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Research Paper

Is Umbilical Cord Blood Bilirubin a Reliable Predictor of Newborn Hyperbilirubinemia?

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Abstract

Neonatal hyperbilirubinemia is the prevailing condition in newborns during the first week of life. Diagnosing substantial hyperbilirubinemia and initiating timely therapy in infants has become challenging due to early release following delivery. Therefore, there is a need to anticipate which newborns are at a high risk of developing hyperbilirubinemia. The motivation behind this study was to investigate whether the bilirubin level in the umbilical cord blood of neonates at birth could serve as a reliable indicator for predicting neonatal hyperbilirubinemia that would require phototherapy. This study utilized a cross-sectional design and included a sample of 208 babies who were healthy and born at full term (gestational age >37 weeks). The newborns were delivered in several hospitals located in Rajahmundry, Andhra Pradesh, India. The colorimetric Diazo technique was used to measure umbilical cord bilirubin (UCB). Hyperbilirubinemia was characterized by bilirubin levels that exceeded the recommended threshold for phototherapy, as outlined in the NICE guidelines. The mean umbilical cord blood (UCB) concentration in the newborns was 1.65±0.75 mg/dL. Approximately 39% of newborns necessitated phototherapy. The cutoff limit of UCB for identifying newborn hyperbilirubinemia was 1.975 mg/dL with an excellent sensitivity (76.54%) and specificity (87.4%). The receiver operating characteristic (ROC) curve demonstrated a high area under the curve (AUC) value of 0.879 for UCB in accurately identifying neonatal hyperbilirubinemia. The Youden measure demonstrated a satisfactory level of fairness in the current investigation. The prediction accuracy of the cutoff point of present study was likewise high. The findings of the current investigation demonstrated that the UCB is an excellent predictor of newborn hyperbilirubinemia and early identification of jaundice.

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KEYWORDS: Neonatal hyperbilirubinemia; umbilical cord blood bilirubin; Diagnosis cutoff

1. INTRODUCTION

Bilirubin is a naturally occurring substance in the body, but it is neurotoxic when its concentration in the blood is very high, a condition known as hyperbilirubinemia. Hyperbilirubinemia in newborn newborns is the most prevalent condition during the 1st week of life in most cases, benign disease in the neonatal period that is generally physiologic, and interventions are not usually

essential. Almost every infant acquires an unconjugated blood bilirubin level of more than 30 µmol/L (1.8 mg/dL) during the first week of life. More than two-third of newborn babies suffer neonatal jaundice. [1] Infants develop clinically jaundiced when the bilirubin level exceeds about 80 µmol/L. [2] On the other hand, neonatal jaundice is a significant clinical trait as it may be a symptom of an underlying condition (*i.e.* hemolytic anemia, infection, an inborn error of metabolism or liver disease).[3] The clinical finding of yellowish staining of the skin and sclera in neonates is owing of buildup of unconjugated bilirubin. In severe situations, excessive unconjugated hyperbilirubinemia can be accumulated in the brain, particularly in the basal ganglia, producing kernicterus. [4] Newborns are especially sensitive to hyperbilirubinemia-induced neurological injury, because in the initial days of life, the still-developing liver is heavily exercised by the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the blood–brain barrier is not as formed. Mildly raised serum bilirubin levels are frequent in infants, and neonatal jaundice is not unusual, but bilirubin levels must be constantly monitored in case they start to climb, in which case more aggressive therapy is needed, usually via light therapy but sometimes even via exchange transfusion. Severe hyperbilirubinemia can occur without apparent reason in healthy newborns, and can be deposited in the brain and may cause kernicterus. [5] The avoidance of serious consequences depends on early diagnosis of newborns who are at risk of developing significant hyperbilirubinemia and good early treatment, yet clinically substantial jaundice may not occur until one or more days after birth. [6] Early discharge of the healthy-term neonates after delivery has become a widespread practice because of both medical and social reasons as well as economic restraints, which may entail delays in recognition and beginning of medical therapy. [5,7] In the period of 'early discharge' in order not to fail to diagnose substantial hyperbilirubinemia and initiate treatment on time, predicting baby at high risk of developing hyperbilirubinemia was required. Current practice of early discharge of healthy term neonate aims to promote a home environment/emotional bonding with the family members and to prevent nursery overcrowding which in turn helps to decrease hospital acquired infection. Identification of biomarkers that might be measured within a few hours following birth, which substantially predict incident jaundice, would constitute a tremendous breakthrough. Follow-up within one to two days of early discharge, umbilical cord bilirubin (UCB) concentration at birth, routine pre-discharge serum bilirubin, and transcutaneous bilirubin measurements, as well as the universal clinical assessment of risk factors for developing jaundice, are various strategies are proposed to predict the likelihood of developing significant hyperbilirubinemia.[8,9] Of these UCB, Umbilical Cord Albumin (UCA) and bilirubin-albumin ratio are recommended as relevant markers.[5] Rosenfeld 1986 and Calkins *et al.*,, 2015 found that there is a connection between UCB and peak postnatal bilirubin levels.[10,11] Categorization of newborn children into low-risk and high-risk groups based on the UCB levels helps to focus attention on high-risk groups hence preventing early discharge and carefully commencing and monitoring of pharmacological therapy for preventing consequences of hyperbilirubinemia.[12] These factors encouraged us to undertake this study was meant to examine whether the bilirubin level in the umbilical cord blood of neonates at delivery might be utilized as a predictor of neonatal hyperbilirubinemia requiring phototherapy.

