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Original Article

Frequency of Hypoalbuminaemia in Preterm Neonates With Sepsis and Its Relation With Mortality

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Abstract

Background: Neonatal sepsis is a leading cause of morbidity and mortality in preterm infants, who are particularly vulnerable due to their immature immune systems. Hypoalbuminemia, a common biochemical abnormality in these neonates, may reflect the severity of infection and the systemic inflammatory response, potentially serving as a prognostic marker for mortality.

Objective: This study aimed to determine the frequency of hypoalbuminemia in preterm neonates with sepsis and to evaluate its sensitivity, specificity, and diagnostic accuracy in predicting mortality within the neonatal period.

Methods: A cross-sectional validation study was conducted at the Department of Paediatrics, Combined Military Hospital, Rawalpindi, from January 2023 to April 2024. A total of 140 preterm neonates with sepsis were included. Neonates with primary liver conditions, significant congenital anomalies, or nephrotic syndrome were excluded. Serum albumin levels were measured upon study enrollment, with hypoalbuminemia defined as a serum albumin level <2.5 g/L. Mortality was monitored for up to 28 days of life. Data were analyzed using SPSS version 25. Quantitative variables were expressed as means/medians, while qualitative variables were presented as frequencies and percentages. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated, and a receiver operating characteristic (ROC) curve was plotted to determine the optimal cut-off value.

Results: Hypoalbuminemia was observed in 57 (40.7%) of the neonates. Mortality occurred in 36 (25.7%) cases. Hypoalbuminemia was significantly associated with mortality ($p<0.001$). The sensitivity, specificity, and diagnostic accuracy of hypoalbuminemia in predicting mortality were 77.78%, 72.12%, and 73.57%, respectively. The optimal serum albumin cut-off value for predicting mortality was 2.45 g/L, with a sensitivity of 73.1% and a specificity of 77.8%.

Conclusion: Hypoalbuminemia is a significant predictor of mortality in preterm neonates with sepsis, demonstrating reasonable diagnostic accuracy. Monitoring serum albumin levels may be valuable in risk stratification and early identification of high-risk neonates. Further studies are recommended to validate these findings in larger cohorts and to explore potential therapeutic interventions.

1 Introduction

Sepsis is a significant contributor to morbidity and mortality in neonates, particularly among preterm infants who are inherently vulnerable due to their underdeveloped immune systems. The prevalence of neonatal sepsis is alarmingly high, with estimates indicating that it occurs in as many as 14.2 per 1000 live births in specific preterm populations, underscoring the critical need for early and accurate identification of at-risk neonates (2). The neonatal period is a time of considerable vulnerability, where even minor disruptions in physiological homeostasis can have severe consequences for survival and long-term health outcomes (3). In this context, sepsis exacerbates this delicate balance, initiating a cascade of systemic inflammatory responses that can compromise multiple organ systems, including the liver, which is integral to the synthesis of albumin (4). Consequently, hypoalbuminemia, a common biochemical abnormality observed in neonates with sepsis, may serve as both a marker of the severity of the infection and a manifestation of the systemic inflammatory response (4).

Hypoalbuminemia in neonates can precipitate a range of serious complications, particularly given the critical roles albumin plays in maintaining oncotic pressure, transporting essential nutrients, and modulating immune function. The development of edema, particularly in the lungs, is one such complication, wherein low albumin levels lead to fluid leakage from blood vessels into surrounding tissues, contributing to respiratory distress and other life-threatening conditions (5, 6). Furthermore, albumin's role in binding and transporting hormones, enzymes, and nutrients is vital for wound healing and the immune response, suggesting that hypoalbuminemia could

exacerbate the risk of infections and impair recovery processes in neonates (7, 8). The deficiency of albumin not only diminishes the transport of critical vitamins and minerals but also potentially compromises the neonate's immune defense mechanisms, thereby increasing susceptibility to infections and further complicating clinical outcomes (9, 10).

Despite its clinical relevance, the precise relationship between hypoalbuminemia and mortality in preterm neonates with sepsis remains inadequately explored, leaving a gap in the understanding necessary for optimizing clinical management strategies. The high prevalence of hypoalbuminemia in this population, coupled with its potential implications for mortality, suggests that it could serve as a valuable prognostic marker. However, the existing literature lacks a comprehensive characterization of this relationship, particularly in the context of preterm neonates who are already at heightened risk for adverse outcomes. Addressing this gap is crucial for the development of evidence-based prognostic models that can guide therapeutic interventions and improve the clinical management of neonatal sepsis.

