Risk of Sarcopenia and Gastrointestinal Toxicity of Older Patients Undergoing Chemotherapy

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Risco de Sarcopenia e Toxicidade Gastrointestinal de Pacientes Idosos em Quimioterapia

Riesgo de Sarcopenia y Toxicidad Gastrointestinal de Pacientes Ancianos Sometidos a Quimioterapia

Hellba Karts Maria e Silva[1]; Lilian de Souza Cavalcante[2]; Giovanna Andrade Souza Almeida[3]; Jarson Pedro da Costa Pereira[4]; Marcella Campos Lima da Luz[5]

ABSTRACT

Introduction: Sarcopenia is a condition associated with poor prognosis, including the risk for worse gastrointestinal toxicity in older patients with cancer undergoing chemotherapy treatment. **Objective:** Evaluate the association between the risk of sarcopenia and gastrointestinal toxicity in older patients undergoing chemotherapy. **Method:** Observational study with cross-sectional data collection involving 60 older patients diagnosed with solid tumors, sampled by convenience, undergoing exclusive or combined chemotherapy regimen. Risk of sarcopenia was assessed using the SARC-F and SARC-CalF questionnaires. Malnutrition diagnosis was evaluated by the Mini Nutritional Assessment short form (MNA-SF). **Results:** Among the patients included, the risk of sarcopenia (SARC-F) was observed in 15%. Using SARC-CalF, this number increased to 33.3%. It was noticed that higher SARC-F scores were independently associated with a greater number of symptoms related to gastrointestinal toxicity. Furthermore, higher SARC-F scores (indicating higher risk) were associated with lower handgrip strength and lower MNA-SF scores. Higher SARC-CalF scores were associated with lower handgrip strength and lower MNA-SF scores as well. **Conclusion:** The findings suggest that SARC-F could be utilized as a guiding tool for interventions to improve muscle condition, potentially mitigating the elevated incidence of chemotherapy-related gastrointestinal symptoms.

Key words: Sarcopenia/diet therapy; Aged; Neoplasms/epidemiology; Nutritional Status/drug effects.

RESUMO

Introdução: A sarcopenia é uma condição associada ao mau prognóstico, incluindo o risco para pior toxicidade gastrointestinal em pacientes com câncer submetidos a tratamento quimioterápico. **Objetivo:** avaliar a associação entre o risco de sarcopenia e a toxicidade gastrointestinal de pacientes idosos em quimioterapia. **Método:** Estudo observacional com coleta transversal, envolvendo 60 idosos diagnosticados com tumores sólidos, selecionados por conveniência, em regime de quimioterapia exclusiva ou combinada. O risco de sarcopenia foi avaliado por meio dos questionários SARC-F e SARC-CalF. O diagnóstico de desnutrição foi avaliado pela mini avaliação nutricional reduzida (MAN-r). **Resultados:** Entre os pacientes incluídos, o risco de sarcopenia (SARC-F) foi observado em 15%. Ao utilizar o SARC-CalF, esse número cresceu para 33,3%. Foi observado que uma maior pontuação do SARC-F esteve independentemente associada ao maior número de sintomas relativos à toxicidade gastrointestinal. Além disso, maiores escores do SARC-F (mais risco) se associaram à menor força de preensão palmar e aos menores escores da MAN-r. Elevados escores do SARC-CalF se associaram à menor força de preensão palmar e menores escores na MAN-r. **Conclusão:** Os achados sugerem que o SARC-F pode ser uma ferramenta guia para intervenções relacionadas à melhora do estado muscular, potencialmente prevenindo o elevado número de sintomas relacionados à quimiotoxicidade gastrointestinal.

Palavras-chave: Sarcopenia/dietoterapia; Idosos; Neoplasias/epidemiologia; Estado Nutricional/efeitos dos fármacos.

