

Circulating Biomarkers and CT-Derived Muscle Indices in Colon Cancer: A Comprehensive Evaluation of Sarcopenia

Costel-George Gherghescu^{1,2†}, Radu Andrei Baz^{2,3†}, Constantin Dina^{3†*}, Catalin Nicolae Grasa^{3,4*}, Andrei Dumitru^{3,5†}, Georgeta Camelia Cozaru^{6†}, Mihaela Manea^{6†}, Ioana Popescu^{3,5†}, Ana-Maria Grigorescu^{3†}, Stere Popescu^{3†}, and Eugen Dumitru^{3,5,6,7†}

¹PhD School of Medicine, Ovidius University of Constanta, Romania

²Clinical Laboratory of Radiology and Medical Imaging, Sf. Apostol Andrei County Emergency Hospital, Constanta, Romania

³Medicine Faculty, Ovidius University of Constanta, Romania

⁴General Surgery Department, Sf. Apostol Andrei Emergency County Hospital, Constanta, Romania

⁵Gastroenterology Department, Sf. Apostol Andrei Emergency County Hospital, Constanta, Romania

⁶Research Center for the Morphological and Genetic Study in Malignant Pathology, Ovidius University of Constanta, Romania

⁷Academy of Romanian Scientist, Bucharest, Romania

*Corresponding author:

Catalin Nicolae Grasa, MD
General Surgery Department
Sf. Apostol Andrei Emergency County
Hospital, 900591 Constanta, Romania
E-mail: catalin.grasa@yahoo.com
Constantin Dina, MD
Anatomy Department
Ovidius University of Constanta
1 University Street, 900470, Romania
E-mail: constantin-dina@365.univ-ovidius.ro

[†]These authors share equal contribution.

Rezumat

Biomarkeri circulanți și indici musculari derivați din CT în cancerul de colon: o evaluare cuprinzătoare a sarcopeniei

Context: Sarcopenia și pierderea masei musculare asociată cancerului reprezintă aspecte relevante din punct de vedere clinic la pacienții cu cancer de colon, însă evaluarea acestora necesită integrarea forței musculare, a cantității sau calității musculare și a performanței fizice. Biomarkerii circulanți și indici musculari derivați din CT pot furniza informații complementare privind modificările musculare, deși performanța lor diagnostică individuală rămâne incertă.

Metode: Acest studiu observațional a inclus 30 de pacienți cu cancer de colon confirmat histologic și 30 de persoane în grupul de control. Participanții au fost evaluați prin tomografie computerizată (CT), măsurători antropometrice și de compoziție corporală, precum și prin analize biochimice. Cantitatea de masă musculară a fost evaluată la nivelul celei de-a treia vertebre lombare (L3), utilizând indicele muscular scheletic (SMI) și indicele mușchiului psoas (PMI), în timp ce biomarkerii circulanți au fost determinați prin metoda imunoenzimatică ELISA (enzyme-linked immunosorbent assay). Analizele statistice au inclus comparații între grupuri, analiza curbei caracteristice de operare a receptorului (ROC), cu estimarea ariei de sub curbă (AUC), analiza precision-recall și un model exploratoriu de regresie logistică binară multivariată.

Rezultate: Pacienții cu cancer de colon au prezentat diferențe moderate ale profilului biomarkerilor circulanți comparativ cu persoanele din grupul de control, inclusiv valori mai scăzute ale osteonectinei și IGF-1 și valori mai ridicate ale P3NP. Indicii musculari derivați din CT au fost, în general, comparabili între grupuri. Analiza ROC a evidențiat o capacitate discriminatorie limitată pentru biomarkerii evaluați, fără diferențe semnificative statistic între grupuri în ceea ce privește valorile AUC. În modelul exploratoriu de regresie logistică multivariată, niciunul dintre biomarkerii

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evaluați și niciunul dintre indicii musculari derivați din CT nu s-a asociat independent cu statusul de cancer de colon.

Concluzii: Biomarkerii circulanți și indicii musculari derivați din CT evaluați au prezentat o capacitate discriminatorie limitată atunci când au fost analizați individual. Aceste rezultate sugerează că parametrii biochimici și cei derivați din imagistică ar trebui interpretați în cadrul unui context clinic mai larg. Deoarece forța musculară și performanța fizică nu au fost evaluate, prezentul studiu nu stabilește un diagnostic de sarcopenie definit conform criteriilor EWGSOP2 și trebuie interpretat ca o evaluare a cantității musculare determinate prin CT și a corelațiilor săi biochimici.

Cuvinte cheie: sarcopenie, cancer de colon, biomarkeri, indice de masă musculară scheletică, indice al mușchiului psoas, tomografie computerizată, atrofie musculară, inflamație

Abstract

Background: Sarcopenia and cancer-associated muscle loss are clinically relevant in patients with colon cancer, but their assessment requires the integration of muscle strength, muscle quantity or quality, and physical performance. Circulating biomarkers and CT-derived muscle indices may provide complementary information regarding muscle-related alterations, although their individual diagnostic performance remains uncertain.

Methods: This observational study included 30 patients with histologically confirmed colon cancer and 30 individuals in a control group. Participants were evaluated using computed tomography (CT), anthropometric and body composition measurements, and biochemical analysis. Muscle quantity was assessed at the level of the third lumbar vertebra (L3) using the skeletal muscle index (SMI) and psoas muscle index (PMI), while circulating biomarkers were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses included between-group comparisons, receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) estimation, precision–recall analysis, and an exploratory multivariable binary logistic regression model.

Results: Patients with colon cancer showed modest differences in circulating biomarker profiles compared with controls, including lower Osteonectin and IGF-1 levels and higher P3NP levels. CT-derived muscle indices were broadly comparable between groups. ROC analysis demonstrated limited discriminatory performance for the evaluated biomarkers, with no statistically significant differences in AUC between groups. In the exploratory multivariable logistic regression model, none of the evaluated biomarkers or CT-derived muscle indices was independently associated with colon cancer status.

Conclusions: The evaluated circulating biomarkers and CT-derived muscle indices showed limited discriminatory performance when considered individually. These findings suggest that biochemical and imaging-derived measures should be interpreted within a broader clinical framework. Because muscle strength and physical performance were not assessed, the present study does not establish an EWGSOP2-defined diagnosis of sarcopenia and should be interpreted as an evaluation of CT-defined muscle quantity and its biochemical correlates.

