International Medicine
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Research Article

Section: Paediatrics

Diagnostic Accuracy of Cord Blood Albumin in Predicting Neonatal Hyperbilirubinemia: A Statistical Evaluation

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ARTICLE INFO

Article History:

Received: 06-01-2025

Accepted: 15-02-2025

Key words:

Neonatal Hyperbilirubinemia
Cord Blood Albumin
ROC Curve Analysis
Phototherapy
Neonatal Jaundice
Bilirubin
Risk stratification
Early Detection.

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ABSTRACT

Aim: This study evaluated the diagnostic accuracy of cord blood albumin (CBA) in predicting neonatal hyperbilirubinemia using ROC analysis and identified an optimal CBA threshold for early risk stratification and phototherapy intervention in term newborns. **Introduction:** Neonatal jaundice affects 60% of term and 80% of preterm newborns, with severe cases risking kernicterus if undetected. Early discharge increases the risk of missed hyperbilirubinemia, especially in low-resource settings. CBA is a potential biomarker for early jaundice prediction, aiding in timely intervention and follow-up. However, variability in CBA cutoff values raises concerns about its diagnostic accuracy, sensitivity, and specificity. **Methods:** This prospective observational study was conducted at Jagannath Gupta Institute of Medical Sciences and Hospital, Kolkata, over 18 months (July 2022 – December 2023). Eighty term newborns meeting the inclusion criteria were enrolled. CBA levels were measured at birth, and TSB was assessed at 72 hours. The need for PT was determined using AAP guidelines. SPSS version 26 was used for statistical analysis, and ROC curve analysis identified the optimal CBA cutoff for predicting NNH requiring intervention.**Results:** Among 80 newborns, 13 (16.25%) developed jaundice requiring phototherapy, while none needed exchange transfusion. CBA ≤2.8 g/dL had an 81.8% jaundice risk, whereas CBA ≥3.4 g/dL had none. A negative correlation ($r = -0.41$, $p < 0.00001$) confirmed lower CBA predicted higher bilirubin. ROC analysis identified CBA ≤2.9 g/dL as the best cutoff (87.5% sensitivity, 89.07% specificity).**Conclusion:** CBA ≤2.9 g/dL predicts neonatal jaundice, while CBA ≥3.4 g/dL indicates minimal risk. Measuring CBA at birth enables early detection and intervention, improving neonatal care, especially in resource-limited settings. Routine CBA screening can enhance management, but larger studies are needed to standardize thresholds for universal screening.

INTRODUCTION

Neonatal jaundice, or neonatal hyperbilirubinemia (NNH), is one of the most common clinical conditions affecting newborns, particularly in the first week of life. It is characterized by elevated levels of serum bilirubin, leading to yellow discoloration of the skin, sclera, and mucous membranes. Although physiological jaundice is a normal transitional process due to immature hepatic function and increased red blood cell turnover, some neonates develop pathological jaundice, which requires timely intervention to prevent bilirubin-induced neurological dysfunction (BIND) and kernicterus [1].

The global incidence of neonatal jaundice varies significantly based on genetic, ethnic, and environmental factors. Approximately 60% of term newborns and 80% of preterm infants experience some degree of jaundice within the first postnatal week [2]. In most cases, jaundice is benign and resolves without treatment. However, in about 10–15% of neonates, the serum bilirubin levels rise excessively, necessitating medical interventions such as phototherapy and, in severe cases, exchange transfusion [3]. Failure to detect and manage neonatal jaundice in a timely manner may result in severe complications such as acute bilirubin encephalopathy (ABE) or its chronic form, kernicterus, which leads to permanent neurological impairment, including cerebral palsy, sensorineural hearing loss, and cognitive disabilities [4].

