ORIGINAL ARTICLE

Serum Albumin as a Predictor of Severity, Morbidity, And Mortality in Neonatal Sepsis

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ABSTRACT

Objective: To evaluate early serum albumin levels as a predictor of disease severity, morbidity, and mortality among neonates with sepsis.

Study design: Prospective cohort study.
Place and duration of study: Neonatal Intensive Care Unit, Dr Ruth K.M. Pfau Civil Hospital, Karachi, over a six-month period

Materials and methods: A total of 218 neonates with culture-confirmed sepsis were enrolled using consecutive sampling. Neonates with prior antibiotic exposure, hypoxic-ischemic encephalopathy, suspected inborn errors of metabolism, or prior blood transfusion were excluded. Serum albumin levels were measured at admission. Demographic, clinical, and laboratory data were recorded, and neonates were followed until discharge or death. Outcomes included morbidity, length of hospital stay, and mortality. Correlation analyses and multivariable regression models were applied.

Results: The mean gestational age was 35.1±2.9 weeks, and 55.5% were preterm. Hypoalbuminemia (<2.5 g/dL) was present in 42.2% of neonates. Overall mortality was 17.4%, and morbidity occurred in 37.2%. Mortality was significantly higher in neonates with hypoalbuminemia compared to those with normal serum albumin (30.4% vs. 7.9%, p <0.001), as was morbidity (56.5% vs. 23.0%, p <0.001). Neonates with hypoalbuminemia had a significantly longer hospital stay (12.6±5.1 vs. 7.8±3.2 days, p <0.001). On multivariable analysis, hypoalbuminemia independently predicted mortality (AOR = 3.21) and morbidity (AOR = 2.87).

Conclusion: Early hypoalbuminemia is common in neonatal sepsis and independently predicts adverse outcomes. Serum albumin is a simple, cost-effective prognostic marker for early risk stratification.
Keywords: *Neonatal sepsis, Serum albumin, Hypoalbuminemia,*

INTRODUCTION

Mortality, Morbidity, Pakistan

Neonatal sepsis is a critical issue of global health concern and it is one of the most common causes of morbidity and mortality in newborns, especially in the low and middle income countries. Approximately 1.4 million neonatal deaths occurring annually worldwide are due to invasive infections of which sepsis is a cause of most (nearly 30-50%). Although perinatal care and neonatal intensive care services have advanced, prevalence of neonatal sepsis in the resource-limited settings is still disproportionately high because of late presentations, lack of diagnostic capacity, and high rates of prematurity and low birth weight.[1,2]

Neonatal sepsis is an inflammatory reaction of the whole body to a suspected or confirmed infection during the first 28 days of life and is categorized as early-onset (<72 hours) or late-onset (>72 hours) or hospital-acquired neonatal sepsis (3). The clinical picture is usually insidious and nonspecific, with such signs as stability of temperature, respiratory distress, apnea, feeding intolerance, lethargy, seizures, hypotonia, and circulatory impairment. The resulting overlap between these features makes it difficult to diagnose them early and emphasizes the necessity of reliable and easy to measure biomarkers to stratify accurately the risks in the initial risk and prognosticate.[4]

Even though laboratory parameters (complete blood count indices, C-reactive protein and procalcitonin) are widely used, the diagnostic and prognostic characteristics cannot be performed optimally, particularly at the beginning of the disease course. Serum albumin is a possible prognostic biomarker due to its intimate association with inflammation in the system, nutrition status, and illness severity. The levels of albumin decrease in acute inflammatory states, as the synthesis decreases and the catabolism and leaks increase. The connection between hypoalbuminemia and a more severe disease, the length of hospitalization and mortality has been relatively steady in critically ill patients, including neonates.[5,6]

Neonatal sepsis is also a leading cause of neonatal mortality in Pakistan. It is therefore necessary to identify simple and cost-effective prognostic markers. The study hypothesized that early serum albumin levels influence disease severity, morbidity, length of hospital stays and mortality among neonates with sepsis admitted to a tertiary care neonatal intensive care unit (NICU)

.MATERIAL AND METHODS

This is a prospective cohort study that was done in Neonatal Intensive Dr Ruth K.M. Pfau Civil Hospital, Karachi, after receiving the consent of the College of Physicians and Surgeons Pakistan and the Institutional Review Board of Dow University of Health Sciences over a period of six months. The ethical principles of the Declaration of Helsinki were met in conducting the study. All the eligible neonates had written informed consent provided by their parents or legal guardians before the enrolment. Non-probability consecutive sampling was used to recruit 218 neonates who were diagnosed with sepsis on admission. Infants of both genders were involved. Neonates were not included in the case of refusal of the consent, history of antibiotic exposure in the last three days, referral to a different healthcare facility, post-admission sepsis, and known hypoxic-ischemic encephalopathy or suspected inborn error of metabolism. Neonates who had been exposed to blood or blood products before sampling and neonates without clinical sepsis were also excluded in order to reduce the confounding.

