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Original Article

Paediatrics Section

Cord Blood Bilirubin as an Early Marker of Hyperbilirubinemia in Term and Late Preterm Newborns at 48 Hours of Life: A Prospective Cohort Study

APARNA GILBERT[1], BABURAJ STEPHENSON[2]

ABSTRACT

Introduction: Jaundice is a common clinical condition present during the neonatal period, which can be either physiological or pathological. Early discharge of newborns is a common practice in our country due to medico-social and economic reasons, making post-discharge follow-up of infants challenging compared to developed countries.

Aim: To determine the correlation between cord blood bilirubin levels and the occurrence of hyperbilirubinemia at 48 hours of life in newborns with a gestational age of ≥35 weeks.

Materials and Methods: This cohort study was conducted in the Department of Pediatrics at Dr SMCSI Medical College, Karakonam, Trivandrum, Kerala, India, over a one-year period from June 2017 to June 2018. The exposure variables included the mother's blood group, baby's blood group, mode of delivery, gestational age, gender, and weight of the baby. The outcome variables included cord blood and 48-hour serum total and direct bilirubin levels. The data was coded and entered into Microsoft Excel and analysed using Statistical Package for Social Science (SPSS) version 16.0. Descriptive measures were calculated, and the correlation between cord and 48-hour bilirubin levels was assessed using Pearson's correlation coefficient formula. Other statistical tests applied were chi-square test and independent t-test.

Results: Total subjects of 500 (243 female and 257 were males) participants were included in the study.Among the 21 babies who underwent phototherapy, 11 were female and 10 were male, and 15 were full term and six were late preterm for their gestational age . Of the 21 babies needing phototherapy, 15 were delivered by normal vaginal delivery, and six were delivered by LSCS. Correlation between cord blood bilirubin and serum bilirubin at 48hr is 0.477 with a p-value <0.001; which indicates mild correlation between the cord blood Total Bilirubin (TB) and serum TB. A cord TB value of 1.45 mg/dL had a sensitivity of 95.2% and specificity of 32.5%. A value of 1.55 mg/dL had a sensitivity of 90.5% and specificity of 40.9%. A cord TB value of 1.65 mg/dL had a sensitivity of 66.7% and specificity of 53.9%. These findings suggest that cord bilirubin levels can be used to predict which babies require further evaluation and treatment.

Conclusion: Cord blood serum bilirubin can serve as a useful screening test for predicting neonatal hyperbilirubinemia and ensuring safe post-natal hospital discharge.

Keywords: Gestational age, Jaundice, Newborn, Phototherapy

INTRODUCTION

Jaundice is a common clinical condition present in the neonatal period. It manifests as a visible discoloration of the skin and sclera due to elevated serum concentration of bilirubin. Neonatal jaundice can occur as both physiological and pathological processes in newborns [1]. Early discharge of newborn babies is a common practice in our country due to various medico-social and economic reasons [2]. However, this practice makes it more difficult to recognise, follow-up, and provide early treatment for neonatal jaundice [3]. As a result, there is an increased risk of hospital readmissions, which incurs extra expenses for the family, early weaning due to emotional problems, exposure of a healthy newborn to a hospital environment, and delay in identifying hyperbilirubinemia, thereby increasing the risk of kernicterus [4].

The American Academy of Pediatrics recommends that newborns discharged within two days should have a follow-up visit after 2-3 days to rule out significant hyperbilirubinemia [5]. However, in our country, post-discharge follow-up of infants is challenging compared to developed countries. There are various risk factors for the development of severe hyperbilirubinemia in infants of 35 weeks or more, such as pre-discharge total bilirubin in the high-risk zone, jaundice within the first hour of life, blood group incompatibility, history of phototherapy in a previous sibling, cephalohematoma or significant bruising, inadequate breastfeeding, excessive weight loss, and East Asian race [5].

