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GLOBAL ONCOLOGY: RESEARCH ARTICLE

Malnutrition at diagnosis and throughout therapy in pediatric patients with solid tumors: A single-institution study in a developing country

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Abstract

Background: Changesin nutritional status can constitute a risk factor for reduced tolerance and effectiveness of antineoplastic treatment. Knowledge of the nutritional status of pediatric patients is important for implementing interventions to improve outcomes. We aimed to evaluate nutritional status at diagnosis and throughout therapy in pediatric patients with solid tumors.

Objectives: To study the prevalence of malnutrition at diagnosis, compare different assessment tools, and examine longitudinal changes in nutritional status during the treatment of pediatric patients with solid tumors in a Brazilian institution.

Methods: This prospective single-center study enrolled patients with solid tumors (age <19 years) from June 2017 to May 2018. Nutritional evaluations were performed at diagnosis and after 3 and 6 months of treatment. *z*-Scores for height for age (H/A) and body mass index for age (BMI/A) were calculated using the Anthro/AnthroPlus software and mid-upper arm circumference (MUAC) percentile was used for nutritional classification.

Results: The prevalence of nutritional status at diagnosis was 29.3% malnourished, 49.5% adequate, and 21.2% overweight/obese. Nutritional status improved during the first 3 months of treatment, with a reduction in the proportion of malnourished patients and an increased number of patients with adequate nutritional status.

Conclusions: The two combined indices, BMI/A and MUAC, facilitated the diagnosis of a greater number of patients with solid tumors who had nutritional alterations. A high prevalence of malnutrition was present at diagnosis. Nutritional status improved in the first 3 months of treatment and could be related to the multidisciplinary institutional approach following the diagnosis.

KEYWORDS
cancer treatment, nutritional status, pediatric solid tumors, prevalence

Abbreviations: BMI, body mass index; BMI/A, body mass index for age; H/A, height for age; INCA, Brazilian National Cancer Institute; LMIC, low- and middle-income countries; MUAC, mid-upper arm circumference; WHO, World Health Organization.

1 | INTRODUCTION

Survival rates in childhood cancer have increased to more than 80% in the last few decades. However, for many of the commonest solid tumors, the 5-year overall survival rate has remained nearly unchanged at approximately 60%–70% and has shown little improvement over the past decades.[1] In low- and middle-income countries (LMICs), where most cancer patients are found, the above-mentioned survival rates have not been achieved yet and need to be greatly improved.[2] The treatment outcomes of pediatric cancer patients in these countries is influenced by the delayed diagnosis, high dropout rates, high prevalence of malnutrition and other comorbidities, and difficulty in accessing healthcare.[3]

Research into treatment options is a priority for most clinical investigators, although some investigators are increasingly exploring the role of supportive care in the context of solid tumors and determining the association of supportive care with treatment-related toxicities and outcomes. A systematic review of articles reporting findings from children and adolescents with solid tumors who were treated in high-income countries found that up to 62% of patients were classified as either overnourished or undernourished at the time of cancer diagnosis, and nutritional status was associated with increased toxicities and poorer outcomes.[4] However, there is limited information on these associations among children with solid tumors who undergo treatment in developing countries.

Nutritional challenges and socioeconomic disadvantages are prevalent in LMICs and have been linked to adverse outcomes in cancer patients.[2,5,6] For example, in Nicaragua, pediatric oncology patients with malnutrition at cancer diagnosis had increased treatment-related morbidity, treatment discontinuation, and inferior event-free survival rates.[7] In Brazil, which is an upper middle-income country, consecutive studies have indicated a high number of malnourished children and adolescents with cancer.[8–10] Viani et al. reported that the prevalence of underweight children at diagnosis varied from 6% to 25% and increased from 10.5% to 52.4% during treatment. The prevalence of overweight and obesity ranged from 4.1% to 35% at diagnosis, and from 7.25% to 57.9% during and after treatment, respectively. The variation in the prevalence of nutritional status reflects the lack of standardized methods to define nutritional status, and most of the studies reported on children with acute leukemia. These factors highlight the need for more information on children with solid tumors who are undergoing treatment in developing countries.[11]

The aim of this study was to evaluate nutritional status at diagnosis and throughout therapy in pediatric patients with solid tumors. The objectives were to compare different nutritional assessment tools, to study the prevalence of malnutrition at diagnosis, and to examine longitudinal changes in nutritional status during the treatment of pediatric patients with cancer in a Brazilian institution.

