Association between nutritional status and muscle strength in pediatric cancer patients

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ABSTRACT:

Background: As in adults, pediatric cancer provides a catabolic state, leading to weight loss and depletion of lean mass, which is accompanied by loss of muscle strength. Low muscle strength is more sensitive to poor prognostic and treatment-related outcomes. Aim: To evaluate the association between nutritional status and muscle strength in pediatric cancer patients hospitalized at the Cancer Hospital I. Methods: A cross-sectional study was carried out with patients aged 6 to 19 years with cancer hospitalized in the period from February 2019 to November 2019. In the first 48 hours of hospitalization, anthropometric and handgrip strength (HGS) assessments were performed. Patients in severe condition, palliative care, hospitalized for bone marrow transplantation, in contact and / or respiratory isolation and unable to perform anthropometry were excluded. The statistical analysis for the data correlation was performed using Pearson's coefficient, and association by $\chi 2$ test. The HGS values were distributed in quartiles. P-value $\leqq 0.05$ was considered significant. Results: The majority of the population had an adequate BMI (45.60%).and the mean HGS was 17.1 kg (SD ± 8.93). There was a strong correlation between HGS and mid-arm muscle circumference (MAMC) and weight. The lowest HGS percentile also showed a statistically significant association with below adequate MAMC. Conclusions: These results show that the use of HGS is feasible in clinical practice to determine low muscle strength and as a prognostic factor for treatment.

Keywords: Neoplasms, children, adolescent, muscle weakness, nutritional status.

1 – INTRODUCTION:

Individuals with cancer usually experience weight loss and lean mass depletion (1), which is an independent risk factor for increased morbidity and mortality, length of hospital stay, risk of treatment toxicity, and worsening quality of life (2,3). Malnutrition is a common complication in pediatric cancer patients (4). Lean mass depletion is accompanied by loss of muscle strength, more appropriately called dinapenia (5).

Among the types of cancer that affect the pediatric age group, leukemia is the most common type of cancer in most populations (6–8). According to the estimates of the National Cancer Institute José Alencar Gomes da Silva (9) for each year of the 2020-2022 triennium, in Brazil, there will be 4,310 new cases of cancer in male children and adolescents, and 4,150 in female.

More recently, dinapenia in children has been studied (10–13), which can be measured by handgrip strength. It has been considered a predictor of nutritional status (14,15), but there is no defined cutoff point for the pediatric population.

According to the European consensus on sarcopenia in older people (16), muscle strength reflects muscle functionality and is the first parameter evaluated for diagnosis, which must be confirmed with other methods to measure muscle mass, but it is highly likely that the individual is sarcopenic when presenting muscle strength reduction. Although there is growing research interest in childhood sarcopenia, there is no consensus until the present moment (17). Thus, this study aims to evaluate the association between nutritional status and muscle strength in pediatric cancer patients hospitalized.

2- METHODS:

2.1 – Study population and design:

A quantitative, observational, descriptive and cross-sectional study was carried out with pediatric cancer patients admitted to the pediatric ward of the National Cancer Institute

José Alencar da Silva (INCA), from February 2019 to November 2019. Children and adolescents from 6 to 19 years, with confirmed oncological diagnosis of solid and / or hematological tumors were included. The exclusion criteria were: patients admitted to the pediatric ICU in a severe clinical condition; patients admitted for bone marrow transplantation; palliative care patients; patients unable to perform anthropometric assessment, either due to the presence of edema, an amputated limb or the impossibility of walking; and patients in contact and / or respiratory isolation.

The sample was stratified by age group: 6 to 9 years, 10 to 14 years and 15 to 19 years. Participants underwent nutritional assessment within the first 48 hours of hospitalization. In nutritional assessment, handgrip strength (HGS) measurements were performed to assess muscle function, and anthropometric measurements were taken to diagnose nutritional status.