On admission, a thorough clinical assessment of all the enrolled neonates was conducted by the attending neonatology unit. Demographic information, such as age and gender, was measured. Perinatal (gestational age) and clinical

variables (weight at birth, mode of delivery, and sepsis as early-onset (<72 hours of life) or late-onset (>72 hours of life) were recorded. Specific clinical features that were suggestive of sepsis were observed such as abnormal temperature, respiratory distress, apnea, cyanosis, difficulty in feeding, lethargy, hypotonia, seizures, bulging fontanelle, and evidence of poor perfusion. All the findings were documented on a designed structured proforma. The severity of the disease was determined on the basis of the clinical assessment of the severity of a disease in relation to the involvement of the systemic processes, intensive supportive treatment, and the occurrence of complications in the course of hospitalization. To evaluate outcomes, which included morbidity, a length of stay in hospital, and mortality, neonates were tracked prospectively since the time of admission up to the time of discharge or death.

At admission, aseptic venous blood samples were taken before the patient received definitive antibiotic treatment. The tests conducted in the laboratory were complete blood count, blood culture, serum albumin, C-reactive protein, serum electrolytes, arterial blood gases, alanine aminotransferase, aspartate aminotransferase, urea, and creatinine. Blood cultures were done by the use of BacT/ALERT(r) 3D system as per the institutional protocols. The serum albumin concentration was determined through standard automated biochemical analyzers and hypoalbuminemia was considered when the serum albumin concentration was less than 2.5 g/dl. Clinical management and research analysis were based on laboratory results, and did not disrupt the standard of treatment protocols.

The data were coded and entered through SPSS software and analyzed. Continuous variables including gestational age, birth weight, serum albumin, inflammatory markers and hospital stay were tested on normality using the Shapiro-Wilk test and were presented as the mean plus-standard deviation or median with the interquartile range as the case. Gender, type of sepsis, clinical signs, the presence of complications, and final outcomes are all categorical variables that were summarized in the form of frequencies and percentages. Bivariate tests were conducted to evaluate the relationship among serum albumin and clinical outcomes. Categorical variables were analyzed with the chi-square test or Fisher exact test and independent t-test or Mann-Whitney U test were used to analyze continuous variables. Correlation between the levels of serum albumin and other continuous variables including C-reactive protein and length of stay was assessed using Pearson or Spearman correlation coefficients. The multivariate logistic regression analysis was performed to determine independent predictors of mortality and morbidity, the linear regression analysis was done to determine the independent predictors of prolonged hospital stay. Subgroup analyses were conducted to compare early-onset and late-onset sepsis, preterm and term babies. Any p-value lower than 0.05 was taken to be statistically significant.

RESULTS

A total of 218 neonates with culture-confirmed sepsis were enrolled. The majority were male (60.6%), preterm (55.5%), and had early-onset sepsis (59.2%). The mean gestational age was 35.1 ± 2.9 weeks and mean birth weight was 2.28 ± 0.61 kg. Hypoalbuminemia (<2.5 g/dL) at admission was present in 92 neonates (42.2%), with a mean serum albumin level of 2.74 ± 0.52 g/dL (Table 1).

Table 1. Baseline demographic and clinical characteristics of neonates with sepsis

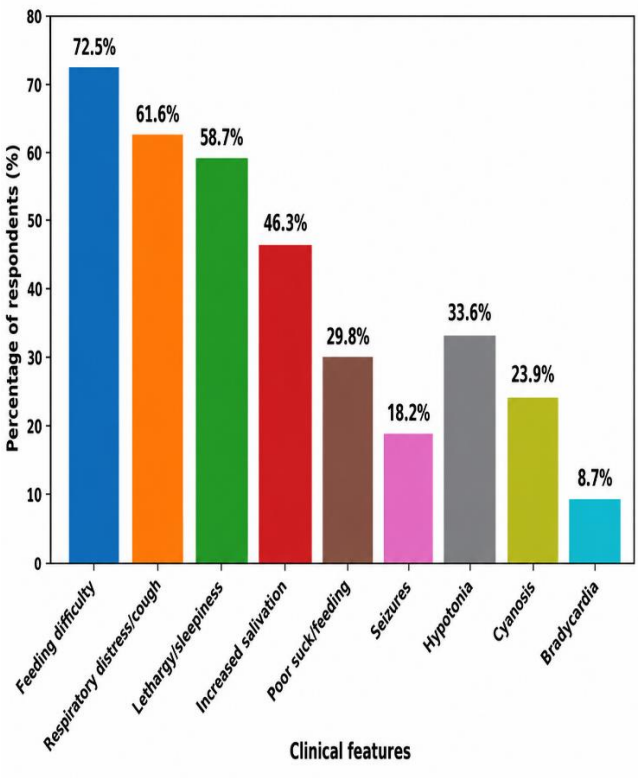
Characteristics	Total (N = 218)
Demographic	
Age at presentation (days), mean ± SD	4.6 ± 3.2
Male, n (%)	132 (60.6)
Female, n (%)	86 (39.4)
Perinatal	
Gestational age (weeks), mean ± SD	35.1 ± 2.9
Preterm, n (%)	121 (55.5)
Term, n (%)	97 (44.5)
Birth weight (kg), mean±SD	2.28 ± 0.61