This study aims to fill this gap by rigorously examining the frequency of hypoalbuminemia in preterm neonates diagnosed with sepsis and evaluating its sensitivity, specificity, and diagnostic accuracy in predicting mortality. Through a methodologically robust cross-sectional validation study, we seek to clarify the prognostic significance of hypoalbuminemia in this vulnerable population and lay the groundwork for future research that could lead to improved risk stratification and targeted treatment strategies in neonatal sepsis. By focusing on serum albumin levels as a potential predictor of mortality, this study contributes to the broader effort to enhance the clinical care of preterm neonates and ultimately reduce the burden of neonatal sepsis (1).

2 Material and Methods

This cross-sectional validation study was conducted to assess the frequency of hypoalbuminemia in preterm neonates diagnosed with sepsis and to evaluate its sensitivity, specificity, and diagnostic accuracy in predicting mortality. The study was carried out at the Department of Paediatrics, Combined Military Hospital, Rawalpindi, over a period from January 2023 to April 2024. A total of 140 preterm neonates, born between 28 and 37 weeks of gestation, who were admitted to the neonatal intensive care unit (NICU) with a clinical diagnosis of sepsis were included in the study. Neonates with primary liver pathologies, significant congenital anomalies, or nephrotic syndrome were excluded to minimize confounding factors that could influence serum albumin levels and mortality outcomes.

Upon admission, comprehensive demographic and clinical data were collected for each neonate, including gestational age, birth weight, APGAR scores, gender, mode of delivery, and antenatal steroid exposure. A thorough clinical examination was conducted, and relevant clinical history was documented. Parental or guardian consent was obtained prior to the enrollment of each neonate, following a detailed explanation of the study's objectives and procedures. The study protocol adhered to the ethical principles outlined in the Declaration of Helsinki and was approved by the ethical committee of Combined Military Hospital, Rawalpindi.

For the assessment of serum albumin levels, a peripheral blood sample of 1 mL was drawn from each neonate using aseptic techniques. The blood sample was transferred to an Ethylene Diamine-Tetraacetic Acid (EDTA) tube to prevent clotting and was subsequently analyzed using an automated point-of-care analyzer (Allegro analyzer, Nova Biomedical, Waltham, USA). Hypoalbuminemia was defined as a serum albumin level of less than 2.5 g/L (13). Mortality was monitored prospectively for each neonate up to 28 days of life or until death, whichever occurred first.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 25 (IBM Corp; Armonk, USA). Quantitative variables such as gestational age, birth weight, APGAR scores, and serum albumin levels were presented as means and standard deviations or medians and interquartile ranges, depending on the distribution of the data. Qualitative variables like gender, mode of delivery, antenatal steroid exposure, presence of hypoalbuminemia, and mortality were expressed as frequencies and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk test.

To compare qualitative variables between groups, the Chi-Square test or Fisher's Exact test was applied as appropriate, while independent samples t-tests or Mann-Whitney U tests were used for the comparison of quantitative variables. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of serum albumin levels in predicting mortality were calculated using 2x2 contingency tables. Additionally, a receiver operating characteristic (ROC) curve was plotted to determine the optimal cut-off value for serum albumin levels in predicting mortality.

All statistical tests were two-tailed, and a p-value of ≤0.05 was considered statistically significant. The study design, data collection, and analysis were conducted with strict adherence to the ethical guidelines to ensure the integrity and validity of the research findings.

3 Results

The study included 140 preterm neonates diagnosed with sepsis, with a median gestational age at delivery of 33.50 weeks (IQR: 3.00) and a median birth weight of 2033.50 g (IQR: 438.00). The distribution of gender was relatively balanced, with males accounting for 53.6%

(n=75) of the study population. The median APGAR score at birth was 7.00 (IQR: 1.00), and 55.7% (n=78) of the neonates received antenatal corticosteroids. Vaginal delivery was the predominant mode of delivery, observed in 72.1% (n=101) of the cases.

