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Is serum albumin associated with prognostic in pediatric cancer patients?

Abstract

Serum albumin has been shown to be associated with clinical indicators in hospitalized patients.

The objective was to study the association of serum albumin with clinical and nutritional indicators in pediatric cancer patients. A prospective cohort study carried out at Pediatric Oncology Institute of Federal University of São Paulo, Brazil. This study follows patients of 1 year old or above, during anti-cancer therapy, from January 2002 to January 2004, enrolled in an enteral nutritional protocol. Exclusion criteria were corticoid therapy, swallowing abnormalities and previous nutritional support. They received two types of oral supplement (industrialized formula and non-industrialized/homemade supplementation) and were followed for three weeks. Serum albumin was collected at admission of the nutritional protocol and after three weeks. The associations of the clinical and nutritional index with the decrease in serum albumin, serum albumin at admission and in week three and the differences between serum albumin in week zero and week three were studied.

Fifty-four patients were analyzed. The analysis showed that episode of hospital stay and fever were associated with the decrease in serum albumin ($p<0.05$); and episode of hospital stay ($p=0.05$) and infection ($p=0.02$) with serum albumin in week three. Nutritional performance showed association with serum albumin: the higher albumin at admission of the protocol, the better nutritional outcome ($p=0.02$). Serum albumin at week three also influenced nutritional outcome: higher serum albumin was associated with reduced tube feeding indication ($p=0.04$). No association was found between serum albumin and anthropometric and body composition indexes. Albumin was more associated with clinical than nutritional index. This confirms adult studies that found association between albumin depletion and prognostic factors.

Keywords: cancer, pediatric, clinical outcomes, nutritional outcomes, serum albumin, hospital stay

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Introduction

Some evidences point that cancer patients demonstrate metabolic changes because of the disease, as well as its treatment and complications.[1] These changes seem to be associated with inflammatory response due to malignance tumor and/or to infectious or organic complications during anticancer therapy. This situation leads to the anorexia-cachexia syndrome.[2,3]

Impaired synthesis of some proteins like albumin, transthyretin and transferrin is expected in inflammatory response because of the increase in pro-inflammatory cytokines production.[4] Some authors suggested an association with cell cytokines production in response to an inflammatory status due to malignance or with a direct cytokines produced by tumor cells.[5]

In spite of these changes, serum albumin has been used in order to evaluate nutritional depletion[6]. However, it has been showed to be a limited nutritional index, because it is influenced by several changes in clinical setting that are frequent in cancer patients, mainly during metabolic stress. Albumin is the primary component of plasma proteins and is synthesized by the liver. It has functions on oncotic pressure regulation between plasma and interstices, protein transport to synthesize hormones, substrates and several other molecules, like medications and toxins.[7] Because of a long half-life (14 to 20 days), serum albumin is not a sensible index to measure nutritional status and its evolution in a short time. Nevertheless, when there are limited resources to nutritional assessment, a common situation in developing world, the association of available methods can improve nutritional diagnosis. For this reason, some authors recommend it for children with cancer to identify nutritional depletion.[6,8]

However, hypoalbuminemia does not seem to be associated with nutritional index in ill patients. Serum albumin is a strong biomarker of disease severity and prognosis in oncology adult patients. In contrast, its value as predictor of outcome in children with cancer has not been established. Previous studies have reported more association between low albumin levels and clinical than nutritional outcomes as longer length of hospital stay, postoperative complications and survival in breast cancer patients.[9–11] In spite of this, we cannot find any study about the association between albumin profile and clinical and nutritional index in children and adolescents with cancer. We aimed to determine whether serum albumin is associated with clinical and nutritional outcome in pediatric cancer patients underwent a nutritional intervention, taking into account the nutritional support, diagnosis, gastrointestinal toxicity and age of the patient.

Methods and materials

This study was a prospective analysis that was part of a broader protocol developed to guide enteral nutritional support. It was carried out at Pediatric Oncology Institute of Federal University of São Paulo,

Brazil; including patients above 1 year old were followed during anti-cancer therapy from January 2002 to January 2004. Inclusion criteria were cancer diagnosis, mild malnutrition (z-score < -1.0 to –2.0 in children and > 5th e < 15th of body mass index in adolescents) and anti-cancer treatment with curative perspective. The exclusion criterion were corticoid therapy or hormonal therapy, swallowing abnormalities, previous enteral or parenteral nutrition support and presence of non-cancer related diseases.

