Association of serum albumin levels with inflammation and clinical outcomes in children with acute bronchiolitis.

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October 26, 2020

Abstract

Objective: To evaluate if hypoalbuminemia on admission predict disease severity in children with acute bronchiolitis (AB). Working hypothesis: Hypoalbuminemia is associated with worse outcome in infants with AB. Study design: Single-centre prospective cohort study. Patient-subject selection: Infants aged <12 month-old with AB. Methodology: Serum albumin levels were determined within the first 24 hours upon inclusion. The primary outcome was the need of pediatric intensive care unit (PICU) admission. Results: We enrolled 90 cases of AB. Serum albumin was independently associated with C-Reactive protein levels (CRP) (rs=-0,28; p=0.002). Fourteen (15.5%) cases required PICU admission. They presented lower serum albumin levels (3.7 (0.11) vs 4 (0.5) g/dl; p=0.034) regarding those patients without severe illness. In the multivariate logistic regression analysis, hypoalbuminemia was independently associated with a higher risk of severe illness (adjusted Odds Ratio 4.1 (1.2-85); p=0.032). The area under the ROC curve for serum albumin to predict adverse outcome was 0.70 (95% Confidence interval of 0.59-0.79). A cut-off point of 3.5 g/dl presented a sensitivity of 0.71, specificity of 0.68, positive predictive value of 0.29, and negative predictive value of 0.92. Conclusion: Low serum albumin levels at admission are significantly associated with higher PICU admission rates in infants with AB. The inflammatory response could play a key role in the occurrence of hypoalbuminemia in AB.

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Type of article: Original article

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Keywords: Acute bronchiolitis; Serum Albumin; Biomarkers; Inflammation

Short title: Rodriguez-Gonzalez et al: Albumin and inflammation in acute bronchiolitis.

Abstract

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Main Text

Introduction

Acute bronchiolitis (AB) is the leading cause of lower respiratory infection and hospital admission among children up to 2 years of age worldwide[1]. Approximately 2-6% cases of AB will develop a severe form of the disease, requiring admission at the pediatric intensive care unit (PICU)[2]. In absence of any definitive treatment, the major goal in AB is the prevention and early identification of infants at risk for develop a severe illness in order to provide the best management options and potentially decrease morbidity[3]. Current guidelines recommend the identification of specific risk factors (congenital heart disease (CHD), chronic lung disease (CLD), prematurity) and the clinical assessment as the best tools to asses severity, predict evolution and tailor the management accordingly[4]. However, most hospitalizations correspond to healthy infants, who can also develop a severe AB[1,2], and most clinical scores for AB are not well validated and fail to predict outcomes[5]. In this context, the identification of novel biomarkers with adequate predictive value for disease severity in AB is an area of increasing research[6-8].

Albumin is a 69kDa protein that is mainly synthesized by the liver and plays an important role in a number of physiological mechanisms. It has long been well established that hypoalbuminemia is a powerful prognostic marker in the general population and many pathological settings, mainly as a result of malnutrition and inflammation[9-13]. During severe AB a reduced energetic intake, impaired nutritional status and an inflammation with a cytokine-mediated acute phase response can coexist, leading to lowered levels of serum albumin. However, the association between albumin and AB severity has been little investigated in this setting[14].

The primary objective of this study was to evaluate if serum albumin levels on admission are associated with severity of illness in infants with AB. A secondary objective was to explore possible causes of these low plasmatic levels in this setting.

Materials and methods

- Design, settings and study population: This was a single-centre prospective cohort study including infants aged less than 12 month-old evaluated at the Pediatric Department of our institution (a tertiary

university-affiliated hospital in Spain) due to AB between October 1, 2018 and October 1, 2019. The diagnosis of AB was based on personal history, clinical symptoms and physical exam. The pediatrician in charge, who followed the recommendations of current AB guidelines, managed all patients. The exclusion criteria were patients previously diagnosed with malnutrition, a previous episode of AB, bacterial superinfection (based on blood or endotracheal cultures), patients that received any intravenous fluids including albumin before the intervention, and patients with incomplete intervention or medical records. Our Institutional Review Board approved the study. Informed consent was obtained for all patients.