Neonatal hyperbilirubinemia requires timely intervention, whether it is caused by physiological or pathological factors. It affects approximately 60% of term and 80% of preterm neonates during the first week of life [4]. Bilirubin enters the brain as unbound bilirubin or bound bilirubin to albumin in the presence of a disrupted blood-brain barrier, which can occur in conditions such as asphyxia, metabolic acidosis, or in premature newborns. It primarily damages brain neurons and subsequently affects astrocytes and microglia [6]. The main complications of hyperbilirubinemia include bilirubin-induced neurological dysfunction, bilirubin encephalopathy, and kernicterus [7]. Acute bilirubin encephalopathy has three phases: an early phase characterised by hypotonia, lethargy, high-pitched cry, and poor suck; an intermediate phase with hypertonia of extensors, fever, irritability, and seizures; and an advanced phase with a shrill cry, apnoea, seizures, coma, and ultimately death [6,8]. Chronic encephalopathy, known as kernicterus, is characterised by athetosis, sensorineural deafness, dental dysplasia, and intellectual defects [9,10].

Neonatal hyperbilirubinemia at 48 hours is considered significant when the serum bilirubin level is greater than or equal to 15 mg/dL in lower-risk newborns (term newborns without risk factors), greater

than or equal to 13 mg/dL in medium-risk newborns (term newborns with risk factors or late preterm newborns without risk factors), and greater than or equal to 11 mg/dL in higher-risk infants (late preterm >35 weeks with risk factors) [1]. Risk factors for hyperbilirubinemia include low birth weight, small for gestational age, prematurity, ABO/Rh incompatibility, sepsis, congenital liver disorders, or infections [11]. A newborn may not appear icteric until the serum bilirubin level exceeds 5-7 mg/dL [1].

Various methods can be used to predict hyperbilirubinemia, including physical examination, cord blood bilirubin level, serum or cutaneous measurements of bilirubin, or end-expiratory CO measurements [12]. The first-line treatment for hyperbilirubinemia is phototherapy [13]. If an association can be found between cord bilirubin and 48-hour bilirubin levels among babies delivered in the southern part of India, it can easily predict whether the newborn will develop hyperbilirubinemia and help determine the need for special care, such as referral to a higher center or neonatal nursery care, especially when delivered in peripheral health centers and remote areas. A nomogram for cord blood bilirubin can help categorise babies into different risk categories and predict the likelihood of hyperbilirubinemia. This information can guide decisions regarding early discharge home in the case of low cord blood bilirubin levels or the need for further monitoring or referral to a higher center in the case of higher values of cord blood bilirubin.

This study primarily aims to determine the correlation between cord blood bilirubin and the occurrence of hyperbilirubinemia at 48 hours of life in newborns ≥35 weeks gestation. It also aims to identify the cord blood bilirubin value above which further investigations and phototherapy would be necessary. The secondary objective is to examine the correlation between cord blood bilirubin and subsequent hyperbilirubinemia in relation to various maternal and neonatal factors.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of Pediatrics at Dr. SMCSI Medical College, Karakonam, Trivandrum, Kerala, India, from June 2017 to June 2018. The study was approved by the Human Ethics Committee of Dr. SMCSI Medical College, Karakonam, Trivandrum (Ethical approval no- SMCSIMCH/EC(PHARM) 30/205 dated 3rd December 2015).

Sample size calculation: The sample size was calculated using the expected correlation coefficient (the positive predictive value (p)-34.9%, precision (r)-5%, desired confidence interval (Z1-α/2)-95%, from a similar study by Hamdi N et al., using the formula [14].

$$n=\frac{(Z1-\alpha/2)^2\ p\ (1-p)}{r^2}$$

The sample size was calculated using online sample size calculators for designing clinical research. With a power of 90%, alpha at 0.05, and the expected correlation coefficient r=0.2, the minimum sample size required was 259.

Inclusion criteria: Those healthy newborns ≥35 weeks of gestation and Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score >7 at 5 minutes were included in the study.