2.2 – Nutritional Assessment:

Anthropometry were performed: body weight measurements on a digital scale calibrated with a scale of 0.1 kg with participants wearing light clothes and without shoes; height, measured by vertical wall stadiometer; mid-upper arm circumference (MUAC), measured by a flexible, inelastic measuring tape, at the midpoint of the distance between the acromion and the olecranon; tricipital skinfold (TSF), performed at the same midpoint of the MUAC, but in the posterior part of the arm, parallel to the horizontal axis, to assess the adipose reserve through the adipometer; and mid-arm muscle circumference (MAMC), obtained indirectly by measuring the TSF and MUAC using the following calculation: MAMC (cm) = MUAC (cm) - TSF (mm) x π / 10 (where π = 3 , 14). MUAC and TSF measurements were obtained in one arm, in three measurements and the value used was the average of these values. HGS was measured using the Jamar hydraulic hand dynamometer (Sammons Preston TM, Canada). The test was applied with the patient seated, with the shoulder abducted and neutrally rotated, elbow flexed at 90° and forearm and wrist in neutral position. Three measurements were taken in each hand alternately (total of six measurements), with a one-minute pause between them, except in case of venous access or catheter in one of the arms. In this case, three measurements were made on the same hand. The patient was asked to exercise as much force as possible and the highest value obtained was considered.

For the diagnosis of nutritional status, the Body Mass Index (BMI) was calculated by the body weight divided by the height squared. The Z-score calculation of the anthropometric ratios "weight for age", "height for age" and "BMI for age" was performed using the WHO AnthroPlus software (version 3.2.2, January 2011) and the classification was performed by the growth curves of the World Health Organization (18). The classifications of MUAC, TSF and MAMC were based on the reference tables of FRISANCHO (1981, 1990).

All equipment for assessing the patients' nutritional status were available at the institution. Information regarding diagnosis and treatment was obtained from medical records.

2.3 – Statistical Analysis:

Continuous variables were expressed as mean and standard deviation (SD) and categorical variables were presented by percentage frequency distribution. The Chi-square test was used to analyze categorical variables and ANOVA with Bonferrini post-hoc test or Student's t-test for continuous variables. Pearson's correlation was used to assess the correlation between muscle strength and nutritional status. Pearson's coefficients were classified as: from 0.1 to 0.39 indicates a weak correlation, from 0.40 to 0.69 indicates a moderate correlation and above 0.70 indicates a strong correlation (19).

The values of HGS were classified in quartiles and the distribution of patients in the percentiles <25, ≧ 25 and <50, ≧ 50 and <75, and ≧ 75 was performed. From this distribution, the chi-square test was performed between HGS percentiles and anthropometric parameters.

The results were considered statistically significant when p-value ≦ 0.05, and 95% confidence intervals. The SPSS (Statistical Package for Social Sciences) program, version 22, was used to analyze the data.

2.4 – Ethical considerations:

The study in question is linked to a larger study called "Construction and validation of a nutritional assessment instrument for pediatric cancer patients". The project has been submitted to the Ethics Committee and approved under CAAE No. 73737317.2.3001.5274.

Those responsible for patients aged 6 to 17 years signed the Informed Consent. The 18 and 19-year-old patients signed the Informed Consent for adolescent patient together with the parents or responsible for them. The Assent term was signed by patients aged 7 to 17 years.

3- RESULTS:

The sample consisted of 63 patients, 52.40% male and 47.60% female. Table 1 shows the general characteristics and the main diagnoses of all patients, stratified by age group.

Most tumors were solid (69.80%), with Central Nervous System (CNS) tumors being the most frequent in the sample (22.20%), followed by Acute Lymphoid Leukemia - ALL (14.30%) and osteosarcoma (11.10%). CNS tumors were also the most frequent for the 10-14 year olds and 15-19 year olds (25% and 31.60%, respectively). In the 6 to 9 year old age group, the most frequent tumors were ALL (18.80%), Burkitt's Lymphoma (12.50%), Osteosarcoma (12.50%) and Retinoblastoma (12.50%).