Despite significant advances in neonatal care, early hospital discharge practices have increased the risk of missed diagnoses of NNH, especially in low-resource settings where routine post-discharge bilirubin monitoring is often inadequate [5]. The American Academy of Pediatrics (AAP) recommends that all newborns discharged within 48 hours undergo a follow-up bilirubin evaluation within 48–72 [6]. However, logistical, socioeconomic, and healthcare accessibility challenges prevent many parents from returning for scheduled follow-up visits, resulting in delayed diagnosis and treatment[7]. Therefore, there is an urgent need for early, cost-effective, and reliable screening tools to identify newborns at risk for hyperbilirubinemia at the time of birth.

Several risk factors have been associated with an increased likelihood of neonatal hyperbilirubinemia, including prematurity, exclusive breastfeeding with inadequate intake, hemolytic diseases such as ABO and Rh incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, sepsis, cephalohematoma, and maternal diabetes[8]. Among these, the role of serum albumin has gained attention due to its ability to bind free bilirubin in circulation, preventing its toxic effects on the neonatal brain[9]. Albumin acts as a carrier protein for bilirubin, limiting its diffusion across the blood-brain barrier. Hence, low levels of albumin may increase the risk of bilirubin-induced neurotoxicity[10].

Cord blood albumin (CBA) has been proposed as an early biomarker for identifying neonates at risk of developing significant hyperbilirubinemia[11]. The rationale behind this approach is that lower CBA levels may indicate a reduced capacity for bilirubin binding, making newborns more susceptible to excessive bilirubin accumulation. Several studies have demonstrated a strong correlation between low CBA levels and increased serum bilirubin levels during the first 72–96 hours of life, suggesting that CBA measurement at birth could serve as a predictive tool for neonatal jaundice [12,13].

However, despite promising results, the clinical utility of CBA in routine neonatal screening remains controversial. While some studies have reported high sensitivity and specificity for different CBA cutoff values, others have found significant variability in predictive accuracy[14]. For instance, some researchers have proposed that CBA ≤2.8 g/dL serves as an effective threshold for predicting neonates requiring phototherapy, while others suggest higher or lower cutoff values depending on population characteristics[15].

Although cord blood albumin (CBA) is a widely studied predictor of neonatal hyperbilirubinemia (NNH), its diagnostic accuracy remains uncertain due to inconsistent sensitivity, specificity, and cutoff values. An ideal screening tool must offer high sensitivity to detect at-risk newborns while maintaining adequate specificity to minimize unnecessary interventions. Receiver Operating Charac-teristic (ROC) curve analysis is commonly used to determine the optimal CBA cutoff, ensuring effective early detection with minimal false positives[15]. This study evaluates CBA's diagnostic accuracy, establishing a clinically relevant threshold to improve risk stratification, reduce readmissions, and enhance neonatal care, especially in resource-limited settings.

MATERIAL AND METHODS

This prospective observational study was conducted over 18 months (July 2022 – December 2023) at Jagannath Gupta Institute of Medical Sciences and Hospital, Kolkata, with ethical approval obtained to assess the diagnostic accuracy of cord blood albumin (CBA) in predicting neonatal hype rbilirubinemia (NNH) using Receiver Operating Characteristic (ROC) curve analysis. The study included 80 term newborns based on criteria such as gestational age ≥37 weeks, birth weight ≥2.5 kg, Apgar score ≥7 at 1 and 5 minutes, and parental consent. Newborns with Rh/ABO incompatibility, birth asphyxia, assisted deliveries (forceps /vacuum), congenital anomalies, neonatal sepsis, G6PD deficiency, or maternal diabetes were excluded. Cord blood samples were analyzed for CBA levels using a semi-auto analyzer (CHOD-PAP method), while total serum bilirubin (TSB) levels were measured at 72 hours. Newborns were monitored for jaundice over 72–96 hours, with treatment decisions based on AAP guidelines for phototherapy (PT) or exchange transfusion (ET).

