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Research Article

Association of Nutritional Status and C Reactive Protein in Admission with Hospitalization Time and Mechanical Ventilation in Children with Cancer in Intensive Care Unit

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Keywords

- Nutritional assessment
- Pediatric intensive care unit
- Cancer
- Mechanical ventilation
- Length of stay

Abstract

Aim: This study aims to evaluate the influence of nutritional status on admission, according to the anthropometric indicator, serum C-reactive protein (CRP) and albumin on length of hospital stay (LHS) and time of mechanical ventilation (MV) in the Pediatric Intensive Care Unit (PICU) in a Oncological Treatment Center.

Methods: It is a longitudinal, observational, retrospective study with all children admitted to the PICU in 2013. The comparison of medians related to LHS and VM was assessed using the nonparametric Mann-Whitney and Kruskal Wallis test. The Kaplan-Meier curve evaluated the influence of body mass index (BMI), CRP and albumin on LHS and VM. The significance value was $p < 0.05$.

Results: A total of 54 patients were selected, median age of 8.02 (2.35-12.79) years. Solid tumors were the most common (92.6%; n = 50), and the most frequent causes of hospitalization in the PICU were respiratory failure (26.4%; n = 14) and sepsis (24.5%; n = 13). The median LHS was 11 (6-18) days and MV median was 11 (6-16.86) days. The frequency of BMI above and below the adequate level was 23.5% (n = 12) and 29.4% (n = 15), respectively.

Conclusion: The criteria used for nutritional assessment were not associated with clinical outcomes LHS and MV.

INTRODUCTION

Often, during therapy, the child with cancer has compromised nutritional status diagnosis. Among the various complications that affect cancer patients, poisoning chemotherapy can cause serious clinical problems as cardiotoxicity, nephrotoxicity, bone marrow depression, and a number of other side effects that compromise various organic functions and that, in many often require intensive support [1].

Mortality is a concern of the team Pediatric Intensive Care Unit (PICU) and its main causal factors are the length hospital stay (LHS) and the need for mechanical ventilation (MV) [2].

Faced with the limitations of anthropometry, biological markers have been used as an alternative method for assessing the degree of malnutrition in the PICU. A systematic review of the literature, in which 2068 children were included in the studies, large observational, found reviews about 16 nutritional biomarkers, being the most used albumin, prealbumin, transferrin and calcium. It was found that hypoalbuminemia at admission was linked to LHS in the PICU, mortality and infection. However, despite hav-

ing a positive association with the outcomes, none of these markers showed consistency in clinical results in pediatric patients in PICU [3].

The C-reactive protein (CRP) is an inflammatory marker of positive acute phase response, whose secretion is regulated by cytokines IL-1, IL-6 and tumor necrosis factor-α, has its increased concentrations depending on the degree of inflammation [4]. In turn, albumin is a negative acute phase protein, which tends to decrease their serum concentrations before an inflammatory process. Both related substances can replace the nutritional inflammatory prognostic index, and is considered an important evaluation criterion in the adult critically ill patients, especially in septic shock [5].

For the critical adult patient, the National Consensus on Nutrition Oncology recommended as a nutritional evaluation criteria the *Prognostic Inflammatory* and *Nutritional Index* (PINI) and as a worsening of the nutritional risk, the increased CRP [6]. For children in intensive care with cancer, this consensus recommends nutritional assessment (NA) based on clinical, dietary and anthropometric data. It is considered an aggravating nutritional risk the presence of one or more of the indicators: weight/height or BMI/age between - 1 standard deviation (SD) and - 2SD in rating Z score; serum albumin < 3.2g/dL; CRP > 2mg/dL ; dietary intake < 70% of the needs for three to five consecutive days, regardless of the anthropometric deficit; recent weight loss > 5% by weight before disease; presence of symptoms of the gastrointestinal tract; comorbidities; Systemic Inflammatory Response Syndrome (SIRS) and sepsis presence [6].

The literature presents studies that address the NA practices in children in intensive care, however, no studies in children with cancer in PICU was found. The patient hospitalized with cancer in intensive care presents a number of aspects that hinder an accurate assessment of their nutritional status [1]. Thus, this article aims to evaluate the influence of nutritional status on admission, according to the anthropometric indicator, serum CRP and albumin on LHS and MV outcomes in children and adolescents admitted to the PICU of Oncological Treatment Center Rio de Janeiro.

METHODS

Design and study population

It is a longitudinal study, observational with retrospective data, whose population consisted of all children and adolescents admitted to the PICU of a reference center for the treatment of cancer patients, in Rio de Janeiro, Brazil, from january to december of 2013, who met the inclusion criteria of the study. They included all children and adolescents diagnosed with malignancy, aged 1 to 18 years of age, with length stay in PICU ≥72 hours (3 days), and made use of ENT (enteral nutrition therapy), during hospitalization in the PICU in 2013. Patients previously diagnosed as out of therapeutic possibilities of cure were not eligible at admission to the PICU and patients who have exclusive use of oral or diet and parenteral nutrition during hospitalization in the PICU.