2 | METHODS

In this cohort study, we prospectively enrolled pediatric patients with solid tumors who were scheduled to receive cancer treatment at the Brazilian National Cancer Institute (INCA) from June 2017 to May 2018 and evaluated prespecified nutrition-related variables both at diagnosis and during treatment.

Patients were routinely followed up by nutritionists in the department of nutrition, and all patients who were at nutritional risk or had malnutrition were started on the nutritional intervention protocol. Oral nutritional supplements are used for patients who have food intake that is less than 75% of the recommended nutritional values for 3–5 consecutive days. Nutritional intervention through the use of a nasoenteral tube occurs when oral feeding is impossible, or when food intake is insufficient (oral intake below 60% of the recommendations) for 3–5 consecutive days. Nutritional supplementation is routinely monitored by nutritionists at the outpatient nutrition clinic once every 15 days and evaluated daily in hospitalized patients. Nutritional supplements were provided by the department of nutrition for use at home.

For this study, all anthropometric assessments were performed by a qualified and trained investigator (Patricia Sasse). Demographic, clinical, and social data were obtained from the medical records. No additional examinations or routine nutritional interventions were performed. This study was approved by the INCA Human Research Ethics Committee (CEP). Based on the inclusion criteria, this study included children and adolescents up to 18 years and 11 months of age who were registered in the Pediatric Oncology Department of INCA. Eligible participants had confirmed diagnosis of a solid tumor, and caregivers provided written informed consent on behalf of all patients; moreover, patients who were older than 12 years provided voluntary informed consent for study participation. The informed consent form was available only in Portuguese, and consent was recorded by the primary investigator; withdrawal of consent was permitted at any time during the study.

We excluded patients who had previously received chemotherapy or radiotherapy, those who had undergone previous diagnostic surgery and had disease progression upon registration at our institution, and patients who did not undergo a nutritional assessment by the study's investigator before initiating cancer treatment and for more than 2 weeks after the scheduled assessment date at the 3- and 6-month time points.

2.1 | Sociodemographic, disease-related, and treatment-related variables

The demographic variables included date of birth, sex, and sociodemographic characteristics, including the mother's age (in years) and maternal education (≥9 or <9 years; because the Brazilian elementary schooling duration is 9 years),[12] and the per capita family income (≥0.25 or <0.25 minimum wage).[13] Clinical variables related to the disease were diagnosed in accordance with the International Classification of Childhood Cancer (ICCC-3),[14] the presence of metastasis at diagnosis, and the type of treatment.[15]

2.2 | Nutritional assessments

Nutritional evaluations were obtained during routine visits to the pediatric oncology outpatient clinic or in the ward at diagnosis as well as at 3 and 6 months after the diagnosis of a solid tumor. Weight, height, and mid-upper arm circumference (MUAC) were collected by a single trained and qualified observer at each designated time point (Patricia Sasse). Three measurements were taken for each patient, and the mean value was determined for MUAC. The ratio of height to age (H/A) and the body mass index to age (BMI/A) were calculated using the World Health Organization (WHO) Anthro and Anthroplus software.[16] The values obtained were expressed as *z*-scores, and the nutritional status was classified according to the WHO 2006–2007 recommendation for each age group. Malnutrition was considered as values below the (−)2 SD *z*-score, either for H/A (stunted) or BMI/A (wasted), in all age groups; children and adolescents with a BMI/A greater than the +2 and +3 *z*-score were classified as overweight and obese, respectively.[17] The MUAC was measured according to the recommendations in guidelines, using a fiberglass tape, to the nearest 1 mm at the halfway point between the acromion and olecranon process of the dependent right upper arm with the forearm held at a right angle.[18] Percentiles ≤5 were classified as malnourished, fifth to 84th as healthy range, and greater than or equal to the 85th as overweight and obese.[19] The categorization of nutritional status based on the BMI/A *z*-score and MUAC percentile was combined to account for the limitations associated with relying upon the body mass index (BMI) alone.[5] The combination of BMI/A and MUAC was used because some studies have shown that arm anthropometry is more effective for detecting malnutrition, especially in patients with solid tumors.[8,10,20–24]

2.3 | Statistical analyses

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 17.0,[25] and demographic variables are expressed as the absolute (*n*) and relative (%) frequencies. The chi-square test was used to compare the frequency of nutritional status and sociodemographic, clinical, and tumor-related characteristics. Statistical significance was set at $p < .05$.