Keywords: sarcopenia, colon cancer, biomarkers, skeletal muscle index, psoas muscle index, computed tomography, muscle wasting, inflammation

Introduction

Sarcopenia, defined as a progressive and generalized loss of skeletal muscle mass and function, has emerged as a significant clinical factor influencing outcomes in patients with colorectal cancer (1). Initially described in the context of aging, sarcopenia is now increasingly recognized in oncological settings, where it reflects a complex interplay between cancer-related inflammation, malnutrition, and metabolic alterations (2,3).

Colorectal cancer remains one of the most common malignancies worldwide and a leading cause of cancer-related mortality, despite advances in multidisciplinary treatment strategies (4).

Globally, colorectal cancer accounted for over 1.9 million new cases and more than 900,000 deaths in

2022, confirming its position as the third most common cancer and the second leading cause of cancer-related mortality worldwide (5,6). Regions such as Europe and North America cluster in the upper-right area of the graph, showing higher incidence values (often exceeding 20–30 cases per 100,000) along with elevated mortality rates, reflecting both increased disease burden and longer life expectancy.

Within this context, nutritional status and body composition have gained increasing attention as prognostic indicators (7,8). Sarcopenia, considered a specific form of cancer-associated malnutrition, has been consistently associated with adverse short-term and long-term outcomes, including increased post-operative complications, prolonged hospitalization, and reduced survival rates (9).

The assessment of sarcopenia has been facilitated by imaging techniques such as computed tomography, which allows precise quantification of skeletal muscle mass and quality at the level of the third lumbar vertebra (10). This objective evaluation has enabled the identification of sarcopenia as an independent predictor of morbidity and mortality following oncologic colon surgery (11). Furthermore, sarcopenia may impair tolerance to surgical and oncological treatments, contributing to worse clinical outcomes and delayed recovery.

Given its high prevalence and prognostic significance, sarcopenia represents a modifiable risk factor that warrants early identification and targeted intervention in patients with colon cancer.

Diagnosing sarcopenia in oncological patients requires the integration of clinical, imaging, and biological approaches, as no single method fully captures the condition. Clinically, tools such as handgrip strength testing, gait speed assessment, and validated screening questionnaires are used to identify probable sarcopenia, in line with the revised consensus criteria proposed by the European Working Group on Sarcopenia in Older People (EWGSOP2), which defines sarcopenia through the combination of low muscle strength, reduced muscle quantity or quality, and impaired physical performance (12). Imaging techniques, particularly CT-derived skeletal muscle and psoas muscle indices measured at the L3 vertebral level, remain the reference standard for quantifying muscle mass in oncological populations, as they can be obtained from staging scans already performed for cancer diagnosis and treatment planning (10). In parallel, circulating biomarkers reflecting muscle catabolism, extracellular matrix turnover, and impaired anabolic signalling have been proposed as complementary, minimally invasive tools capable of capturing the biological dimension of muscle wasting that imaging alone cannot resolve, although their individual diagnostic accuracy remains inconsistent across studies (13). In patients with colon cancer specifically, these three dimensions, clinical, imaging, and biological, are closely interrelated: tumour-related systemic inflammation and metabolic dysregulation drive biochemical alterations detectable through circulating biomarkers, which in turn parallel the structural muscle loss visible on CT and the functional decline observed at the bedside, underscoring the rationale for a multidimensional diagnostic approach rather than reliance on any single modality (14).

The clinical implications of accurately diagnosing sarcopenia in colon cancer are substantial. Beyond serving as a marker of nutritional and functional decline, sarcopenia has been consistently associated

with increased postoperative morbidity, prolonged hospitalization, and reduced tolerance to surgical and oncological treatment (15). With respect to survival, cohort studies and meta-analyses have shown that sarcopenic patients with colorectal cancer experience significantly shorter overall, disease-free, and recurrence-free survival compared with non-sarcopenic patients, independent of tumour stage (16). A recent international multicentre cohort further demonstrated that sarcopenia and myosteatosis retain independent prognostic value even in early-onset colorectal cancer, reinforcing the relevance of this condition across age groups and disease stages (7). Nevertheless, because currently available diagnostic methods show variable and often limited standalone accuracy, a combined evaluation of imaging-derived muscle indices and circulating biomarkers, as pursued in the present study, is warranted to better characterize sarcopenia in this patient population and to justify the choice of this research topic.

Materials and Methods

Study Design

This observational study was carried out at the Sf. Apostol Andrei County Emergency Clinical Hospital of Constanta, Romania, between January 2024 and March 2026. Both the colon cancer group and the control group were recruited and evaluated during this same period. The study protocol was approved by the institutional Ethics Committee (approval no. 05/04.02.2022), and all procedures were performed in accordance with the ethical standards of the Declaration of Helsinki.

Study Population and Eligibility Criteria

The study population consisted of 30 patients with histologically confirmed colon cancer, alongside a control group of 30 individuals without known malignancy, recruited from national screening program "Systemic Measures for the Implementation, Assurance, and Quality Control of the Colorectal Cancer Screening Program" conducted at the Sf. Apostol Andrei County Emergency Clinical Hospital of Constanta, as a local component. Participants were eligible if they were adults with complete clinical, biochemical, and imaging data available. Baseline demographic and clinical variables, including age, sex, body weight, height, and body mass index (BMI), were obtained from medical records.

Exclusion criteria included severe immobilization, autoimmune diseases, uncontrolled endocrine disorders, advanced heart failure, uremia, septic conditions, or

other comorbidities that could significantly influence muscle metabolism or overall clinical status.

Imaging Assessment and Body Composition Analysis

Skeletal muscle mass and quality were evaluated using CT scans performed as part of routine oncological assessment. Quantitative analysis was conducted at the level of the third lumbar vertebra (L3), which is considered a validated anatomical landmark for whole-body muscle estimation.

Skeletal muscle area was measured through manual delineation of regions of interest on axial CT images at the time of diagnosis. The SMI and PMI were calculated by normalizing muscle area to patient height (cm^2/m^2). Muscle quality was assessed using attenuation values expressed in Hounsfield Units (HU).