Exclusion criteria: Those babies with gestational age <35 weeks, birth weight <2.5 kg, those with significant illness requiring NICU admission, major congenital malformations, birth asphyxia, or ecchymosis/cephalohematoma were excluded from the study.

A sample of 500 babies was included.

Study Procedure

All mothers who fulfilled the inclusion criteria and were admitted to Dr. SMCSI Medical College were approached. Those who consented were interviewed for information collection at a convenient time for them. Clinical information was collected through one-to-one interviews using a pre-designed and pre-tested questionnaire that was formatted and approved by the institution. This process continued until the required sample size was obtained. Maternal and neonatal characteristics, along with anthropometry, were obtained from the neonatal receiving area adjacent to the labor room and obstetric operation theater.

Detection of the cord blood bilirubin: When the umbilical cord was cut after delivery, 2 mL of umbilical venous blood was immediately collected from the placental umbilical cord stump for examination. To avoid hemolysis, the sample was kept at room temperature of 37°C for 30 minutes. Once the blood fully solidified, it was placed in a centrifugal machine with a speed of 2000 turns/min to separate the serum for five minutes. The serum was then tested using the VITROS Calibrator kit 4, and the results were followed-up.

All healthy term and late preterm newborns included in the study were observed for 48 hours of life. Babies who were sick or fell under the exclusion criteria were excluded from the study. At 48 hours, the baby was clinically evaluated again, and blood was taken for serum estimation of total and direct bilirubin levels under strict aseptic precautions. 2 mL of venous blood was collected in a plain bottle containing a clot accelerator. To avoid hemolysis, after the sample was sent to the clinical laboratory, it was promptly placed at room temperature of 37°C for 30 minutes. Once the blood fully solidified, it was placed in a centrifugal machine with a speed of 2000 turns/min to separate the serum for 5 minutes. The serum was then tested using the VITROS Calibrator kit 4.

The pre-designed and pre-tested questionnaire, formatted and approved in our institution after a pilot study, was used. It contained the following sections:

Section A: Details of the mother, including the gestation at which the baby was born, risk factors, type of delivery, and gender of the baby were recorded in this section.

Section B: Laboratory investigation reports, including baby blood group, cord total bilirubin (TB), cord direct bilirubin (DB), 48-hour TB, and 48-hour DB. An infant was considered at lower risk when the gestational age at delivery was >38 weeks and the baby was well. The cutoff for phototherapy at 48 hours was considered as serum bilirubin <15 mg/dL. An infant was considered at medium risk when the gestational age at delivery was >38 weeks+risk factors or 35 weeks-37 weeks+6 days and the baby was well. The cutoff for phototherapy at 48 hours was considered as serum bilirubin <13 mg/dL. An infant was considered at higher risk when the gestational age at delivery was 35 weeks-37 weeks+6 days+risk factors. The cutoff for phototherapy at 48 hours was considered as serum bilirubin <11 mg/dL [1].

All the required fields were entered in the pre-designed and pre-tested proforma. It was filled out through one-to-one questioning by the enumerator. The results of the total bilirubin were plotted on the bilirubin for gestational age and hour-specific chart by the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia for infants 35 or more weeks of gestation [2]. Based on this chart, the need for phototherapy was determined. If the result fell within the range for phototherapy, the baby was placed under the phototherapy sub-unit.

If the baby's bilirubin levels were within the normal range, the baby was discharged and re-assessed within 48 hours. The exposure variables in this study include the mother's blood group, baby's blood group, mode of delivery, gestational age, gender, and weight of the baby. The outcome variables include cord blood and 48-hour serum total and direct bilirubin levels.

STATISTICAL ANALYSIS

The data was coded and entered into Microsoft Excel and analysed using SPSS version 16.0. Descriptive measures were calculated, and correlation was assessed by calculating the correlation coefficient. Other statistical tests, such as chi-square test and independent

t-test, were applied. Pearson's correlation was used to find the correlation between cord blood total bilirubin and total bilirubin after 48 hours, and a p-value <0.005 was considered statistically significant.