To exclude the possibility of selection bias, we used the chi-square test to compare the baseline variables of the included participants and the patients who were excluded.

The concordance between nutritional alteration at diagnosis and in the follow-up was assessed by the kappa coefficient ($\varkappa$) and classified according to the method described by Landis and Koch.[17,26] Concordance was considered poor, mild, moderate, substantive, and almost perfect (0.00–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00, respectively).

3 | RESULTS

3.1 | Sample characterization

From June 1, 2017 to May 31, 2018, a total of 333 patients were registered at the institution with a diagnosis or high suspicion of neoplasia (Figure 1). Of these, 168 were diagnosed with a solid tumor and 99 patients were included in the study cohort and underwent nutritional assessments before commencing cancer treatment. There was no statistically significant difference in the clinical and demographic characteristics between the study participants and the 53 patients who were excluded on the basis of the study inclusion/exclusion criteria (Table S1).

At the 3- and 6-month assessments, 88 and 69 patients, respectively, were evaluated. There was no statistically significant difference in the clinical and demographic characteristics between the patients who were evaluated at 3 and 6 months and the losses due to death or the unevaluabilty of patients who did not have a scheduled appointment during the study period (Table S2).

The demographic characteristics of the study cohort are shown in Table 1. Most patients were younger than 5 years (44.4%), and the commonest type of cancer was central nervous system tumors (33.3%).

3.2 | Prevalence of nutritional status according to the joint BMI/A *z*-score and MUAC percentile definition at diagnosis

Participants were classified using individual nutritional indicators, as well as a combination of the BMI/A and MUAC aspects of nutritional status. Using the combination of BMI/A and MUAC at diagnosis, 29.3% and 21.2% of participants were classified as malnourished and overweight/obese, respectively. The combined classification resulted in a 37% reduction in children classified as eutrophic (Table 2). The concordance of the classification of nutritional status analysis between the BMI/A *z*-score and MUAC achieved a kappa value of .496 with a $p < .001$ (Table 3), suggesting moderate to low concordance between the indicators.

3.3 | Association between nutritional status at diagnosis and tumor-related sociodemographic and clinical characteristics

Contrary to the reports in the literature,[6,10] we did not observe an association between the nutritional status and the type of tumor or any other demographic or clinical characteristics (Table S3).