Study design

The patients received two types of nutritional intervention, according to protocol of nutritional support: (1) oral supplementation formula (OSF), and (2) homemade oral supplementation (HOS). The patients were followed for three weeks; serum albumin was collected on admission of the nutritional protocol and after three weeks. Clinical and nutritional outcome were evaluated. The clinical outcome were overall hospitalization (hospitalization for any reason), hospitalization for complications (organic and infectious), length of hospital stay, fever, fever combined with leucopenia, positive blood culture and clinical or laboratorial documented blood infections. Nutritional outcome were tube feeding indication and to achieve the ideal body weight (IBW). These variables were used to make an association analysis with the decrease in serum albumin after a three-week period, serum albumin at admission of the nutritional protocol, serum albumin at week three of the protocol and difference in serum albumin between week zero and three of the protocol. The relationship between serum albumin (week zero and three) and nutritional status were also analyzed.

Nutritional status assessment

The weight was taken by means of a digital weight machine (150 kg and 50g of accuracy), in a flat surface. The height was taken by a stadiometer or anthropometer. These measurements were taken by the same nutritionist. Mild malnutrition was classified based on Lusky's (1996) published data for adolescents,[12] but for children we proposed a cut-off based on St. Jude Children Research Hospital published algorithm.[8]

Triceps skinfold thickness (TSFT), mid-upper arm circumference (MUAC) and muscle arm circumference (MAC) were the indicators used for follow-up and analysis. In order to determine skin thickness the Harpenden Skinfold Caliper (Cescorf) was used. These variables were performed and interpreted in accordance with the Frisancho recommendations[13] using the percentile charts and the percentage of the ideal, as obtained in this equation: observed value /ideal value × 100.

The assessments were performed at admission of the nutritional protocol and weekly thereafter. The data considered for analysis were those from week zero and week three.

Laboratory analysis

Blood sampling for laboratory analysis was collected at admission of the nutritional protocol and after three weeks in order to measure serum albumin. This analysis was performed by turbimetric method. Serum albumin was considered abnormal when below 3.5mg/dl[8].

Clinical assessment

In order to study association between serum albumin and clinical outcomes, episode of overall hospitalization, hospitalization for complications, length of hospital stay, fever, fever combined with leucopenia, positive blood culture and clinical or laboratorial documented blood infections were evaluated during the three-week of protocol. Episodes of nausea, vomiting and mucositis were evaluated as confounder variables. They were assessed weekly by the nutritionist, and noted in accordance with toxicity grade.[14]

Nutrition intervention

Patients also received nutritional counseling and were encouraged to eat better at home, according to their individual habits. The group was randomized to receive OSF or HOS for three weeks. OSF was *Nutren Jr* for children and *Nutren 1.0* for adolescents (Nestlé-Clinical Nutrition). This supplement was a whole powder formulation with macro (52% carbohydrates, 12% proteins and 36% lipids), vitamins trace elements, macroelements and taurine and L-carnitine that presents 1.0 kcal/ml. HOS was composed by milk, ice cream, sugar milk, boiled white egg, and lipids (oil or margarine); sometimes they put some fruits or chocolate powder. The supplements were offered to cover 45% of daily-recommended energy, according to recommendations for oncology pediatric patients.[15,16] The amount offered was based in previous test.

Ethics committee

Medical Ethics Committee of Federal University of Sao Paulo approved the nutritional protocol which this analysis was part (protocol number 1097/02). The correspondent consent from all parents, guardians or patients was obtained after the study protocol was explained to them.

Statistical analysis

The analyses were performed with the use of NCSS/PASS 2000 statistical software[17]. Descriptive statistics were used to summarize the characteristics of the sample. Because normality tests from serum albumin data were rejected, the results are expressed as medians and interquartile. For comparison of the prevalence between OSF and HOS, chi-square test was performed. *Wilcoxon* signed-rank test was applied to analyze differences between serum albumin medians at week zero and three.