Sepsis-related	
Early-onset sepsis, n (%)	129 (59.2)
Late-onset sepsis, n (%)	89 (40.8)
Laboratory parameters	
Serum albumin (g/dL), mean ± SD	2.74 ± 0.52
Hypoalbuminemia (<2.5 g/dL), n (%)	92 (42.2)
Normal albumin (≥2.5 g/dL), n (%)	126 (57.8)

Table 2. Association of serum albumin levels with clinical outcomes

The most frequent clinical manifestations were feeding difficulty (72.5%), respiratory distress/apnea (61.9%), lethargy (58.7%), and temperature instability (46.3%), as shown in Figure 1.

Graph 1. Frequency of clinical manifestations among neonates with sepsis



Distribution of presenting clinical features among neonates diagnosed with sepsis.

Overall mortality was 17.4%, and morbidity occurred in 37.2% of neonates. Mortality was significantly higher in neonates with hypoalbuminemia compared to those with normal serum albumin levels (30.4% vs. 7.9%, $p < 0.001$). Similarly, morbidity was more frequent in the hypoalbuminemia group (56.5% vs. 23.0%, $p < 0.001$) (Table 2).

Outcome	Hypoalbuminemia (n=92)	Normal albumin (n=126)	P-value
Mortality,n (%)	28 (30.4)	10 (7.9)	**<0.001***
Morbidity, n (%)	52 (56.5)	29 (23.0)	**<0.001***
Hospital stays (days), mean ± SD	12.6 ± 5.1	7.8 ± 3.2	**<0.001***
Preterm birth, n (%)	63 (68.5)	57 (45.2)	**0.001***

Neonates with hypoalbuminemia had a significantly longer hospital stay than those with normal albumin levels (12.6 ± 5.1 vs. 7.8 ± 3.2 days, $p < 0.001$). Serum albumin levels showed a significant negative correlation with duration of hospital stay ($r = −0.46$, $p < 0.001$) and C-reactive protein levels ($r = −0.39$, $p < 0.001$).

On subgroup analysis, preterm neonates had significantly lower serum albumin levels and higher mortality than term neonates ($p < 0.05$). Late-onset sepsis was associated with a higher frequency of hypoalbuminemia and morbidity. On multivariable logistic regression, hypoalbuminemia independently predicted mortality (AOR = 3.21; 95% CI: 1.51–6.84; $p = 0.002$) and morbidity (AOR = 2.87; 95% CI: 1.63–5.05; $p < 0.001$). Lower serum albumin levels also independently redicted prolonged hospitalization ($\beta = −0.41$, $p < 0.001$) (Table 3).

Table 3. Multivariable regression analysis of predictors of adverse outcomes

Predictors	Adjusted OR / β	95% CI	P-value
Hypoalbuminemia (mortality)	3.21	1.51–6.84	**0.002***
Preterm birth (mortality)	2.08	1.01–4.27	**0.041***
Elevated CRP	2.74	1.29–5.80	**0.008***
Serum albumin (hospital stay)	−0.41	—	**<0.001***
Preterm birth (hospital stay)	0.29	—	**0.003***

Logistic regression for mortality and linear regression for prolonged hospital stay.

DISCUSSION

This research was mainly aimed at assessing the level of early serum albumin as an indicator of severity, morbidity, and mortality of neonatal sepsis. The current research paper proves that pre-admission hypoalbuminemia is closely linked with a negative prognosis. Low serum albumin had a great impact, as infants with low serum albumin levels suffered higher rates of mortality, morbidity, and extended hospitalization. Furthermore, hypoalbuminemia was a significant independent predictor of both mortality and morbidity when potential confounding factors were taken into account, thus demonstrating serum albumin to be a useful prognostic biomarker in sepsis among newborns.[7]

The general mortality rate of 17.4% that was found in the current study is similar to that reported in Pakistan, where mortality in neonatal sepsis cases admitted to tertiary care hospitals is 15% to 30% and higher in the cases of preterm

and low-weight babies.[8] The mortality rate due to neonatal sepsis ranges between 8-12 and 20-35 percent in high- and low- and middle-income nations, respectively.[9, 10] This vast gap indicates variations in early identification, admission to the intensive care unit, and access to laboratory support, and highlights how neonatal sepsis continues to be a burden in resource-limited environments.