- **Intervention, Data Collection and Definitions:** All patients underwent clinical, laboratory, and microbiologic evaluation. Characteristic data were recorded from medical records of the patients during hospitalization. The attending physician assessed clinical presentation. The bronchiolitis score of Sant Joan de Déu (BROSJOD) score[15] was the clinical score used to assess the respiratory state severity at admission. A BROSJOD score greater than 10 points is indicative of severe clinical state. The blood collection was drawn within the first 24 hours upon inclusion of the patient in the study. Biochemical data including serum albumin levels were recorded. PCR analysis of nasopharyngeal mucus for respiratory viruses was routinely analyzed in all patients. Blood culture was performed only in cases with clinically suspected bacterial sobreinfection .

- **Research outcome:** The primary outcome were the need of PICU admission during the episode of AB, mortality and the length of stay (LOS) hospitalization. PICU admission criteria for AB in our institution are the presence of apnea, extreme bradycardia, need of respiratory support greater than high-flow nasal cannula oxygen therapy, or need of inotropic support. According to these data, patients that required PICU admission were classified as severe AB group.

- **Statistical analysis:** Continuous data are presented as median (range) or mean (standard deviation) after testing for normality with the Shapiro-Wilk test. Categorical data are presented as frequencies and percentage. Mean comparison was performed using Student's t test or Wilcoxon Mann-Whitney test as appropriate. Proportions were compared using Chi-square test or exact methods as necessary. Pearson and Spearman coefficients were used to assess correlations between continuous data. Multiple linear regression analysis was performed to identify variables independently associated with the dependent variable serum albumin. Only statistically significant variables in the correlation tests were entered into the multivariate analysis. Because the absence of clear normal range values for serum albumin in infants, the serum albumin level was dichotomized at the 25th percentile of the entire cohort and defined as hypoalbuminemia if the level was minor or equal of 3.5 g/dL. Multivariate logistic regression analysis was used to determine if hypoalbuminemia was independent predictor for adverse outcome. Significant variables detected in the univariate analysis and which were considered to be clinically relevant (known risk factors for severe AB) were entered into this multivariate analysis. Collinearity between variables was evaluated. The relative risks were expressed as odds ratios (OR) and 95% confidence intervals (95%CI). A receiver operator curve (ROC) analysis was used to determine the diagnostic accuracy of serum albumin for adverse outcome. The values of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for serum albumin cut-off point of < 3.5 g/dl. All the statistical analyses were performed using the Stata software (StataCorp. 2014. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). A P value minor than 0.05 was considered statistically significant.

Results

- **Baseline Data:** A total of 107 infants aged 12 months or less with AB were assessed for eligibility. Of them, 101 patients accepted to participate, and we excluded 11 cases because of the presence of a previous AB episode (5) and bacterial superinfection (6), resulting in a sample size of 90 cases of AB (median age of 1 (0.5-7) months; 57 (60%) male). The most prevalent causative agent was respiratory syncytial virus (RSV) (59 cases; 65%). A total of 13 (14.5%) of cases presented a known comorbidity associated to the development of a severe disease (1 case of congenital heart disease, 1 case of chronic pulmonary disease and 11 cases of prematurity). The patients consulted after 1 (0-7) days from the beginning of the symptoms, with a median BROSJOD score of 6 (2-14) points. Up to 10 (11%) patients were classified as severe clinical state accordingly with BROSJOD score (>10) at admission. A total of 80 (89%) cases required hospital

admission with a median length of stay of 3 (0-19) days. Up to 14 (15.5%) patients required PICU admission during a median of 6.5 (3-16) days. Regarding the respiratory support, a total of 55 (61%) cases required oxygen therapy throw nasal cannula, 10 (11%) cases required non-invasive ventilation (NIV), and 3 (3.5%) cases required mechanical ventilation (MV). No cases required inotropic support. There were no cases of mortality.Table 1 summarizes the baseline characteristics of the entire population and comparison between those with and without severe illness.