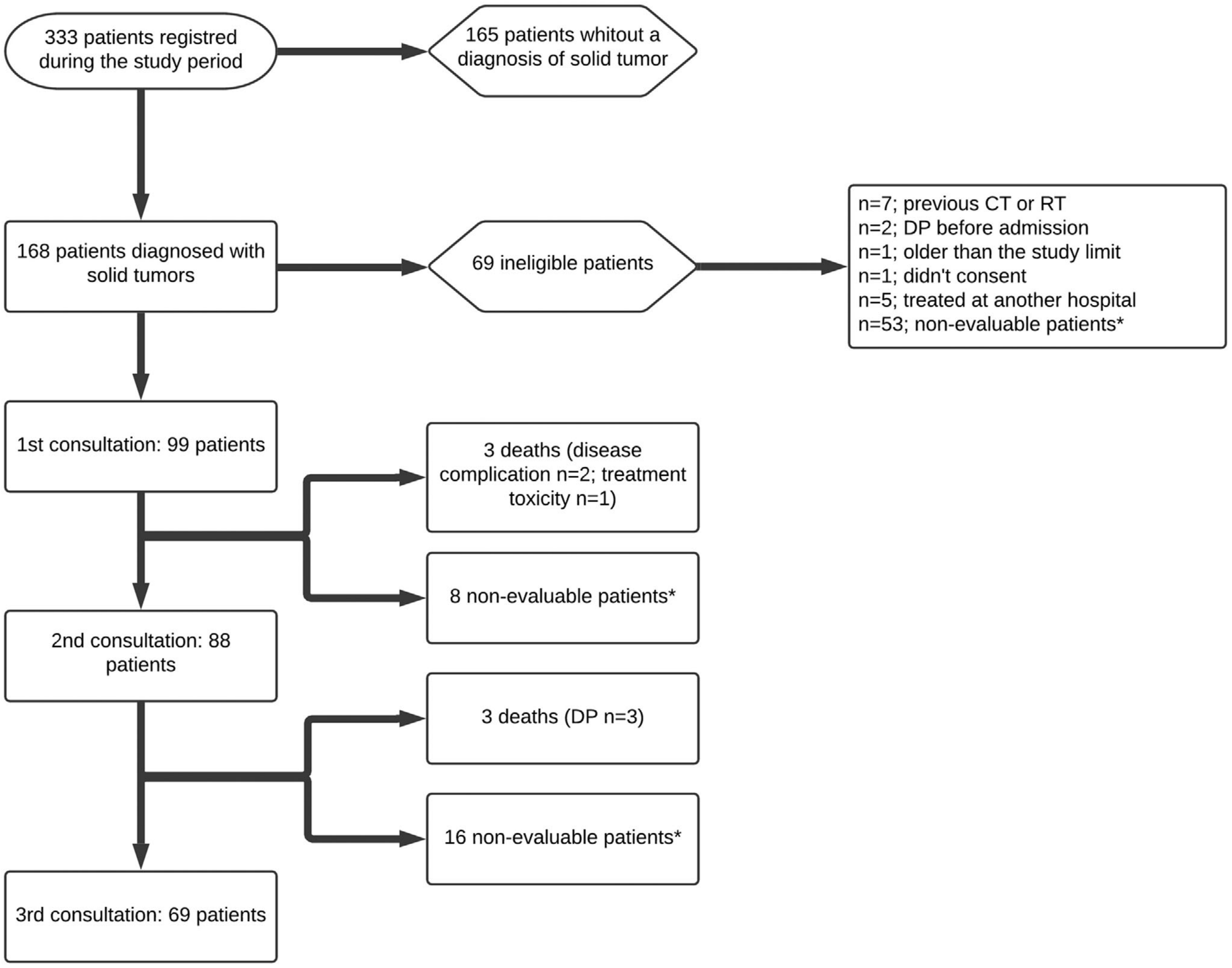

FIGURE 1 Study flowchart. CT, chemotherapy; DP, disease progression; RT, radiotherapy. *Patients who were unevaluable did not have a scheduled consultation during the study period

3.4 | Nutritional evaluation of pediatric patients with solid tumors during treatment and at the end of 3 and 6 months of treatment

At the end of 3 months of treatment, of the 26 children who were malnourished at diagnosis, 10 were adequately nourished (38.5%), and four were overweight/obese (15.4%). Of the 45 patients who were eutrophic at diagnosis, 31 remained adequately nourished (68.9%), eight were malnourished (17.8%), and six developed overweight/obesity (13.3%). Of the 17 overweight/obese patients at diagnosis, six were adequately nourished (35.3%), and 11 remained overweight/obese (64.7%) ($p < .001$; Table 4).

At the end of 6 months, 21 of the 26 malnourished children were evaluable. Ten were adequately nourished (47.6%), and two were overweight/obese (9.5%). Thirty-three patients were eutrophic at diagnosis, with four subsequently becoming malnourished (12.1%), 22 remaining adequately nourished (66.7%), and seven becoming overweight/obese (21.2%). Of the 15 overweight/obese patients at diagnosis, five were adequately nourished (33.3%), and 10 remained overweight/obese (66.7%; $p < .001$). Figure 2 shows the results from the evaluation of the patients at the 3- and 6-month time points.

4 | DISCUSSION

To our knowledge, this is the first prospective cohort study of the nutritional status of children with solid tumors in Brazil and the correlation with the outcomes. Few studies have addressed the nutritional assessment of pediatric patients with solid tumors.[4,22,24,27] In the present study, combination of the anthropometric indices, BMI/A *z*-score and MUAC percentile, to assess nutritional status highlighted the limitations of using BMI alone, especially in children with solid tumors who were undergoing treatment in an LMIC where large tumor masses are often present, which further limits the usefulness of the BMI/A for accurately assessing nutritional status. We found a higher number of children in at-risk nutritional categories when both indices

TABLE 1 Sociodemographic, clinical, and disease characteristics at diagnosis ($n = 99$)

