



## Original article

## Muscle function loss is associated with anxiety in patients with gastrointestinal cancer



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## ARTICLE INFO

## Article history:

Received 25 October 2018

Accepted 2 November 2018

## Keywords:

Cancer  
Sarcopenia  
SARC-F  
Anxiety  
Depression

## SUMMARY

**Objective:** To verify the prevalence of patients with muscle function loss (MFL) and whether it is associated with anxiety and depression scores in gastrointestinal (GI) cancer patients.

**Methods:** A cross-sectional study with seventy-one adult GI cancer patients was conducted. The MFL was evaluated by the SARC-F questionnaire, and participants were divided into MFL (cut-off  $\geq 4$  SARC-F) and normal muscle function (NMF) groups (cut-off  $< 4$  SARC-F). Anxiety and depression were analyzed using the Hospital Anxiety and Depression Scale (HADS).

**Results:** From 71 patients, 25.4% ( $n = 18$ ) were classified as MFL and 74.6% ( $n = 53$ ) as NMF. Body weight was lower in the MFL group when compared to the NMF group (MFL:  $57.6 \pm 11.3$  vs. NMF:  $64.8 \pm 11.6$  kg,  $p = 0.032$ ). MFL showed higher anxiety (MFL: 7.5 (0–21) vs. NMF: 2 (0–17),  $p = 0.030$ ) and depression scores (MFL: 6.5 (0–13) vs. NMF: 2 (0–17),  $p = 0.034$ ) compared to NMF. A positive correlation between the SARC-F and the anxiety ( $r = 0.34$ ,  $p = 0.004$ ) and depression score ( $r = 0.32$ ,  $p = 0.006$ ) was found. When adjusted by sex and body weight, MFL saw an increase with the anxiety score (OR: 1.15 95%CI(1.01–1.31),  $p = 0.023$ ), but not with the depression score. In addition, LMF was responsible for anxiety in 12% of the population.

**Conclusion:** In our study, 25% of GI cancer patients presented LMF and an association with the anxiety score.

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## 1. Introduction

Cachexia is a multifactorial syndrome defined by involuntary weight loss with depletion of skeletal muscle mass (with or without loss of fat mass) that leads to the damage of muscle function [1,2]. When the weight loss involves muscle mass, there is sarcopenia and this is associated with a higher frequency of clinical complications, less favorable prognosis, muscle function, increase in the rate of mortality, and poor quality of life [3–5]. Changes in body composition are common in patients with gastrointestinal cancer (GI) due to anorexia and severe weight loss that may have a negative impact on the individual's body perception [6]. Combined

with loss of muscle mass, cancer patients often experience weakness and muscle function loss (MFL) which adversely affects their functional status and independence [7–9]. Thus, weight loss can negatively influence aspects related to daily activities, as well as the patients' physical and emotional well-being [3,6].

In addition to the behavioral, social, and environmental factors that lead to the appearance of psychological disorders, such as depression and anxiety in cancer patients. The loss of lean mass has also been identified as a trigger in the initial stages of psychological disorders [3,10,11]. However, no evidence shows that (SARC-F) [12], which is commonly used on the Brazilian population to evaluate the presence of sarcopenia [13] could also serve to predict anxiety and depression. In addition, no studies evaluated if a validated Hospital Anxiety and Depression Scale (HADS) [14,15] is associated with muscle function.

Magnetic resonance imaging (MRI) and computed tomography (CT) are considered good techniques to estimate muscle mass.

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However, some aspects complicate the use of MRI or CT for research and clinical practice, due to high cost, limited access to equipment and the radiation exposure [16]. In addition, the DXA has been the preferred method to evaluate muscle mass, due to its ability to quantify the bone mineral and lean tissue mass with minimal radiation. However, this equipment is not portable, nor useful in clinical routine [16]. Alternatively, the BIA estimates the volume of fat mass and lean body mass. BIA is considered a good portable alternative for dual-energy X-ray absorptiometry (DXA), and its measurements are used under standard conditions [16]. Questionnaires are used to evaluate muscle function, due to the ease of use in the clinical routine, as well as the inexpensive scientific investigations. Likewise, the SARC-F is useful to measure the loss of muscle strength and/or performance in cancer patients as a first step of screening using imaging systems and gold standard methods [17], such as DXA, BIA, MRI or CT [16]. Thus, the aim of this study was to verify the prevalence of MFL and its association with anxiety and depression scores in GI cancer patients.