In order to study some correlation between serum albumin and TSFT, MUAC and MAC at week zero and three, Spearman correlation test was performed.

Multiple logistic regressions were applied to estimate odds ratios (ORs) between: (1) serum albumin (albumin in week zero, albumin at week three and difference between the albumin at week zero and three - continuous variables) and clinical outcomes (overall hospitalization, hospitalization for organic and infectious complications, fever, fever combined with leucopenia, positive blood culture and clinical or laboratorial documented blood infections – categorical variables); (2) serum albumin (continuous variables) and nutrition outcomes (tube feeding indication and to achieve ideal weight - categorical binary variables) at the end of the three-weeks program.

Regression analysis was also applied to determine if serum albumin and difference between the serum albumin at week zero and three as outcome variables could be associated with oral supplementation (OSF vs HOS). Odds Ratio (OR) with 95% confidence intervals (CIs) described the magnitude of effects for each categorical variable studied.

Logistic regression models were also employed to analyzed nutritional outcomes. These analyses were performed to study an

association of the difference in albumin between week zero and three (albumin 3 – albumin 0; numerical variables) with nutritional and clinical outcomes (categorical binary variables). For these purposes, only the probability of the test and regression coefficient were used to confirm the association.

Oral supplementation formula (yes or not), specific diagnosis, age (children and adolescents) and gastrointestinal toxicity grade (nausea/vomiting and mucositis) were investigated as explanatory variables. Both adjusted and unadjusted ORs were performed, but only final analyses after adjustments are presented. All of the statistical tests were two-sided; $p < 0.05$ was considered significant.

Results

Descriptive analysis of data

The patients' characteristics are shown in Table 1. Sixty-seven patients were enrolled, but fifty-four were analyzed. Eight patients had to be excluded because abandonment of the follow up and four because they did not collect laboratory analysis. Thirty-two patients were in OSF group and 22 in HOS group.

Table 2 presents median (interquartile) and prevalence of albumin depletion in 54 patients. The decrease in serum albumin was observed in nineteen patients (35.2%) after three weeks of the nutrition protocol; 11/32 in OSF group (34.4%) and 8/22 (36.4%) in HOS group (p=NS).

Table 1 Demographic characteristics of pediatric cancer patients (n = 54)

Characteristic	Number OSF group	Percentage HOS group	Number OSF group	Percentage HOS group
Age category				
Children	20	62.5	16	72.7
Adolescents	12	37.5	6	27.3
Gender				
Male	17	46.9	12	54.5
Female	15	53.1	10	45.5
Diagnostics:				
ALL[a]	4	12.5	3	13.6
AML[b]	0	0	1	4.5
NHL[c]	1	3.1	1	4.5
HD[d]	1	3.1	1	4.5
CNS[e]	3	9.4	1	4.5
Neuroblastoma	3	9.4	2	9.1
Wilms tumor	3	9.4	1	4.5
Bone tumors	7	21.9	5	22.7
Rabdomyosarcoma	2	6.3	2	9.1
Germ cells tumor	2	6.3	1	4.5
Carcinomas	0	0	1	4.5
Retinoblastoma	3	9.4	1	4.5

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Table 2 Median and percentage of albumin depletion (n = 54)

	OSF W0	OSF W3	HOS W0	HOS W3	Total group W0	Total group W3
Median and min and max	4 (3.1– 5)	4(3.6–5.1)	4 (3-4.9)	4.1(3.2-4.8)	4 (3 – 5)	4 (3.2 – 5.1)
Prevalence of depletion	6.25%	0	18.2%	9.1%	11.1%	3.7%

OSF, oral supplementation formula; HOS, homemade oral supplement; W0, week zero; W3, week three Minimum and maximum: min and max

The hypothesis that tested difference in median of the serum albumin at weeks zero and week three (albumin zero – albumin three < 0) did not demonstrate to be statistically significant (p=0.099).

Nutritional indexes and serum albumin correlation

The analysis showed a significant, but weak correlation between serum albumin and TSFT at week three (0.22; p=0.012), without correlation with other anthropometrical indices.