Newborns were classified into three groups based on CBA levels: Group A (≤2.8 g/dL), Group B (2.9–3.3 g/dL), and Group C (≥3.4 g/dL). Statistical analysis was conducted using SPSS version 26, employing Chi-square tests for associations, Student's t-test and ANOVA for group comparisons, and Pearson correlation analysis to evaluate the relationship between CBA and TSB levels. ROC curve analysis determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CBA, with the Youden Index identifying the optimal CBA cutoff. Ethical approval was granted by the Institutional Ethics Committee, and parental informed consent was obtained in accordance with the Declaration of Helsinki..

RESULTS

This study included 80 term newborns, of whom 43 (54%) were male and 37 (46%) were female. The mean gestational age was 38.2 weeks, with 48% born at 38 weeks, 31% at 39 weeks, and 11% at 40 weeks. The mean birth weight was 3.07 kg (SD 0.33), with 46% of newborns weighing between 3.0–3.5 kg. Regarding the mode of delivery, 61% were delivered via LSCS, while 39% were delivered via normal vaginal delivery (NVD)(Figure 1).

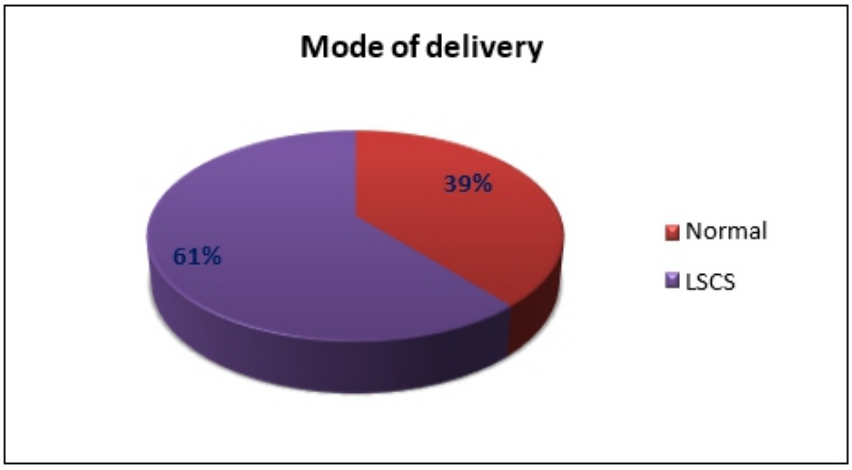

Figure 1: Pie Diagram Showing Distribution of the Newborns Based on Mode of Delivery

The mean cord blood albumin (CBA) level in this study was 3.09 g/dL (SD 0.28), with values ranging from 2.3 to 3.6 g/dL. Based on CBA levels, newborns were classified into three groups: Group A (≤2.8 g/dL) comprising 14% of the newborns, Group B (2.9–3.3 g/dL) representing 54%, and Group C (≥3.4 g/dL) making up 32% (Figure 2).

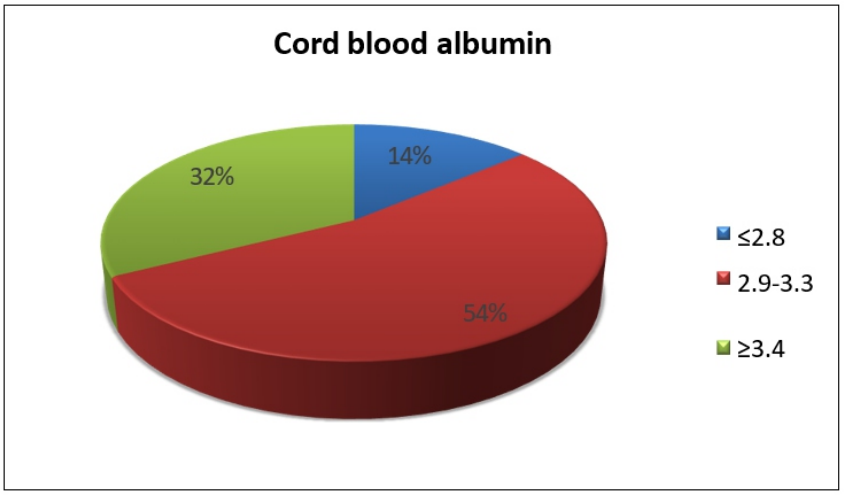

Figure 2: Pie Diagram Showing Distribution of the Newborns Based on Cord Blood Albumin