Data collect

Data were collected from physical and electronic records of patients, using a form drawn up exclusively for this search. To characterize the demographic data were used age, expressed in years and months, and gender.

For the anthropometric assessment of nutritional status on admission to the PICU was used the body mass index for age (BMI/A), as recommended by the World Health Organization [7,8]. The BMI/A was calculated from the body weight in kilograms and height in meters by dividing body weight by height squared (weight (kg) x height m^2). Then, it w as calculated the Z score of BMI/A through the WHO Antro and Antroplus software; Antro for children up to 5 years old and Antroplus for children 5 years and adolescents up to 18 years in version 3.2.2 [9]. The adopted cutoff points were: below the appropriate (low weight and nutritional risk) <-1 z score; Suitable > -1 and < +1 DP z score; and abovey the appropriate> + 1SD Z score [10].

Serum concentrations of albumin and CRP were evaluated, considering inadequate when the values were below 3.2g/dL for albumin and above 2.0mg/dL for CRP. Clinical evaluation was done for information regarding the reason for admission to the PICU and clinical diagnostic base (type of cancer). The outcome measures were LHS and MV in the PICU.

Type variables

Independent variables:

BMI - This variable was assessed continuously and categorically. When categorized was defined as: below the appropriate (low weight or low birthweight) with z score < -1; appropriate (eutrophic) with z score> -1 and ≤ +1 ; above the appropriate (overweight and obese) with z score > +1.

CRP - This variable was assessed continuously and categorically. It was considered the benchmark recommended by the National Consensus in Oncology Nutrition, which defines as risk CRP levels greater than 2 mg/dL.

Albumin - This variable was assessed continuously and categorically. It was considered the benchmark recommended by the National Consensus in Oncology Nutrition serum albumin < 3.2g/dL.

Dependent variables (Clinical Outcomes):

Length of Hospital Stay (LHS) - was defined by the number of days of hospital stay, from admission to the PICU to discharge the unit.

Mechanical ventilation (MV) - was considered the number of days of mechanical ventilation during hospitalization in the PICU.

Statistical analysis

After the collection of information from medical records, data were reviewed by the researcher in order to minimize errors and lack of relevant data population and were entered into the *Statistical Package for Social Sciences* (SPSS) *for Windows* version 23.0.

In the description of the sample, data for numerical variables were expressed as median and interquartile range as the curve of distribution of the samples and for categorical variables

expressed as a ratio. In the distribution of quartiles, they and securities were divided into 4 groups considering the period of stay: ≤ 7; > 7 and ≤ 14; > 14 and ≤ 21 and > 21 days for LHS and ≤ 5 ; > 5 and ≤ 10; > 10 and ≤ 20 and > 20 for MV.

The comparison of medians of continuous variables related to outcomes (IT and TMV) were evaluated using the nonparametric Mann- Whitney test (two groups) and Kruskal Wallis (more than 2 groups) as the distribution of variables.

The survival curve of *Kaplan-Meier* method was constructed to evaluate the influence of BMI, serum concentrations of CRP and albumin on IT in the PICU (< 14 days and ≥ 14 days) and TMV (< 10 days and ≥ 10 days), followed by *Log Rank test, Breslow* and *Tarone-Ware* to verify the equality of survival distributions for the different levels of classification, according to the respective above-mentioned variables. For all analyzes, the significance value was $p < 0.05$.

The Bonferroni Post Hoc tests were performed to evaluate the sample size power to detect differences in the prevalence of malnutrition in cancer children. The sample size in this study has a power of 80% to detect differences of prevalence of malnutrition in PICU. Moreover, with this sample size (at least 50), the study has a power of 95% to detect differences of prevalence of malnutrition in cancer children patients.

Ethical aspects

The study followed the rules laid down in the National Health Council Resolution 466/2012 – CNS[11] and approved by the Ethics Commitee of the Clementino Fraga Filho University Hospital (HUCFF) and the INCA Ethics Commitee under 37601214.5 protocols. and 37601214.5.3001.5274 0000.5257, respectively.

RESULTS

178 records of patients admitted to the PICU were found, considering all hospitalizations in the year 2013, 54 children and adolescents, have been selected, according to the inclusion criteria. Figure 1 in supplementary material depicts the flowchart for obtaining the sample.

