0.001$) [15]. In a study with kidney-transplanted patients, dos Reis et al. showed that PhA was associated with HGS but not with muscle mass or GS [39]. In the oncology study by Norman et al. mentioned above, PhA was moderately and significantly correlated with strength ($r = 0.59$ and 0.48 for men and women, respectively, $p < 0.0001$) [1]. In a study with breast cancer survivors PhA accounted for 22% of variance in strength ($R^2 = 0.22$, $p < 0.01$) but remained a borderline predictor after adjustments for age and physical activity level ($R^2 = 0.36$, $p = 0.05$) [29]. We found that PhA accounted for 26% ($R^2 = 0.26$) and also remained a predictor for strength variance independently of age, sex, BMI, performance status, comorbidities and cancer stage ($R^2 = 0.64$, $p < 0.001$). Similar to our study, PhA had a weak correlation with GS ($r = 0.24$; $p = 0.023$) in older women [30]. Looijaard et al. found a high positive correlation between CT-derived SMD ($r = 0.70$, $p < 0.001$) with PhA in critically ill patients [14]. On the other hand, some studies using ultrasound to assess muscle quality found a weak association between PhA and echogenicity of the quadriceps femoris muscle in older [11] and healthy adults [27]. It is worth noting that only three of the studies mentioned above used CT to assess muscle mass [14,15,28]. The majority used BIA to estimate muscle mass [9,11–13,39,40].

According to our study, PhA had a good diagnostic accuracy for detecting low SMI and low SMI and HGS combined. These results suggest that PhA is a marker of muscle mass and function in this subset of patients. Hirose et al. found similar results in male hospitalized patients with cardiovascular disease (AUC = 0.82 for males and 0.77 for females) [16]. Some studies found a moderate predictive ability of PhA for incident disability in older adults (AUC = 0.76 for male and 0.71 for female) [10], in patients with cirrhosis [15] and kidney-transplanted patients [13] (AUC = 0.70 and 0.73, respectively). To the best of our knowledge, this is the first study comparing PhA to SMI and SMD combined and SMD and HGS combined. The fact that PhA had a good diagnostic accuracy for detecting low muscle mass and radiodensity and low muscle radiodensity and strength confirms the utility of PhA as a novel muscle quality tool.

Although the majority of studies found a positive association between muscle mass and function with PhA, in a study with older women, low PhA was not associated with muscle mass and strength [30]. Similarly, Gomes et al. found that patients with cancer with PhA above 4° had no risk for fatigue in a multiple logistic regression analyses controlled for weight loss, age, sex, and hydration [41]. In kidney-transplanted patients, PhA was associated with strength but

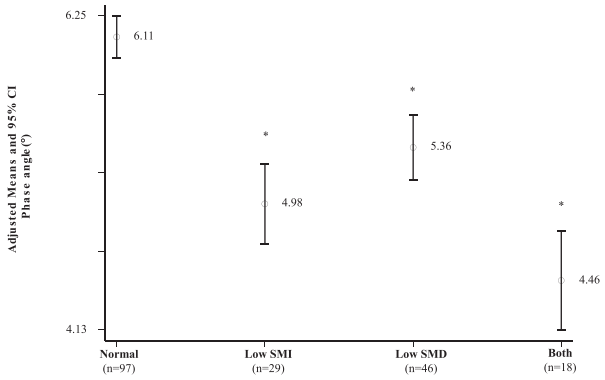

Fig. 2. Box plot of phase angle adjusted by sex according to muscle abnormalities categories (n=190). Results are shown as median (IQR Q1–Q3); Normal = 6.11° (5.96°; 6.25°); Low SMI = 4.98° (4.71°; 5.25°); Low SMD = 5.36° (5.14°; 5.58°); Both = 4.46° (4.13°; 4.79°). SMI: skeletal muscle mass; SMD: skeletal muscle radiodensity; $^{*}p < 0.001$ when compared to normal group.