Among the tumors in the “other” category, there are tumors that presented 2 times or less. They are: desmoid tumor of the mandible, Ewing's sarcoma, Fibrohistiocytoma, Synoviosarcoma, Teratoma, Hepatocarcinoma, Pheochromocytoma and Willms tumor.

Among CNS tumors are: Medulloblastoma, Astrocytoma, Primitive neuroectodermal tumor (PNET), Glioma, Germinoma, Craniopharyngioma, Chordoma clivus and Ependimoma.

Table 1: General characteristics and main diagnoses for general population and by age group.

Variables		General	6 - 9 years	10- 14 years	15 - 19 years
Sex**					
	Male	52,40%	68,80%	60,70%	26,30%
	Female	47,60%	31,30%	39,30%	73,70%
Age (years) – mean (SD)		13,01 (3,83)	8,03 (1,14)	12,80 (1,56)	17,50 (1,58)
Hospitalization reason					
	Emergency	52,40%	37,50%	53,60%	63,20%
	Elective	47,60%	62,50%	46,40%	36,80%
Tumors types					
	Solids	69,80%	62,50%	71,40%	73,70%
	Hematological	30,20%	37,50%	28,60%	26,30%
Diagnoses					
	ALL	14,30%	18,80%	14,30%	10,50%
	AML	1,60%	-	-	5,30%
	Hodgkin's lymphoma	4,80%	6,30%	3,60%	5,30%
	Non-Hodgkin's lymphoma	6,30%	-	10,70%	5,30%
	Burkitt's lymphoma	3,20%	12,50%	-	-
	CNS tumors	22,20%	6,30%	25,00%	31,60%
	Thyroid carcinoma	3,20%	6,30%	3,60%	-
	Osteosarcoma	11,10%	12,50%	10,70%	10,50%
	Rhabdomyosarcoma	4,80%	6,30%	7,10%	-
	Oro/nasopharynx	7,90%	-	10,70%	10,50%
	Retinoblastoma	3,20%	12,50%	-	-
	Others	17,50%	18,80%	14,30%	21,10%

**P-value ≦ 0.05, using the Chi-square test. SD: standard deviation; ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid Leukemia; CNS: central nervous system.

Table 2 shows the mean and standard deviation of the parameters of nutritional assessment. The mean weight of the patients was 44.88 kg (SD ± 19.53) and the mean HGS was 17.1 kg (SD ± 8.93). The weight and MAMC variables showed a statistically significant difference between the three age groups.

Table 2: Mean and standard deviation (SD) of nutritional assessment parameters for the entire sample and by age group

Nutritional Assessment		General	6 - 9 years	10- 14 years	15 - 19 years
Weight (Kg)	*#º	44,88 (19,53)	26,73 (5,60)	46,99 (16,74)	59,70 (18,75)
Height (cm)	*º	148,76 (17,65)	125,44 (7,08)	155,50 (12,09)	161,56 (6,95)
BMI (Kg/m²)	º	19,49 (5,30)	16,84 (2,30)	19,09 (5,06)	22,75 (6,28)
MUAC (cm)	#º	22,45 (5,36)	18,72 (2,29)	22,14 (5,02)	26,04 (5,52)
TSF (mm)		16,57 (10,55)	13,25 (6,22)	15,33 (10,42)	21,17 (12,39)
MAMC (cm)	*#º	17,24 (3,18)	14,55 (1,43)	17,32 (2,73)	19,39 (3,25)
HGS (Kg)	*º	17,10 (8,93)	8,88 (3,65)	18,89 (9,14)	21,37 (7,34)

* P-value ≦ 0.05 between 6-9 years and 10-14 years; # P-value ≦ 0.05 between 10-14 years and 15-19 years; º P-value ≦ 0.05 between 15-19 years and 6-9 years, using ANOVA with Bonferroni post-hoc test. BMI: body mass index; MUAC: mid-upper arm circumference; TSF: tricipital skin fold; MAMC: mid-arm muscle circumference of the arm; HGS: handgrip strength.