In addition to CT-derived indices, anthropometric and body composition parameters were determined by multi-frequency bioelectrical impedance analysis (BIA) using the InBody 770 analyzer (InBody Co., Seoul, South Korea). Measurements were performed with participants in a fasting state, as per manufacturer protocol, on the same day as the clinical evaluation, to ensure methodological reproducibility. These parameters were included as complementary, descriptive indicators of overall nutritional and metabolic status rather than as EWGSOP2 diagnostic criteria for sarcopenia: body water percentage is a required normalization factor in bioimpedance-derived muscle mass estimates, visceral fat relates to the sarcopenic-obesity phenotype increasingly recognized in colorectal cancer, and bone mineral content reflects concurrent osteosarcopenia risk; their comparison across groups therefore contextualizes the SMI/PMI-based muscle-quantity findings within a broader body-composition profile rather than serving as standalone diagnostic endpoints.

Biomarker Assessment

Peripheral venous blood samples were collected pre-op by standard venipuncture, and biomarker measurements were performed promptly after collection. Any remaining plasma was aliquoted and preserved at -80°C for later analyses. Serum concentrations of SPARC, CAF, procollagen type III N-terminal propeptide (P3NP), myostatin (MSTN), and insulin-like growth factor-1 (IGF-1) were quantified using enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturers' instructions.

Muscle mass and quality were evaluated using upper abdominal computed tomography imaging.

Skeletal Muscle Index and Psoas Muscle Index were calculated from non-contrast CT images. Low CT-derived muscle mass, corresponding to the muscle-quantity component of sarcopenia, was defined using established threshold values of $52\text{--}55 \text{ cm}^2/\text{m}^2$ for men and $39\text{--}41 \text{ cm}^2/\text{m}^2$ for women for SMI, while PMI cut-off values were $\leq 6.31 \text{ cm}^2/\text{m}^2$ in men and $\leq 3.91 \text{ cm}^2/\text{m}^2$ in women.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 30.0) (14) and Microsoft Office Excel. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), depending on data distribution (19,20). Categorical variables were presented as absolute frequencies and percentages. The normality of data distribution was assessed using the Shapiro-Wilk test. Differences between groups were evaluated using independent samples t-tests or Mann-Whitney U tests, as appropriate (17). For comparisons involving multiple groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis test was applied (17). Receiver operating characteristic curve analysis was used to assess the diagnostic performance of the evaluated biomarkers. Statistical significance was defined as a p-value < 0.05 (18).

To further explore whether biomarkers and CT-derived indices could jointly discriminate colon cancer patients from controls, a multivariable binary logistic regression model was fitted, with group (colon cancer = 1, control = 0) as the dependent variable and age, sex, Osteonectin, CAF, P3NP, MSTN, IGF-1, PMI, and SMI entered simultaneously as independent variables (Enter method). Results are reported as odds ratios (OR) with 95% confidence intervals (CI). Overall model fit was assessed with the omnibus likelihood-ratio test and Nagelkerke R^2 , and apparent discrimination with the AUC of the predicted probabilities. Because the dependent variable of this model is group membership, the model was intended to assess discrimination between colon cancer patients and controls, not to identify independent predictors of sarcopenia.

With 30 events and nine candidate variables (approximately 3.3 events per variable, below the commonly recommended threshold of ten), the multivariable binary logistic regression model carries a substantial risk of overfitting and unstable parameter estimates. Its results, together with the univariable comparisons presented below, should therefore be regarded as exploratory and hypothesis-generating rather than confirmatory.

Table 1. Descriptive statistics of age distribution according to study groups and sex

		(n=60)		Mean	SD	Median	95.0% Lower CL	95.0% Upper CL
Group	Control group	Sex	Female (14)	Age	65	2	67	61
			Male (16)	Age	62	2	62	56
	Colon cancer group	Sex	Female (7)	Age	64	3	64	60
			Male (23)	Age	61	2	58	56

Results

The Control group consisted of 30 individuals and the Colon cancer group of 30 patients. *Table 1* presents the descriptive statistical analysis of age distribution stratified by study group and sex. The analysis includes mean values, SD, median, and 95% CI for both the control group and patients diagnosed with colon cancer. This stratification allows for the evaluation of potential demographic differences between groups, as well as sex-related variations within each cohort.

The analysis revealed comparable age distributions between the control and colon cancer groups, with no clinically significant differences observed. Median values and confidence intervals showed a similar pattern across all subgroups, indicating a relatively homogeneous age distribution.

In the control group, the mean age was slightly higher in females (65 ± 2 years) compared to males (62 ± 2 years), while in the colon cancer group, females also demonstrated marginally higher mean values (64 ± 3 years) than males (61 ± 2 years).

Table 2 summarizes the mean values of circulating biomarkers and imaging-derived body composition parameters in the control group and in patients with colon cancer. The evaluated variables include Osteonectin, CAF, P3NP, MSTN, IGF1, as well as PMI and SMI, allowing a comparative assessment of metabolic and muscular profiles between the two groups.

The analysis revealed modest differences between the two groups across both biomarkers and body composition parameters. Patients with colon cancer

exhibited slightly lower mean values of Osteonectin and IGF1, alongside reduced MSTN levels compared to the control group. In contrast, CAF and P3NP levels were marginally higher in the colon cancer group, suggesting a trend toward increased extracellular matrix turnover and muscle remodelling.

Regarding body composition, both PMI and SMI values were slightly increased in patients with colon cancer compared to controls (PMI: 5.4 vs. 5.2 cm²; SMI: 44.8 vs. 43.0 cm²), indicating relatively preserved muscle mass in this cohort. The observed differences were small, suggesting that, at a descriptive level, biomarker profiles and muscle indices remain relatively comparable between groups, with subtle variations that may warrant further statistical validation.

Table 3 presents the ROC curve analysis of the evaluated biomarkers, including Osteonectin, CAF, P3NP, MSTN, and IGF1, in both the control group and patients with colon cancer. The area under the curve values were calculated to assess the diagnostic performance of each biomarker in distinguishing between the two groups.

The ROC analysis demonstrated limited diagnostic performance for all evaluated biomarkers. In the colon cancer group, P3NP (AUC = 0.597) and Osteonectin (AUC = 0.590) showed the highest discriminatory ability, although their values remained below the threshold typically considered clinically relevant. MSTN (AUC = 0.535) and CAF (AUC = 0.486) exhibited poor diagnostic accuracy, with values close to 0.5, indicating minimal discriminative capacity.