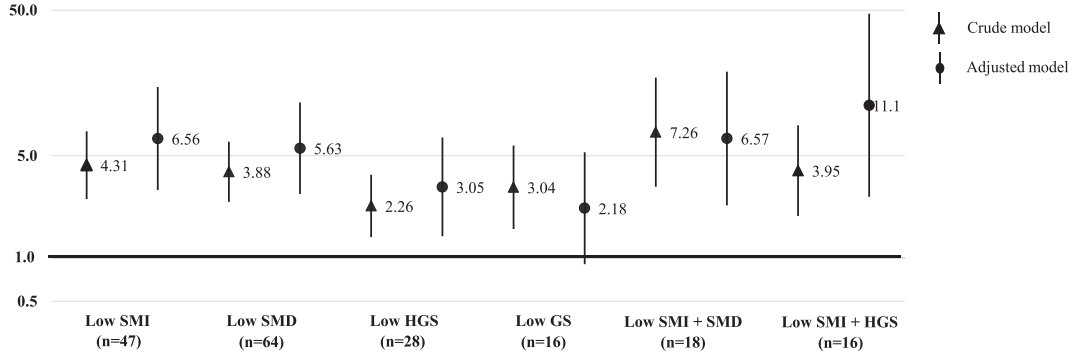

Fig. 3. Muscle abnormalities and function odds ratio for 1-degree decrease in phase angle (n = 190). Results are shown as odds ratio and 95% confidence interval. Model adjusted for sex, age, body mass index, performance status, comorbidities and cancer stage. SMI: skeletal muscle mass; SMD: skeletal muscle radiodensity; HGS: handgrip strength; GS: gait speed.

not with muscle mass and strength combined [39]. These discrepancies may be explained by the use of different BIA devices and prediction equations to estimate muscle mass [42], incorrect use of population cut-off [41], use of PhA as a dependent variable [30,39,41], inappropriate selection of confounding variables in multivariable regression models among studies [41], differences in target group studied [30,39], and in the outcome measures explored [41].

Although CT is frequently used as a gold-standard tool to assess body composition in oncology populations, these images can only be used opportunistically for this purpose. As such, availability of images and of the landmark of interest (i.e. L3), and the need for training limit the use of CT for body composition research purposes. On the other hand, BIA is a portable, non-invasive and an inexpensive method. Although BIA has limited applicability in patients with obesity and those with edema [43], BIA vector analysis has emerged as a relatively novel technique for assessing hydration status in patients with cancer and can overcome BIA conventional limitations [44]. Phase angle is an objective measure determined by BIA and can be calculated directly without a regression equation [6]. Nonetheless, the relationship between PhA and muscle mass and function is not completely understood. Phase angle is a predictor of cell membrane integrity and alterations in fluid balance, and a marker of the amount and quality of soft tissue which reflects muscle cell damage and functional impairment [6,45]. Possible mechanisms explaining abnormal muscle composition and muscle function include changes in muscle size and density including loss of myofibers, changes in architecture and fiber types, alteration in mitochondrial function and neural activation, increases in extracellular fluid, fat infiltration and/or fibrosis [23]. These may potentially explain the association between PhA and muscle mass, muscle radiodensity and strength [23].

As mentioned above, our study was the first to explore association of PhA with function and muscle abnormalities in cancer, the latter using a state-of-the-art technique for measuring both muscle mass and radiodensity. Images were analyzed by a single trained researcher, in a representative and relatively large sample of patients with CRC. However, some limitations should be acknowledged. First, the cross-sectional nature of the study precluded a causal–effect relationship between PhA, muscle abnormalities and function. Second, because this was a convenient sample including patients across various points in the cancer care trajectory, we are unable to draw conclusions regarding the impact of treatment on PhA, muscle mass and/or physical function. Third, we lack Brazilian population-specific reference values for low muscle mass so we are uncertain if the cutpoint used is ideal for our cohort. Fourth, contrast-enhanced CT images could influence SMD values.

In conclusion, the present study provided evidence that PhA was a predictor of muscle abnormalities and function and had a good diagnostic accuracy for detecting low muscle mass, low muscle mass and radiodensity, low muscle radiodensity and strength, and low muscle mass and strength. Therefore, PhA may be a practical alternative marker to reflect abnormalities in muscle mass and function in clinical practice. Future longitudinal studies are needed

to investigate the impact of low and change in PhA on muscle mass, muscle radiodensity and strength and subsequent adverse clinical outcomes in cancer.

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Authors' contribution

NCS: Investigation, Formal analysis, Visualization, Writing- Original draft preparation. CMA: Conceptualization, Methodology, Visualization, Writing- Original draft preparation. CMP: Visualization, Writing- Original draft preparation. RBM: Supervision, Writing- Reviewing and Editing. VDR: Resources, Writing- Reviewing and Editing. NBP: Resources, Writing- Reviewing and Editing. SBH: Visualization, Writing- Original draft preparation. MCG: Conceptualization, Methodology, Formal analysis, Visualization, Writing- Original draft preparation.

Conflict of interest

CMP reports grants from Campus Alberta Innovation Program during the conduct of the study; personal fees from Consultancy, personal fees from Payment for lectures including service on speakers' bureaus, outside the submitted work. SBH reports personal fees from Tanita Corporation, Medical Advisory Board, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.06.013.

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