The median age was 8.02 (2.35 to 12.79), years, being solid tumors the most common (92.6%; n = 50), median time to diagnosis of 0.04 (0, 02 to 1.02), years. Considering the cause of hospitalization in the PICU, stood out the clinical condition of respiratory failure (26.4%; n = 14), and sepsis (24.5%; n = 13). The median HST was 11 (6-18) days, and about 87% (n = 47), of patients required ventilatory support, with MV median 11 (6 to 16.86) days. Table 1 in supplementary material presents the characteristics of the study population.

According to the anthropometric assessment, based on BMI at admission, the frequency of patients classified as nutritional status below the suitable was 23.5% (n = 12), 47.1% (n = 24), classified as appropriate nutritional status (NS), and 29.4% (n = 15), above as appropriate. Figures 2 and 3 in supplementary material show the variation in BMI, CRP and albumin, according to LHS and MV. The criteria for NA critical cancer patient in the unit where the study was conducted (BMI, serum albumin and CRP), were not associated with clinical outcomes LHS and MV, as

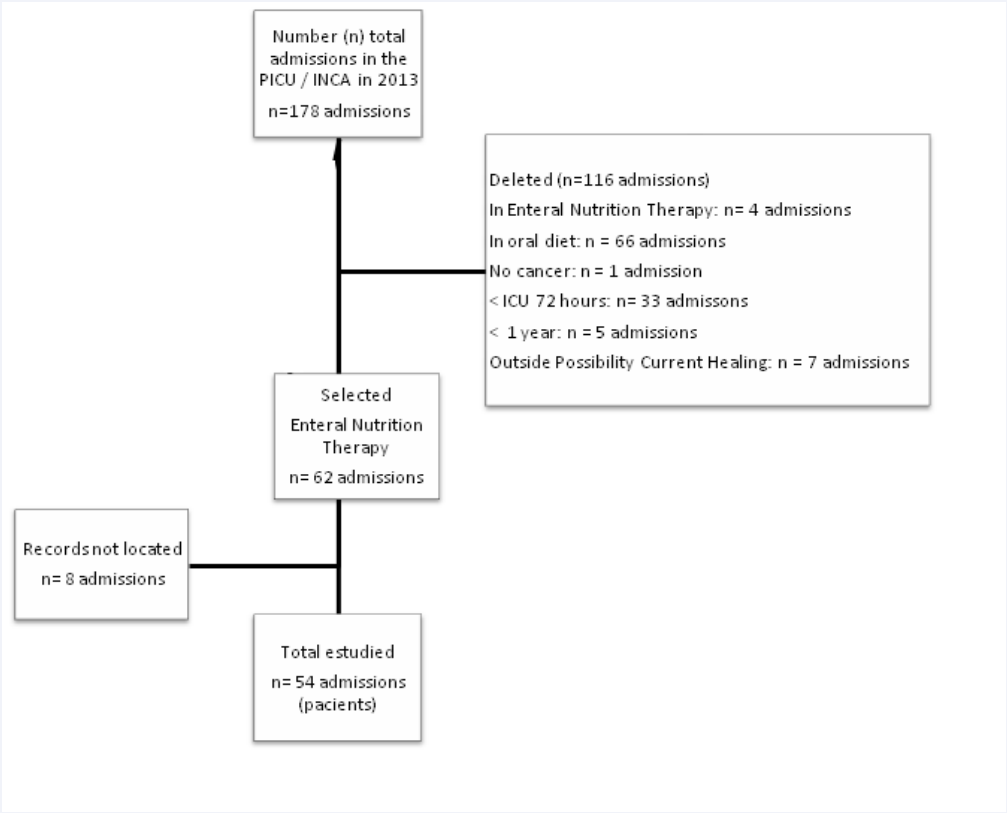

Figure 1 Flowchart obtain a sample.

