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Original Research Article

CORD BLOOD ALBUMIN AS A PREDICTIVE BIOMARKER FOR NEONATAL HYPERBILIRUBINEMIA: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Neonatal jaundice, caused by elevated bilirubin levels, affects 60–80% of newborns, with severe hyperbilirubinemia risking kernicterus and neurological damage. Early prediction is critical, and cord blood albumin (CBA) has emerged as a potential biomarker due to its role in bilirubin transport.

Materials and Methods: This prospective observational study included 98 late preterm and term neonates (gestational age ≥34 weeks). CBA levels were measured at birth and categorized: Group A (<2.5 g/dL), Group B (2.6–3.5 g/dL), and Group C (>3.6 g/dL). Serum bilirubin was assessed at 72 hours, and phototherapy need was recorded. Statistical analysis used Fisher's exact test, ROC curves, and Youden's Index.

Results: 26.5% of neonates had low CBA (<2.5 g/dL), correlating with higher bilirubin levels 28.5% required phototherapy, predominantly in Group A. ROC analysis showed 80.76% sensitivity, 94.44% specificity, and AUC 0.385 (Youden's Index: 0.752). CBA <3 g/dL predicted hyperbilirubinemia (PPV: 84%, NPV: 93%).

Conclusion: Low CBA levels (<3 g/dL) are a strong predictor of neonatal hyperbilirubinemia, enabling early intervention. Routine CBA screening could optimize postnatal care and reduce severe outcomes.

Keywords: Neonatal jaundice, cord blood albumin, hyperbilirubinemia, kernicterus, phototherapy, bilirubin prediction.

INTRODUCTION

Jaundice originates from the French word jaune, meaning yellow. It manifests as a yellowish discoloration in the skin, sclera, and mucous membranes due to elevated bilirubin levels in the bloodstream.[1] Neonatal jaundice, characterized by yellowish skin discoloration, occurs commonly in newborns due to elevated bilirubin levels.[2,3] This condition arises due to elevated levels of bilirubin, a by- product of the breakdown of red blood cells. In the neonatal period, jaundice is typically benign and self-limiting; however, if not adequately monitored and managed, it can progress to severe hyperbilirubinemia. Severe hyperbilirubinemia can lead to acute bilirubin encephalopathy and kernicterus, which are associated with permanent neurological damage and, in extreme cases, death.[3]

Bilirubin is produced from the breakdown of fetal hemoglobin in the reticuloendothelial system. In newborns, bilirubin metabolism—which includes production, liver uptake, conjugation, and excretion—is often impaired due to immature liver function. Specifically, the enzyme UGT1A1, responsible for converting bilirubin into a water-soluble form for excretion, is underdeveloped. This immaturity leads to elevated levels of unconjugated (lipophilic) bilirubin, which can cross the blood-

brain barrier and cause neurotoxicity. While the placenta clears bilirubin before birth, the newborn's liver must assume this role after delivery, increasing the risk of hyperbilirubinemia.[4,5]

Approximately 60-80% of term infants develop jaundice in the first week of life. It is one of the most common reasons for hospital readmission during this period. The incidence is higher among preterm infants, affecting up to 85% of them in the first week. Prematurity often correlates with increased susceptibility to jaundice due to factors like immature liver function and increased red blood cell breakdown.[3,4] In term infants, TSB levels above 5 mg/dL within the first 24 hours, 10-12 mg/dL by the second to the third day, and 15 mg/dL at any time during the first week are considered significant and may require treatment.[4]

Several factors contribute to the risk of developing neonatal jaundice. These include prematurity, low birth weight, breastfeeding difficulties, dehydration, and genetic conditions such as G6PD deficiency. Infants of East Asian or Mediterranean descent are also at higher risk. Other maternal and perinatal factors, such as maternal diabetes, use of oxytocin during labor, and blood group incompatibilities (e.g., ABO or Rh incompatibility), can also predispose neonates to jaundice.