Serum albumin and nutritional outcomes

Low serum albumin at admission of nutritional protocol demonstrated to be associated with nutritional outcome only for tube feeding indication when unadjusted analysis was performed (OR=7.83 (95%CI: 1.00-61.46; p<0.05). However, adjusted analysis did not demonstrated association with tube feeding indication (Table 3).

Table 3 Multiple Logistic Regression Analysis of Clinical Factors Associated with Serum Albumin (OSF and HOS group)

Variable	OR	Multivariate for Decrease of the Albumin 95% CI	*p*	OR	Multivariate for Albumin at week 3 95% CI	*p*
OH	4.54	1.15–17.85	0.03	13.73	1.71-109.98	0.001
Fever	6.53	1.76–24.28	< 0.01	-	-	NS
HSC	-	-	NS	53.6	12.87-1000.47	< 0.01
PBC	-	-	NS	15.71	0.66-376.16	0.09
Infection	-	-	NS	49.0	3.02-794.52	< 0.01

OH, Overall hospitalizations; HSC, Hospitalization for complications (organic or infectious); PBC, Positive blood culture

Serum albumin at admission of the protocol demonstrated to influence nutritional outcome (to achieve the IBW). The higher the albumin, the better nutritional outcome (regression coefficient=1.60; p=0.02). Nutritional outcome also demonstrated to be influenced by serum albumin at week three: the higher serum albumin, the less tube feeding indication (regression coefficient=-2.67; p=0.04).

There was not any association between type of supplement intake (OSF vs HOS) and albumin.

Serum albumin and clinical outcome

Multiple logistic regression analysis of albumin with clinical indices showed that overall hospitalization (OR=4.54; 95%CI: 1.15–17.85; p=0.03) and fever (OR=6.53; 95%CI: 1.76–24.28; p<0.01) were associated with the decrease in serum albumin. When the decrease in serum albumin was analyzed with hospitalization for complications (organic or infectious), no association was found. When OSF group was analyzed alone, the same was observed. The relationship of the decrease in serum albumin and overall hospitalization demonstrated an OR=13.73 (95%CI: 1.71-109.98; p=0.01), but it did not demonstrate any association with hospitalization for complications (Table 3).

Low serum albumin at week three was also associated with clinical outcome: low albumin was associated with increased hospitalization for complications (OR=53.6; 95%CI: 12.87-1000.47; p=0.009) and infection (OR=49.0; 95%CI: 3.02-794.52; p=0.006). Positive blood culture (OR=15.71; 95%CI: 0.66-376.16; p=0.09) presented a borderline association with low albumin at week three (Table 3).

Discussion

Cancer patients are vulnerable to metabolic changes due to disease process, and because of the treatment and its complications. This situation is characterized by decrease in the syntheses of visceral protein and increase in acute phase protein syntheses. Various conditions, as infections, organic complications as liver and renal toxicity and changes in hydration status for edema, water retention or dehydration can modify metabolic responses and impair the nutritional assessment.[18]

Serum albumin is a significant and independent prognostic factor in patients with colorectal cancer and its effect is maintained across tumor–node–metastasis (TNM) stages and other well defined prognostic factors.[19] This study aimed to evaluate the association between the decrease in serum albumin and some clinical and nutritional outcomes. It can be easily used in prognostic models and should be employed to stratify prognosis in therapeutic randomized clinical trials. Although some associations had been found, serum albumin levels did not demonstrate to be severely depleted in this study (Table 2). Lis et al. (2003) observed the median level of serum albumin was 3.85 g/dl, with a range of 2.5 to 5.8 g/dl in patients with breast cancer. The authors demonstrated that survival improved from

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the lowest quartile of albumin to the highest quartile, showing that the five-year survival of patients declined from 79% with normal albumin levels to 47% with low levels. Interestingly, the analysis detected that low levels of serum albumin identified patients with the most severe disease within each tumor stage. The author data suggest that serum albumin is a marker for patients with severe disease.