Variables	*N* (%)
Age range (years)	
<5	44 (44.4)
≥5 to <10	22 (22.2)
≥10	33 (33.3)
Sex	
Female	44 (44.4)
Male	55 (55.6)
Maternal schooling	
<9 Years of study	16 (16.1)
≥9 Years of study	76 (76.8)
Missing data	7 (7.1)
Family income per capita	
Below poverty (<0.25 minimum wage)	33 (33.3)
Above poverty (>0.25 minimum wage)	55 (55.6)
Missing data	11 (11.1)
Cancer diagnosis - ICCC-3	
Intracranial or intraspinal neoplasia	33 (33.3)
Neuroblastoma	10 (10.1)
Renal tumors	6 (6.1)
Liver tumors	4 (4.0)
Retinoblastoma	7 (7.1)
Bone tumors	9 (9.1)
Tumors of soft tissue	17 (17.2)
Germ cell tumors	10 (10.1)
Epithelial malignant neoplasms	1 (1.0)
Other malignancies, unspecified	2 (2.0)
Metastases at diagnosis	
No	83 (83.8)
Yes	16 (16.2)
Proposed treatment	
Surgery	22 (22.2)
Surgery, CT and/or RT	42 (42.4)
CT and/or RT, without surgery	35 (35.4)

Abbreviations: CT, chemotherapy; ICCC-3, International Classification of Childhood Cancer; RT, radiotherapy.

were utilized, further underscoring the importance of this approach in the solid tumor pediatric setting.

Our results confirm the findings of Garófolo et al.[8] who performed a retrospective chart review in Sao Paolo, Brazil and found that 35.4% of children with solid tumors were malnourished at diagnosis when using only the MUAC percentile; this figure decreased to 18.9% when the BMI/A *z*-score was applied. Lemos et al.[10] reported that 10.85% of children with cancer were malnourished at diagnosis when assessed using the BMI/A *z*-score, and this proportion increased to 24.74% when applying the MUAC. Our results are aligned with the findings reported by Garófolo et al. in that a higher proportion of malnutrition was observed among children with solid tumors. In contrast, Lemos et al. included patients with both hematologic and solid tumors.[1]

TABLE 2 Nutritional status assessment at diagnosis according to anthropometric data ($n = 99$)

Nutritional status	BMI/A *N* (%)	H/A *N* (%)	MUAC *N* (%)	BMI/A + MUAC *N* (%)
Malnourished	8 (8.1)	4 (4)	27 (27.3)	29 (29.3)
Adequately nourished	77 (77.8)	95 (96)	55 (55.6)	49 (49.5)
Overweight/ obese	14 (14.1)	–	17 (17.2)	21 (21.2)
Total	99 (100.0)	99 (100)	99 (100.0)	99 (100.0)

Note: Weight and height *z*-score, MUAC percentile, and combination of BMI/A and MUAC.
Abbreviations: BMI/A, body mass index for age; H/A, height for age; MUAC, mid-upper arm circumference.

Similarly, a study in Latin American countries showed that the prevalence of malnutrition in children with cancer is similar to that of the prevalence in other developing countries, with 28% of patients categorized as malnourished at diagnosis by using the BMI/A *z*-score, whereas the use of arm anthropometry revealed 18% and 45% of moderately and severely depleted patients, respectively, which was associated with adverse oncological outcomes.[22] The study in Guatemala showed a similar incidence of malnutrition and that low socioeconomic status may be responsible for high prevalence of severe nutritional depletion. This study underscores the importance of diverting limited clinical resources to this highly susceptible group of children.[6]

The prevalence of malnutrition in the healthy pediatric population in Brazil is low and corresponds to approximately 4.1% in children aged 5–9 years. On the other hand, there has been a profound increase in the prevalence of overweight and obesity in recent years. According to data from the national survey of family budgets of the Brazilian population, 33.5% and 14.3% of children between 5 and 9 years of age were overweight or obese children, respectively. Among adolescents aged 10–19 years, the prevalence of overweight and obesity was 20.5% and 4.9%, respectively. The nutritional status of the participants in our study did not align with the findings of national surveys in Brazil. In our cohort, 27.3% of children aged 5–10 years and 24.2% of adolescents older than 10 years were classified as malnourished, suggesting that the disease itself can exert an influence and alter the nutritional status of children and adolescents who are diagnosed with a solid tumor. On the other hand, 22.7% of study participants aged 5–10 years and 22.7% of adolescents older than 10 years were classified as overweight and obese, respectively, which might reflect the general tendency in our population.[29] Future studies and clinical interventions may need to be established in order to meet the needs of this growing population because poor outcomes and increased treatment-related toxicities have been associated with overweight and obesity in several cancers in the pediatric population.[30]