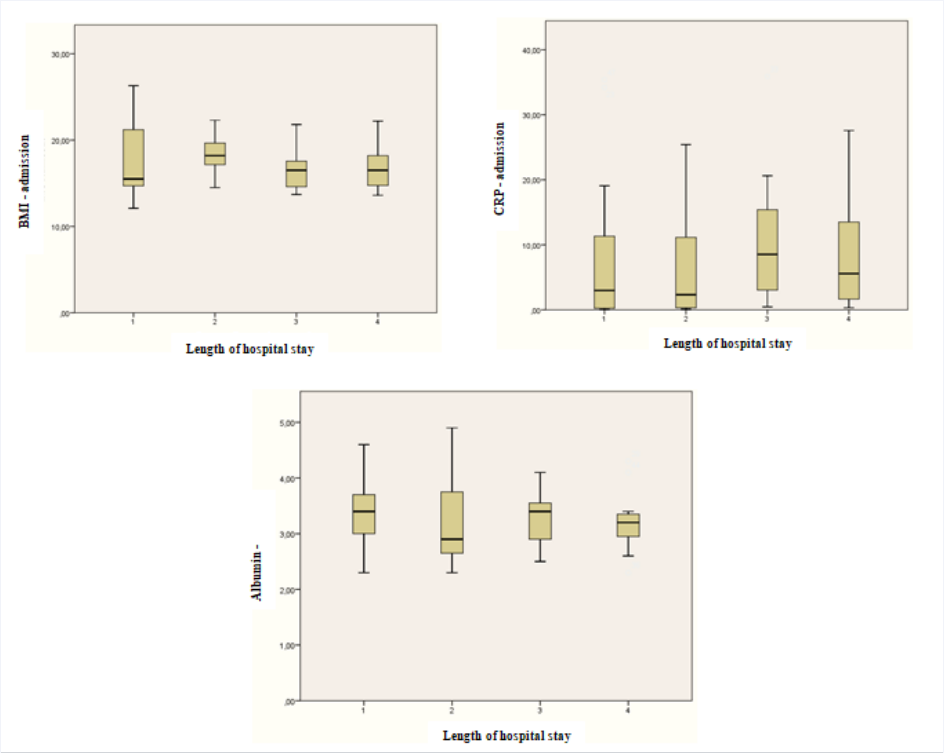

Figure 2 Distribution of changes in BMI (Body Mass Index), serum CRP (C-reactive protein) and albumin on admission to the PICU (intensive pediatric care unit) according to in children and adolescents hospitalized in an Oncological Treatment Center from Rio de Janeiro. Rio de Janeiro, 2013.

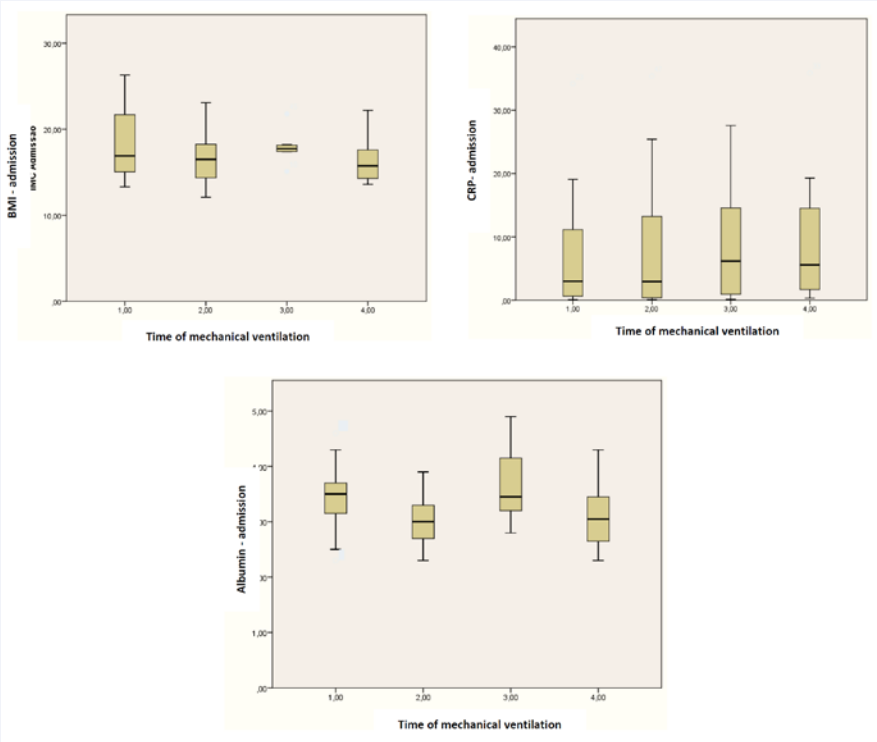

Figure 3 Distribution of changes in BMI (Body Mass Index), serum CRP (C-reactive protein) and albumin on admission to PICU (intensive pediatric care unit) according to mechanical ventilation in children and adolescents hospitalized in an Oncological Treatment Center from Rio de Janeiro. Rio de Janeiro, 2013.