Deaths of neonates with hypoalbuminemia were almost four times more frequent than the deaths of their counterparts with normal serum albumin levels (30.4% vs. 7.9%) [11]. The literature on neonates has also given mortality rates of 25-45% of septic neonates with hypoalbuminemia against 8-15% of those with normal albumin levels. The South Asian data on regional data reflect that over one-third of low serum albumin septic neonates fail to survive.[12, 13] All these results confirm that hypoalbuminemia is a good prognostic indicator of neonatal sepsis.

This study found that 37.2% of neonates were morbid, and the morbidity was significantly higher in cases of hypoalbuminemia. Complication rates of 30-50% of the neonates with sepsis are reported by national reports, and the morbidity in cases of sepsis is described at 28-60%, especially in preterm infants and in those with late-onset sepsis. Hypoalbuminemia and disease severity are closely linked, as the augmented workload, respiratory dysfunction, and multiorgan dysfunction among the low serum albumin neonates emphasize.[14]

Neonates with hypoalbuminemia had a significantly longer hospital stay than those with normal serum albumin levels. Previous studies have similarly reported prolonged hospitalization among septic neonates with hypoalbuminemia, reflecting greater disease severity, persistent inflammation, and increased risk of complications. Pakistani neonatal units generally report hospital stays of 8-14 days for neonatal sepsis, which is consistent with our findings. Furthermore, serum albumin demonstrated a moderate negative correlation with hospital stay, indicating that lower albumin levels are associated with prolonged hospitalization and more severe clinical illness [15, 16].Prematurity proved to be a significant predictor of poor outcomes. Over 60% of neonatal sepsis-related deaths in Pakistan occur among preterm or low-birth-weight infants.[17] It is also important to recognize that serum albumin concentrations are physiologically lower in preterm neonates because of immature hepatic protein synthesis and increase progressively with advancing gestational age. In a study of 195 newborn infants ranging from 25 to 42 weeks' gestation, Cartlidge and Rutter demonstrated that serum albumin concentrations ranged from 1.9 to 3.1 g/dL and increased with gestational age, independent of infection.[18] Therefore, hypoalbuminemia in preterm infants may reflect physiological immaturity as well as the inflammatory response to sepsis. To account for this potential confounding, gestational age was included in our multivariable regression model, in which hypoalbuminemia remained an independent predictor of mortality. Nevertheless, residual confounding related to prematurity cannot be completely excluded, and future studies using gestational age-specific reference ranges for serum albumin may better define its independent prognostic value in neonatal sepsis.[19]

Late-onset sepsis was linked to increased occurrence of hypoalbuminemia and increased morbidity. According to data on national NICUs, late-onset sepsis comprises approximately 35-45% of the cases and is often linked to increased hospitalization duration and increased morbidity [20]. It has been reported internationally that 40-60% of late-onset cases of sepsis develop major complications, as compared to 25-35% of early-onset cases [21]. This greater morbidity is probably due to extensive hospitalization, invasive procedures, and cumulative inflammatory load.

Although this study has made vital findings, several limitations ought to be noted. It was a single-center study, which may limit the generalizability of the findings to other healthcare settings. Serum albumin was measured only at admission, and no serial measurements were performed; therefore, changes in albumin levels over time could not be assessed. Furthermore, although multivariable analysis was performed, residual confounding by factors such as nutritional status, maternal characteristics, and timing of antibiotic administration cannot be completely

excluded. In addition, serum albumin concentrations may be influenced by non-septic neonatal conditions, including necrotizing enterocolitis, respiratory distress syndrome, and hepatic dysfunction, which were not systematically evaluated in this study and may have affected albumin levels independent of sepsis. However, the prospective study design, standardized data collection, and clinically relevant outcome measures strengthen the validity of our findings. Future multicentre studies with larger sample sizes, serial albumin measurements, and adjustment for important neonatal comorbidities are warranted to further clarify the prognostic role of serum albumin and evaluate albumin-guided risk stratification strategies. The incorporation of serum albumin into the routine evaluation of neonatal sepsis may facilitate earlier identification of high-risk neonates, optimize monitoring and supportive care, and improve utilization of neonatal intensive care resources.

CONCLUSION

Hypoalbuminemia at admission is common in neonatal sepsis and is independently associated with increased mortality, higher morbidity, and prolonged hospital stay. Early serum albumin measurement provides a simple and cost-effective prognostic marker for risk stratification in neonates with sepsis

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Author's Contribution

1: Proposed topic, basic study design, methodology and manuscript writing
1-4: Collected data and di the manuscript writing
5-6: Did the Statistical analysis, interpretation, results section and manuscript review**.**

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.