- Serum Albumin in infants with AB: The mean value of serum albumin in the entire group study was 4 (0.47) g/dl, and 15 (16%) patients presented hypoalbuminemia (levels under 3.5 g/dl). The scatter plot of serum albumin displayed a significantly correlation with age (r_s=0.50; p < 0.001), weight for age percentile (r_s=0.33; p= 0.002), CRP (r_s=-0.27; p =0.008), pCO2 (r_s=-0.32; p=0.003), and HCO3 (r=-0.24; p=0.029) levels (Figure 1). Multiple-linear regression analysis confirmed the age, the weight for age percentile and CRP levels as the variables independently associated with serum albumin (Table 2). The patients with a severe AB presented lower serum albumin levels at admission than those patients without a severe illness (3.7 (0.11) g/dl vs 4 (0.5) g/dl; p=0.034) (Figure 2A). Those patients with serum albumin <3.5 g/dl presented a five-fold risk of PICU admission (OR 5.5 (CI95% 1-55-19); p =0.008). After adjusting for potential confounders (age, weight for age, presence of comorbidity, BROSJOD score, respiratory acidosis and CRP) in a multivariate logistic regression analysis, serum albumin level less than 3.5 g/dl remained independently associated with a higher risk of severe AB (aOR 4.1 (1.2-24); p = 0.032). The ROC curve for serum albumin to predict a severe AB was generated, yielding an AUC of 0.70 (95% CI 0.59-0.79) (Figure 3). A cut-off point of 3.5 g/dl presented a sensitivity of 0.71, specificity of 0.68, positive predictive value of 0.29, and negative predictive value of 0.92. Finally, lower levels of serum albumin at admission correlated with the length-of-stay (LOS) hospitalization (r=-0.20; p = 0.036) (Figure 2B).

Discussion

In this observational prospective study involving 90 infants with AB, an observational correlation has been observed between severity of illness and serum albumin levels; the children who had higher severity of illness, requiring PICU admission and longer hospitalizations had lower albumin levels at admission. Although the predictive value of hypoalbuminemia was only moderate, these results highlight a possible role for albumin as a biomarker for severity in this setting.

Serum albumin is considered as a marker of disease severity in critically ill adult patients, with low serum albumin concentrations being reported in 30%-50% of cases[12, 13]. Some studies have investigated the incidence and the prognostic value of hypoalbuminemia in critically ill children, reporting a higher incidence (60% approximately) in cases requiring PICU admission[11,16-22]. In our study, hypoalbuminemia, defined as serum levels less than 3.5 g/dl, was observed in approximately 15% of cases of AB at presentation. There are no clear reference values of serum albumin in children. Therefore, the lower incidence of hypoalbuminemia that we observed could be explained because the albumin level used to define hypoalbuminemia varies widely between the different studies. Also, we did not included patients with previously diagnosed malnutrition, a known facilitating factor for hypoalbuminemia. Furthermore, the inflammatory response in AB, another important determinant of hypoalbuminemia, is usually of lower intensity than in conditions such as cardiac surgery, bacterial pneumonia or sepsis, that were the most frequent diseases included in those studies[23].

The presence of hypoalbuminemia has been previously shown as a significant marker of mortality and increased stay in children admitted to pediatric intensive care unit[11,16-22], but to our knowledge this is the second study that have investigated the role of hypoalbuminemia as biomarker for severity in children with AB. Mansbach et al. studied 1016 infants with AB and found that those cases of AB presenting with hypoalbuminemia had a four-fold risk to develop apnea during hospitalization[14]. Results consistent with aforementioned study were found in the present study. Thus, we found a four-fold risk to present a severe illness in infants with AB and serum albumin less than 3.5 g/dl at presentation. Also, we found that lower levels of serum albumin were correlated with a prolonged LOS hospitalization. It is noteworthy that the incidence of hypoalbuminemia in the study of Mansbach et al. (38%) was higher than the incidence that we found (16%). This could be explained by the different cut-off that we used to define hypoalbuminemia (3.5 g/dl vs 3.8 g/dl).

Using the same definition of hypoalbuminemia (3.8 g/dl), the incidence in our population would raise up to 28% (data not shown). Despite our differences, the incidence of hypoalbuminemia seems to be lesser in AB than conditions with a more important inflammatory component, as mentioned previously.

The discriminatory value of serum albumin level for predicting PICU admission in our study was fair (AUC ROC 0.70), and sensitivity and specificity were relatively low (71% and 68% respectively) for hypoalbuminemia (<3.5g/dl). However, based on the very high NPV observed (92%), serum albumin levels equal or higher than 3.5 g/dl could help clinicians to identify those infants with AB at lower risk for developing a severe disease. The advantage of using of serum albumin levels for predicting outcomes is that it would be an objective, inexpensive and widely available biomarker to use in conjunction with current clinical scores to assess disease severity.