The lowest level of albumin detected in patients of our study was 3 g/dl; this level was higher than that found in Lis' study, suggesting low deficit or less inflammation in patients of this study. On the other hand, the higher level found in our study (5.1 g/dl) was lower than Lis' study (5.8g/dl) and 35% presented reduction in the serum albumin after three weeks.[11] Serum albumin is not a good marker of the nutritional deficit in children with cancer, mainly when compared to anthropometrical methods.[4,20]

Since there was a significant, but low relationship between serum albumin and TSFT at week three in the present study, we could believe that nutritional status would have a little direct or indirect effect on albumin. However, we can not do any inference about causality.

Although it was found association between overall hospitalization and fever with the decrease in serum albumin, hospitalization specifically for complications did not demonstrate significant association with this variable. However, albumin at week three showed to be associated with hospitalization for complications and infections. Therefore, the association could be related to many situations that promote an acute inflammatory response, due to surgeries and hospitalizations for chemotherapy administration, in addition to infections and organic complications. It is probably that the episode of hospitalization for procedures, fever and infection lead to a serum albumin depletion by means of this inflammatory response and catabolism generated for this situation. In the same way, Kyle et al.[9] found low serum albumin was significantly associated with length of hospital stay≥11 days in adult patients with various diagnosis and Leite et al. (2016) found that hypoalbuminemia at admission to the intensive care unit (ICU) is associated with higher mortality, and longer ICU stay and duration of mechanical ventilation. These associations were independent of systemic inflammatory response, disease severity, and nutritional status.[21]

Although hypoalbuminemia has traditionally been linked to malnutrition, it is not a specific nutritional marker. The mechanisms implicated in the genesis of hypoalbuminemia are multifactorial, involving process of synthesis, catabolism, amino acid supply, water retention and losses to the extravascular space due to the disruption of endothelial permeability.[4] Therefore, in addition to being an indicator of malnutrition, low levels of albumin seem to represent an organic adaptation to aggressive events in several clinical settings.

Nevertheless, it is also important to consider the hypothesis that serum albumin depletion could represent a protein catabolism, what impairs cellular proliferation, mainly cells of rapid growth, decreasing immune and gastrointestinal function and impairing wound healing. This is a detrimental condition to the patient's prognosis. Many studies have demonstrated that patients with cancer are malnourished[22-26] and it could impair prognostic.[27-29] Some evidences point that preoperative albumin correlated inversely with complications and length of hospitalization in postoperative and intensive care patients and with mortality in hospitalized patients.[30,31]

In the present study, it was possible to observe an association between nutritional outcome and serum albumin. Improvement in nutritional status (recovery of ideal weight and reduction of tube feeding indications) was associated with a higher serum albumin value at week zero and three, respectively. Since no association was found between type of supplement intake and serum albumin, to achieve IBW could be related to patients with better prognostic and/or with less intense inflammatory response, demonstrated by serum albumin at week zero. This condition could be more propitious to improve the nutritional evolution of the patients.

On the other hand, the positive outcome about tube feeding and its association with serum albumin at week three can be partially related to nutritional status. Maybe, higher levels of albumin after three weeks could really reflect an improvement of the nutritional status. Meantime, we did not analyze any marker of inflammatory response, like C-reactive protein (CRP), thus it is not possible to confirm these hypotheses.

The lack of association between supplementation and serum albumin can be explained by short time of nutritional support, as well as by low severity of malnutrition (mild malnutrition group).

These results seem to suggest that the role of serum albumin can be prognostic, but that does not role out the importance of the nutritional depletion on albumin.

The main methodological limitations of our study are the relatively small number of patients and the heterogeneity of the group regarding the different diagnosis and treatment phase. On the other hand, the patients in this study are mildly malnourished which has allowed us to believe that albumin depletion could be more involved with the clinical than nutrition condition. In addition, serum albumin values were not as low.

The present research is a preliminary study highlighting the role of serum albumin as a likely prognostic indicator in oncology pediatric clinical setting. Although some professionals recommend serum albumin as a nutritional indicator, the evidences can provide some information about its importance as a prognostic marker in pediatric oncology patients undergoing anti cancer treatment.

Conclusion

Serum albumin index were more associated with clinical than nutritional outcomes. These results confirm adult studies that found association between serum albumin depletion and prognostic factors. Serum albumin probably does not only reflect nutritional status during disease conditions, especially in cancer patients with some degree of inflammation.

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Conflicts of interest

None.

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