IGF1 showed the lowest performance, particularly in the colon cancer group (AUC = 0.271), suggesting an

Table 2. Comparative analysis of biomarkers and body composition parameters between the control group and colon cancer group

Variable	Control (mean $\pm$ SD)	Colon cancer (mean $\pm$ SD)	p-value
Osteonectin (ng/mL)	578.6 $\pm$ 133.6	557.7 $\pm$ 118.9	0.525
CAF (pg/mL)	1603.8 $\pm$ 965.9	1636.6 $\pm$ 1147.9	0.905
P3NP (ng/mL)	5.25 $\pm$ 0.86	5.58 $\pm$ 0.70	0.111
MSTN (ng/mL)	22.66 $\pm$ 41.28	18.91 $\pm$ 37.01	0.712
IGF1 (ng/mL)	107.67 $\pm$ 25.60	100.30 $\pm$ 39.46	0.395
PMI (cm ²)	5.18 $\pm$ 1.45	5.42 $\pm$ 1.28	0.503
SMI (cm ²)	43.02 $\pm$ 10.16	44.77 $\pm$ 8.03	0.461

Note: Between-group comparisons were performed using the independent samples t-test, following confirmation of normal distribution for all variables via the Shapiro-Wilk test

Table 3. Receiver operating characteristic curve analysis of biomarkers in the control group and colon cancer group

Test Result Variable(s)	Area Under the ROC Curve				
	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
P3NP ng/ml	.620	.073	.099	.477	.763
CAF pg/ml	.523	.075	.757	.375	.671
MSTN ng/ml	.404	.074	.197	.259	.550
IGF1 ng/ml	.363	.073	.061	.219	.506

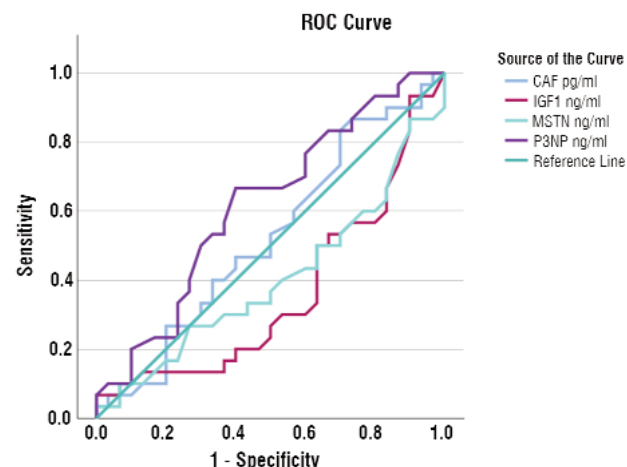
The test result variable(s): P3NP ng/ml, CAF pg/ml, MSTN ng/ml, IGF1 ng/ml has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

^a Under the nonparametric assumption; ^b Null hypothesis: true area = 0.5

inverse or non-informative relationship in this context (Fig. 1). Similarly, AUC values in the control group were generally low across all biomarkers, further supporting the lack of strong predictive capability. These findings indicate that none of the analyzed biomarkers demonstrate sufficient accuracy as standalone diagnostic tools for differentiating patients with colon cancer from controls, highlighting the need for combined biomarker approaches or integration with imaging and clinical parameters.

The ROC curves demonstrate an overall limited discriminative capacity of the evaluated biomarkers. Most curves closely follow the reference line, indicating poor diagnostic performance. Among the analyzed variables, P3NP and Osteonectin show a slightly improved trend toward discrimination, as their curves deviate modestly above the diagonal line, particularly in the colon cancer group. In contrast, CAF and MSTN exhibit curves that remain close to the reference line, suggesting minimal predictive value. IGF1 demonstrates inconsistent behavior, with curves indicating weak or inverse discriminatory ability.

Table 4 presents the independent-group comparison of AUC differences for the evaluated biomarkers, including Osteonectin, CAF, P3NP, MSTN, and IGF1. The analysis includes z-scores, significance values, standard error differences, and 95% CI, allowing assessment of whether the diagnostic performance of each biomarker differs significantly between the two groups.

**Figure 1.** Receiver operating characteristic curves of evaluated biomarkers in the control group and colon cancer group. ROC curves illustrating the diagnostic performance of CAF, IGF1, MSTN, Osteonectin, and P3NP in both the control group and patients with colon cancer. The diagonal reference line represents the line of no discrimination (AUC = 0.5). Curves closer to the upper left corner indicate better diagnostic performance, reflecting higher sensitivity and specificity.

The comparative analysis of AUC differences revealed no statistically significant differences between the control group and the colon cancer group for any of the evaluated biomarkers. All p-values were above the threshold for statistical significance, indicating

Table 4. Independent-group comparison of AUC differences for evaluated biomarkers between the control group and colon cancer group

Test Result Variable(s)	Independent-Group Area Difference Under the ROC Curve					
	Asymptotic		AUC Difference	Std. Error Difference ^b	Asymptotic 95% Confidence Interval	
	z	Sig. (2-tail) ^a			Lower Bound	Upper Bound
Osteonectin ng/ml	-1.383	.167	-.229	.165	-.553	.095
CAF pg/ml	-.020	.984	-.004	.198	-.392	.384
P3NP ng/ml	-.432	.666	-.082	.189	-.452	.289
MSTN ng/ml	-.137	.891	-.026	.188	-.395	.343
IGF1 ng/ml	.678	.498	.095	.140	-.180	.370

^a Null hypothesis: true area difference = 0; ^b Under the nonparametric assumption

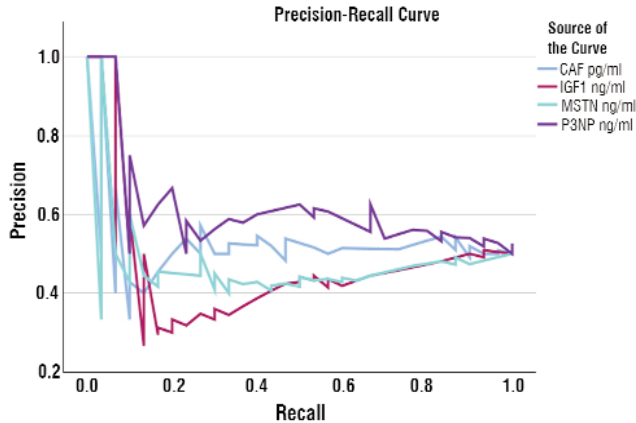


Figure 2. Precision–recall curves of evaluated biomarkers in the control group and colon cancer group. Precision–recall curves illustrating the performance of CAF, IGF1, MSTN, Osteonectin, and P3NP in both the control group and patients with colon cancer. Precision (positive predictive value) is plotted against recall (sensitivity), highlighting the balance between true positive detection and false positive rates across different thresholds.

that the diagnostic performance of Osteonectin, CAF, P3NP, MSTN, and IGF1 did not differ meaningfully between groups.