RESUMEN

Introducción: La sarcopenia es una condición asociada con un mal pronóstico, incluido el riesgo de una mayor toxicidad gastrointestinal en pacientes con cáncer sometidos a tratamiento de quimioterapia. **Objetivo:** El objetivo del estudio fue evaluar la asociación entre el riesgo de sarcopenia y la toxicidad gastrointestinal en pacientes ancianos sometidos a quimioterapia. **Método:** Estudio observacional con recolección transversal de datos que involucró a 60 pacientes ancianos diagnosticados con tumores sólidos, seleccionados por conveniencia, que recibían un régimen de quimioterapia exclusivo o combinado. El riesgo de sarcopenia se evaluó utilizando los cuestionarios SARC-F y SARC-CalF. El diagnóstico de desnutrición se evaluó mediante la evaluación nutricional abreviada (MNA-SF). **Resultados:** Entre los pacientes incluidos, se observó un riesgo de sarcopenia (SARC-F) en el 15%. Al utilizar SARC-CalF, este número aumentó al 33.3%. Se observó que puntajes más altos de SARC-F estaban independientemente asociados con un mayor número de síntomas relacionados con la toxicidad gastrointestinal. Además, puntajes más altos de SARC-F (indicando un mayor riesgo) se asociaron con una menor fuerza de agarre manual y puntajes más bajos de MNA-SF. Puntajes más altos de SARC-CalF también se asociaron con una menor fuerza de agarre manual y puntajes más bajos de MNA-SF. **Conclusión:** Los hallazgos sugieren que el SARC-F podría ser una herramienta de orientación para intervenciones dirigidas a mejorar el estado muscular, potencialmente mitigando el elevado número de síntomas gastrointestinales relacionados con la quimiotoxicidad gastrointestinal.

Palabras clave: Sarcopenia/dietoterapia; Ancianos; Neoplasias/epidemiología; Estado Nutricional/efectos de los fármacos.

[1,2,5]Universidade Federal de Pernambuco, Hospital das Clínicas de Pernambuco. Recife (PE), Brasil. E-mails: hellbakarts@gmail.com; lilian.2610@hotmail.com; cellacamposlima@gmail.com. Orcid iD: https://orcid.org/0000-0003-2880-8426; Orcid iD: https://orcid.org/0000-0002-1887-8917; Orcid iD: https://orcid.org/0000-0001-9226-1387

[3,4]UFPE, Departamento de Nutrição. Recife (PE), Brasil. E-mails: nutri.giovannandrade@gmail.com; jarson.costa@ufpe.br. Orcid iD: https://orcid.org/0000-0002-3836-3363; Orcid iD: https://orcid.org/0000-0001-5412-6467

Corresponding author: Marcella Campos Lima da Luz. Avenida Prof. Moraes Rego, 1235, bloco C, 3º andar – Cidade Universitária. Recife (PE), Brasil. CEP 50670-901. E-mail: cellacamposlima@gmail.com

INTRODUCTION

Populational ageing-induced demographic transition has caused a remarkable epidemiological change with increase of chronic non-communicable diseases, standing out cancer[1], that continues to be a significant cause of impairment and early death globally. Due to its inflammatory nature, this disease can aggravate deterioration and damage the muscle-protein synthesis. In addition, the treatment usually associated with immunosuppression, ageing and the disease itself intensifies risk factors and worsening of the nutritional status, leading to malnutrition and sarcopenia[2].

Sarcopenia is a muscle syndrome characterized by progressive loss of muscle mass with decline of strength. When severe, physical performance can be compromised[3]. Old age, sedentarism and comorbidities are the main risk factors for primary sarcopenia[4]. The prevalence of sarcopenia depends on the clinical condition and method of evaluation[5]. The syndrome is frequently associated with less autonomy of older patients, worst quality of life and poor clinical outcomes as prolonged hospitalization and lower global survival[6,7].

Due to operational difficulties for the diagnosis of sarcopenia in clinical practice, the SARC-F was proposed as a tool to identify its risk[8,9]. It is a low-cost method with a self-reported questionnaire[3,8,9] being possible to provide insights about the functional and muscle capacity, allowing the application of the correct intervention[3,8,9]. Later, calf circumference was incorporated to SARC-F (SARC-CalF) to improve the sensitiveness of the tool as a muscle mass marker[8,10,11].

Sarcopenia in older patients with oncologic diagnosis can be associated with dose-limiting chemotoxicity, postoperative complications and lower survival in cases of malignant diseases[2,7]. Nevertheless, the relation of risk of sarcopenia measured by SARC-F and SARC-CalF with chemotoxicity is still little explored. Hypothetically, whether this association exists, it will strengthen the utilization of these tools in clinical practice, facilitating the development of assertive strategies. The objective of this study was to evaluate the risk of sarcopenia and its association with gastrointestinal toxicity in older patients submitted to chemotherapy treatment. The secondary objective was to verify the association between risk of sarcopenia with variables of nutritional status.