A total of 13 (16.25%) newborns developed neonatal hyperbilirubinemia (NNH) requiring phototherapy (PT), but none required exchange transfusion (ET). Among newborns in Group A (CBA ≤2.8 g/dL), 81.8% (9/11) developed NNH, while only 9.3% (4/43) of newborns in Group B (CBA . 2.9–3.3 g/dL) developed jaundice. In contrast, none of the 26 newborns in Group C (CBA ≥3.4 g/dL) developed NNH, indicating a significantly lower risk of hyperbilirubinemia in this group (Figure 3)

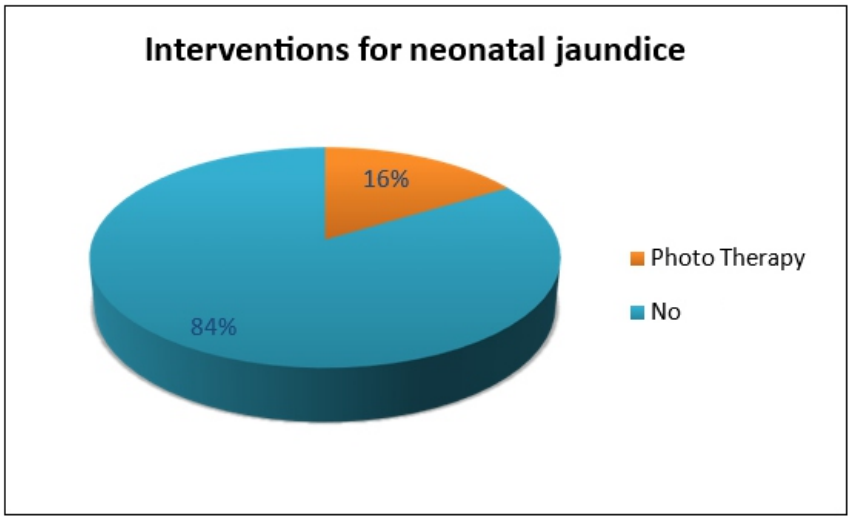

Figure 3: Pie Chart Showing Intervention Given for Neonatal Jaundice in this Study.

A negative correlation (r = -0.41, p < 0.0001) was observed between cord blood albumin (CBA) levels and total serum bilirubin (TSB) at 72 hours, indicating that lower CBA levels were associated with higher bilirubin levels (Figure 4).

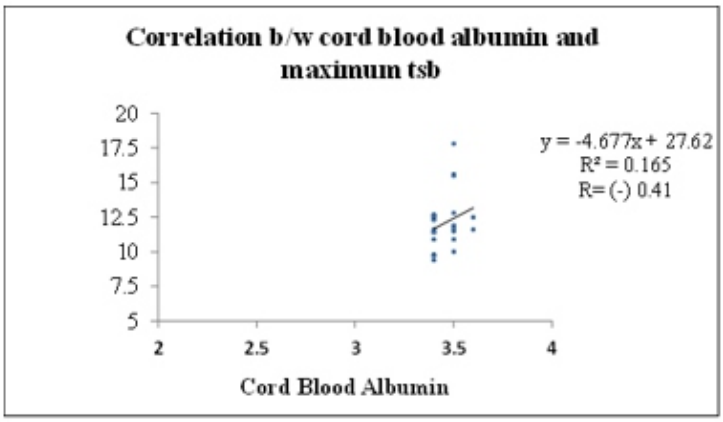

Figure 4: Correlation of Cord Blood Albumin with Total TSB (Maximum Value)

The mean TSB levels were 17.64 mg/dL (SD 1.44) in Group A (CBA ≤2.8 g/dL), 12.33 mg/dL (SD 3.35) in Group B (CBA 2.9–3.3 g/dL), and 12.16 mg/dL (SD 1.92) in Group C (CBA ≥3.4 g/dL) (Figure 5).