Although IGF1 showed a positive AUC difference, while Osteonectin, CAF, P3NP, and MSTN demonstrated negative values, these variations were minimal and not statistically relevant. Furthermore, the 95% CI for all biomarkers included zero, reinforcing the absence of significant differences in discriminatory ability.

The precision–recall curves (*Fig. 2*) indicate an overall modest predictive performance of the evaluated

biomarkers, with considerable variability across thresholds. P3NP and Osteonectin demonstrate relatively better performance, maintaining higher precision values across a broader range of recall, particularly in the colon cancer group. MSTN also shows moderate stability, with curves suggesting a balanced trade-off between precision and recall.

In contrast, CAF and IGF1 exhibit more fluctuating patterns, with lower precision values at increasing recall levels, indicating reduced reliability in identifying true positive cases. The dispersion of the curves and their proximity across groups further suggest limited discrimination between control subjects and patients with colon cancer.

A multivariable binary logistic regression model including age, sex, all evaluated circulating biomarkers, and CT-derived muscle indices was fitted to assess their combined ability to discriminate colon cancer patients from controls (*Table 5*). The overall model was not statistically significant (omnibus $\chi^2(9) = 9.64$, $p = 0.380$; Nagelkerke $R^2 = 0.198$). The apparent AUC of the model was 0.718, with 65.0% of participants correctly classified; because these estimates were derived from the same data used to fit the model, they are likely to overestimate its true discriminative performance.

The decreased cross-sectional muscle area visible in both images reflects a reduction in skeletal muscle mass, consistent with low CT-defined muscle mass (the muscle-quantity component of sarcopenia). None of the nine covariates reached statistical significance (all $p > 0.05$): age (OR 0.99, 95% CI 0.91–1.08, $p = 0.843$), sex (OR 4.34, 95% CI 0.81–23.16, $p = 0.086$), Osteonectin (OR 1.00, 95% CI 0.99–1.00, $p = 0.332$), CAF (OR 1.00,

Table 5. Multivariable binary logistic regression analysis of circulating biomarkers, CT-derived muscle indices, age, and sex for the discrimination of colon cancer patients from controls

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Step 1 ^a								
Age	-.009	.045	.039	1	.843	.991	.908	1.082
Sex(1)	1.468	.855	2.949	1	.086	4.338	.813	23.163
Osteonectin ng/ml	-.003	.003	.943	1	.332	.997	.990	1.003
CAF pg/ml	.001	.001	.864	1	.353	1.001	.999	1.003
P3NP ng/ml	.477	.523	.830	1	.362	1.611	.578	4.491
MSTN ng/ml	-.013	.023	.331	1	.565	.987	.944	1.032
IGF1 ng/ml	-.007	.015	.224	1	.636	.993	.964	1.023
PMI cm ²	-.217	.298	.528	1	.468	.805	.449	1.445
SMI cm ²	.000	.038	.000	1	.991	1.000	.928	1.077
Constant	-.401	4.858	.007	1	.934	.670		

a. Variable(s) entered on step 1 (Enter method): Age, Sex, Osteonectin ng/mL, CAF pg/mL, P3NP ng/mL, MSTN ng/mL, IGF-1 ng/mL, PMI cm², SMI cm².

Note: Dependent variable: group (colon cancer = 1; control = 0). Omnibus $\chi^2(9) = 9.64$, $p = 0.380$; Nagelkerke $R^2 = 0.198$. The model assesses discrimination between colon cancer patients and controls and does not identify predictors of sarcopenia. Events per variable = 3.3; estimates are exploratory. B, regression coefficient; S.E., standard error; Exp(B), odds ratio; C.I., confidence interval.

Table 6. Comparative analysis of anthropometric and body composition parameters between the control group and colon cancer group

Group		Weight kg	Height cm	BMI	Visceral fat	Body fat %	Body water %	Muscular mass kg	Bone minerals kg
		Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Group	Control	78	174	26	10.4	28.7	48.4	48.2	2.6
	Colon cancer	80	174	27	11.2	28.1	47.5	46.0	2.6

95% CI 1.00–1.00, $p=0.353$), P3NP (OR 1.61, 95% CI 0.58–4.49, $p=0.362$), MSTN (OR 0.99, 95% CI 0.94–1.03, $p=0.565$), IGF-1 (OR 0.99, 95% CI 0.96–1.02, $p=0.636$), PMI (OR 0.81, 95% CI 0.45–1.45, $p=0.468$), and SMI (OR 1.00, 95% CI 0.93–1.08, $p=0.991$).

Table 6 presents the mean values of anthropometric and body composition parameters in the control group and in patients with colon cancer. The evaluated variables include weight, height, BMI, visceral fat, body fat percentage, body water percentage, muscular mass, and bone mineral content, providing an overview of overall nutritional and body composition status in both groups.

The analysis demonstrated similar anthropometric characteristics between the two groups, with identical mean height values and only slight differences in weight and BMI, which were marginally higher in the colon cancer group. Patients with colon cancer also exhibited slightly increased visceral fat levels, suggesting a modest shift toward greater adiposity.

In contrast, body composition analysis revealed a reduction in body water percentage and muscular mass in the colon cancer group compared to controls, indicating a potential trend toward altered hydration status and decreased lean tissue. Body fat percentage showed minimal variation between groups, while bone mineral content remained identical.

