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The Use of Cord Blood Bilirubin as an Early Marker of Hyperbilirubinemia: A Prospective Cohort Study

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Abstract

Introduction:

A significant number of neonates are affected by neonatal jaundice, which is predominantly caused by elevated bilirubin levels. Severe cases may result in bilirubin encephalopathy and Kernicterus. The expeditious detection and management of neonates are complicated by their early discharge. Cord blood bilirubin (CBB) has been identified as a potential non-invasive predictor of neonatal hyperbilirubinemia.

Objective:

To assess the predictive utility of CBB for neonatal hyperbilirubinemia, determine its correlation with subsequent serum bilirubin levels, and establish a threshold for intervention.

Methods:

A prospective investigation was conducted at Mata Gujri Memorial Medical College & LSK Hospital on 511 neonates. Healthy neonates with postnatal hospital stay that exceeded two days were included in the inclusion criteria. CBB levels were evaluated at birth, and venous serum bilirubin was measured at 48–72 hours. Statistical analyses, including ROC curves, assessed sensitivity, specificity, and correlations.

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Results & discussion:

In neonates who required phototherapy, there was a significant correlation between CBB levels and subsequent bilirubin levels ($r = 0.752$, $p = 0.018$). The sensitivity and specificity of neonates with CBB >1.95 mg/dL were 86.7% and 63.9%, respectively, indicating a high risk of severe hyperbilirubinemia. The risk of hyperbilirubinemia was substantially influenced by gestational age ($p = 0.002$), while there was no significant association between gender and birth weight.

Conclusion:

CBB is a non-invasive, effective predictor of neonatal hyperbilirubinemia that enables early risk stratification and resource optimization. The integration of CBB assessments into routine neonatal care has the potential to enhance outcomes, particularly in cases of early discharge. Additional multicenter validation is advised.

Keywords: Neonatal jaundice, Cord blood bilirubin (CBB), Neonatal hyperbilirubinemia, Phototherapy

Introduction:

Neonatal jaundice, a clinical condition marked by noticeable yellowish staining of the skin and sclera due to elevated bilirubin levels, is one of the most common medical issues in infants. [1] Hyperbilirubinemia, which affects around 60% of term neonates and 80% of preterm neonates in the first week of life, can manifest in both healthy and pathological forms.[2] Physiological jaundice heals spontaneously; however, pathological jaundice may lead to grave outcomes, including neurological impairment, if not addressed swiftly.[3] In the Indian healthcare context, the early discharge of neonates within 48 hours post-delivery is a prevalent practice due to economic and infrastructural limitations.[4] This technique presents difficulty in promptly identifying and managing newborn jaundice, resulting in heightened readmission rates. These readmissions inflict financial and emotional hardships on families while exposing otherwise healthy newborns to nosocomial diseases. [5] Paediatricians must promptly identify infants at risk for hyperbilirubinemia to avert problems such as bilirubin encephalopathy and Kernicterus.[3]

Bilirubin, a metabolic consequence of hemoglobin degradation, circulates in the bloodstream complexed with albumin. When serum bilirubin levels exceed the albumin-binding capacity, unbound bilirubin may penetrate the blood-brain barrier, potentially resulting in neurotoxicity. Conditions such as hypoxia, metabolic acidosis, or preterm heighten this risk. [6, 7] Kernicterus,

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the persistent variant of bilirubin encephalopathy, presents with cognitive impairments, sensorineural hearing loss, dental anomalies, and athetoid cerebral palsy. [3,8]

Numerous prenatal and neonatal factors affect the probability of hyperbilirubinemia. Risk factors encompass prematurity, low birth weight, small for gestational age, ABO/Rh blood group incompatibility, cephalohematoma, insufficient nursing, and East Asian ancestry.[3,9,10] Clinically severe hyperbilirubinemia at 48 hours is characterized by serum bilirubin levels of ≥15 mg/dL in term infants without risk factors, ≥13 mg/dL in term infants with risk factors, and ≥11 mg/dL in late preterm newborns with risk factors. Visible jaundice often manifests when bilirubin levels are above 5–7 mg/dL. [10]

The fundamental approach to managing hyperbilirubinemia is phototherapy, which efficiently lowers bilirubin levels by transforming them into a water-soluble form for elimination. In critical instances, exchange transfusion may be required. [11] Nevertheless, emphasis must be placed on prevention and early detection to avert the advancement of serious problems. Predictive techniques, like cord bilirubin testing and predischarge bilirubin assessments, including maternal education regarding breastfeeding and jaundice indicators, could substantially diminish morbidity and death. The American Academy of Pediatrics (AAP) advises that neonates discharged within 48 hours should have a follow-up appointment within 2 to 3 days.[10] Nevertheless, inadequate follow-up infrastructure in low-resource environments frequently hinders adherence to this rule. Notwithstanding progress in newborn care, the identification of high-risk neonates continues to be a difficulty. Physical examination is often inadequate; dependence on total serum bilirubin (TSB) values is customary.[12] In these situations, economical, non-invasive prediction techniques such as CBB testing could be crucial in reconciling early discharge with appropriate follow-up.