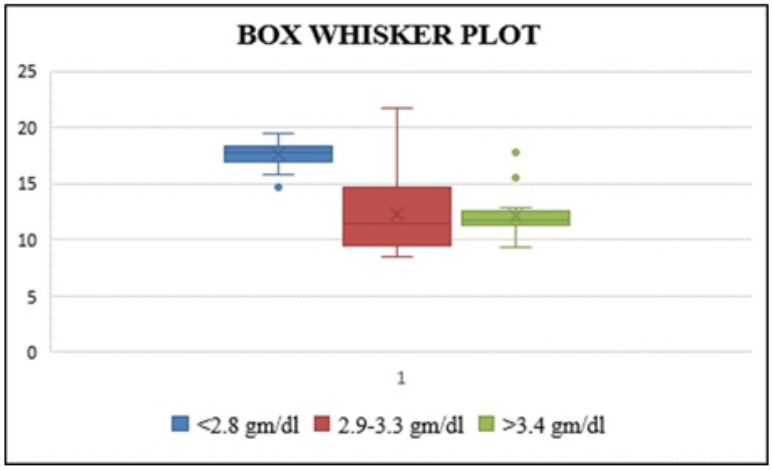

Figure 5: Distribution of TSB (Maximum) Among the Term Newborns with Different Cord Blood Albumin Groups

ANOVA analysis confirmed a statistically significant difference (p<0.001) in TSB levels among the three groups (Table 1)

Table 1: One way ANOVA test Data Summary: Comparison of Maximum Total Serum Bilirubin in Different Cord Blood Albumin Groups (> 2 Groups).

Data summary of Cord Blood Albumin Groups(gm/dl)				
	≤2.8	**2.9-3.3**	**≥3.4**	**Total**
N	11	43	26	80
ΣX	194	530.1	316.2	1040.3
Mean	17.64	12.32	12.16	13.00
ΣX^2	3442.2	7006.57	3937.78	14386.55
SD	1.44	3.35	1.92	3.29

Receiver Operating Characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of CBA in predicting NNH. The area under the ROC curve (AUC) was 0.91, indicating excellent diagnostic performance of CBA (Figure 6). The optimal CBA cutoff value for predicting neonatal jaundice was ≤2.9 g/dL, which had a sensitivity of 84.6% and specificity of 85.1%. The positive predictive value (PPV) was 72.2%, and the negative predictive value (NPV) was 92.8%, indicating that newborns with CBA ≤2.9 g/dL are at high risk of developing NNH, while those with CBA >2.9 g/dL are unlikely to develop clinically significant jaundice (Figure 6).

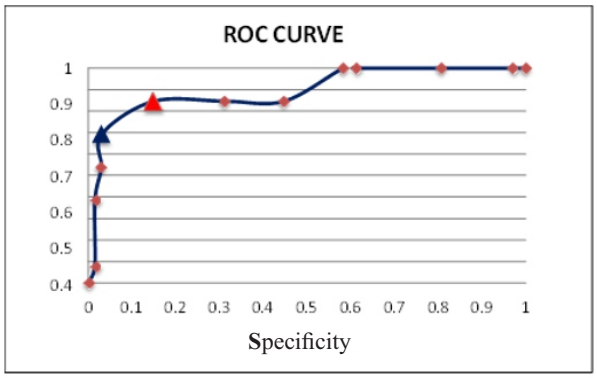

Figure 6: The ROC Curve Analysis Identifies two Optimal Cutoff Points for Cord Blood Albumin (CBA) Levels in Predicting Neonatal Jaundice Requiring Phototherapy

The blue delta point (CBA ≤2.8 g/dL) has a sensitivity of 69.2% and specificity of 97.02%, while the red delta point (CBA ≤2.9 g/dL) has a higher sensitivity (84.6%) with an acceptable specificity (85.1%). To minimize missed cases and prevent complications, CBA ≤2.9 g/dL is identified as the best cutoff value for predicting neonatal jaundice requiring intervention.