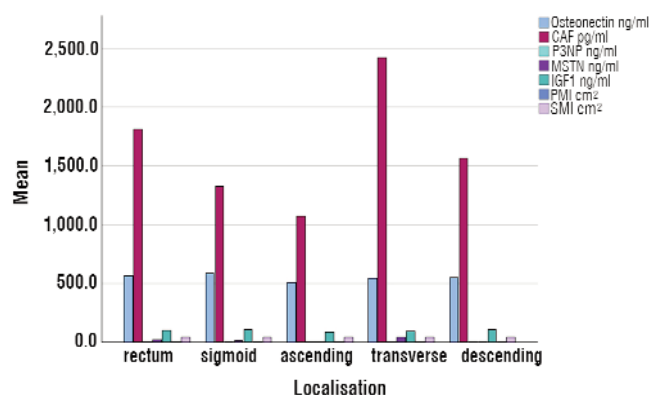
**Figure 3.** Mean values of biomarkers and body composition parameters stratified according to tumor localization in patients with colon cancer

Fig. 3 presents the mean values of biomarkers and body composition parameters stratified according to tumor localization in patients with colon cancer. Given the small number of patients within each tumor-localization subgroup, these comparisons should be regarded as exploratory and hypothesis-generating rather than confirmatory.

The analysis revealed variability in biomarker levels and body composition parameters depending on tumor localization. CAF values were highest in tumors located in the transverse colon, followed by rectal and descending locations, suggesting increased neuromuscular junction degradation or muscle remodelling in these subgroups. Similarly, MSTN levels were markedly elevated in transverse colon tumors, indicating a potential association with enhanced muscle catabolism. P3NP levels were also higher in transverse and descending localizations, reflecting increased extracellular matrix turnover. In contrast, Osteonectin and IGF1 values showed moderate variation across locations without a clear trend.

Regarding body composition, PMI and SMI values were relatively stable across tumor sites, suggesting preserved muscle mass regardless of localization. However, psoas muscle density was notably higher in descending and transverse tumors, indicating potential differences in muscle quality.

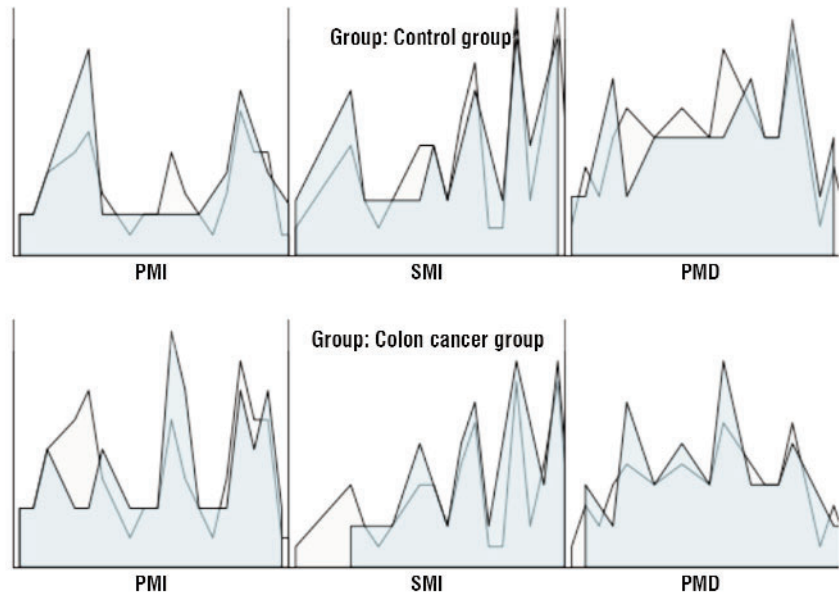
Fig. 4 demonstrates a heterogeneous distribution of PMI, SMI, and PMD values within the control group and colon cancer group. PMI values show moderate variability, with fluctuations indicating differences in psoas muscle area among individuals. SMI presents a broader dispersion, suggesting variability in overall skeletal muscle mass even in the absence of malignancy.

PMD values exhibit relatively higher peaks and variability compared to PMI and SMI, reflecting differences in muscle quality and composition across subjects. Despite these variations, the distributions do not suggest extreme outliers, indicating a relatively balanced muscle profile within the control group.

Figs. 5 and 6 show CT images with a reduction in skeletal muscle mass.

The decreased cross-sectional muscle area visible in both images reflects a reduction in skeletal muscle mass, consistent with sarcopenia. Attenuation values measured within the delineated ROI fall within the

Figure 4. Distribution of PMI, SMI, and PMD values in the control group and colon cancer group. Graphical representation of the distribution patterns of PMI, SMI, and PMD in the control group. The plots illustrate the variability and dispersion of muscle-related parameters, highlighting differences in muscle mass and quality within the control population.



typical range for skeletal muscle tissue (29–150 HU), confirming appropriate tissue identification.

In image (A), segmentation encompasses the entire abdominal skeletal musculature, enabling calculation of SMI, whereas in image (B), the analysis is restricted to the bilateral psoas muscles for the determination of PMI.

Relative to normal anatomical standards, both

images demonstrate a decrease in cross-sectional muscle area along with reduced muscle bulk, findings consistent with low CT-defined muscle mass. The attenuation values recorded within the segmented regions fall within the expected range for skeletal muscle tissue, supporting the accuracy and reliability of the measurements. The present analysis highlights that

Figure 5. Native axial CT images demonstrating SMI values of 25.56 cm²/m² (A) and PMI values of 3.27 cm²/m² (B).