Cord blood bilirubin (CBB) is an essential indicator for forecasting serum bilirubin patterns. Newborns with excessive CBB levels face a heightened risk of severe hyperbilirubinemia, requiring intervention. Integrating CBB testing into regular neonatal care enables healthcare practitioners to make more informed early discharge decisions for low-risk infants while ensuring watchful monitoring for those at elevated risk.

Multiple studies have demonstrated a correlation between bilirubin concentrations in umbilical cord blood and the subsequent risk of hyperbilirubinemia. [10, 12, 13] The authors aimed to evaluate the potential utility of cord blood bilirubin in predicting hyperbilirubinemia in newborns

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and its relationship with serum bilirubin levels assessed on the second day as an indicator of this condition.

Materials & method:

The study was planned collaboratively by the Department of Pediatrics and the Department of Biochemistry, Mata Gujri Memorial Medical College & LSK Hospital, Kishanganj. The study was done from August 1st, 2022, to July 31st, 2013.

Inclusion Criteria:

Healthy neonates born at the Department of Pediatrics who were hospitalized for more than two days after birth; whose mothers are willing to give written consent.

Criteria for Exclusion:

Clinical jaundice noted on the first postnatal day, ill neonates or those hospitalized in the NICU, neonates who received drugs that may affect serum bilirubin concentrations, neonates exhibiting substantial congenital abnormalities, maternal gestational diabetes mellitus, pathological jaundice of newborns, Rh incompatibility.

Five hundred and eleven neonates were selected for the study based on these criteria. Informed written consent was acquired from the parents of all participants. Data was gathered using a systematic proforma incorporating a questionnaire, maternal case files, and physical examinations of the neonates.

Maternal factors, such as a history of jaundice, first-trimester hemorrhage, gestational hypertension, delivery method, and pharmacological interventions throughout pregnancy, were documented. Furthermore, information regarding labor, delivery, APGAR scores, and maternal blood type was obtained from the maternal case file. Neonates were assessed daily for jaundice, infection, sickness, or birth trauma. The birth weight and gestational age of all infants were recorded. Daily observations took place during the first five days after delivery, as peak serum bilirubin levels typically occur between the first and second days.

Cord blood was obtained from the placental side at birth, and serum bilirubin concentrations were measured using these samples within four hours post-delivery. Follow-up venous blood samples were collected 48 to 72 hours later. These blood samples were protected from light and stored at 2–8 °C until analysis of bilirubin levels using the diazotized sulfanilic assay.

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The main objective of the study was to determine the incidence of hyperbilirubinemia. Neonates with serum bilirubin levels of 15 mg/dL or higher after 48 hours were identified as hyperbilirubinemic. The IAP-NNF recommends phototherapy when bilirubin levels reach or exceed 15 mg/dL after two days. In this study, newborns with serum bilirubin levels equal to or above this threshold after 48 hours were classified as hyperbilirubinemic and in need of phototherapy. Maternal, neonatal, and natal factors were evaluated in relation to newborns after two days of follow-ups. **Statistical Examination:**

The data were examined using the independent sample 't' test, descriptive analysis, and chi-square testing. The tests' sensitivity, specificity, and positive and negative predictive values were computed. The cord bilirubin level with the most incredible sensitivity and specificity was identified by the Receiver Operating Characteristic (ROC) curve analysis. Cord serum bilirubin and first-day serum bilirubin levels were employed to create a "prediction test." Sensitivity and specificity were assessed to forecast hyperbilirubinemia.

Results:

This study considered the gender of the baby, gestational age, neonatal birth weight, and the number of babies requiring phototherapy, among other general characteristics.

Table 1: Frequency distribution of neonatal sex

	Phototherapy		Percent
	Yes	No	
Female (N=267)	20	247	52.3
Male (N=244)	15	229	47.7
Total	35	476	100

Of the 511 neonates in this study, 267 were female and 244 were male. Of the 35 babies requiring phototherapy, 20 were female and 15 were male.

Table 2: Frequency distribution according to gestational age

	Phototherapy		Percent
	Yes	No	

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Preterm	13	94	20.94
Term	22	382	79.06
Total	35	476	100

Among the 511 neonates, it was shown that 35 babies needed phototherapy treatment, out of which 13 were preterm and 22 were term neonates. The chi-square test showed statistically significant association between gestational age and the requirement of phototherapy (chi square = 11.273, p = 0.002).