2. MATERIALS AND METHODS

From July to December 2023, 208 healthy term neonates with gestational age greater than 37 weeks delivered by either natural birth or caesarean section in either natural or tertiary hospitals Rajahmundry, Andhra Pradesh, India. The institutional ethical committee (IEC) approved the study. The study excluded preterm newborns and infants with additional issues including respiratory discomfort syndrome, Rh incompatibility, newborn sepsis, cholestasis, and kids with hemodynamic instability. The newborn's parents signed informed permission before they were registered in the study .

Study Method: Interviewing the mother from her prenatal card and using a structured questionnaire, demographic profile and pertinent data were gathered. Mother's prenatal card allowed one to evaluate gestational age. The hospital carried out clinical assessments for the mother as well as the newborn. A sterile syringe emptied three milliliters of umbilical cord blood; it was then transferred straight to the hospital's Laboratory of the Year under clean caps. Hemolyzed samples were not included into the study; blood samples were kept dark during processing and storage. The colorimetric Diazo technique was used to project umbilical cord bilirubin (UCB).Using the NICE guidelines for care of neonatal hyperbilirubinemia, hyperbilirubinemia was defined as the bilirubin levels exceeding phototherapy requirements. [13]

Statistical Analysis

The mean and SD were utilized for continuous variables; frequency and percentage was used for categorical variables to characterize the data. The cut-off with sensitivity and specificity of UCB was determined using the receiver operator characteristic (ROC) curve analysis in order to forecast newborn hyperbilirubinemia. Ranging from zero to a perfect value of 1, Youden's index (J) is a general indication of the sensitivity and specificity. Using the formula [J= (sensitivity plus specificity) – 1] the index was computed. MedCalc statistics programme (version 22.030) was used for statistical analysis.

3. RESULTS

This cross-sectional study included 208 children with gestational age >37 weeks who were delivered by the Department of Obstetrics and Gynecology in different hospitals Rajahmundry, Andhra Pradesh, India. Table 1 shows participant characteristics. The mother's average age, weight, and BMI during pregnancy were 23.4±3.8 years, 51.24±8.12 kg, and 20.82±3.43 kg/m2 correspondingly. The mother's average hemoglobin and blood pressure during pregnancy were 11.22±0.94 mg/dl, 107.9±10.76 mmHg, and 68.61±8.18 mmHg, respectively. The maternal

anemia prevalence was considerable (45.67%). The prevalence of hypotension and hypertension among them was 23.08% and 16.83%, respectively. The average gestational age of the study participants was 39.51±1.44 weeks. The newborn infants' mean birth weight was 2.83±0.45 kg, with a 12.5% prevalence of low birth weight (LBW).The average umbilical cord blood bilirubin (UCB) level in the newborns was 1.65±0.75 mg/dL. Among the total number of neonates born, 81 (38.94%) required phototherapy. The average UCB for newborns requiring phototherapy was 2.23±0.45 mg/dL, while the average UCB for infants not requiring phototherapy was 1.26±0.65 mg/dL, which was substantially different ($p<0.001$).