METHOD

Observational, cross-sectional study conducted from March to August 2023 at the oncology ward of "*Hospital das Clínicas da Universidade Federal de Pernambuco*" with older than 60 years of age adults, both sexes, with solid tumors in exclusive or combined chemotherapy regimen selected by convenience. Older patients with oncohematological diagnosis or physical impairment, with severe edema, ascites and associated metabolic diseases (cardiac failure, chronic renal disease, peripheral obstructive pulmonary disease and chronic liver disease) were excluded. Individuals with cognitive impairment unable to respond to questionnaires were excluded too.

Clinical and sociodemographic data were collected through an interview and obtained from electronic charts as: age, sex, skin color, diagnostic, tumor location, comorbidities, including systemic arterial hypertension (SAH) and diabetes *mellitus* (DM). For gastrointestinal chemotoxicity, xerostomia, dysgeusia, odynophagia, dysphagia, nausea, vomits, constipation and diarrhea were considered, further to the type of neoplasm and treatments performed (chemotherapy or chemotherapy and radiotherapy, surgery).

Weight (kg) and height (m) were measured to calculate the body mass index (BMI), in addition to calf and arm circumference. BMI classification was determined by the cutoff proposed by the Pan American Health Organization (PAHO) in 2002[12]; the calf circumference was measured at its widest part, it is deemed reduced when ≤ 34 cm for males and ≤ 33 cm for females[8]. As it is influenced by the body mass, specially adiposity, a BMI-adjustment was made, consisting in the subtraction of 3 cm of CC for individuals with BMI between 25 and 29 kg/m², 7 cm for BMI between 30 and 39 kg/m² and 12 cm for BMI equal or above 40 kg/m²[13]. The arm circumference was measured according to Frisancho[14], its appropriateness was classified pursuant to percentile 50[15]. Weight loss (WL) was calculated with the formula: (regular weight – current weight) x 100/regular weight; the percent was classified as severe when > 2% in one week, > 5% in one month, > 7.5% in three months or > 10% in six months[16].

The risk of sarcopenia was measured with SARC-F and SARC-CalF. SARC-F has five questions evaluating the patient's perception of his/her strength, walking, standing up from a chair, climb stairs and falls in the last year; those with scores ≥ 6 were considered at risk of sarcopenia[8]. For SARC-CalF, patients with scores ≥ 11 were considered at risk of sarcopenia, and 10 points were added should the patient had reduced calf circumference[8].

The six-items (letters A to F) Mini Nutritional Assessment-Short Form (MNA-SF) was applied to identify the nutritional risk or diagnosis of malnutrition, it evaluates food intake, WL, mobility, presence of emotional factors, neuropsychologic issues and BMI[17]. Scores ≥ 12 were indicative of regular nutritional status, between 8 and 11, risk of malnutrition and < 8, were deemed as malnutrition[17].

Muscle strength was measured by handgrip strength (HGS) with digital dynamometer Jamar® following the recommendations of the American Society of Hand Therapists[18]. With the patient seated and arm flexed at 90 degrees, HGS was measured with three repetitions in the dominant hand, with 30 seconds interval between one another. The maximum value reached was utilized for the analysis. Strength was considered low when < 30 kg for men and < 16 kg for women[19].

Microsoft Office Excel 2013 was utilized to organize the data and exported to SPSS[20] version 20.0. The normality of the continuous variables was tested with the Shapiro-Wilk test, and expressed as mean and standard deviation if the distribution was normal. Median and interquartile range (IQR) were calculated for non-normal distribution. Categorical variables were expressed as absolute (n) and relative (%) frequency and compared with Pearson's Chi-Square test with Yates correction or Fisher's Exact test.

Raw and adjusted linear regression model was constructed to identify the association among risk of sarcopenia (SARC-F and SARC-CalF) and the variables of interest. The adjustments were made for sex, age, tumor site and chemotherapy regimen and were considered significant for the final model whether $p < 0.05$ and range of statistical significance for p between 0.05 and 0.10.

The hospital's Institutional Review Board (IRB) approved the study, report number 5,878,262 (CAAE (submission for ethical review): 66748623.3.0000.8807) in compliance with Directive 466/12[21] of the Ministry of Health. All the participants signed the informed consent form.