Table 3: Frequency distribution according to gestational weight

Gestational age	Phototherapy		Percent
	Yes	No	
2.5 kg to 2.99 kg	15	214	44.81
3 kg to 3.49 kg	18	224	47.36
3.5 kg or more	2	38	7.83
Total	35	511	100

In this study, there were 229 babies in the weight band of 2.5 kg to 2.9 kg, out of which 15 babies needed phototherapy. Among the weight bands of 3 to 3.4 kg, there were 242 babies, and 18 of them required phototherapy. Lastly, in the weight band >3.5 kg, there were 40 babies, and only 2 babies needed phototherapy. The chi-square test showed no statistically significant association between the weight band and the requirement of phototherapy (chi square = 0.638, p=0.837).

Table 4: Frequency distribution according to mode of delivery

	Phototherapy		Percent
	Yes	No	
Vaginal delivery	23	308	64.77
Caesarean section	12	168	35.23
Total	35	476	100

When we analyzed the relation of the mode of delivery with the requirement of phototherapy, it was found that 331 babies were delivered by normal delivery, whereas 180 babies were delivered

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via lower segment caesarean section (LSCS). Out of these, 23 babies delivered by vaginal delivery and 12 babies delivered by LSCS required phototherapy. The chi-square test showed no statistically significant association between the mode of delivery and the requirement of phototherapy (chi-square = 1.727, p = 0.242).

Table 5: Comparison of umbilical cord bilirubin and day 3 bilirubin levels among newborns

Phototherapy	Total bilirubin	Mean	Std. dev	p-value
Yes	Cord blood	2.15	0.571	0.003
	Venous blood after 48 hours	17.23	1.037	
No	Cord blood	1.25	0.343	0.021
	Venous blood after 48 hours	8.62	1.438	

$p<0.05$ is statistically significant.

Table 5 compares total bilirubin levels in neonates undergoing phototherapy versus those without. After 48 hours, neonates receiving phototherapy had significantly higher mean bilirubin levels in venous blood (17.23 ± 1.037 mg/dl) than in cord blood (2.15 ± 0.571 mg/dl, p = 0.003). Non-phototherapy neonates also showed similar statistically significant differences but with lower levels (cord blood: 1.25 ± 0.343 mg/dl, venous blood: 8.62 ± 1.438 mg/dl, p = 0.021).

Table 6: Correlation between umbilical cord blood bilirubin and day 2 serum total bilirubin

Pearson's correlation	Phototherapy	
	Yes	No
r-value	0.752	0.643
p-value	0.018	0.068

Among the neonates who developed significant hyperbilirubinemia requiring phototherapy, cord blood bilirubin and day 2 bilirubin were positively correlated with an r-value of 0.752 (table 6) and were statistically significant with Pearson's correlation analysis.

Figure 1: ROC curve depicting specificity and sensitivity of cord TB and 48-hour TB

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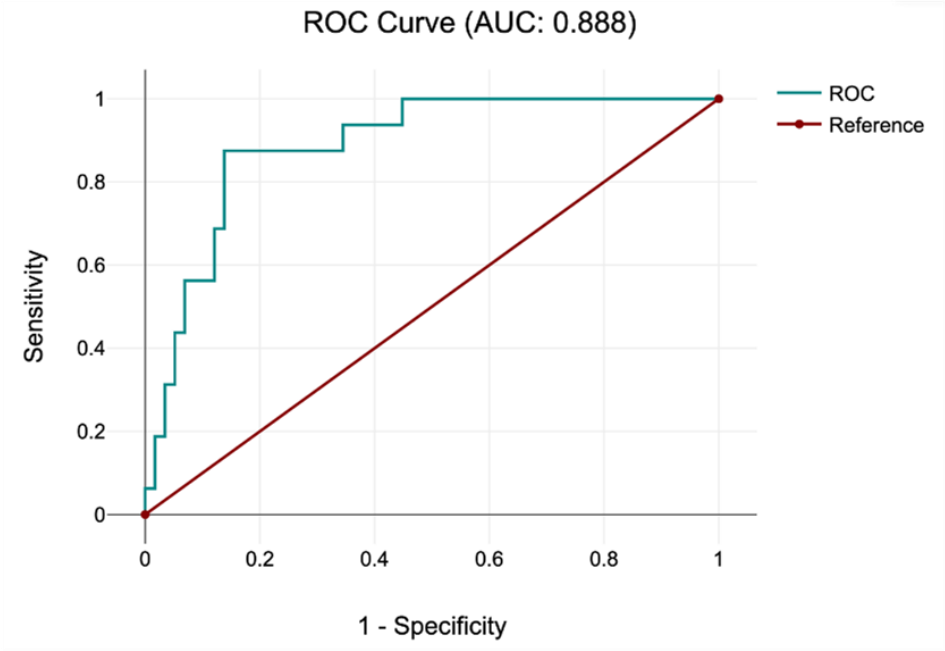