Table 1: Descriptive characteristics of the study participants (n = 208)

Parameters		**Mean±SD / f (%)**
Age at Pregnancy (years)		23.4±3.8
Mother Height (cm)		154.07±5.84
Mother weight (kg)		51.24±8.12
Mother BMI (kg/m^2)		20.82±3.43
Gestational age (weeks)		39.51±1.44
Mother Haemoglobin (mg/dl)		11.22±0.94
Anaemia		95 (45.67%)
Mother blood pressure	SBP (mmHg)	107.9±10.76
	DBP (mmHg)	68.61±8.18
Blood pressure category	Hypotension	48 (23.08)
	Hypertension	35 (16.83)
No of pregnancy	1	154 (74.04)
	2 or more	54 (25.96)
Birth weight (kg)		2.83±0.45
LBW		26 (12.5%)
UCB (mg/dL)		1.65±0.75
UCB (mg/dL)	Phototherapy require	2.23±0.45
	Phototherapy not-require	1.26±0.65

SBP: Systolic blood pressure;
DBP: Diastolic blood pressure;
LBW: Low birth weight;
UCB: Umbilical cord blood bilirubin

Table 2: Optimal cut-off value of umbilical cord blood bilirubin to predict neonatal hyperbilirubinemia based on ROC analysis

Neonatal hyperbilirubinemia	
Cutoff	>1.975
Sensitivity	76.54
Specificity	87.40
J	0.639
AUC	0.879
95%CI	0.826 to 0.92
z statistic	16.551 (0.000)
PPV	79.5
NPV	85.4
+LR	6.08
-LR	0.27

J- Youden's index,
AUC- Area Under Curve,
95th CI- 95% Confidence Interval;
PPV- Positive predictive value (%),
NPV- Negative predictive value (%),
+LR- Positive likelihood ratio,
−LR- Negative likelihood ratio

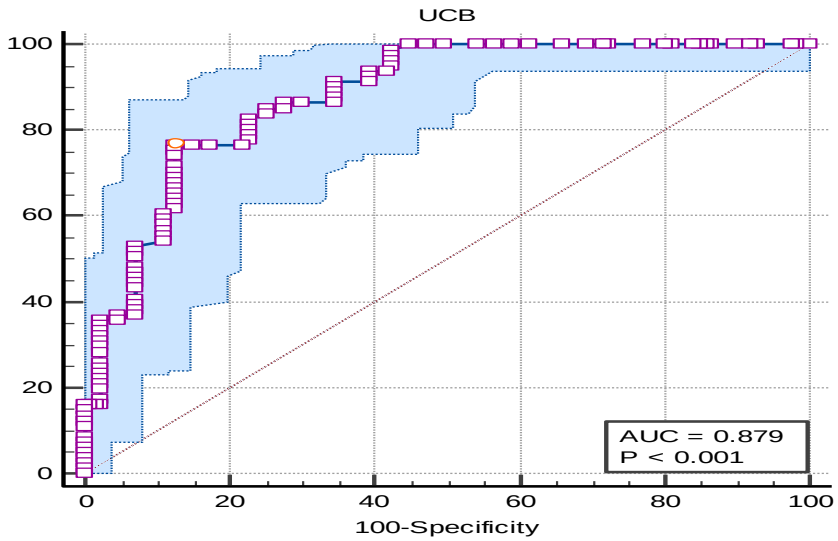

Figure 1: ROC curves of umbilical cord blood bilirubin (UCB) to predict neonatal hyperbilirubinemia

Table 3: Comparison of UCB cut-off values define neonatal hyperbilirubinemia among earlier survey and present study