RESULTS

The final study sample consisted in 60 patients. The risk of sarcopenia was 15% measured by SARC-F and increased to 33.3% when SARC-CalF was applied. Risk of malnutrition was found in 40% of the patients, while 25% were malnourished according to MNA-SF. 31.6% of the sample was classified as low weight according to BMI (not included in the tables). Females were predominant (53.3%) with mean age of 69.4±6.9 years and 48.3% presented SAH. The most frequent oncologic diagnostic was gastrointestinal tumor (GIT) with 46.7% of the cases. Chemotoxicity of GIT was found in 90% of the individuals, the most common symptoms were nausea (58.3%), dysgeusia (46.7%) and xerostomia (43.3%) (Table 1).

Associations among risk of sarcopenia and gastrointestinal toxicity related symptoms as diarrhea and/or constipation were revealed when SARC-F was utilized. In addition, a tendency of association between the risk and diagnosis of malnutrition (MNA-SF) and risk of sarcopenia ($p = 0.055$) was noticed. Patients with reduced muscle strength had more frequency of risk of sarcopenia ($p = 0.017$) (Table 2). With this tool, associations with symptoms of gastrointestinal toxicity were found. Individuals with risk of sarcopenia presented high frequency of odynophagia and/or dysphagia ($p = 0.050$) (Table 3). Overweight was associated with low frequency of risk of sarcopenia ($p = 0.006$) according to BMI and reduced muscle strength was associated with high frequency of risk of sarcopenia ($p = 0.005$).

Higher scores of SARC-F were independently associated with high number of gastrointestinal chemotoxicity related symptoms even after age-adjustment for age, sex, tumor site and chemotherapy regimen [β 0.25 (0.06;0.04) $p = 0.011$]. In addition, it was noticed that scores of SARC-F and SARC-CalF presented reversed association with HGS and MNA-SF scores (Table 4).

DISCUSSION

The objective of this study was to evaluate the relation between risk of sarcopenia measured by SARC-F and SARC-CalF and gastrointestinal chemotoxicity in older patients diagnosed with cancer and association with other nutritional status related variables. It is aligned with a restricted portion of researches which explored the relation between risk of sarcopenia and chemotoxicity in older patients diagnosed with cancer in Brazil. The main results indicated that higher scores of SARC-F, although not for SARC-CalF, were independently associated with higher number of gastrointestinal toxicity symptoms. In addition, higher scores for both SARC-F and SARC-CalF associated with less muscle strength (HGS) and lower score of MNA-SF (indicative of risk and/or diagnosis of malnutrition) were observed.

A recent systematic review[22] concluded that sarcopenia in patients with colorectal cancer appears to have a stronger association with reduction of intolerance to the treatment compared with other diagnostic methods and nutritional screening as index of nutritional risk, subjective global assessment (SGA) and other tools. Although the study has not approached directly the instruments (SARC-F and SARC-CalF), these findings reinforce the importance of identifying the prognostic value related to chemotherapy, utilizing simple low-cost tools as SARC-F and SARC-CalF.

A study conducted by Celik *et al.*[23] with mean-60 years old patients and oncologic diagnoses on gastrointestinal tract showed that sarcopenia emerged as sole predictor of chemotherapy-related toxicity. Given that natural ageing[3]

Table 1. Characteristics of older patients with cancer in chemotherapy treatment (n = 60))

Variables	n or mean	(%)	CI 95% or ±SD
Sex			
Male	28	46.7	33.3-60.0
Female	32	53.3	40.0-66.7
Age	69.4	-	±6.99
Ethnicity/Race			
White	28	46.7	35.0-60.0
Brown	23	38.3	25.0-50.0
Black	9	15.0	6.7-25.0
Comorbidities			
SAH	29	48.3	35.0-60.0
DM	3	5.0	0.0-11.7
SAH+DM	13	21.7	11.7-31.7
None	15	25	15.0-36.7
Tumor location			
Gastrointestinal	28	46.7	33.0-60.0
Gynecological	16	26.7	15-38.3
Urologic	8	13.3	5.0-23.3
Others*	8	13.3	5.0-21.7
Chemotherapy regimen			
Paclitaxel + carboplatin	14	2.3	13.3-35.0
FOLFOX	12	20.0	10.0-31.7
Docetaxel	5	8.3	1.7-15.0
Others**	29	48.3	36.7-61.7
Oncologic surgery			
Yes	30	50	36.7-63.3
No	30	50	36.7-63.3
Gastrointestinal toxicity			
Present	54	90	81.7-96.7
Absent	6	10	3.3-18.3
Type of gastrointestinal toxicity			
Nausea	35	58.3	45.0-70.0
Vomits	20	33.3	21.7-45.0
Diarrhea	25	41.7	28.3-55.0
Constipation	22	36.7	23.3-48.3
Xerostomia	26	43.3	31.7-55.0
Dysgeusia	28	46.7	33.3-58.3
Dysphagia	9	15	6.7-25.0
Odynophagia	2	3.3	0.0-8.3
Anorexia	15	25.0	13.4-36.7

