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Research Article

Cord Blood Biomarkers for Predicting Significant Hyperbilirubinemia in Apparently Healthy Term Neonates: A Prospective Observational Study

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Article Info

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Abstract

Objectives: To evaluate cord blood albumin, bilirubin, bilirubin-to-albumin ratio, and alkaline phosphatase as early predictors of significant hyperbilirubinemia in apparently healthy term neonates.

Methods: In this prospective observational study, 250 apparently healthy term neonates were enrolled consecutively. Cord blood bilirubin, albumin, and alkaline phosphatase were measured at birth, and the bilirubin-to-albumin ratio was calculated. Total serum bilirubin was measured at 72–96 h. Significant hyperbilirubinemia was defined as total serum bilirubin ≥17 mg/dL. Predictive performance was evaluated using receiver operating characteristic curves.

Results: Significant hyperbilirubinemia developed in 38 (15.2%) neonates. Affected neonates had lower cord albumin and higher cord bilirubin, bilirubin-to-albumin ratio, and alkaline phosphatase (all $P < 0.001$). The respective areas under the curve were 0.909, 0.983, 0.984, and 0.906.

Conclusions: Cord blood bilirubin and the bilirubin-to-albumin ratio showed the strongest predictive performance. These markers may help identify apparently healthy term neonates who need closer surveillance. External validation of the study-derived cut-offs is required.

Keywords: Bilirubin-albumin ratio; Cord blood; Neonatal hyperbilirubinemia; Screening; Term neonates

Introduction

Neonatal hyperbilirubinemia is common during the first week of life because newborns have increased bilirubin production and immature hepatic uptake, conjugation, and excretion. Although most cases are benign, excessive unconjugated bilirubin can cause acute bilirubin encephalopathy or kernicterus and permanent neurological disability [1,2]. Timely recognition and treatment can prevent most bilirubin-related injury [2].

Risk factors such as prematurity, hemolytic disease, blood-group incompatibility, sepsis, and birth asphyxia prompt closer surveillance. However, apparently healthy term neonates without obvious risk factors may also develop significant hyperbilirubinemia. Clinical assessment of jaundice is affected by skin pigmentation, ambient lighting, and observer variation and can underestimate bilirubin levels [3]. Bilirubin levels may rise after discharge, when opportunities for observation are limited. Repeated serum measurements require blood sampling and laboratory support, which may be difficult in busy, resource-constrained settings.

A marker available at birth could help identify neonates who need closer surveillance or earlier follow-up. Cord blood can be collected without additional invasive sampling and has been studied for this purpose, particularly when early discharge is planned [4]. Cord bilirubin reflects the bilirubin level at birth, whereas albumin is the main binding protein for unconjugated bilirubin. The bilirubin-to-albumin (B/A) ratio may therefore reflect the balance between bilirubin concentration and binding capacity [5,6]. Cord alkaline phosphatase (ALP) has also been evaluated as a supplementary marker [7].

This study evaluated cord blood bilirubin, albumin, the B/A ratio, and ALP as early predictors of significant hyperbilirubinemia in apparently healthy term neonates.

Materials and Methods

This prospective observational study was conducted at Shri Dada Dev Matri Avum Shishu Chikitsalaya, New Delhi, from February to December 2021. Healthy term neonates (37 to <42 wk of gestation) with birth weight ≥2500 g and an Apgar score ≥7 at 1 min were eligible. Exclusion criteria were preterm or post-term birth, instrumental delivery, jaundice within the first 24 h, intrauterine growth restriction, Rh or ABO incompatibility, birth asphyxia, neonatal sepsis, respiratory distress syndrome, meconium-stained amniotic fluid, and major congenital anomalies. Neonates whose parents did not consent were also excluded. Eligible neonates were enrolled consecutively until the sample size of 250 was reached.

The minimum sample size was 236, based on an anticipated incidence of 19%, a 95% confidence level, and 5% absolute precision. Allowing 5% attrition yielded 249; this was rounded to 250.

At delivery, cord blood was analyzed for albumin, bilirubin, and ALP, and the B/A ratio was calculated. Total serum bilirubin (TSB) was measured at 72–96 h of postnatal life. A TSB level ≥17 mg/dL after 72 h was considered significant neonatal hyperbilirubinemia.

The study protocol was approved by the Institutional Ethics Committee of the hospital, and written informed consent was obtained from the parents. Confidentiality was maintained throughout the study.