The mechanisms of hypoalbuminemia in critical illness is complex and may involve a number of mechanisms such as an imbalance between albumin synthesis and degradation, increased capillary leakage, and altered intravascular and tissue albumin distribution[9,10]. Interestingly, the presence of hypoalbuminemia seems to be associated with a severe illness independently of the underlying respiratory process. Thus, we did not document a worse respiratory state at admission in relation with hypoalbuminemia, as the BROSJOD clinical score, pCO2, pH, serum bicarbonate and serum lactate levels at admission were not associated to serum albumin levels in the multivariate analysis. In the light of our results, the levels of serum albumin in infants with AB are associated with the age, the weight for age percentile, and the inflammatory response. Accordingly, the positive correlation observed between the age and the serum albumin level has been previously recognized in neonates and small infants[24], and malnutrition and inflammation are considered to play a major role in occurrence of hypoalbuminemia[9]. Although it has traditionally been linked to malnutrition and we observed that the weight for age percentile was independently associated to serum albumin levels, hypoalbuminemia is not considered a specific nutritional marker[9]. Thus, serum albumin concentration is influenced also by various non-nutritional factors, impairing its validity as a nutritional parameter in patients who have acute-phase response and metabolic stress. Furthermore, a decrease in serum albumin concentration develops usually late in the course of malnutrition and, as a consequence, in the most severe cases that were excluded for this study. Therefore, we think that low serum albumin levels may not be due to the nutritional status of our patients.

Conversely, we think that inflammation could play a key role in the occurrence of hypoalbuminemia in AB. Albumin is assumed as a negative acute phase protein. Inflammation mediated by cytokines leads to decreased synthesis of albumin and causes albumin redistribution associated with increased capillary permeability[9,10]. The multivariate linear regression showed an independent inverse association between CRP and albumin levels, suggesting that hypoalbuminemia in AB is associated with the acute inflammatory response. The association of low serum albumin levels with high concentrations of inflammatory markers such as CRP, or IL-6 has been previously demonstrated in adults[25-27]. Of note, among the inflammatory mediators that have been described to play an essential role in the Respiratory Syncytial Virus pathology are cytokines[6,28]. Among these, the pro-inflammatory cytokine IL-6 is has been described to be critical for regulating disease severity during RSV infection in mice models, and has been related with the development of neurologic alterations in infants[28-30]. Thus, it could be possible that the increase of inflammatory mediators such as IL-6 during AB leads to an increase in the hepatic production of positive acute phase reactants, such as CRP, while conversely decreasing the production of negative acute phase reactants such as albumin. Because, measurement of IL-6 is usually not readily available and expensive, serum albumin could serve as a low-cost and easily measured biochemical parameter of inflammation in AB.

Limitations: The study has some limitations. This is an observational relatively small size and single centre study; therefore it may not be representative of outcomes at other sites because of special circumstances such as physician quality, hospital features, different resources or hospitalization/PICU admission criteria. A control group was not used to establish normal reference levels of serum albumin. We used the 25th percentile as an arbitrary definition of hypoalbuminemia. We used the initial serum albumin level measured when patients presented to the ED. Strength of this approach was that the initial serum albumin level was

unlikely to be affected by fluid resuscitation or other possible treatment during ED. However, we did not investigate the trends in serum albumin level, which could reveal more kinetic information and should be a subject of the further research. Although we attempted to collect extensive covariates data and avoid introducing potential bias, unknown confounding factors may have influenced the associations between the predictive and outcome variables.

Conclusion: An observational correlation has been observed between severity of illnessas determined by PICU admission and serum albumin levels; the children who had higher severity of illness had lower albumin levels at hospital admission. Specifically, serum albumin levels higher than 3.5 g/dl could help clinicians to identify those infants with AB at lower risk of develop a severe illness. Hypoalbuminemia in patients with AB seems to be associated to the acute inflammatory response of the disease. The results of this study suggest that inflammation has a role in severity of illness in the setting of AB.

Acknowledgements:

This work has been awarded the Best Clinical Research Annual Prize grated by Cadiz's Medical Association.

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