Table I presents the characteristics of the study population stratified by the presence of hypoalbuminemia. Of the total neonates, 57 (40.7%) were identified with hypoalbuminemia, defined as a serum albumin level of less than 2.5 g/L. The median serum albumin level in the hypoalbuminemia group was significantly lower at 2.30 g/L (IQR: 0.30) compared to 3.10 g/L (IQR: 0.50) in those without hypoalbuminemia (p<0.001). Mortality was significantly higher in the hypoalbuminemia group, with 49.1% (n=28) of these neonates succumbing to sepsis, compared to only 9.6% (n=8) in the non-hypoalbuminemia group (p<0.001).

Table 1: Patient Characteristics and Study Outcomes Stratified by Hypoalbuminemia

Variable	Hypoalbuminemia Present (n=57)	Hypoalbuminemia Absent (n=83)	p-value
Gestational age (weeks)	33.00 (IQR: 2.00)	34.00 (IQR: 3.00)	0.324
Gender			
Males	32 (56.1%)	43 (51.8%)	0.614
Females	25 (43.9%)	40 (48.2%)	
Birth-Weight (g)	2019.00 (IQR: 413.00)	2043.00 (IQR: 442.00)	0.314
APGAR Score at Birth	7.00 (IQR: 1.00)	7.00 (IQR: 1.00)	0.457
Antenatal Steroid Exposure	34 (59.6%)	44 (53.0%)	0.437
Mode of Delivery			
Vaginal Delivery	41 (71.9%)	60 (72.3%)	0.963
Caesarean Section	16 (28.1%)	23 (27.7%)	
Serum Albumin (g/L)	2.30 (IQR: 0.30)	3.10 (IQR: 0.50)	<0.001
Mortality	28 (49.1%)	8 (9.6%)	<0.001

Table II displays the 2x2 contingency table for hypoalbuminemia in predicting mortality among preterm neonates with sepsis. Hypoalbuminemia demonstrated a sensitivity of 77.78% and a specificity of 72.12% for predicting mortality. The positive predictive value was 49.12%, while the negative predictive value was 90.36%, resulting in an overall diagnostic accuracy of 73.57%.

Table 2: 2x2 Contingency Table for Serum Albumin in Predicting Mortality in Neonatal Sepsis

Outcome	Mortality Present (n=36)	Mortality Absent (n=104)	Total
Hypoalbuminemia Present (<2.5 g/L)	28 (True Positive)	29 (False Positive)	57
Hypoalbuminemia Absent (≥2.5 g/L)	8 (False Negative)	75 (True Negative)	83
Total	36	104	140

Table III summarizes the test characteristics of hypoalbuminemia for predicting mortality in this cohort. The ROC curve analysis determined that the optimal cut-off value for serum albumin was 2.45 g/L, yielding a sensitivity of 73.1% and a specificity of 77.8%.

Table 3: Diagnostic Performance of Serum Albumin in Predicting Mortality

Test Parameter	Value
Sensitivity	77.78%
Specificity	72.12%
Positive Predictive Value	49.12%
Negative Predictive Value	90.36%
Diagnostic Accuracy	73.57%

These findings indicate that hypoalbuminemia is a significant predictor of mortality in preterm neonates with sepsis, demonstrating reasonable diagnostic accuracy. The association between low serum albumin levels and increased mortality risk underscores the potential utility of hypoalbuminemia as a prognostic marker in this vulnerable population.

4 Discussion

The findings of this study provide valuable insights into the prognostic significance of hypoalbuminemia in preterm neonates with sepsis. Hypoalbuminemia was found to be prevalent in this cohort, affecting 40.7% of the neonates, and was significantly associated with an increased risk of mortality. This relationship underscores the potential of serum albumin levels as a prognostic marker in the management of neonatal sepsis, particularly in preterm infants who are already at heightened risk due to their underdeveloped immune systems.

Previous studies have similarly highlighted the prevalence of hypoalbuminemia in neonates, though the reported frequencies vary depending on the population studied and the specific conditions of the neonates. For instance, Akram et al. found a higher prevalence of hypoalbuminemia in their study, with 68.8% of neonates affected, which they attributed to the critical nature of the neonatal intensive care unit population they studied (14). In contrast, Watchko et al. reported a lower prevalence of 29%, which could be due to differences in the gestational ages and underlying conditions of the neonates in their cohort (15). The variation in prevalence across studies suggests that while hypoalbuminemia is common in neonates with sepsis, its occurrence may be influenced by multiple factors, including gestational age, birth weight, and the presence of comorbidities.