When the genders are compared, there was a statistical difference between the HGS for male and female in the general population (p-value = 0.009). However, in the different age groups, was found statistical difference only between the two sexes in the age group of 14 to 19 years (p-value = 0.002). In both sexes, the HGS increased with age, but it was only significant in the 6 to 9 year old age group compared with the other two age groups, showing a greater increase in the HGS from the school phase to the adolescent phase and a decreasing from the 10 years old. This also occurs with male patients, but in females there is only a statistical difference between the age groups of 6 to 9 years and 15 to 19 years.

Table 3 shows the classification of anthropometric indexes and anthropometric measures in the total population and stratified by sex and age. The majority of the population had an appropriate weight for their age (81.30%), an adequate height for their age (94.20%) and adequate BMI (45.60%). However, in the age group of 15 to 19 years, in the male population, the frequency of adequate BMI, overweight and marked thinness was similar (33.30%). Most also had adequate MUAC, TSF and MAMC (58.70%, 50.80% and 55.60%, respectively). However, in the age groups 10 to 14 and 15 to 19 years old, the highest frequency of MUAC was lower than that suitable for males (47.10% and 60.00%, respectively), and in the age group 15 to 19 years old, also in the male population, the most frequent MAMC classification was below the adequate level (60.00%). In addition, in the age group of 15 to 19 years, in the female population, the frequencies of MAMC below the adequate and adequate were similar (42.90%).

Table 3: Classifications of anthropometric indexes and anthropometric measures for the entire sample and by sex and age group

					6 - 9 years		10 – 14 years		15 - 19 years	
		Geral	**Masculino**	**Feminino**	**Masculino**	**Feminino**	**Masculino**	**Feminino**	**Masculino**	**Feminino**
Z-score W/A	Low	6,30%	9,10%	-	9,10%	-	NA	NA	NA	NA
	Nutritional risk	12,50%	18,20%	-	18,20%	-	NA	NA	NA	NA
	Adequate	81,30%	72,70%	100,00%	72,70%	100,00%	NA	NA	NA	NA
Z-score H/A	Low	5,80%	-	12,50%	-	-	-	20,00%	-	11,10%
	Adequate	94,20%	100,00%	87,50%	100,00%	100,00%	100,00%	80,00%	100,00%	88,90%
Z-score BMI/A	Marked thinness	8,80%	10,30%	7,10%	-	-	13,30%	10,00%	33,30%	7,70%
	Thinness	7,00%	6,90%	7,10%	9,10%	-	6,70%	-	-	15,40%
	Nutritional risk	10,50%	17,20%	3,60%	9,10%	-	26,70%	10,00%	-	-
	Overweight	15,80%	10,30%	21,40%	27,30%	20,00%	-	10,00%	-	30,80%
	Obesity	12,30%	13,80%	10,70%	9,10%	-	13,30%	10,00%	33,30%	15,40%
	Eutrophic	45,60%	41,40%	50,00%	45,50%	80,00%	40,00%	60,00%	33,30%	30,80%
MUAC	Below adequate (< P5)	33,30%	39,40%	26,70%	18,20%	20,00%	47,10%	27,30%	60,00%	28,60%
	Above adequate (> P95)	7,90%	12,10%	3,30%	-	-	17,60%	-	20,00%	7,10%
	Adequate (P5-95)	58,70%	48,50%	70,00%	81,80%	80,00%	35,30%	72,70%	20,00%	64,30%
TSF	Below adequate (< P5)	4,80%	6,10%	3,30%	-	-	11,80%	-	-	7,10%
	Nutritional risk (P5-15)	12,70%	15,20%	10,00%	27,30%	20,00%	5,90%	18,20%	20,00%	-
	Obesity risk (P85-95)	14,30%	12,10%	16,70%	27,30%	-	-	27,30%	20,00%	14,30%
	Above adequate (> P95)	17,50%	21,20%	13,30%	27,30%	20,00%	17,60%	9,10%	20,00%	14,30%
	Adequate (> P15 e < P85)	50,80%	45,50%	56,70%	18,20%	60,00%	64,70%	45,50%	40,00%	63,30%
MAMC	Below adequate (< P5)	41,30%	42,40%	40,00%	27,30%	20,00%	47,10%	45,50%	60,00%	42,90%
	Above adequate (> P95)	3,20%	-	6,70%	-	-	-	-	-	14,30%
	Adequate (P5-95)	55,60%	57,60%	53,30%	72,70%	80,00%	52,90%	54,50%	40,00%	42,90%