RESULTS

The general characteristics considered in this study were the gender of the baby, gestational age, neonatal birth weight, and hyperbilirubinemia needing phototherapy. Maternal risk factors, such as the type of delivery and mother's exposure to oxytocin during induced vaginal delivery, as well as the mother's blood group (ABO/RH blood group), were also considered.

Among the 500 normal singleton neonates included in the study, 243 were female and 257 were male. Among the 21 babies who underwent phototherapy, 11 were female and 10 were male [Table/Fig-1].

	Phototherapy		Percent
	Yes	No	
Female (N=243)	11	232	48.6
Male (N=257)	10	247	51.4
Total	21	479	100

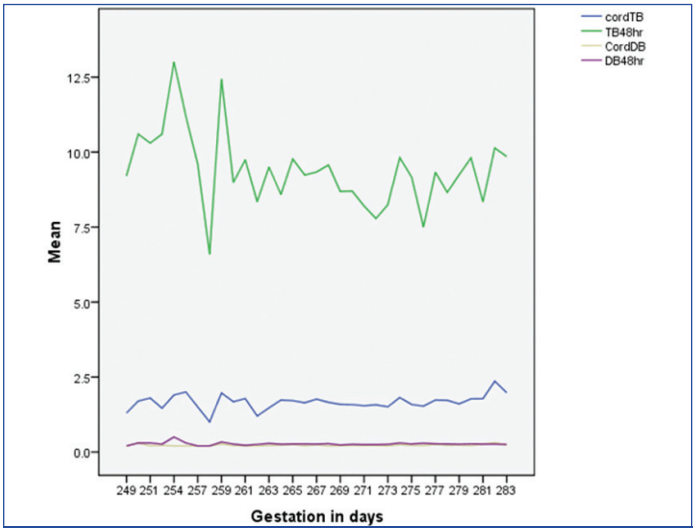
[Table/Fig-1]: Frequency distribution of neonatal sex.
Among the 500 babies who had undergone phototherapy, ratio 1.1:1 female: male

Of the 500 term and late pre-term delivered neonates, it was shown that 21 babies needed treatment in the form of phototherapy. Out of these, 15 were full term and six were late preterm [Table/Fig-2].

	Phototherapy		Percent
	Yes	No	
Late preterm	3	9	2.4
Term	18	470	97.6
Total	21	479	100

[Table/Fig-2]: Gestational age categories.
1 in 26 term baby had received phototherapy whereas in late preterm it was 1 in 3

A nomogram prepared using the present study group showed a peak in the earlier part of gestation, from 35 weeks to 37 weeks, compared to the later part of gestation [Table/Fig-3].



[Table/Fig-3]: Nomogram prepared using peaking of bilirubin with gestation.
This nomogram was prepared using the present study group, which showed peaking in the earlier part of the gestation as compared to the later part of the gestation

In this study, there were a total of 214 babies in the weight band of 2.5 to 2.9 kg, and out of these, 10 (4.7%) babies needed phototherapy. Among the weight band of 3 to 3.4 kg, there were a total of 236 babies, and out of these, 10 (4.2%) babies needed phototherapy. Among the weight band of 3.5 to 4 kg, there were a total of 50 babies, and only one baby (2%) needed phototherapy.

The association between weight band and the need for phototherapy was not found to be statistically significant according to the chi-square test, χ^2=0.721 (p-value of 0.697) [Table/Fig-4].

Gestational weight	Phototherapy		Percent
	Yes	No	
2.5 to 2.999 kg	10	204	42.8
3 to 3.499 kg	10	226	47.2
3.5 to 4 kg	1	49	10
Total	21	479	100

[Table/Fig-4]: Gestational weight categories.