Neonatal jaundice risk is influenced by factors such as prematurity, low birth weight, dehydration, breastfeeding challenges, and genetic conditions like G6PD deficiency. Infants of East Asian or Mediterranean descent and those with maternal conditions like diabetes, oxytocin use, or blood group incompatibility are also at increased risk. Early prediction of hyperbilirubinemia is crucial for timely intervention. While current methods involve monitoring total serum bilirubin (TSB) and using nomograms, more accurate early biomarkers are needed. Prompt detection enables effective phototherapy, preventing severe outcomes like kernicterus and long-term neurological damage.[6]

Cord blood albumin (CBA) plays a crucial role in the pathophysiology and prediction of neonatal hyperbilirubinemia. Synthesized in the liver, albumin is a carrier protein for bilirubin, binding to unconjugated bilirubin and aiding in its transport. This binding process reduces the potential toxicity of bilirubin to tissues and competes with tissue binding sites, thereby influencing the severity and duration of jaundice in newborns.[4,7]

Cord blood albumin levels are categorized to assess the risk of neonatal hyperbilirubinemia. Levels below 2.5 g/dL indicate a high risk, often reflecting poor liver function or nutritional status, and typically require close monitoring and possible phototherapy. Levels between 2.5–3.5 g/dL suggest a moderate risk, with an increased likelihood of jaundice and need for treatment compared to higher levels. Levels above 3.5 g/dL are considered normal and are associated with a low risk of hyperbilirubinemia, indicating better bilirubin-binding capacity and healthier liver function in newborns. These classifications help clinicians predict which neonates might develop hyperbilirubinemia and allow timely interventions to prevent severe complications.[8-10]

Research focusing on CBA aims to explore its predictive value in identifying neonates at risk of developing significant hyperbilirubinemia, which can lead to complications such as kernicterus if untreated. Kernicterus, characterized by bilirubin deposition in the brain, can result in long-term neurological impairments. Therefore, early identification of at-risk infants through markers like CBA is critical for initiating timely interventions such as phototherapy or exchange transfusion, effectively reducing bilirubin levels and mitigating kernicterus risk.

MATERIALS AND METHODS

This prospective observational analytical study was conducted over eighteen months in the Neonatal Intensive Care Unit and postnatal ward of the Department of Pediatrics at Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan. The study included late preterm (34–37 weeks) and term neonates (37–42 weeks) who met specific inclusion criteria such as gestational age over 34 weeks, birth weight above 2 kg, and an APGAR score ≥7 at one minute. Exclusion criteria included Rh and ABO incompatibility, neonatal sepsis, birth asphyxia, instrumental delivery, meconium-stained amniotic fluid, pathological jaundice, NICU admissions (beyond observation), major congenital anomalies, or denial of consent. Based on assumptions of 85% sensitivity and specificity with 95% confidence and 80% power, the calculated minimum sample size was 98, adjusted to 104 considering a 5% dropout rate. Cord blood samples were collected immediately after birth to measure albumin levels. Newborns were monitored daily for jaundice using the Krammer index and had serum bilirubin measured at 72 hours or earlier if clinical jaundice was suspected. Babies with bilirubin ≥12 mg/dl were followed clinically, treated according to NICU protocols, and monitored until discharge or the seventh day of life. Those discharged earlier were recalled for follow-up. Maternal and neonatal details were recorded, and all laboratory investigations were carried out at the institute's hematology and biochemistry departments. Data were analyzed using descriptive statistics, Pearson's correlation, and ROC analysis. A p-value <0.05 was considered statistically significant, and data analysis was performed using Microsoft Office and SPSS software.

RESULTS

Table 1: Number of Studied Neonates

S. No.	Final Studied Neonates	Numbers
1.	No. of Neonates Estimated with Cord Albumin,	168
2.	No. of Neonates Lost to Follow-Up/Excluded	70
3.	No. of Neonates Included in the Study	98

Table 2: Distribution of Participants According to Cord Blood Albumin Levels(N=98)

S. No.	Cord Blood Albumin Levels	Numbers
1.	Group A (<2.5 g/dl)	26 (26.5 %)
2.	Group B (2.6-3.5 g/dl)	40 (40.8 %)
3.	Group C (>3.6 g/dl)	32 (32.65 %)

The table presents the distribution of participants based on cord blood albumin levels. The largest group, comprising 40.8% of participants, had albumin levels between 2.6-3.5 g/dl (Group B). A smaller proportion (32.65%) had levels greater than 3.6 g/dl (Group C), while 26.5% of participants had albumin levels below 2.5 g/dl (Group A). This shows that most participants had cord blood albumin levels within the 2.6-3.5 g/dl range.

Table 3: Distribution of Serum Bilirubin Levels at 72 Hrs. Of Age Among Participants(N=98)

S. No.	Serum Bilirubin Level at 72 hrs. of age	Numbers
1.	<10 mg/dl	68 (69.3 %)
2.	10-15 mg/dl	18 (18.3 %)
3.	15-20 mg/dl	10 (10.2 %)
4.	>20 mg/dl	2 (2.04 %)

The table shows the distribution of serum bilirubin levels at 72 hours of age among participants. The majority (69.3%) had bilirubin levels below 10 mg/dl, while 18.3% had levels between 10-15 mg/dl. A smaller proportion had levels between 15-20 mg/dl (10.2%), and only 2.04% had levels exceeding 20 mg/dl. This indicates that most participants had lower bilirubin levels at 72 hours.