W/A: weight for age; H/A: height for age; BMI/A: body mass index for age; MUAC: mid-upper arm circumference; TSF: tricipital skin fold; MAMC: mid-arm muscle circumference.

Table 4 shows the correlation between HGS and anthropometric measurements. The correlation between HGS and weight was strong and significant for the total sample, but it was moderate to weak when stratified by age group. The correlation between HGS and MAMC was also strong and significant for the general population and for the 10 to 14 age group. There was moderate to weak correlation between HGS and BMI, MUAC and TSF.

In addition, classification in HGS quartiles was performed, creating 25th, 50th and 75th percentiles for each sex and age group. Of the 26 children with low MAMC, 16 had an HGS below the 50th percentile, and of the 35 children with adequate MAMC, 29 had an HGS above the 50th percentile (p = 0.003). This significance was maintained in all age groups. There was no association between the HGS percentiles and the other parameters.

Table 4: Correlation of HGS with anthropometric measurements

Variables	**General**		**6 - 9 years**		**10 - 14 years**		**15 - 19 years**	
	r^2	**p**	**r^2**	**p**	**r^2**	**p**	**r^2**	**p**
HGS X Weight	0,706	0,000	0,680	0,004	0,670	0,000	0,360	0,171
HGS X BMI	0,485	0,000	0,516	0,041	0,436	0,029	0,278	0,297
HGS X MUAC	0,569	0,000	0,547	0,028	0,473	0,011	0,364	0,125
HGS X TSF	0,208	0,102	0,196	0,468	0,131	0,508	0,040	0,872
HGS X MAMC	0,743	0,000	0,605	0,013	0,714	0,000	0,572	0,010

Pearson's correlation; r^2 between 0.40 and 0.69: moderate correlation; r^2> 0.70 strong correlation. HGS: hand grip strength; BMI: body mass index; MUAC: mid-upper arm circumference; TSF: tricipital skin fold; MAMC: mid-arm muscle circumference.

4-DISCUSSION

In the study, the highest prevalence was of solid tumors, and most patients had an adequate nutritional status, according to the WHO classification, except in some age groups that had a higher prevalence of nutritional status below the adequate level. Moreover, a strong correlation of HGS with MAMC and weight was found, as well as a statistically significant relationship of the distribution of HGS in percentiles with MAMC.

Leukemia and lymphomas are known to be the most common types of cancer in the pediatric population (6–8). Despite this, the current study had a higher prevalence of children with solid tumors (69.80%). This is probably due to the low turnover of the pediatric hematology ward of Cancer Hospital I, which has few beds, and in which most patients are admitted multiple times for chemotherapy protocols, in addition to having a prolonged hospital stay.

In the current study, the sample mostly presented adequate nutritional status according to all anthropometric parameters, and was compatible with the study by Moreira et al. (2019), who assessed the nutritional status of pediatric patients newly diagnosed with Acute Lymphoblastic Leukemia. These findings were also consistent with those of Jensen et al. (2017) and Lifson et al. (2017) in relation to anthropometric indexes, however they differed from this second author when it comes to the classifications of MUAC, TSF and MAMC, whose findings showed a higher prevalence of malnutrition. However, in the current study, despite the general population presenting the appropriate classification for such measures, when the sample was stratified, it was possible to observe that in certain age groups the frequency of classifications below the appropriate level is higher, especially for males.