## 2. Materials and methods

### 2.1. Study design and participants

This cross-sectional study was conducted between December 2017 and June 2018 at the Araujo Jorge Hospital of the Goiás Association to Combat Cancer (ACCG), Goiania, Brazil. A total of 85 patients of an outpatient clinic, diagnosed with GI cancer, aged 29–82 years, of both sexes, undergoing surgery, chemotherapy and/or radiotherapy treatment were screened. However, 14 patients were excluded because they did not complete the HADS questionnaire. Thus, 71 patients had completed data and were included in the study.

The study was approved by the Research Ethics Committees at the Federal University of Goiás (number 2.259.702) and Araujo Jorge Hospital (number 2.289.067) and after agreeing to participate in the study, they signed the appropriate Consent Form. Patients were interviewed while waiting for their outpatient medical appointment at the hospital. Patients also answered a questionnaire to investigate the demographic data: age, sex, and clinical information from medical records, such as the location of the primary and/or secondary tumor, and what type of treatment was being performed.

### 2.2. Anthropometric measurement

Body weight (kg) and height (m) measurements were taken and then input into the Body Mass Index (BMI, kg/m<sup>2</sup>). For taking weight, a Toledo<sup>®</sup> electronic weighing scale with a maximum capacity of 150 kg was used, which was installed in a flat location and the patients were instructed to remove outer garments, accessories, and shoes before weighing.

Height measurement was performed with the Sanny<sup>®</sup> wall stadiometer. The patients were instructed to be barefoot and positioned with their back straight, arms extended along the body, heels together and the head forming a 90° angle with the upper base of the stadiometer [18,19].

### 2.3. Evaluation of muscle function

Loss of muscle strength and/or performance was performed using SARC-F, a questionnaire validated on the Brazilian population [13,20]. This questionnaire is considered a quick and easy evaluation tool to predict sarcopenia and to evaluate MFL in patients aged 50.6 ± 12.6 years old [2]. It has five questions related to strength, the need for help to walk, ability to lift a chair, climb stairs and

frequency of falls that demonstrate the presence of sarcopenia. Each question has a scale that ranges from 0 to 10, that is, 0–2 points for each component, 0 = no difficulty/frequency and 10 = lots of difficulty/high frequency. From the answers obtained, it was possible to identify patients with MFL (cut-off ≥4 SARC-F) and those with normal muscle function (NMF) (cut-off <4 SARC-F) [13,20]. Thus, we divided the sample in two groups, MFL or NMF.

### 2.4. Evaluation of anxiety and depression

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). It is a questionnaire that has 14 items, seven of them related to anxiety and seven of them to depression. The cut-off points are 0–8 (without anxiety) and ≥9 (with anxiety); 0–8 (without depression) and ≥9 (with depression) [14]. This scale is used on outpatients and on the general population, and is considered a reliable instrument with good reproducibility for the identification of emotional disorders related to anxiety and depression [15].

### 2.5. Statistical analyses

The normality of data was tested using the Kolmogorov–Smirnov test and to verify the differences between groups, the Mann–Whitney test was performed for non-parametric variables and T Student for parametric variables. Fisher's exact test was used to verify differences in categorical variables.

For the association of LMF with anxiety and depression scores, a logistic or linear analysis regression was performed with three models, crude, adjusted for sex (model 1) and/or adjusted for sex and body weight (model 2). Medcalc<sup>®</sup>, Seoul, Korea software was used for all analyses.  $p < 0.05$  was considered statistically significant.

## 3. Results

Of the 71 patients evaluated, 18 (25.35%) were classified as MFL (cut-off ≥4 SARC-F) and 53 (74.65%) with NMF (cut-off <4 SARC-F). MFL showed higher SARC-F score [4 (4–9)] when compared to NMF [1 (0–3)],  $p < 0.0001$  (Table 1).