The distribution was plotted by comparing the bilirubin levels in cord blood. Two hundred forty-seven infants exhibited levels exceeding 1.9 mg/dL, of which only 26 received phototherapy. A total of 152 infants exhibited levels ranging from 1.5 to 1.9 mg/dL, with 6% of this cohort (9 infants) need phototherapy. A total of 112 infants exhibited cord blood bilirubin levels below 1.5 mg/dL, and none required intervention for early newborn hyperbilirubinemia. Consequently, infants with cord blood bilirubin concentrations exceeding 1.5 mg/dL are deemed at risk for early neonatal hyperbilirubinemia. The incidence of neonates with severe hyperbilirubinemia rose alongside elevated cord bilirubin levels. The ROC curve was developed to establish the threshold value of cord total bilirubin necessitating phototherapy. The cord's total bilirubin level of 1.65 mg/dL exhibited a sensitivity of 94.2% and a specificity of 36.5%. A result of 1.75 mg/dL exhibited a sensitivity of 91.5% and a specificity of 42.6%. The cord's total bilirubin level of 1.95 mg/dL exhibited a sensitivity of 86.7% and a specificity of 63.9%.

Discussion:

In the context of early discharge, neonatal jaundice is a common condition that frequently requires timely and precise intervention. With an emphasis on risk stratification based on biochemical and demographic factors, the objective of this study was to assess the predictive value of umbilical cord bilirubin for neonatal hyperbilirubinemia. This study's results are in accordance with prior

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research, which further supports the practicality and non-invasive nature of cord bilirubin as a predictive marker.

The results of this study indicated that a higher risk of significant hyperbilirubinemia was associated with cord bilirubin levels exceeding 1.5 mg/dL. While infants with cord bilirubin levels below 1.5 mg/dL did not develop jaundice necessitating phototherapy, those with levels between 1.5 and 1.9 mg/dL were at a moderate risk of developing jaundice (6% required phototherapy). It was most probable for neonates to develop severe hyperbilirubinemia when their levels exceeded 1.9 mg/dL. 1.95 mg/dL was determined to be a critical threshold by ROC curve analysis, with a specificity of 63.9% and a sensitivity of 86.7%. This discovery is consistent with the results of comparable investigations, which determined that 2.0 mg/dL is a dependable threshold for hyperbilirubinemia necessitating intervention, with sensitivities and specificities exceeding 85%. [12,14-16] Vasudevan et al. conducted an additional study that revealed a strong correlation between neonatal hyperbilirubinemia and cord blood bilirubin levels of 1.5 mg/dL in comparison to other cut-off levels. In contrast to our findings, 1.5 mg/dl was regarded as a relatively safe bilirubin level by them. [17] Another study by Patil et al. found that cord blood bilirubin levels of 2.5 mg/dL were relatively safer for predicting neonatal hyperbilirubinemia. [13]

There were gender disparities in hyperbilirubinemia in this study, with females having a slightly higher prevalence than males, although the difference was not statistically significant. This outcome is consistent with the findings of Bernaldo AJ and Segre CA, as well as Newman TB et al., who also indicated that there were minimal gender-based disparities in hyperbilirubinemia prevalence. [18, 19]

Hyperbilirubinemia was demonstrated to be significantly influenced by gestational age, with preterm neonates being at a significantly higher risk than term newborns ($p=0.002$). The necessity of vigilant monitoring of preterm neonates is emphasized by this discovery, as their immature liver function elevates the likelihood of bilirubin accumulation. However, no significant correlation was observed between the necessity of phototherapy and the weight of the neonate at birth. This suggests that gestational maturity may be a more significant factor in developing hyperbilirubinemia than birth weight. Another study conducted by Gilbert et al. corroborates these results. [10]

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In addition, the risk of hyperbilirubinemia was influenced by the mode of delivery, with neonates who were delivered vaginally having a higher likelihood of requiring phototherapy than those who were delivered by Caesarean section.

The predictive value of cord bilirubin is further underlined by the significant positive correlation between subsequent venous bilirubin levels (r=0.752 in phototherapy cases). Especially in environments where early discharge is prevalent, these results suggest that cord bilirubin assessment should be incorporated into routine neonatal care. Healthcare providers can alleviate the burden of severe hyperbilirubinemia by implementing targeted surveillance and timely interventions to identify at-risk neonates.

Limitations:

Parameters like umbilical cord blood albumin and bilirubin albumin ratio were not measured.

Conclusion:

Umbilical cord bilirubin is practicable and effective for predicting neonatal hyperbilirubinemia. A 1.9 mg/dL threshold effectively segregates neonates into low- and high-risk groups, thereby enabling safer discharge practices and optimised resource utilization. Additional multicenter studies are required to validate these thresholds across diverse populations and refine their implementation in clinical settings.

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