Many authors have considered HGS as an indicator of nutritional status, sarcopenia and bone fragility (14,22). The findings of this article show that the HGS increased with age, but this increase was not significant between the 10-14 year old and 15-19 year old, evidencing that there is a significant increase from the school to the adolescent phase, slowing down from 10 years old. Another study also observes this phenomenon, but the author points out that the greatest increase in HGS occurs between 9 and 11 years in girls and between 13 and 14 years in boys (12). Ploegmakers et al. (2013) found that HGS also increases with age, accelerating above 12 years in boys and from 11 years in girls. Both studies were conducted with healthy children and adolescents.

In assessing the correlation of HGS with anthropometric parameters, a strong correlation was observed with weight, which was not maintained in any of the three age groups, and with MAMC, which persisted only in the 10 to 14 age group. In addition, by distributing the HGS in quartiles, it was possible to identify a significant association between the adequacy of the MAMC and the percentile of HGS. This result points that HGS can be a good predictor of nutritional status related to muscle mass. Three other authors found a relationship between HGS and muscle mass, either through MAMC or BIA (11,12,23).

According to Marrodán Serrano et al. (2009), in addition to the correlation with MAMC, correlations were also found with height, age, weight, MUAC, total arm area and muscular arm area for males, but only weight, age, MAMC and height for the women. However, when the effects of age and height are eliminated, the correlations with the other parameters are not maintained. de Souza et al. (2014), in a study also carried out with healthy children, identified a correlation between HGS and height, weight and fat-free mass, obtained through BIA. Ploegmakers et al. (2013) observed an association between HGS and weight, in addition to age, height and sex.

Bouma et al. (2016), in a study with children after hematopoietic cell transplants, observed that patients with malnutrition, classified according to BMI for age, had lower HGS values than those who had an adequate or high BMI for their age. In addition, he observed that children with HGS below the 10th percentile, had a significant association with BMI, indicating that this may possibly be a good cutoff point for this population.

It is important to note that the weight in patients with solid tumors may be overestimated due to the presence of the tumor mass. However, there was a correlation of strength with other anthropometric parameters, whether moderate or strong.

The HGS in this study was distributed in quartiles, but it was not possible to diagnose dinapenia, since there is no cutoff point validated for the pediatric population with cancer in Brazil. The studies that define cutoff points use varied methodologies, such as the ROC curve, which requires a representative sample, the LMS method, which takes into account the mean, coefficients of variation and Box-Cox transformations, for the distribution in percentiles and definition of the extreme values, and the classification of two standard deviations below the mean (10,14,24,25). Steffl; Chrudimsky; Tufano (2017) proposes the use of an index created from the ratio between HGS and BMI and concludes, through the data, that it is able to identify children at risk of being diagnosed with sarcopenic obesity. All of these studies are carried out with healthy children.

No studies were found to assess HGS and its relationship with anthropometric parameters in pediatric cancer patients. In recent years, a lot of research has been done evaluating sarcopenia in children, however, such studies do not evaluate HGS, but muscle mass through CT or DEXA. This shows the innovative character of the research and its relevance to clinical practice, since HGS is an easy-to-use and low-cost method.

Nevertheless, some limitations must be considered. Patients from the emergency room were included. Often the HGS of these children may be reduced due to symptoms that led them to seek care and not to malnutrition related to the disease and treatment.

5-CONCLUSION:

The study demonstrated a positive and strong correlation between HGS and MAMC, showing that it reflects nutritional status related to lean mass. Therefore, its use in clinical practice is feasible, especially in children with cancer, since they will be submitted to aggressive treatments such as radiotherapy and chemotherapy and will be subject to unsatisfactory outcomes related to muscle mass loss.

However, further studies are still needed, mainly to define a cutoff point for each age group and to use HGS as a predictor of sarcopenia and as a prognostic factor for treatment. However, at first, its use for follow-up is suggested in order to assess dinapenia during antineoplastic therapy or hospitalization.

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