Newborns with CBA ≤2.8 g/dL had a significantly higher need for phototherapy compared to those with CBA >2.8 g/dL (69.2% vs. 3%, $p < 0.05$). The mean CBA levels among newborns who received PT were significantly lower (2.77 g/dL, SD 0.22) compared to those who did not receive PT (3.4 g/dL, SD 0.24, $p < 0.01$) (Figure 7).

Figure 7: Box Plot Showing Distribution of Cord Blood Albumin (gm/dl) Among Different Treatment Groups.

Additional ROC analysis was performed to determine the optimal CBA cutoff for identifying newborns whose TSB levels at 72–96 hours would be within 2 mg/dL of the phototherapy threshold. The best cutoff was found at ≤2.9 g/dL, with a sensitivity of 87.5% and specificity of 89.07% (Figure 8). This suggests that newborns with CBA ≤2.9 g/dL should undergo repeat bilirubin testing within 12–24 hours to prevent late detection of significant hyperbilirubinemia (Figure 8).

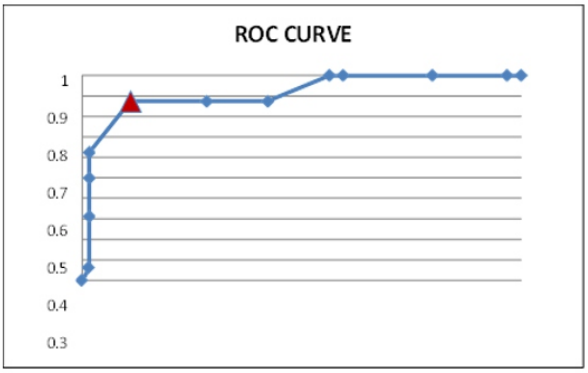

Figure 8: The ROC curve identifies the red delta point (CBA 2.9 g/dL) as the optimal threshold, with 87.5% sensitivity and 89.07% specificity for detecting TSB levels within 2 mg/dL of the phototherapy cutoff. Since this bilirubin level is close to the treatment threshold, newborns in this category require repeat TSB testing within 12–24 hours, as per AAP guidelines, to ensure early detection and timely management of neonatal jaundice.

DISCUSSION

Neonatal hyperbilirubinemia (NNH) is a common clinical condition that, if undetected or untreated, can lead to bilirubin-induced neurological dysfunction (BIND) and kernicterus. Early identification of neonates at risk of developing significant hyperbilirubinemia is crucial to prevent delayed intervention, prolonged hospitalization, and potential neurotoxicity. While cord blood albumin (CBA) levels have been studied as a predictor of neonatal jaundice, their diagnostic accuracy, optimal cutoff value, and clinical applicability remain subjects of ongoing research. This study aimed to determine the diagnostic performance of CBA using Receiver Operating Characteristic (ROC) curve analysis and establish an optimal CBA threshold for identifying neonates requiring phototherapy.

In this study, 16.25% of newborns (13/80) developed significant neonatal hyperbilirubinemia requiring phototherapy (PT), while none required exchange transfusion (ET). A negative correlation ($r = -0.41$, $p < 0.0001$) was observed between CBA and total serum bilirubin (TSB) at 72 hours, indicating that lower CBA levels were strongly associated with higher bilirubin levels. Similar findings have been reported in previous studies, where low CBA levels (<2.8 g/dL) correlated with a higher risk of hyperbilirubinemia and increased phototherapy requirements[16].

The mean TSB levels were significantly different across CBA groups, with newborns in Group A (≤2.8 g/dL) showing the highest mean TSB (17.64 mg/dL, SD 1.44) compared to Group B (12.33 mg/dL, SD 3.35) and Group C (12.16 mg/dL, SD 1.92). ANOVA analysis confirmed a statistically significant difference ($p < 0.001$) in TSB levels among the groups, reinforcing that lower CBA levels predict higher bilirubin accumulation.