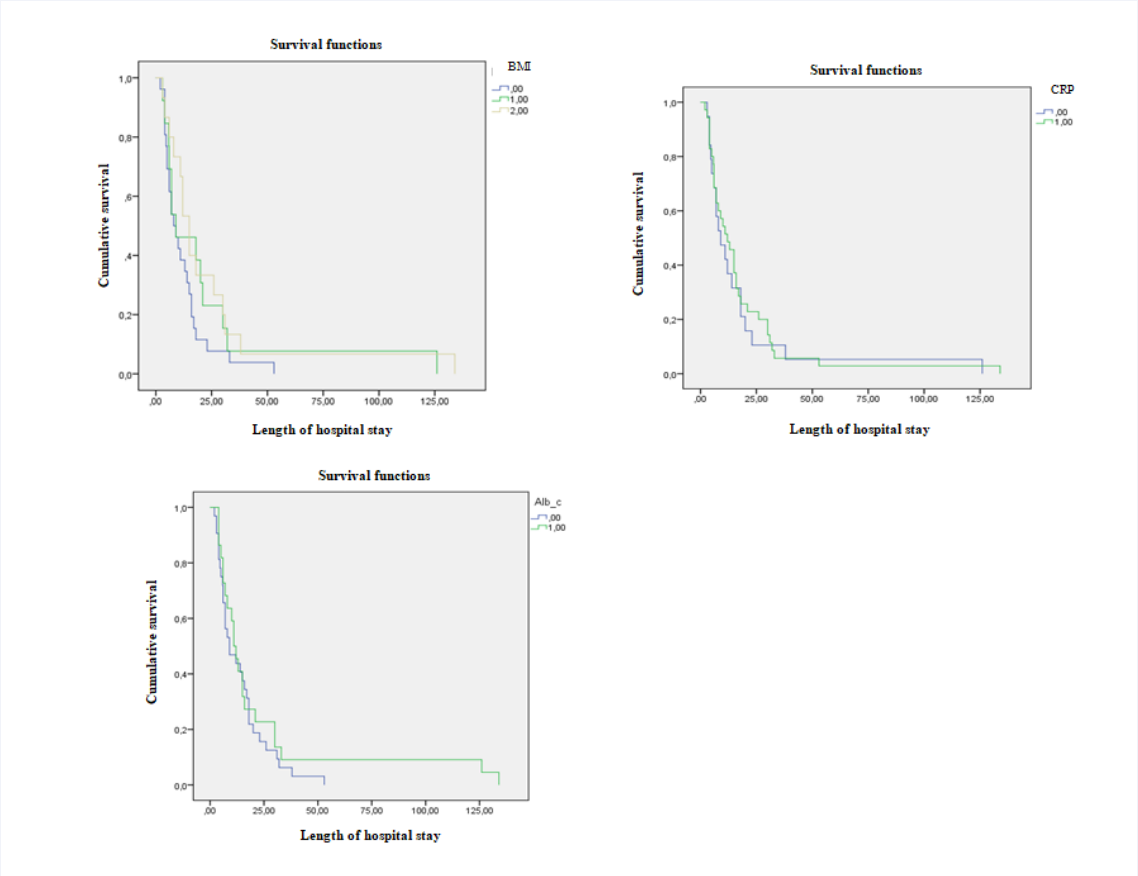

Figure 4 Kaplan-Meier curves of the association between BMI (body mass index), serum concentrations of CRP (C-reactive protein) and albumin, with Length of hospital stay in children and adolescents with cancer admitted to the PICU (Care Unit intensive Pediatric) hospitalized in an Oncological Treatment Center from Rio de Janeiro. Rio de Janeiro, 2013.

shown in Tables 2 and 3. The percentage of children with serum CRP levels > 2 mg/dL and albumin < 3.2 g/dL was 64.8% (n = 35), and 40.7% (n = 22), respectively.

Regarding the association between BMI and biochemical data, with LHS and MV, survival curves were calculated using the *Kaplan-Meier* method (Figures 4 and 5).

DISCUSSION

In this study there was no correlation between BMI, serum albumin and CRP with clinical outcomes studies, LHS and MV, in children with cancer in the PICU. One of the major challenges in pediatric critical patients NA is to choose the best method of evaluation, since there is no concrete evidence to guide this decision. The difficulties are found in different types of assessment, whether the clinical condition of the patient, either in terms of hemodynamic alterations, body composition modification or even the lack of staff awareness of the importance of practice and appropriate measurement data [12]. These difficulties are even greater in children with chronic diseases such as cancer, given the need for intensive care.

It is noteworthy in our group the high percentage of weight deviation (overweight and underweight or nutritional risk) represented by 52.9 % of the sample in the NA, according to BMI. Although malnutrition is a major concern in pediatric oncology, overweight has become a new reality these patients, especially patients with central nervous system tumors, the more prevalent solid tumor in childhood. Similar results were found by Bechard *et al.* 2016, in a cohort study that aimed to evaluate the association of BMI with morbidity and mortality in children with MV in the PICU, whose percentage of overweight and obesity was higher than that of malnutrition. Probably, this seems to be a new reality in the care of pediatric critical patients [13,14].

Moreover, in the literature, malnutrition in pediatric patients is still quite critical reported, with a negative impact on clinical outcomes ranging from 9.8% to 65% [15]. De Menezes *et al.,* 2013 identified 49.9% of malnourished patients on admission in the PICU and found an association of this condition with longer duration of mechanical ventilation and longer length of stay in PICU, although not associated with mortality [16]. Studies in the context of intensive care show that the variation in the nutritional status during hospitalization in the PICU seems to have confirmed an association with clinical outcomes [17-19].