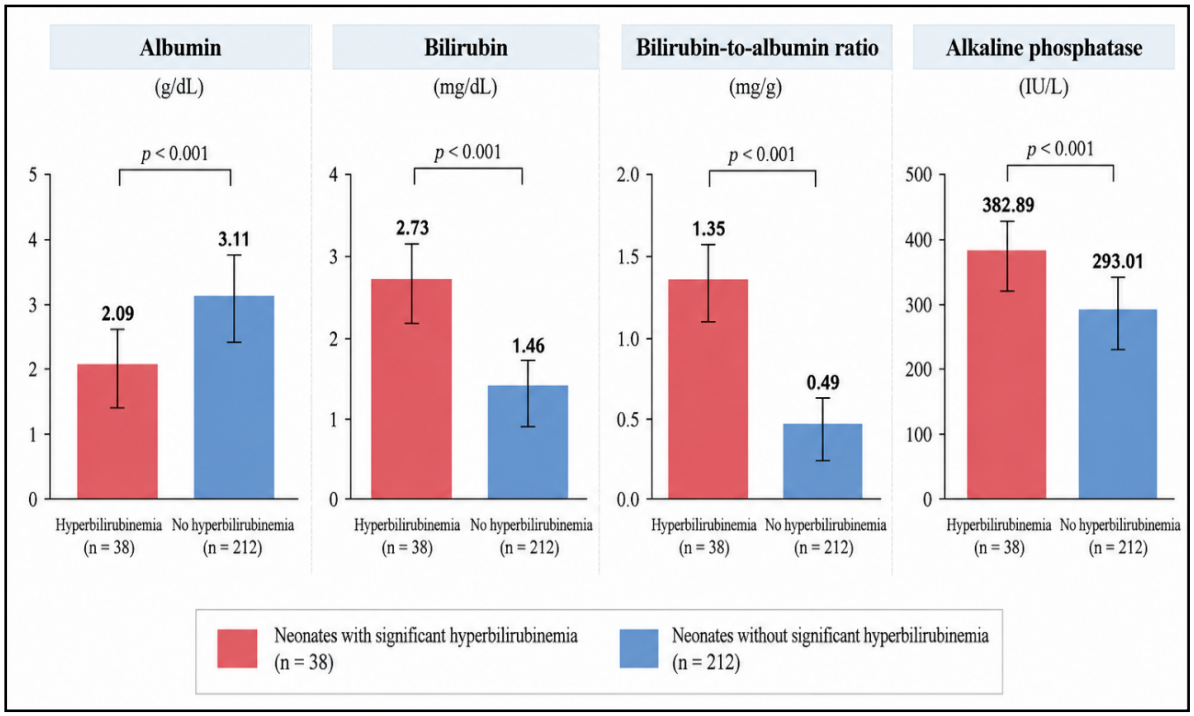
Statistical analysis: Categorical variables were expressed as counts (percentages) and continuous variables as mean ±standard deviation (SD). An unpaired Student's t test was used to compare biomarker levels between neonates with and without significant hyperbilirubinemia. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive ability of cord bilirubin, albumin, the B/A ratio, and ALP. Areas under the curve (AUCs), sensitivities, specificities, and cut-off values were calculated. A P value <0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics version 22.

Results

The study resulted that, Mean cord blood albumin, bilirubin, B/A ratio, and ALP values were 2.95 ±0.70 g/dL, 1.66 ±0.64 mg/dL, 0.63 ±0.38 mg/g, and 306.66 ±63.67 IU/L, respectively.

At 72–96 h, 38 of 250 neonates (15.2%) met the study definition of significant hyperbilirubinemia (total serum bilirubin ≥17 mg/dL). Observed Cord blood albumin was lower in affected neonates than in those without 3.11 ±0.63 g/dL; P < 0.001). Cord bilirubin (2.73 ±0.39 vs 1.46 ±0.47 mg/dL), B/A ratio (1.35 ±0.32 vs 0.49 ±0.20 mg/g), and ALP (382.89 ±34.61 vs 293.01 ±57.79 IU/L) were higher in the affected group (all P < 0.001; Fig.

Figure. 1 Comparison of cord blood biomarker levels in neonates with and without significant hyperbilirubinemia.



Bars represent mean ±standard deviation; all between-group differences were statistically significant (P < 0.001)

significant hyperbilirubinemia (2.09 ±0.35 vs 1).

ROC analysis showed similar discrimination for cord bilirubin and the B/A ratio. For cord bilirubin, a cut-off of ≥2.41 mg/dL gave 94.7% sensitivity and 98.6% specificity (AUC 0.983; 95% CI 0.960–1.000). For the B/A ratio, a cut-off of ≥1.04 mg/g gave 84.6% sensitivity and 97.6% specificity (AUC 0.984; 95% CI 0.966–1.000).

Cord albumin and ALP had AUCs of 0.909 (95% CI 0.871–0.946) and 0.906 (95% CI 0.859–0.952), respectively. Table 1 summarizes the cut-offs and predictive performance of all four biomarkers.

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Albumin	<2.46 g/dL	81.1	84.2	0.909 (0.871-0.946)
Bilirubin	≥2.41 mg/dL	94.7	98.6	0.983 (0.960-1.000)
Bilirubin-to-albumin ratio	≥1.04 mg/g	84.6	97.6	0.984 (0.966-1.000)
Alkaline phosphatase	≥356.5 IU/L	84.2	84.0	0.906 (0.859-0.952)

Table 1. Predictive performance of cord blood biomarkers

AUC, area under the receiver operating characteristic curve; CI, confidence interval

Discussion

Neonates who later develop significant hyperbilirubinemia may appear healthy at birth [2]. In busy units, early discharge can make it difficult to identify those who need closer observation. Cord blood markers may help guide follow-up and timely bilirubin measurement.