Table 4: Need for Phototherapy among the Participants(N=98)

S. No.	Phototherapy requirement	Number
1.	Phototherapy Required	28 (28.5 %)
2.	Phototherapy not Required	70 (71.4 %)

The table indicates the need for phototherapy among participants. A majority, 71.4%, did not require phototherapy, while 28.5% of participants needed it. This shows that less than one-third of the participants required phototherapy for managing elevated bilirubin levels.

Table 5: Correlation of Cord Blood Albumin Levels with Serum Bilirubin Levels at 72 Hrs. Of Birth(N=98)

S. No.	Serum bilirubin levels at 72 hrs. of birth	Group A (N=26)	Group B (N=40)	Group C (N=32)
1.	<10 mg/dl	1(1.02 %)	35 (35.7 %)	32 (32.6 %)
2.	10-15 mg/dl	13 (13.2 %)	5 (5.1 %)	0
3.	15-20 mg/dl	10 (10.2 %)	0	0
4.	>20 mg/dl	2 (2.04 %)	0	0

The Fisher's exact test for the correlation between cord blood albumin levels and serum bilirubin levels at 72 hours resulted in an odds ratio of infinity, indicating a very strong association between low cord blood albumin levels and elevated serum bilirubin levels (>15 mg/dl). The p-value is 1.19×10−81.19 \times 10^ {-8}1.19×10−8, suggesting this correlation is highly statistically significant. This means that the odds of developing high bilirubin levels are significantly higher in Group A compared to Groups B and C.

Table 6: Distribution of Participants as Per the Cut-Off Value of Cord Blood Albumin

S. No.	Cord blood albumin <3 g/dl	Cord blood albumin >3 g/dl
1	30	68

Table 7: Distribution of Participants as Per the Cut-Off Value of Serum Bilirubin at 72 Hours of Age

S. No.	Serum bilirubin >12.5 mg/dl at 72 hrs. of age	Serum bilirubin <12.5 mg/dl at 72 hrs. of age
1	26	72

Table 8: Correlation of Cord blood albumin levels with Serum Bilirubin Levels

S. No.	Patient group	Number
1	CBA <3 g/dl and S. Bilirubin Levels above 12.5 mg/dl (True Positive)	21
2	CBA <3 g/dl and S. Bilirubin Levels below 12.5 mg/dl (False Negative)	5
3	CBA >3 g/dl and S. Bilirubin Levels above 12.5 mg/dl (False Positive)	4
4	CBA >3 g/dl and S. Bilirubin Levels below 12.5 mg/dl (True Negative)	68

Table 9: Two by Contingency Table for Correlation Between Cord Blood Albumin Levels with Serum Bilirubin Levels

Test status	Disease positive	Disease Negative
Test Positive	21(True Positive)	4(False Positive)
Test Negative	5(False Negative)	68(True Negative)