Among the total of 500 deliveries considered in this study, 306 were normal vaginal deliveries, and 194 were Lower Segment Caesarean Sections (LSCS). Out of the babies who needed phototherapy, 15 were delivered by normal vaginal delivery, and six were delivered by LSCS [Table/Fig-5].

	Phototherapy		Percent
	Yes	No	
Vaginal delivery	15	291	61.2
LSCS	6	194	38.8
Total	21	500	100

[Table/Fig-5]: Mode of delivery categories.

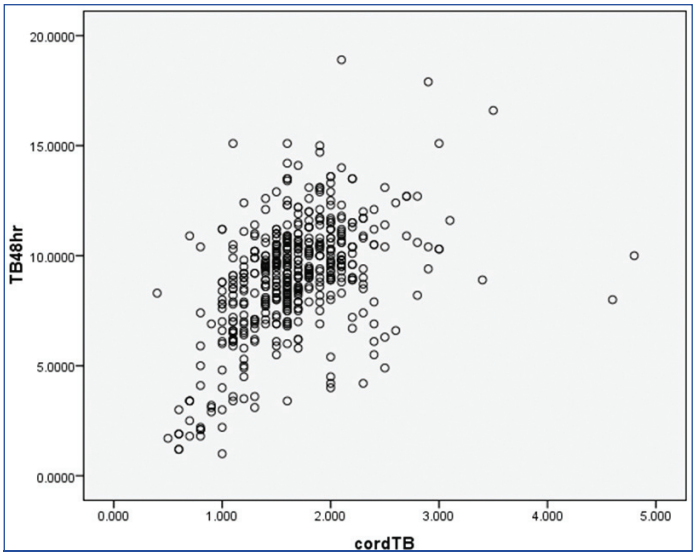
Out of the total 500 babies, 15 babies were born to B negative mothers, and two of them underwent phototherapy. The percentage of significant hyperbilirubinemia among B negative mothers was 13.3%. This was followed by mothers with O positive blood group, which included 181 in total, and 17 of them needed phototherapy, showing 9.4% of significant hyperbilirubinemia. Among mothers with O negative blood group, which included 23 in total, one of them needed phototherapy, showing 4.2% of significant hyperbilirubinemia. Among mothers with A positive blood group, which included 91 in total, one of them needed phototherapy, showing 1.1% of significant hyperbilirubinemia. However, babies born to mothers with blood groups A negative, B positive, AB positive, and AB negative did not need phototherapy. This difference in proportion was Pstatistically significant using the Chi-square test, χ^2=25.696 (p-value of 0.001). This indicates that ABO and Rh incompatibility are major risk factors to be considered, and the probability of mothers with B negative and O positive blood group having a higher chance of significant hyperbilirubinemia [Table/Fig-6].

	Normal	Phototherapy	Total	Cumulative percent
A+	91	1	92	18.4
A-	5	0	5	19.4
B+	146	0	146	48.6
B-	13	2	15	51.6
O+	164	17	181	87.8
O-	23	1	24	92.6
AB+	32	0	32	99
AB-	5	0	5	100
Total	479	21	500	

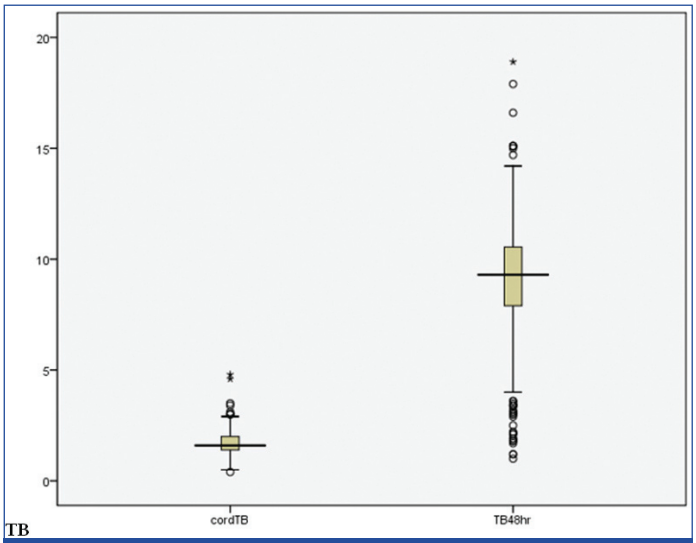
[Table/Fig-6]: Mother's blood group and its relation with hyperbilirubinemia.