A classic study conducted with 108 children in intensive care, which evaluated the nutritional status and the length of hospital stay, showed 47% of malnutrition and showed no significant difference between LHS malnourished patients compared to eutrophic [20].

Table 1: Socio-demographic characteristics, clinical, anthropometric, serum concentrations of C-reactive protein and albumin children and adolescents with cancer hospitalized in PICU (Pediatric Intensive Care Unit) in an Oncological Treatment Center from Rio de Janeiro . Rio de Janeiro, 2013.

Variables (n)	Median (IR) ou % (n)
Age (years; n= 54)	8,02 (2,35-12,79)
Sex (n= 54)	
Female	50 (n=27)
Male	50 (n=27)
Type of tumor (n=54)	
Hematological	7,4 (n= 4)
Solid tumors	92,6 (n=50)
PRISM (pontos; n=47)	4,95 (1,45-15,73)
Diagnosis at PICU admission (n=53)	
Sepsis	24,5 (n=13)
Lowered level of consciousness	17,0 (n= 9)
Respiratory failure	26,4 (n= 14)
Postoperative	20,8 (n=11)
Outhers	11,3 (n= 6)
Weight (Kg; n=54)	23,0 (14,35-36,75)
Height (cm; n=52)	1,18 (0,96-1,42)
BMI (Kg/m^2; n=52)	16,7 (14,85-18,53)
Serum concentrations of CRP (mg/dL; n= 53)	4,33 (0,62-12,45)
Serum concentrations of albumin (g/dL; n=46)	3,29 (2,9-3,68)

IR= Interquartile Range; BMI: Body Mass Index; CRP: C - reactive protein; PRISM: *Pediatric Risk of Mortality*; PICU: Pediatric Intensive Care Unit.

Table 2: BMI z score distribution, serum concentrations of CRP and albumin on admission second children hospital stay and adolescents with cancer admitted to the PICU (Pediatric Intensive Care Unit) in an Oncological Treatment Center from Rio de Janeiro. Rio de Janeiro, 2013.

Variables (n)	Hospital stay				P[a]
	≤7 days [IQ]	8≤14 days [IR]	14≤21 days [IR]	>21 days [IR]	
BMI Z score (n=54)	-0,16 [-1-0,5]	0,32[-0,25-1,26]	-0,12 [-0,99-0,73]	0,61 [-0,74-1,56]	0,392
Serum concentrations of CRP (mg/dL; n= 53)	2,98 [0,23 - 11,32]	2,32 [0,32 - 11,15]	8,52 [3,04 - 15,4]	5,57 [1,65 -13,51]	0,249
Serum concentrations of albumin (g/dL; n=46)	3,4 [3 - 3,7]	2,9 [2,65 - 3,75]	3,4 [2,9 - 3,55]	3,2 [2,95 - 3,35]	0,926

BMI: Body Mass Index; CRP: C- Reactive Protein; IR= Interquartile Range; a: Adopted statistical test *Kruskal Wallis*.

Table 3: Z score distribution of BMI, serum albumin and CRP at admission second mechanical ventilation of children and adolescents with cancer admitted to the PICU (Pediatric Intensive Care Unit) of Oncological Treatment Center of Rio de Janeiro . Rio de Janeiro, 2013.

Variables (n)	Time on mechanical ventilation				P[a]
	≤5 days [IR]	6≤10 days [IR]	11≤20 days [IR]	>20 days [IR]	
BMI Z score (n=54)	-0,13 [-0,87 - 0,92]	0,09 [-0,62 - 0,45]	0,68 [-0,21 - 1,15]	0,04 [-1,55 - 1,22]	0,629
Serum concentrations of CRP (mg/dL; n= 53)	2,98 [0,64 - 11,15]	2,94 [0,39 - 13,22]	6,18 [1,26 - 11,55]	5,59 [1,86 - 14,1]	0,716
Serum concentrations of albumin (g/dL; n=46)	3,5 [3,15- 3,7]	3 [2,7-3,3]	3,45 [3,3- 4,13]	3,05 [2,68 - 3,38]	0,051

BMI: Body Mass Index; CRP: C- Reactive Protein; IR= Interquartile Range. a: Adopted statistical test *Kruskal Wallis*.

The use of BMI to assess patients in PICU has been questioned, although it is widely reported in the literature, for its practicality and low cost. However, studies using anthropometry NA in these patients found that body composition measures, such as arm circumference and triceps skinfold thickness were better predictors of mortality when compared to BMI [21-23].