Captions: CI 95% = confidence interval 95%; SD = standard deviation; SAH = systemic arterial hypertension; DM = *diabetes mellitus*.
*neoplasms of lung, head and neck; **FLOT, cisplatin + gemcitabine, xelox, folfirinox, docetaxel + cyclophosphamide.

Table 2. Association among risk of sarcopenia (SARC-F) with patient's characteristics (n = 60)

Variables	SARC-F				p*
	Without risk		With risk		
	n	%	n	%	
Sex					0.412
Male	23	92.1	5	17.9	
Female	28	87.5	4	12.5	
Gastrointestinal toxicity					0.640
Present	46	90.2	8	88.9	
Absent	5	9.8	1	11.1	
Type of gastrointestinal toxicity					
Nausea and/or vomits	29	66.7	6	56.9	0.582
Diarrhea and/or constipation	32	62.7	2	22.2	**0.029**
Xerostomia and/or dysgeusia	35	68.6	8	88.9	0.205
Odynophagia and/or dysphagia	7	13.7	3	33.3	0.163
Anorexia	12	80	3	20.0	0.399
BMI					0.113
Overweight	13	25.5	3	33.3	
Regular	6	66.7	38	74.5	
AC (%)					0.954
< 90	18	35.3	3	33.3	
Between 90-110	20	39.2	4	44.4	
> 110	13	25.5	2	22.2	
CC					0.203
Reduced	23	45.1	6	66.7	
Normal	28	54.9	3	33.3	
CC corrected to BMI					0.475
Reduced	41	80.4	8	88.9	
Normal	10	19.6	1	11.1	
% WL					0.153
Severe	35	68.6	4	44.4	
Without loss	16	31.4	5	55.6	
MNA-SF					0.055
Normal nutritional status	20	39.2	1	11.1	
Risk of malnutrition	21	41.2	3	33.3	
Malnutrition	10	19.6	5	55.6	
Muscle strength					**0.017**
Reduced	17	33.3	7	77.8	
Normal	34	66.7	2	22.2	

Captions: AC = arm circumference; CC = calf circumference; BMI = body mass index; MNA-SF = mini nutritional assessment – short form; WL = weight loss.
* Fisher's Exact test

Table 3. Association among risk of sarcopenia (SARC-CalF) with patient's characteristics (n = 60)

Variables	SARC-CalF				$p^{a,b}$
	No risk		With risk		
	n	%	n	%	
Sex					0.360[a]
Male	17	60.7	11	39.3	
Female	23	71.9	9	28.1	
Gastrointestinal toxicity					0.089[b]
Present	38	95.0	16	80.0	
Absent	2	5.0	4	20.0	
Type of gastrointestinal toxicity					
Nausea and/or vomits	23	57.5	12	60.0	0.853[a]
Diarrhea and/or constipation	27	67.5	7	35.0	**0.017[a]**
Xerostomia and/or dysgeusia	31	77.5	12	60.0	0.156[a]
Odynophagia and/or dysphagia	4	10.0	6	30.0	**0.050[b]**
Anorexia	11	27.5	4	20.0	0.383[b]
BMI					**0.006[b]**
Overweight	15	37.5	1	5.0	
Regular	25	62.5	19	95.0	
AC (%)					0.068[a]
< 90	10	25.0	11	55.0	
Between 90-110	18	45.0	6	30.0	
> 110	12	30.0	3	15.0	
% WL					0.566[a]
Severe	25	62.5	14	70.0	
No loss	15	37.5	6	30.0	
MNA-SF					0.377[a]
Normal nutritional status	14	35.0	7	35.0	
Risk of malnutrition	18	45.0	6	30.0	
Malnutrition	8	20.0	7	35.0	
Muscle strength					**0.005[a]**
Reduced	11	27.5	13	65.0	
Normal	29	72.5	7	35.0	

[a] Pearson's chi-square; [b]Fisher's exact test.
Captions: AC = arm circumference; BMI = body mass index; MNA-SF; WL = weight loss.

and antineoplastic treatments can induce sarcopenia[24], it is evident that early identification of risk of developing sarcopenia plays a crucial role in preventing chemotoxicity and possible discontinuation of the treatment, reinforcing the importance of SARC-F as an invaluable tool to be routinely included on the clinical assessment of older patients with cancer diagnoses.