In this study, 38 of 250 term neonates with normal birth weight (15.2%) developed significant hyperbilirubinemia, defined as TSB ≥17 mg/dL at 72–96 h. This was similar to the 15.5% reported by Nahar et al. using the same bilirubin threshold [8]. Thus, a substantial proportion of neonates developed significant hyperbilirubinemia despite appearing healthy at birth.

Cord bilirubin measures the bilirubin concentration at birth, while albumin provides an indication of bilirubin-binding capacity. The B/A ratio relates these two measures. Unbound bilirubin is the fraction most closely associated with neurotoxicity, but its direct measurement is technically demanding and not widely available [5]. ALP has several neonatal tissue sources and was included as a supplementary marker.

Mean cord albumin was lower in neonates with significant hyperbilirubinemia than in those with TSB <17 mg/dL (2.09 ±0.35 vs 3.11 ±0.63 g/dL; $P < 0.001$). Lower albumin may indicate reduced bilirubin-binding capacity, and similar associations have been reported [6,9]. At a cut-off of <2.46 g/dL, cord albumin had 81.1% sensitivity, 84.2% specificity, and an AUC of 0.909. Mishra and Sanyasi Naidu reported ≤2.8 g/dL as a useful level [9]. Differences in analytical methods, sample size, and study populations may explain the lower cut-off in our cohort.

Mean cord bilirubin was higher in neonates with significant hyperbilirubinemia than in those with TSB <17 mg/dL (2.73 ±0.39 vs 1.46 ±0.47 mg/dL; $P < 0.001$). At a cut-off of ≥2.41 mg/dL, sensitivity was 94.7%, specificity 98.6%, and AUC 0.983. Other studies have reported thresholds within a similar range, including 2.5 mg/dL by Nahar et al. and 2.0 mg/dL by Taksande et al. [8,10]. These findings support cord bilirubin as a marker for selecting neonates who need closer surveillance after discharge.

The mean cord B/A ratio was also higher in affected neonates (1.35 ±0.32 vs 0.49 ±0.20 mg/g; $P < 0.001$). A cut-off of ≥1.04 mg/g gave 84.6% sensitivity, 97.6% specificity, and an AUC of 0.984. This AUC was almost identical to that of cord bilirubin and does not establish that the ratio is a better predictor. Reported cut-offs vary: Sharma et al. reported 0.719 mg/g, and Kosigi and Gokul Krishnan reported 0.630 mg/g [11,12]. Differences in study populations, outcome definitions, and the timing of bilirubin measurement may account for this variation.

Mean cord ALP was higher in neonates who developed significant hyperbilirubinemia (382.89 ±34.61 vs 293.01 ±57.79 IU/L; $P < 0.001$). At a cut-off of ≥356.5 IU/L, sensitivity was 84.2%, specificity 84.0%, and AUC 0.906. Ahmadpour-Kacho et al. also reported higher cord ALP in neonates who subsequently developed jaundice [7]. Because ALP has multiple physiological sources, it should be considered a supplementary rather than a stand-alone marker.

Cord bilirubin and the B/A ratio had the highest AUCs. At the selected cut-offs, cord bilirubin had the highest sensitivity and specificity of the four markers in this cohort.

The study was limited to a single center and a modest sample of healthy term neonates with normal birth weight. The findings therefore need validation in larger, multicenter cohorts. G6PD status was not assessed, and unrecognized G6PD deficiency may have contributed to significant hyperbilirubinemia in some neonates.

Significant hyperbilirubinemia was defined as TSB ≥17 mg/dL at 72–96 h. Current treatment thresholds vary with postnatal age, gestational age, and neurotoxicity risk factors [2]. The predictive cut-offs identified here should not be interpreted as treatment thresholds or substitutes for age- and risk-specific clinical recommendations.

Conclusion

Cord bilirubin and the B/A ratio may help identify apparently healthy term neonates who need closer surveillance, particularly after early discharge. Cord bilirubin had the highest sensitivity and specificity at the selected cut-off in this cohort.

DECLARATIONS

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Shri Dada Dev Matri Avum Shishu Chikitsalaya, New Delhi, before commencement of the study. The ethics committee approval/reference number and date should be provided by the authors.

Informed Consent

Written informed consent was obtained from the parents or legal guardians of all participating neonates before enrolment in the study.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable institutional and ethical requirements.

Use of Artificial Intelligence

The authors used AI-assisted tools solely for grammatical correction, language refinement, and improving the readability of the manuscript. No AI tools were used to generate research data, perform statistical analyses, interpret findings, or draw scientific conclusions. The authors take full responsibility for the accuracy and integrity of the manuscript.

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