Calculation 1- Sensitivity

$$Sensitivity = \frac{True\ Positive}{True\ positive + False\ Negative}$$

$$Sensitivity = \frac{21}{21+5} = 80.76\ \%$$

Calculation 2- Specificity

$$Sensitivity = \frac{True\ Negative}{True\ Negative + False\ Positive}$$

$$Sensitivity = \frac{68}{68+4} = 94.4\%$$

Calculation 3- Positive Predictive Value

$$PPV = \frac{True\ Positive}{True\ Positive + False\ Positive}$$

$$PPV = \frac{21}{21+4} = 84\ \%$$

Calculation 4- Negative Predictive Value

$$NPV = \frac{True\ Negative}{True\ negative + False\ Negative}$$

$$NPV = \frac{68}{68+5} = 93.1\ \%$$

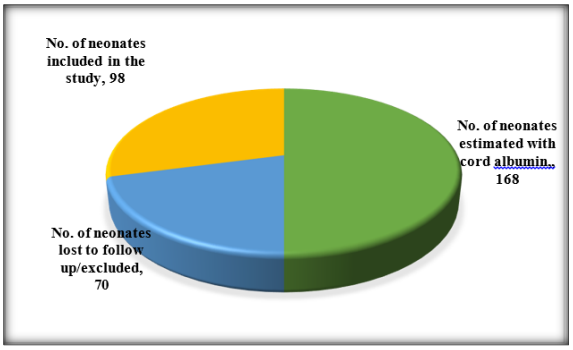

Figure 1: Number of Studied Neonates

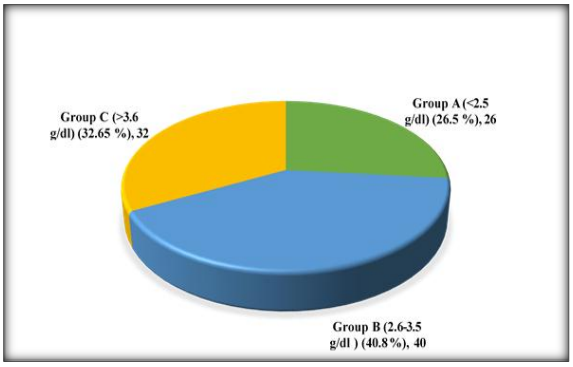

Figure 2: Distribution of Participants As Per Cord Blood Albumin Levels

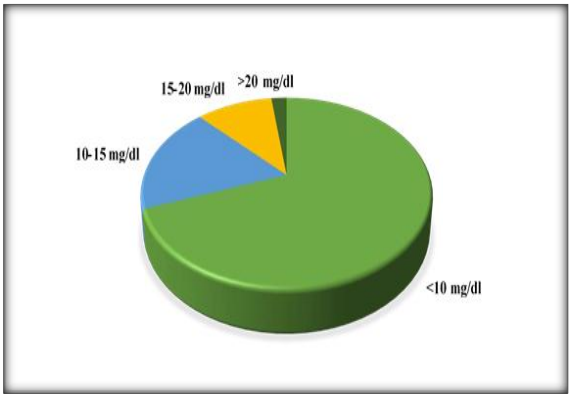

Figure 3: Distribution of Serum Biliirubin

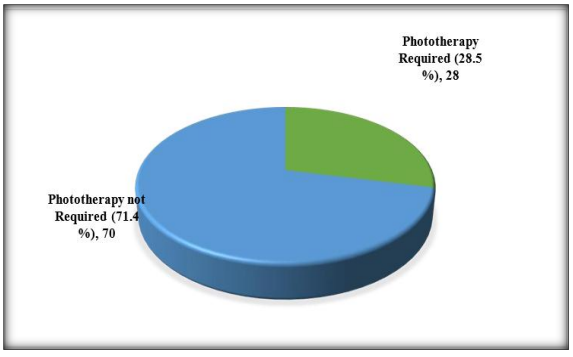

Figure 4: Requirement of Phtotherapy Among the Participants

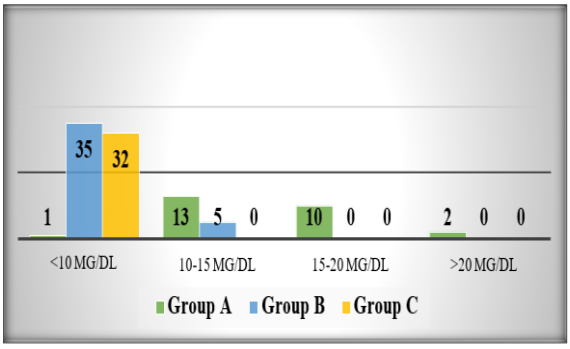

Figure 5: Correlation of Cord Blood Albumin Levels with Serum Bilirubin Levels

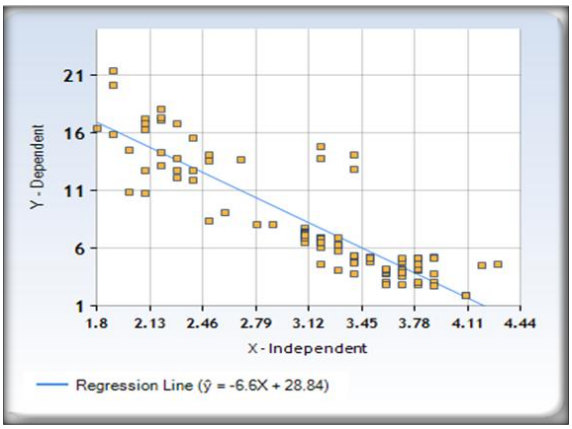

Figure 6: Scatter Diagram of Correlation of Cord Blood Albumin and Serum Bilirubin at 72 Hours' Age