The non-association among SARC-CalF and chemotherapy-associated gastrointestinal tract symptoms can be attributed to a potential sampling bias as the sample is small. Another explanation for GIT toxicity specifically is the utilization of an anthropometric marker which can impact the sensitiveness and specificity of the tool. In addition, it is essential to consider variations of the sample as age, sex, type of tumor and treatments performed, all of them possibly influencing the results of the present analysis, nevertheless, the validity of SARC-F and SARC-CalF as simple tools able to assign prognostic values to older patients with cancer is reinforced[25,26].

These findings have also revealed a reverse and independent association among higher scores of SARC-F and SARC-CalF and muscle strength measured by HGS. It is evident that individuals with higher scores, indicative of elevated risk of sarcopenia presented lower muscle

Table 4. Associations among sarcopenia risk scores (SARC-F and SARC-CalF) with gastrointestinal toxicity, muscle strength and scores of malnutrition of older adults in chemotherapy (n = 60)

	Symptoms of gastrointestinal toxicity			Muscle strength (HGS)			MNA-SF		
SARC-F	**β**	**CI 95%**	***p***	**β**	**CI 95%**	***p***	**β**	**CI 95%**	***p***
Raw	0.11	-0.08;0.31	0.253	-1.23	-1.80;-0.65	**<0.001**	-0.53	-0.79;-0.27	**< 0.001**
Adjusted[a]	0.25	0.06;0.04	**0.011**	-1.22	-1.72;-0.72	**<0.001**	-0.53	-0.81;-0.24	**<0.001**
SARC-CalF	**β**	**CI 95%**	***p***	**β**	**CI 95%**	***p***	**β**	**CI 95%**	***p***
Raw	-0.04	-0.13;0.05	0.429	-0.35	-0.63;-0.07	**0.016**	-0.19	-0.32;-0.07	**0.003**
Adjusted[a]	0.01	-0.08;0.10	0.867	-0.38	-0.63;-0.13	**0.004**	-0.19	-0.32;-0.06	**0.006**

Captions: β = beta coefficient of linear regression; CI 95% = confidence interval 95%; HGS = handgrip strength; MNA-SF = Mini Nutritional Assessment-SF. [a]SARC-F and SARC-CalF adjusted for sex, age, tumor site and chemotherapy regimen.

strength. These results strengthen HGS as an indicator of muscle strength[27] in the present sample supporting the hypothesis that SARC-F can reflect strength and muscle function[28].

The reverse and independent association among higher scores of SARC-F and SARC-CalF with MNA-SF indicates that higher risk of sarcopenia can be related to increased risk or diagnosis of malnutrition for this group of individuals. These results are significant, since sarcopenia and malnutrition coexist frequently[29], exposing a severer scenario associated with adverse outcomes, including chemotoxicity, treatment discontinuation and high morbimortality[30-32]. These findings highlight the importance of utilizing SARC-F and MNA-SF to help the diagnosis of nutritional syndromes in older patients submitted to chemotherapy treatment.

The study limitations are the small sample size, the cross-sectional observational design and selection by convenience in a single site, which impede to determine a causal relation and generalized results. Additionally, some non-measured variables (disease staging and definition of chemotherapy: neoadjuvant, adjuvant or palliative) may lead to important results for the models of regression, with influence on the findings. Cautious is advised while generalizing the results for other clinical populations. Future studies with larger samples and longitudinal design are recommended to explore and validate comprehensively this association.

CONCLUSION

The findings suggest that SARC-F can be a guiding tool for interventions related to the improvement of muscle status, potentially preventing the high number of chemotoxicity related gastrointestinal symptoms. Although additional studies with larger and representative samples to validate these findings are required, the present study contributes to the rising number of evidences indicating SARC-F as a potential prognostic invaluable screening tool of sarcopenia in regard to gastrointestinal chemotoxicity.

CONTRIBUTIONS

All the authors contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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Associate-Editor: Lívia Costa de Oliveira. Orcid iD: https://orcid.org/0000-0002-5052-1846
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