The correlation between cord blood bilirubin and serum bilirubin at 48 hours is 0.477, with a p-value <0.001, which indicates a mild correlation between cord TB and serum TB [Table/Fig-7,8].

By comparing the cord blood bilirubin, the distribution was plotted. 235 babies had levels higher than 1.7 mg/dL, out of which only approximately 15 babies underwent phototherapy. A total of 145 babies had values between 1.3 to 1.7 mg/dL, and 4% of them (6 babies) required phototherapy. There were a total of 120 babies whose cord blood bilirubin levels were less than 1.3 mg/dL, and



[Table/Fig-7]: Scatterplot showing distribution of cord TB and 48 hour TB.
**There is stronger correlation between cord and 48 hour bilirubin



[Table/Fig-8]: Boxplot showing distribution of cord TB and 48 hour.

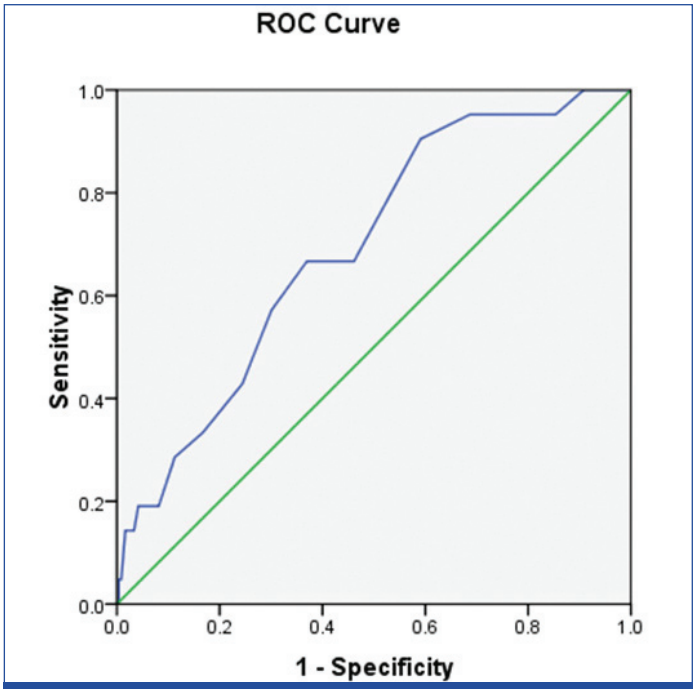
none of them needed treatment for early neonatal hyperbilirubinemia. Hence, babies with cord blood bilirubin levels above 1.3 mg/dL can be considered at risk for early neonatal hyperbilirubinemia.

The mean cord bilirubin level in the present study is 1.66±0.504 mg/dL. The number of newborns with significant hyperbilirubinemia increased with increasing cord bilirubin levels. The ROC curve was created to determine the cutoff value of cord total bilirubin above which phototherapy was needed [Table/Fig-9]. The cord total bilirubin value of 1.45 mg/dL had a sensitivity of 95.2% and a specificity of 32.5%. The value of 1.55 mg/dL had a sensitivity of 90.5% and a specificity of 40.9%. The cord total bilirubin value of 1.65 mg/dL had a sensitivity of 66.7% and a specificity of 53.9%. The correlation between cord DB and 48-hour DB is 0.070, with a p-value of 0.117, indicating no significance between cord DB and serum DB [Table/Fig-10,11].