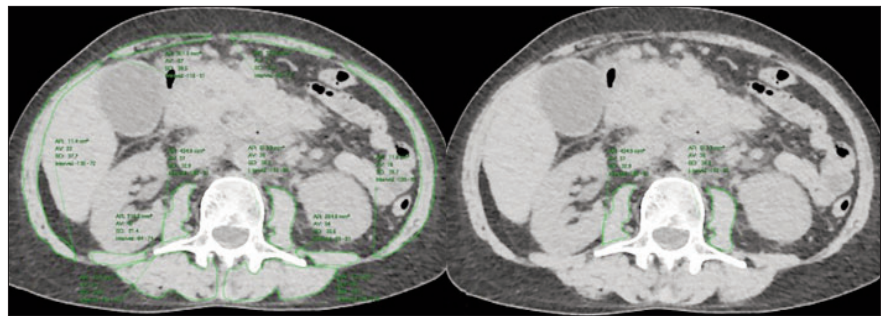
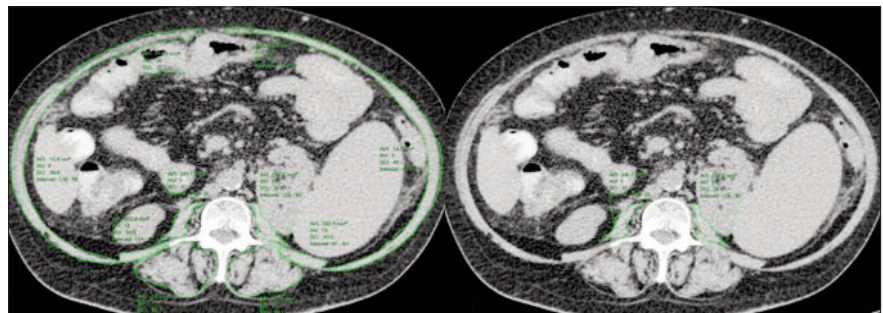


Figure 6. Native axial CT images showing SMI values of 30 cm²/m² (A) and PMI values of 2.35 cm²/m² (B).



while patients with colon cancer exhibit subtle variations in biomarker profiles, inflammatory parameters, and body composition, most differences compared to the control group remain modest and lack strong discriminatory power when assessed individually. ROC and precision–recall analyses further confirmed the limited diagnostic performance of the evaluated biomarkers, with no significant differences in AUC between groups. Additionally, stratification by tumor localization revealed heterogeneity in inflammatory and metabolic parameters, particularly for CRP and alkaline phosphatase, as well as variability in body composition; however, muscle-related indices such as PMI and SMI remained relatively stable across subgroups.

Discussions

This study compared circulating biomarkers of muscle catabolism and extracellular matrix turnover (Osteonectin, CAF, P3NP, MSTN, IGF-1) with CT-derived muscle indices (SMI, PMI) between patients with colon cancer and controls. Overall, the two groups showed only modest, statistically non-significant differences across all evaluated biomarkers and muscle indices (*Table 2*), and ROC analysis confirmed limited standalone diagnostic performance, with AUC values not exceeding 0.62 for any individual marker (*Table 3, Fig. 1*). Biomarker levels also varied according to tumor localization (*Fig. 3*), suggesting that tumor-related biological heterogeneity may partly underlie the inconsistent discriminative performance of individual markers, while SMI and PMI remained comparatively stable across tumor sites. Taken together, these findings indicate that, in this cohort, none of the evaluated circulating biomarkers reliably distinguished patients with colon cancer from controls when considered in isolation. Sarcopenia is well established in the broader literature as being associated with adverse postoperative and oncologic outcomes in colorectal cancer (2,28,29); however, as the present study was not designed to test this association, the discussion below situates our biomarker- and imaging-based findings within that literature context rather than presenting them as direct evidence of a prognostic relationship.

Although biomarkers such as CAF, P3NP, Osteonectin, and MSTN showed detectable variations, their overall diagnostic performance was limited, as reflected by modest AUC values and lack of significant intergroup differences (see below for a comparison with combined-panel approaches). CAF and P3NP demonstrated trends consistent with previous studies by Landi et al. (25) and Qaisar et al. (26), although

their variability across patients highlights the influence of confounding factors such as inflammation, comorbidities, and tumor biology.

CT-derived indices such as SMI and PMI remain reliable and reproducible tools for assessing muscle mass, in line with Schneider et al. (28), but they primarily reflect structural rather than functional or metabolic alterations. The observed heterogeneity according to tumor localization further supports the hypothesis that systemic inflammation and tumor-specific metabolic activity contribute to the variability of sarcopenia expression, as also suggested in prior oncological studies.

In the multivariable binary logistic regression model, none of the circulating biomarkers or CT-derived indices was independently associated with colon cancer status after simultaneous adjustment for age, sex, and the other covariates, and the model as a whole did not reach statistical significance. Sex showed the largest, though non-significant, effect estimate (OR 4.34, 95% CI 0.81–23.16, $p = 0.086$), a trend worth re-evaluating in a larger cohort. This model was built to discriminate colon cancer patients from controls. Because its dependent variable is group membership rather than sarcopenia status, its results cannot, in themselves, be taken as evidence for or against independent predictors of sarcopenia. In addition, with nine covariates and 30 events (approximately 3.3 events per variable, well below the commonly recommended threshold of ten), the model is underpowered and prone to overfitting, and its estimates should be interpreted as exploratory rather than confirmatory.

The modest diagnostic performance of the biomarkers assessed in our cohort should be interpreted in light of prior work exploring combined biomarker panels rather than isolated determinations. Kwak et al. demonstrated that no single circulating biomarker (interleukin-6, SPARC/osteonectin, macrophage migration inhibitory factor, or insulin-like growth factor-1) achieved an area under the curve above 0.70 for sarcopenia prediction, whereas a composite risk score integrating all four markers reached an AUC of 0.763 overall (0.812 in men and 0.739 in women) (24). Similarly, Qaisar et al. showed that a six-marker panel combining P3NP, the C-terminal agrin fragment, osteonectin, irisin, fatty acid-binding protein 3, and macrophage migration inhibitory factor achieved substantially higher discriminative accuracy (AUC up to 0.793) than any individual marker (26). The importance of comorbidity burden and systemic inflammatory status in clinical risk assessment is also supported by recent real-world evidence in patients with advanced chronic kidney disease, in whom renal dysfunction,

inflammation, and coexisting cardiovascular conditions substantially influenced bleeding and treatment-related outcomes (27). These findings parallel our own results, in which P3NP showed the highest yet still modest discriminative value (AUC = 0.597), while osteonectin, myostatin, CAF, and IGF-1 performed even more poorly (AUC 0.590, 0.535, 0.486, and 0.271, respectively).