Study	Sample size	UCB cut-off (mg/dL)	Sensitivity (%)	Specificity (%)
Sharma *et al*., 2020	388	1.9	97.4	40.6
Elfaragy *et al.*, 2021	90	1.8	89	78
Aktas *et al*., 2019	418	1.67	82	99
Ipek *et al*., 2021	350	1.7	78.57	54.76
Khairy *et al.*, 2019	175	1.84	100	87
Arulparithi *et al.*, 2023	50	1.95	75	68
Present Study	208	1.975	76.54	87.4

A ROC curve was drawn to determine the cutoff values of UCB to predict neonatal hyperbilirubinemia and result was described in Table 2. The finding of the present study demonstrated that there was statistically significant predictability of UCB to predict phototherapy require among the newborn newborns. The cut-off points and areas under the ROC curve (AUC) of UCB to characterize newborn hyperbilirubinemia were 1.975 mg/dL and 0.879 correspondingly. The UCB cutoff related with neonatal hyperbilirubinemia exhibited an excellent sensitivity and specificity which were 76.54% and 87.4% respectively (Fig 1).

4. DISCUSSION

Hyperbilirubinemia is a frequent clinical disease in neonates, affecting about 60% of term and 80% of preterm infants during their first week. [14] It is the leading cause of hospital readmission during the early newborn period. Severe jaundice, and even kernicterus, can occur in full-term healthy newborns with no obvious hemolytic, jaundice in the first 24 hours, or any other reason other than breastfeeding hyperbilirubinemia.[1] Kernicterus incidence is unknown. As a result, classifying a specific bilirubin level as physiological can be inaccurate and perhaps harmful. Neonatal hyperbilirubinemia is potentially treatable, and kernicterus is avoidable. [15] The requirement for early identification of hyperbilirubinemia in babies discharged from the hospital is so critical. Knowing which newborns are at danger of developing jaundice enables for the implementation of simple bilirubin-lowering therapies before bilirubin levels reach critical levels. The challenge is that predicting jaundice becomes increasingly difficult. Consideration of UCB as a measure for predicting phototherapy requirements in newborn newborns is not a novel concept. It has been a topic of attention since the 1950s, and most studies have found it to be an accurate predictor of newborn hyperbilirubinemia. A comparison of multiple earlier studies found significant variances in sensitivity and specificity scores, which could simply represent the utility of various arbitrary cutoffs (Table 3). Khairy *et al.*, (2019) and Elfaragy *et al.*, (2021) found similar UCB cutoffs of 1.84 mg/dL and 1.8 mg/dL as early predictors of newborn hyperbilirubinemia. [5,16] Aktas *et al.*, (2019) established a threshold of 1.67 mg/dL for predicting neonatal hyperbilirubinemia.[17] Similarly, Ipek *et al.*, (2021) established a cutoff point of 1.7 mg/dL for neonatal hyperbilirubinemia.[18] In another study [19], it was discovered that using a cutoff of 1.9 mg/dL to predict newborn hyperbilirubinemia had extremely high sensitivity (97%) and medium specificity (41.4%), but another study revealed that a UCB cutoff of 1.95 mg/dL had good sensitivity (75%) and intermediate specificity (68%).[20] However, both studies demonstrate a comparable limit for UCB in predicting neonatal hyperbilirubinemia. The current study's cutoff (1.975 mg/dL) was similar with the results of both investigations; however, the present study had a greater predictive accuracy than those studies. The current study demonstrated a good AUC (0.879) for UCB in defining neonatal hyperbilirubinemia, which is a measure of diagnostic test

accuracy. AUCs between 0.6 and 0.7 appear to be low, 0.70-0.80 reasonable, 0.80-0.90 moderate, and 0.90-1 exceptional. [21] Another ROC curve accuracy index, the Youden index (J), which gives an important and direct assessment of diagnostic accuracy at the ideal threshold (Yin J and Tian 2014), performed similarly in the current investigation. [22] The purpose of this study was to determine the predictive usefulness of umbilical cord bilirubin in identifying newborns at full term who will have hyperbilirubinemia later. The current study advocated using the UCB 1.975 mg/dL to define neonatal hyperbilirubinemia. The predicted accuracy of the cutoff point in the current investigation was also high. The current study found that the UCB is a good predictor of neonatal hyperbilirubinemia and early identification of jaundice.

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