The ROC curve analysis demonstrated that CBA is a strong diagnostic marker for neonatal jaundice. The optimal CBA cutoff for predicting NNH was ≤2.9 g/dL, which had a sensitivity of 84.6% and specificity of 85.1%. The positive predictive value (PPV) was 72.2%, indicating that newborns with CBA ≤2.9 g/dL had a high probability of developing significant jaundice. The negative predictive value (NPV) was 92.8%, suggesting that newborns with CBA >2.9 g/dL were unlikely to require phototherapy.

ROC Analysis Identified two key Cutoff Values Figure 6:

- CBA ≤2.8 g/dL (Blue Delta Point): 69.2% sensitivity, 97.02% specificity
- CBA ≤2.9 g/dL (Red Delta Point): 84.6% sensitivity, 85.1% specificity

Since high sensitivity is crucial in neonatal screening to avoid missing high-risk cases, CBA ≤2.9 g/dL was determined as the best predictive threshold for PT (Figure 6. This is consistent with studies by Trivedi et al. and Kumar et al., which reported similar sensitivity and specificity values for CBA in predicting neonatal hyperbilirubinemia [17,18].

Newborns with CBA ≤2.8 g/dL had a significantly higher requirement for phototherapy (69.2%) than those with CBA >2.8 g/dL (3%). Additionally, the mean CBA levels among newborns requiring PT (2.77 g/dL, SD 0.22) were significantly lower than those who did not need intervention (3.4 gm/dL, SD 0.24, $p < 0.01$) (Figure 7). These findings support the clinical utility of CBA as a risk-stratification tool to guide early discharge decisions and targeted follow-up assessments [19].

Additionally, ROC analysis identified another key threshold (CBA ≤2.9 g/dL), which had a sensitivity of 87.5% and specificity of 89.07% in detecting newborns whose TSB levels at 72–96 hours would be within 2 mg/dL of the phototherapy cutoff (Figure 8). This suggests that newborns with CBA ≤2.9 g/dL should undergo repeat bilirubin testing within 12–24 hours, as per AAP guidelines, to prevent late detection of significant jaundice requiring intervention.

Several studies have evaluated the predictive role of CBA in neonatal jaundice, with reported cutoff values ranging between 2.8–3.0 g/dL. A study by Meshram et al. (2018) found that CBA ≤2.8 g/dL had a sensitivity of 72% and specificity of 94% for predicting phototherapy requir - ements, while Shah et al. (2020) reported similar findings with CBA ≤2.9 g/dL showing the highest predictive value [20].

A meta-analysis by Harisha et al. (2019) concluded that CBA ≤2.9 g/dL had a pooled sensitivity of 82.5% and specificity of 88.3%, reinforcing the findings of the current study [21]. However, variations in cutoff values across studies may be attributed to differences in sample size, genetic and ethnic factors, and hospital discharge policies.

CONCLUSION

Neonatal hyperbilirubinemia is a common condition requiring early identification to prevent bilirubin-induced neurological dysfunction. This study confirms that cord blood albumin (CBA) levels at birth can predict neonatal jaundice risk. Newborns with CBA ≤2.8 g/dL had a significantly higher risk, while those with CBA ≥3.4 g/dL did not develop jaundice. A negative correlation between CBA and TSB at 72 hours reinforces its predictive value. CBA screening at birth could guide early discharge decisions and targeted follow-ups. Integrating CBA-based risk stratification into neonatal care can optimize management, though larger studies are needed to establish standardized thresholds.

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How to cite: Debabrata Debnath, Manas Kumar Mahapatra Joydeep Das. Diagnostic Accuracy of Cord Blood Albumin in Predicting Neonatal Hyperbilirubinemia: A Statistical Evaluation *International Medicine,* 2025; 11 (1) :1-7