Receiver opening characteristic curve

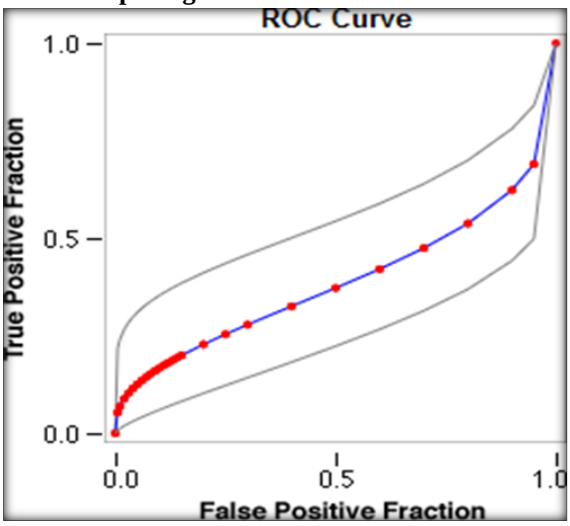

Figure 7: ROC Analysis

RED symbols and BLUE line: Fitted ROC curve.
GRAY lines: 95% confidence interval of the fitted ROC curve Area under curve=0.385

Youden's Index Formula

Youden's Index=Sensitivity+Specificity−1

Substituting the values

Youden's Index=0.8076+0.944−1

Calculation

Youden's Index=1.7516−1=0.7516

The Youden's Index for the given results is approximately 0.752. Interpretation:

A Youden's Index of 0.752 indicates that the estimation of cord blood albumin has a good balance of sensitivity and specificity. The value suggests that the test effectively identifies both true positives and negatives, making it a reliable diagnostic tool for the condition being tested.

DISCUSSION

The present study reported a mean cord blood albumin level of 3.12 gm/dl, which closely aligns with findings from several previous studies. For instance, Maisels MJ et al,[11] (1986) and Bhutani VK et al,[12] (1999) both reported mean levels of 3.2 gm/dl, while Seidman DS et al,[13] (1995) observed a slightly higher level of 3.3 gm/dl. Similarly, Sarici SU et al,[14] (2004) found a slightly lower mean of 3.1 gm/dl. These findings collectively suggest a consistent range of cord blood albumin levels across different studies, with only minor variations.

The analysis of multiple studies comparing the predictive accuracy of cord blood albumin (CBA) levels in identifying neonates at risk of developing significant hyperbilirubinemia reveals consistent and promising findings. The sensitivity values across studies ranged from 72% to 85%, indicating that a considerable proportion of at-risk neonates could be correctly identified using CBA as a predictive tool. Sarici et al,[14] (2004) reported a sensitivity of 72% and a specificity of 79%, suggesting moderate predictive ability, while Alpay et al,[15] (2007) reported balanced sensitivity and specificity values (77%/81% and 77%/88% respectively), suggesting stronger diagnostic value. Notably, Alpay et al.'s study also demonstrated a relatively high PPV of 69% and NPV of 88%, indicating both a good capacity to identify true positives and to rule out those not at risk. Taksande et al,[16] (2012) showed sensitivity and specificity values of 78.2% and 77.5%, respectively, with a PPV of 72.6% and NPV of 82.5%, reinforcing the utility of cord albumin in a clinical setting.

These findings underline the robustness of cord blood albumin as a predictive biomarker, particularly due to its high negative predictive value, which allows clinicians to confidently identify neonates who are unlikely to develop significant hyperbilirubinemia. Such predictive reliability makes it an effective tool for guiding early discharge decisions and ensuring timely interventions to prevent bilirubin-related complications like kernicterus. Overall, this comparison across multiple studies confirms that while slight variations exist, cord blood albumin consistently demonstrates strong predictive performance, and its implementation in clinical protocols could enhance neonatal care outcomes. However differences may be due to variations in sample size, demographic factors, clinical settings, or analytical techniques used in each study. Overall, the present study's findings contribute further evidence to the stability of cord blood albumin levels in neonates.

CONCLUSION

This study highlights the significant predictive role of cord blood albumin (CBA) in neonatal hyperbilirubinemia. Neonates with CBA levels <2.5 g/dL had a markedly higher risk of severe hyperbilirubinemia, while those with levels >3.6 g/dL were at minimal risk. The strong inverse correlation between CBA and serum bilirubin, along with high diagnostic accuracy (Youden's Index = 0.752), supports CBA as a cost-effective, early biomarker for identifying at-risk infants. Incorporating routine CBA screening into postnatal care could enhance early detection, guide phototherapy decisions, and prevent complications like kernicterus. Future studies with larger cohorts could further validate these findings and refine risk stratification protocols.

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