The association between hypoalbuminemia and mortality observed in this study aligns with the findings of other researchers who have also reported a significant relationship between low serum albumin levels and adverse outcomes in neonates. For example, Yang et al. demonstrated that hypoalbuminemia was progressively more common in neonates with increasing severity of infection and was associated with an elevated risk of mortality and other severe complications (17). Similarly, Torer et al. found that serum albumin levels below 2.72 g/L were associated with an increased risk of mortality, with a sensitivity of 71.0% and a specificity of 86.0% for predicting death (18). These studies, along with the current findings, suggest that hypoalbuminemia may serve as a useful biomarker for identifying neonates at higher risk of mortality, particularly in the context of sepsis.

The diagnostic performance of serum albumin in predicting mortality, as evidenced by the sensitivity of 77.78% and specificity of 72.12%, is noteworthy. While these values indicate a reasonable level of accuracy, they also highlight the need for caution in relying solely on serum albumin levels for clinical decision-making. The positive predictive value of 49.12% suggests that while hypoalbuminemia is a significant risk factor, not all neonates with low serum albumin will succumb to sepsis. This finding underscores the importance of considering hypoalbuminemia as part of a broader clinical assessment that includes other risk factors and clinical indicators.

Despite the strengths of this study, including its rigorous methodology and the inclusion of a well-defined cohort of preterm neonates with sepsis, several limitations should be acknowledged. The study was conducted at a single center, which may limit the generalizability of the findings to other populations with different demographic and clinical characteristics. Additionally, while the study accounted for several important variables, other potential confounders, such as the severity of sepsis and the presence of additional comorbidities, were not fully controlled for, which could influence the outcomes. The sample size, although adequate for the analyses performed, may have limited the ability to detect smaller effect sizes or to explore the interaction between hypoalbuminemia and other clinical factors in greater detail.

Future research should aim to validate these findings in larger, multicenter cohorts to enhance the generalizability of the results and to explore the mechanistic pathways linking hypoalbuminemia to increased mortality in neonatal sepsis. Studies that incorporate a broader range of clinical and laboratory variables may also help to refine the prognostic models and improve the accuracy of risk stratification. Additionally, research into the potential benefits of therapeutic interventions aimed at correcting hypoalbuminemia could provide important insights into whether improving serum albumin levels could translate into better clinical outcomes for these high-risk neonates.

In conclusion, this study provides evidence supporting the utility of hypoalbuminemia as a prognostic marker for mortality in preterm neonates with sepsis. The findings highlight the importance of monitoring serum albumin levels in this vulnerable population and suggest that hypoalbuminemia could be incorporated into existing risk stratification tools to improve early identification of neonates at heightened risk of adverse outcomes. However, further research is needed to validate these findings and to explore the potential for therapeutic interventions to mitigate the risks associated with hypoalbuminemia in neonatal sepsis.

5 Conclusion

In conclusion, this study provides significant evidence supporting the role of hypoalbuminemia as a reliable predictor of mortality in preterm neonates suffering from sepsis. The findings highlight the high prevalence of hypoalbuminemia in this vulnerable population and its strong association with increased mortality risk. With a sensitivity of 77.78% and a specificity of 72.12%, serum albumin levels offer a valuable diagnostic tool for early risk stratification, enabling clinicians to identify neonates at heightened risk and potentially guiding more aggressive therapeutic interventions. While the diagnostic accuracy of hypoalbuminemia underscores its utility, it is important to acknowledge the need for further research to validate these findings in larger, multicenter studies and to explore the potential for hypoalbuminemia correction as a therapeutic strategy. Additionally, integrating serum albumin levels into existing clinical scoring systems could enhance the precision of neonatal care, ultimately improving outcomes in this high-risk group. The study also emphasizes the importance of a holistic clinical assessment that considers multiple factors, including hypoalbuminemia, in the management of neonatal sepsis, advocating for a multifaceted approach to care that addresses the complex needs of preterm infants.

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