Studies of NA and body composition in children with cancer in intensive care were not found in literature. However, when using skin measures for evaluation of body reserves was observed that the isolated use of BMI may underestimate malnutrition in this patient population [10,24-26]. Thus, attention is drawn to the use of body composition measures in clinical practice as a possible alternative in the process by the search for more reliable parameters of AN for this group of patients, since the vast majority of global institutions, which deal pediatric oncology, this is not a reality [27].

Systematic review recently published in order to review the evidence on the impact of nutritional status of critical pediatric patients in outcomes in PICU, need for mechanical ventilation and mortality, reinforces that assessment by skinfolds,

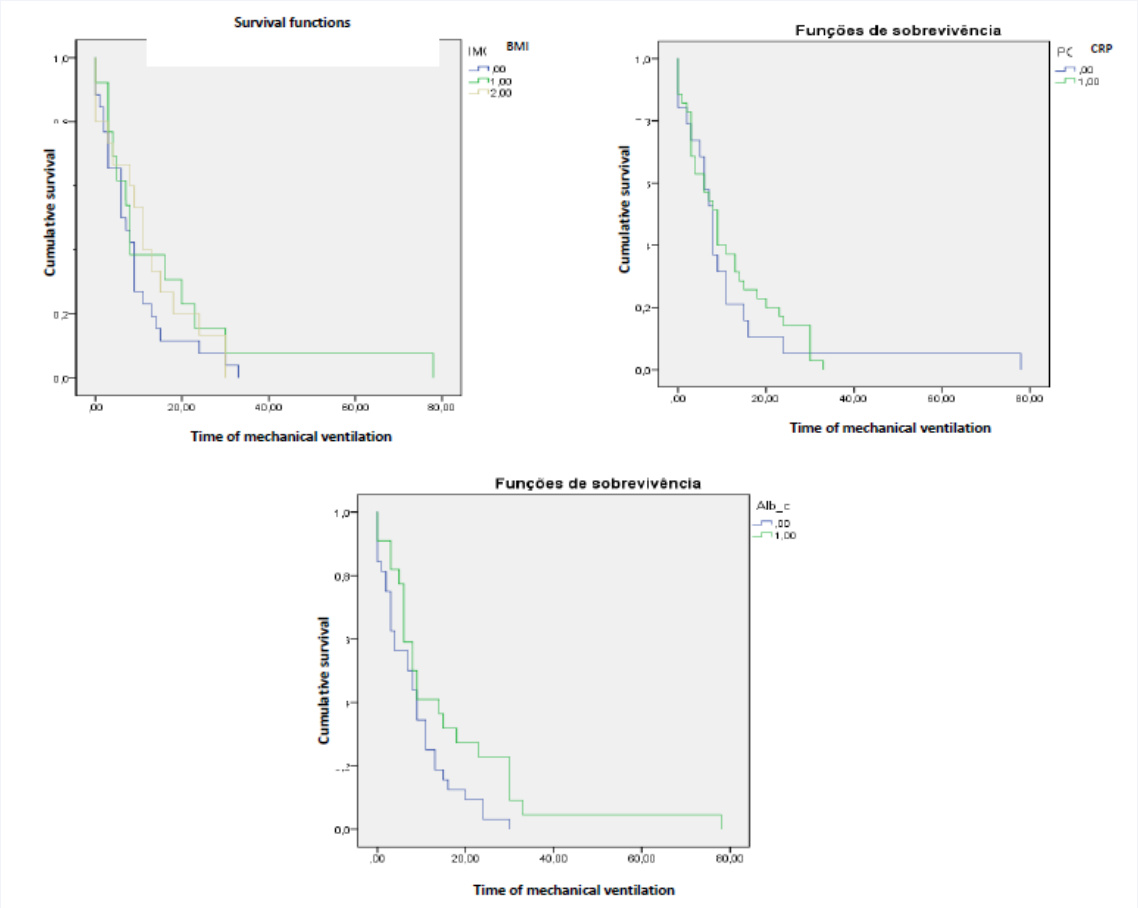

Figure 5 Kaplan-Meier association between BMI (body mass index), serum concentrations of CRP (C-reactive protein) and albumin, with MV (mechanical ventilation) in children and adolescents hospitalized cancer in PICU (Care Unit intensive Pediatric) hospitalized in an Oncological Treatment Center from Rio de Janeiro. Rio de Janeiro, 2013.

circumferences or by bioelectrical impedance analysis (BIA) can be a good alternative for children in this situation and provide data on the reserve fat and lean mass [12].

Lee et al. 2015 presented/ or suggested the BIA as a proposal for adult NA in critical condition [28]. Other authors also with adult study, compared the nutritional status assessment by BIA and by BMI and concluded that the fat free mass values provided by BIA were related to survival of patients using home MV [29].