TABLE 3 Concordance analysis between combination *z*-score BMI/A + MUAC percentile and *z*-score BMI/A nutritional alteration at diagnosis ($n = 99$)

		z-Score BMI/A + MUAC percentile			
		Malnourished	Adequately nourished	Overweight/obese	Total
	Malnourished	8 (100.0%)	0 (0.0%)	0 (0.0%)	8 (100.0%)
z-Score BMI/A	Adequately nourished	21 (27.3%)	49 (63.6%)	7 (9.1%)	77 (100.0%)
	Overweight/obese	0 (0.0%)	0 (0.0%)	14 (100.0%)	14 (100.0%)

Note: Kappa: .496; *p*-value <.001.
Abbreviations: BMI/A, body mass index for age; MUAC, mid-upper arm circumference.

TABLE 4 Concordance analysis between nutritional alteration at diagnosis and after 3 months (combination *z*-score BMI/A + MUAC percentile)

	3 Months	Malnourished	Adequately nourished	Overweight/obese	Total
	Malnourished	12	10	4	26
Diagnostic	Adequately nourished	8	31	6	45
	Overweight/obese	0	6	11	17

Note: $n = 88$; *p*-value <.001.
Abbreviations: BMI/A, body mass index for age; MUAC, mid-upper arm circumference.

Nutritional assessment after 3 and 6 months of treatment in our cohort showed improvement in some patients, although a large proportion of patients remained malnourished and developed overweight or obesity. This finding corroborates the results of the study carried out by Brinksma et al.,[31] where the authors observed an initial decrease in the BMI in patients with solid tumors, but noticed a rapid recovery within a 3-month period, similar to what was observed in our study. In the previous study,[31] weight loss was followed by weight gain during the 3-month assessment, with the risk of the patients becoming overweight during treatment and long-term follow-up. The hypothesis suggested by the authors for this rapid increase in BMI was growth recovery and the possibility of overfeeding, which is compounded by reduced physical activity.

This study has several limitations. The limited availability of personnel did not allow us to conduct nutritional evaluations for every newly diagnosed patient presenting at the INCA, thus there is a potential selection bias in the study results. The sample size of the study was limited and could compromise the statistical associations. Finally, food security was not evaluated in our study and could have affected the duration of malnutrition observed throughout the study period. Our study is strengthened by its prospective design and the homogeneous nutritional care that was provided to participants with diverse solid tumors.

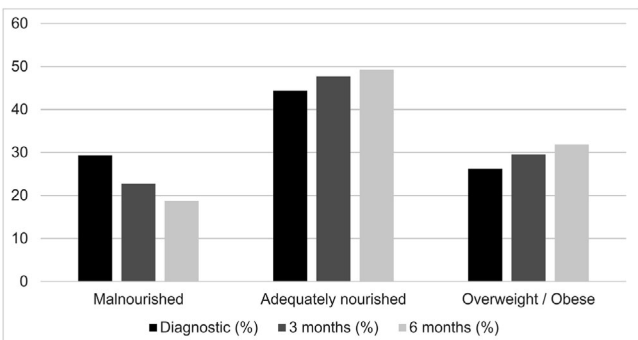

FIGURE 2 Nutritional evaluation of pediatric patients with solid tumors at diagnosis and during treatment, at the end of 3 and 6 months of treatment

5 | CONCLUSION

The combined use of the two indices allowed a more accurate diagnosis of nutritional status in pediatric patients with solid tumors, which is essential for implementing early interventional strategies and for identifying children and adolescents at high risk for nutritional depletion. Our study underscores the importance of systematic nutritional assessment and warrants additional research to evaluate the association with clinical outcomes and to test effective interventions to mitigate both under- and over-nutrition. Importantly, future studies should consider sociodemographic variables and its effect on nutritional outcomes. Effective solutions may lead to better outcomes and reduce acute toxicities and late side effects.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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