Although not directly assessed in our cohort, the clinical relevance of sarcopenia in colorectal cancer is supported by substantial meta-analytic evidence from other, larger studies. In a systematic review and meta-analysis of 23 studies, Trejo-Avila et al. (2021) found that sarcopenic patients undergoing colorectal cancer surgery had significantly higher rates of total postoperative complications (OR = 1.84, 95% CI 1.35–2.49), postoperative mortality (OR = 3.21, 95% CI 2.01–5.11), and infectious complications (OR = 1.40, 95% CI 1.12–1.76), together with shorter overall survival (HR = 1.83, 95% CI 1.57–2.14), disease-free survival (HR = 1.55, 95% CI 1.29–1.88), and cancer-specific survival (HR = 1.77, 95% CI 1.40–2.23) compared with non-sarcopenic patients (29). These findings were corroborated by He, whose updated meta-analysis of 20 studies estimated a pooled sarcopenia prevalence of 34% among colorectal cancer patients and confirmed its independent association with reduced overall survival (HR = 1.72), disease-free survival (HR = 1.42), and cancer-specific survival (HR = 1.48) (30). Mechanistically, sarcopenia in oncological patients appears closely intertwined with systemic inflammation: Fleming et al. showed that low skeletal muscle area independently more than doubled five-year recurrence risk (HR = 2.30, 95% CI 1.41–2.89) and correlated with elevated pro-inflammatory markers (CRP, IL-6, VEGF) and reduced anti-inflammatory mediators (IL-10, IFN- γ), supporting a bidirectional relationship between muscle depletion, chronic low-grade inflammation, and tumor progression (2). Chen and Gao further emphasized that sarcopenia, present in 12–60% of colorectal cancer patients across the studies reviewed, independently predicts both short-term surgical morbidity (e.g., OR = 3.12 for complications in stage IV disease) and long-term oncologic outcomes, including overall survival (HR = 2.15) and recurrence-free survival (13).

According to the revised European Working Group on Sarcopenia in Older People (EWGSOP2) consensus, an accurate diagnosis requires the integration of low muscle strength, muscle quantity/quality, and, when relevant, physical performance (12). Because sarcopenia influences perioperative risk, chemotherapy tolerance, and long-term survival, its systematic assessment could meaningfully inform individualized management in colon cancer, from prehabilitation and nutritional

optimization to tailored surgical and oncological decision-making (21). Our findings are consistent with this framework: none of the individually assessed circulating biomarkers or imaging indices captured the full sarcopenic phenotype in this cohort. Because muscle strength and physical performance were not measured, however, the present data address only the muscle-quantity component of the EWGSOP2 definition.

This study has several important limitations. First, its single-center design and relatively small sample size (30 patients per group) limit statistical power and the generalizability of the findings. Although a multi-variable binary logistic regression model was fitted, the small sample relative to the number of covariates (approximately 3.3 events per variable) limits the power, stability, and interpretability of this model; its estimates, as well as the subgroup comparisons by tumor localization, should therefore be considered exploratory and hypothesis-generating. Second, and most importantly, no functional assessment of muscle strength or physical performance (handgrip dynamometry, chair-stand test, gait speed) was performed. Under the EWGSOP2 consensus, sarcopenia is identified by low muscle strength, confirmed by low muscle quantity or quality, and graded as severe when physical performance is also impaired (12). In the absence of strength and performance measurements, the present study does not fully document an EWGSOP2 diagnosis of sarcopenia: the cohort was characterized only for the muscle-quantity/quality component, through CT-derived indices, complemented by circulating biomarkers. Our results should therefore be interpreted as reflecting CT-defined low muscle mass and its biochemical correlates rather than EWGSOP2-confirmed sarcopenia. Third, the present study was not designed, and was not statistically powered, to evaluate the association between sarcopenia and oncologic prognosis (postoperative complications, recurrence, or survival); although this association is discussed extensively in relation to the existing literature, it was not investigated in our cohort and our results should not be extrapolated to these outcomes. Fourth, potential confounders such as nutritional intake, physical activity, and systemic inflammation markers were not comprehensively controlled.

An additional limitation concerns the incomplete characterization of oncological staging and treatment status in our cohort. TNM stage was not systematically recorded for all patients, and biomarker and imaging assessments could not be stratified according to disease stage, which may have introduced additional heterogeneity given the known association between

tumor stage and the severity of cancer-associated sarcopenia. Similarly, the temporal relationship between assessment and oncological treatment (surgery, chemotherapy) was not explicitly documented; since cytotoxic therapy and major abdominal surgery are themselves recognized drivers of secondary sarcopenia, it cannot be excluded that some measurements reflect treatment-related muscle depletion rather than tumor-intrinsic effects alone. Likewise, the control group was defined broadly as individuals without known malignancy, without further stratification by comorbidity profile (e.g., patients hospitalized for non-oncological digestive or surgical conditions), community-based healthy volunteers, or subjects with a negative screening colonoscopy, and without systematic documentation of functional status (frailty or mobility impairment) in either group; this lack of granularity limits the ability to fully disentangle disease-specific effects from those attributable to hospitalization, comorbidity burden, functional reserve, or selection bias. Future prospective studies should incorporate TNM staging, pre- versus post-treatment timing, and a more precisely defined, ideally age- and sex-matched, control population to strengthen causal inference regarding sarcopenia in colon cancer.

From a clinical perspective, whether an integrated approach combining imaging, biochemical profiling, and clinical parameters can provide superior diagnostic and prognostic value to individual biomarkers remains to be established. Future large-scale, prospective studies are needed to test such multimodal strategies and to establish standardized thresholds for clinical implementation.

Conclusions

The present study evaluated circulating biomarkers and CT-derived muscle indices in patients with colon cancer and controls. Although modest differences in biomarker levels and body composition parameters were observed between groups, the evaluated biomarkers showed limited discriminatory performance when considered individually, and none demonstrated statistically significant differences in AUC between groups. CT-derived SMI and PMI provided complementary information regarding muscle quantity but did not demonstrate independent associations with colon cancer status in the exploratory multivariable model. These findings suggest that isolated biochemical or imaging-derived parameters are unlikely to adequately characterize the complex muscle-related phenotype observed in patients with colon cancer. Future prospective studies should investigate integrated approaches combining CT-derived muscle

measures, circulating biomarkers, muscle strength, physical performance, nutritional status, and relevant clinical variables. Importantly, because muscle strength and physical performance were not assessed in the present study, the findings should not be interpreted as validation of a complete diagnostic assessment of sarcopenia according to EWGSOP2 criteria.

Conflict of Interests

The authors declared no potential conflicts of interest.

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