The mean age was (NMF: 62.32 ± 11.19 vs. MFL: 64.58 ± 8.35 years), with no difference between groups ( $p = 0.378$ ). In addition, no differences were found between groups regarding gender (NMF: 37 vs. MFL: 9;  $p = 0.555$ ), height (NMF: 1.64 ± 0.06 vs. MFL: 1.62 m ± 0.09;  $p = 0.479$ ), BMI (NMF: 23.98 ± 4.34 vs. MFL: 21.00 ± 4.70;  $p = 0.054$ ), treatment with chemotherapy ( $p = 0.762$ ), radiotherapy ( $p = 0.762$ ) and surgery ( $p = 1.000$ ). However, MFL group showed lower body weight (57.63 ± 11.34 vs. 64.83 kg ± 11.62 kg,  $p = 0.032$ ) when compared to NMF, respectively (Table 1). When we evaluated HADS questionnaire, higher anxiety scores (MFL: 7.5 (0–21) vs. NMF: 2 (0–17),  $p = 0.030$ ) and depression scores (MFL: 6.5 (0–13) vs. NMF: 2 (0–17);  $p = 0.034$ ) were found in MFL group (Table 1). Additionally, a positive association between the SARC-F score and the anxiety score ( $r = 0.34$ ,  $p = 0.004$ ) and depression score ( $r = 0.32$ ,  $p = 0.006$ ) were found (Fig. 1).

Although, the logistic regression analysis showed positive association among the LMF and anxiety and depression scores in the Crude Model after adjustment for sex (Model 1), after adjusting for sex and body weight (Model 2), this association remained only for anxiety (OR: 1.15, 95% CI(1.01–1.31),  $p = 0.023$ ), but not for depression (OR: 1.17 95% CI(0.99–1.37),  $p = 0.051$ ) (Table 2). In addition, MFL was responsible for anxiety in 12% of the population ( $r^2: 0.12$ ,  $p = 0.002$ ) (Table 3).

#### 4. Discussion

In this study, 25% of patients with GI cancer were classified as having MFL and higher scores for anxiety and depression. In the present study, patients with MFL also had lower body weight and higher anxiety and depression scores than those with NMF. However, in this study when the logistic regression was adjusted for sex and body weight, only the MFL group was associated with anxiety.

Anxiety and depression are very common among cancer patients. The diagnosis of cancer is associated with fears of suffering and death which lead to anxiety. Besides, during and in the end cancer treatment, patients show signs of depression due to several symptoms caused by diseases and/or treatments, such as anorexia, fatigue and sleep disruptions [21,22].

Likewise, it is widely understood that the maintenance of muscle function has important neuronal and immunological effects that can improve mood [23]. Recently, it has been found that among the factors involved in the development of emotional diseases are the reduction of brain-derived neurotrophic factor (BDNF) and

tumor growth that induces the release of proinflammatory cytokines, such as the tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6) [11,24].

BDNF is known as a neurotrophin, which acts as a growth and survival factor for neurons, playing an important role in the central and peripheral nervous system. BDNF acts as a survival factor for motor neurons during regeneration and thus may be able to reduce denervation-induced muscle atrophy [25]. Likewise, it is probable that patients of our present study are suffering from emotional stress, since depression and anxiety can reduce BDNF synthesis leading to a decrease in neuromotor signaling, compromising muscle function [26].

The presence of systemic inflammation, common in cancer patients, also promotes the onset of psychic diseases and negatively affects muscle function. In this case, tumor growth stimulates the release of inflammatory cytokines (TNF- $\alpha$  and IL-6), which cause alteration in the neuroendocrine control of appetite, promoting anorexia. Once anorexia has been established, the patient has an involuntary reduction of appetite and reduced food intake. Thus,