In the pediatric population, Pileggi et al. 2016, in a study with the aim to report the prevalence of child malnutrition in the University Hospital of Brazil, concluded that the NA by the BIA was more sensitive than the WHO criteria in the diagnosis of malnutrition at admission [30]. The authors suggest the need for implementation of a BIA protocol for all children on admission. It may also be a possibility to practice NA in seriously ill children.

Martinez et al., 2014 assessed the body composition of children in the use of MV home through the BIA and identified a high prevalence of malnutrition and significant depletion of fat-free mass [31]. In this context, although research with phase angle in children in the PICU are still scarce, given the increasing number of works with adults, the BIA can be a NA alternative also in the pediatric population [32-34].

As for biochemical markers, until the finalization of this manuscript, there are no consensus in the literature about the best index associated with the most prevalent clinical outcomes in children in critical condition [4,23] , either in patients with cancer. Although guidelines in pediatric oncology recommend the use of biochemical and inflammatory markers such as nutritional risk assessment criteria in children with cancer, there are no studies available in the literature to support this practice and it cannot be confirmed in this study. It is observed in the guidelines that the data were extrapolated from studies in adults or experts indication. In critical patients it is more complex the use of the NA by means of biochemical indicators depending on the organic changes involved in diseases [12].

Albumin and CRP may be useful in an overall assessment of the context for consideration of high nutritional risk, but not alone. It is known that CRP is a positive acute phase protein which increases in serum according to the degree of inflammation, whereas the albumin is a negative acute phase protein which tends to decrease its serum concentrations before a process of inflammation [35]. A study with 334 adult patients in the ICU showed that the relationship CRP/albumin was an independent predictor of mortality in 90 days and it is considered a more

consistent scorer for this outcome [36]. The present study did not aim to study mortality, because there is no evidence of cutoff for CRP/albumin ratio in studies with children.

Recently, Leite *et al.,* 2016 in a study carried out in a teaching hospital in order to assess whether hypoalbuminemia at admission was associated with the most prevalent clinical outcomes in PICU - mortality at 60 days, IT and MV, hypoalbuminemia was found in 64.2% of patients [37]. The authors emphasize that hypoalbuminemia was associated with mortality in 60 days, larger LHS and MVT. This association was an independent factor of the magnitude of the inflammatory response, disease severity and nutritional status. However, the authors point values below 3.0 g/dL were more associated with the studied outcomes. Delgado *et al.,* 2008 evaluated the relationship of malnutrition and inflammatory response with outcomes in critical pediatric patients and concluded that there was no significant difference between IT severely malnourished patients, moderate and eutrophic [38].

Ong *et al.,* 2014 in a literature review, highlighted that only one study significantly associated hypoalbuminemia at the time of admission to the ICU with the length of stay and mortality of children in intensive care, which may reflect severity in these patients [3]. However, in this study we found no association of biochemical and inflammatory markers with clinical outcomes. The use of albumin is widely questioned in clinical practice, because of its long half life, which does not make it an excellent marker of the current nutritional status, and particularly in situations such as dehydration, sepsis, trauma and liver dysfunction, commonly found in pediatric patients in critical condition, especially cancer, when factors of the disease and treatment may reflect such changes.

In an attempt to enhance the practice of NA in children in critical condition, another NA method understudied in critically ill patients is the Nutritional Assessment Subjective Global Pediatric-NASGP, which was reliable for use in critically ill children by their agreement with anthropometry, despite the low correlation with biochemical evaluation. However, this study also showed no predictive value with the measured results studied as LHS and mortality [39]. Note that this tool has been translated and transculturally adapted, for use in children with cancer in Brazil [40].

The small sample was the main limitation of this study, unprecedented in pediatric oncology in critically ill patients, however, justified by the prevalence limit. Other limitations are related to mortality data not covered in this research; difficulty of working with retrospective data and; the classification of anthropometric nutritional status been carried out exclusively by BMI/age.

CONCLUSION

The NA in children with cancer, considered at constant nutritional risk, both by disease severity as by treatment intensity, need to be held in PICU. The criteria used in this study for NA were not associated with clinical outcomes assessed more critically ill patients - LHS and MV. It is suggested that they should not be neglected in clinical practice however; it is believed that other NA methods, such as the assessment of body composition, the phase angle and the subjective global assessment, should be studied in children with cancer in PICU.

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned in protocols 37601214.5, by the Ethics Committee of the Clementino Fraga Filho University Hospital (HUCFF), and 37601214.5.3001.5274 0000.5257, by the INCA Ethics Committee, have been explained.

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AUTHORSHIP

All authors contributed to the literature search, analysis of the data published, manuscript writing and revisions of the article.

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