**Table 1**  
Characteristics between the groups.

Variables	NMF (<4 SARC-F) n = 53 (74.65%)	MFL ( $\geq$ 4 SARC-F) n = 18 (25.35%)	p
Age (y) <sup>a</sup>	62.32 $\pm$ 11.19	64.58 $\pm$ 8.35	0.378
Body weight (kg) <sup>a</sup>	64.83 $\pm$ 11.62	57.63 $\pm$ 11.34	<b>0.032</b>
Height (m) <sup>a</sup>	1.64 $\pm$ 0.06	1.62 $\pm$ 0.09	0.479
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	23.98 $\pm$ 4.34	21.00 $\pm$ 4.70	0.054
Gender (n) <sup>b</sup>			0.158
Male	37	9	
Female	16	9	
Age (n) <sup>b</sup>			0.555
$\geq$ 60	38	11	
<60	15	7	
Chemotherapy (n) <sup>b</sup>			0.166
Yes	50	15	
No	3	3	
Radiotherapy (n) <sup>b</sup>			0.762
Yes	15	4	
No	38	14	
Surgery (n) <sup>b</sup>			1.000
Yes	25	7	
No	28	7	
Primary diagnostic (n) <sup>b</sup>			0.574
Esophagus	3	2	
Stomach	8	4	
<b>Small Intestine</b>	16	4	
Rectum	9	3	
Colon	11	1	
Pancreas	2	1	
Liver	2	2	
Gall bladder	2	1	
<b>Secondary organs affected (metastases number)<sup>b</sup></b>			0.748
Esophagus	0	1	
Stomach	0	1	
<b>Small Intestine</b>	2	3	
Rectum	10	0	
Colon	1	0	
Pancreas	2	0	
Liver	1	0	
Gall bladder	1	0	
Breast	1	0	
Kidney	1	1	
Lung	1	1	
Lymph node	1	0	
Bone	1	0	
SARC-F (score) <sup>c</sup>	1 (0–3)	4 (4–9)	<b>&lt;0.0001</b>
Anxiety (score) <sup>c</sup>	2 (0–17)	7.5 (0–21)	<b>0.030</b>
Depression (score) <sup>c</sup>	2 (0–17)	6.5 (0–13)	<b>0.034</b>

p < 0.05 was considered as significant; MFL: muscle function loss; NMF: normal muscle function.

<sup>a</sup> Student's t test.

<sup>b</sup> Chi-square test.

<sup>c</sup> Mann–Whitney test.

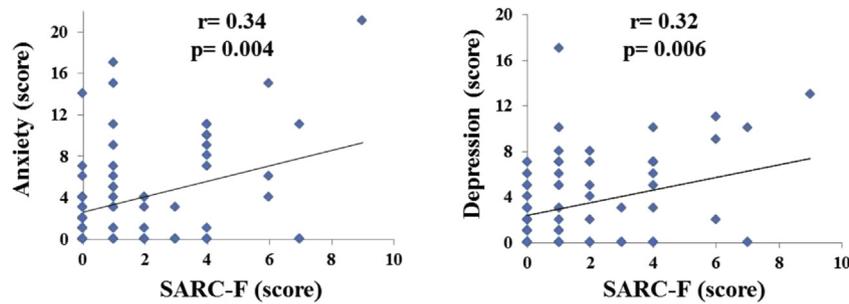


Fig. 1. Pearson's correlation among the SARC-F score and Hospital Anxiety and Depression Scale (HADS).

**Table 2**

Logistic regression (OR, association) between the muscle function loss ( $\geq 4$  SARC-F) and anxiety and depression scores.

Continuous variable	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Anxiety (score)	1.16 (1.04–1.30)	1.16 (1.03–1.31)	1.15 (1.01–1.31)
P value	<b>0.008</b>	<b>0.010</b>	<b>0.023</b>
Depression (score)	1.18 (1.02–1.37)	1.18 (1.02–1.37)	1.17 (0.99–1.37)
P value	<b>0.019</b>	<b>0.024</b>	0.051

OR: odds ratio. Model 1: adjusted by sex. Model 2. Adjusted by sex and body weight.  $p < 0.05$  was considered as significant.

**Table 3**

Linear multiple regression backward between the muscle function loss ( $\geq 4$  SARC-F) and anxiety and depression scores.

Continuous variable	$r^2$	p
Anxiety (score)	0.119	0.002
Depression (score)	0.087	0.008

$p < 0.05$  was considered as significant.

cytokines derived from the tumor can indirectly cause MFL by reducing skeletal muscle mass and strength [27].

Not only the inflammation and anorexia derived from cancers, but also the low level of physical activity can increase the symptoms of anxiety and lead to MFL. In the present study, 100% of the patients have a sedentary lifestyle. In contrast, physical activity exerts a neurophysiological effect on the central nervous system, which promotes adaptations that favor the increase of BDNF concentrations associated with the release of endocannabinoids, substances related to analgesia, anxiolysis and sense of well-being [28,29].

In our study, 28% of the GI patients was diagnosed with cancer in the small intestine. This cancer location is very rare among GI cancers and presents non-specific symptoms. In addition, the screening of small intestine cancer is not easy to detect in the cancer's early stages. Thus, the diagnostic in the majority of cases, is made in advanced stages [30].

In this study, 38% of the patients with MFL undergoing some type of cancer treatment presented tumors in other locations. However, there was no association with anxiety and depression. Indeed, cancer treatment has not been found to be associated with psychological disorders in metastatic cancer [31].

In this study, MFL was associated with a higher anxiety score in GI cancer patients independently of treatment type (post-surgery, and/or undergoing chemotherapy and/or radiotherapy). Some conventional chemotherapeutic agents, immunotherapies, radiotherapies and oncological surgeries are recognized for their adverse effects that induce neurological sequelae such as neuropathy, cognitive deficit, anxiety and depression. Likewise, patients become more vulnerable to psychological disorders, which manifest in symptoms such as fatigue, constant preoccupations,

decreased willingness to perform daily activities, and a sense of worthlessness [32,33].

However, the probable mechanisms that may explain the increased risk of anxiety during treatment are not well understood. What is known is that the patient goes through stages from diagnosis to treatment in which the events related to the disease can explain the psychological problems, promoting an acute stress or posttraumatic disorder [34].

The explanation regarding the association between anxiety and cancer-induced sarcopenia, is likely due to the fact that chemoradiotherapy is often very aggressive and leads to uncomfortable effects such as nausea, vomiting, hair loss, anorexia, non-intentional weight loss, sarcopenia and muscle function damage. These discomforts can provoke the feeling of anxiety in these patients [21,35,36]. However, in the present study, cancer treatments did not associate with higher MFL or anxiety depression scores.

There are few studies that evaluate the presence of anxiety and depression among patients with GI cancer. Thus, it is the anxiety in these patients that over time change the perception of their emotional well-being and trigger the onset of depression. Studies have shown that anxiety is more prevalent among younger patients and those who have a shorter treatment time, while depression is more evident among older individuals with longer treatment times [37]. However, in the present study, in which we evaluated older patients, it seems that anxiety was more associated with MFL than depression was.

Furthermore, anxiety and depression are commonly reported by cancer patients and there is highest prevalence of anxiety in hospitalized patients. This prevalence is reflected predominantly in severely ill inpatients, along with high levels of physical discomforts and increased mortality [38]. However, we assessed outpatients and therefore, they did not suffer the influence of hospitalization on the development of anxiety and depression.

To our knowledge, this is the first study that associated muscle function with anxiety and depression among cancer patients. In addition, the use of the SARC-F and HADS questionnaires to assess muscle function and anxiety and depression, respectively, is important in clinical practice, since they are easily accessible, applied, interpreted and validated tools. Additionally, our sample was homogeneous regarding age, sex, type of treatment and tumor location, which allows a greater reliability in our findings.

However, our study did not evaluate the skeletal muscle mass using gold standard body composition tools. Thus, we believe that the evaluation of muscle mass concomitant with the SARC-F questionnaire may be assessed for further studies. Moreover, evaluation of blood cytokine concentrations could strengthen and confirm this data. In conclusion, MFL is present in 25% of the GI cancer patients and it is associated with anxiety independently of the medical treatment performed.

### Statement of authorship

JDPS and GDP contributed to the study design. JDPS, TLNG, JMS, and ICLO collected the data of the manuscript. JDPS, TLNG, JMS, ICLO, JFM, AL and GDP performed the literature search and participated in the discussion of manuscript. JDPS and GDP drafted the manuscript. All authors read and approved the final version of the article.

### Conflict of interest

None.

### Funding sources

JDPS receives scholarships supported by Capes, Brazil. JMS receives scholarships supported by CNPq, Brazil.

### Acknowledgements

We would like to thank all the patients of the oncology clinic at the Araujo Jorge Hospital of the Goiás Association to Combat Cancer (ACCG).

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