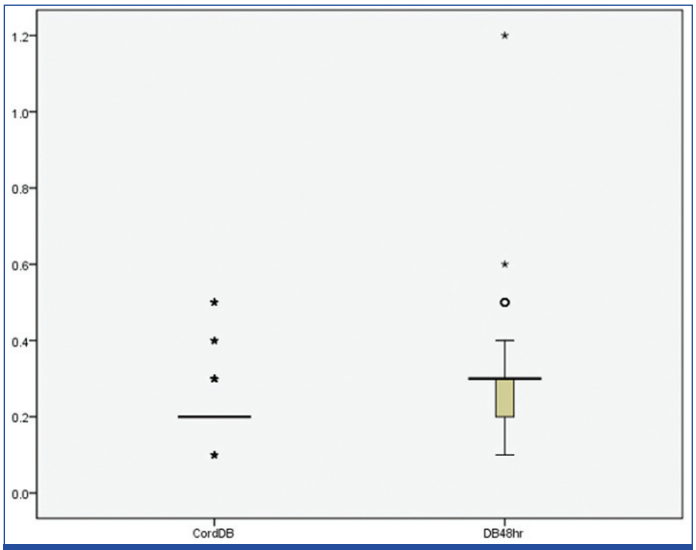
DISCUSSION

Jaundice is a common clinical condition in the neonatal period that requires timely intervention. In the current era of early discharge [15], cord blood parameters are a more practical and useful method of assessing the risk for hyperbilirubinemia, particularly in the early neonatal period [8].

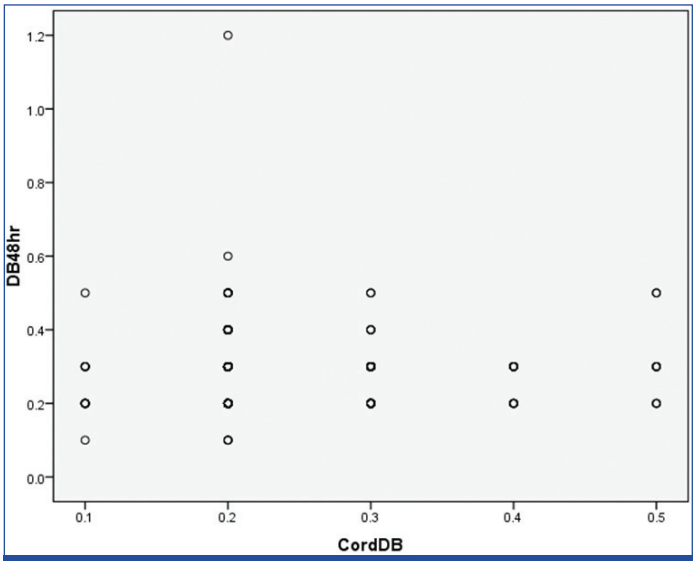
The present prospective cohort study was conducted among 500 term and late preterm babies born in a tertiary care hospital. The objective was to identify whether umbilical cord serum bilirubin values soon after birth could predict the risk of significant neonatal hyperbilirubinemia in the early neonatal period. The mechanisms of



[Table/Fig-9]: ROC curve depicting specificity and sensitivity Cord TB and 48 hour TB.



[Table/Fig-10]: Boxplot showing distribution of cord DB and 48 hour DB.



[Table/Fig-11]: Scatterplot showing distribution of cord DB and 48hour DB.

jaundice development in the early post-natal period have already occurred in late foetal life. Most foetal bilirubin is unconjugated due to a decreased ability of the foetal liver to conjugate bilirubin.

In the present study, ROC curve analysis showed that a cord total bilirubin value of 1.45 mg/dL had a sensitivity of 95.2% and a specificity of 32.5%. The value of 1.55 mg/dL had a sensitivity of 90.5% and a specificity of 40.9%. The cord total bilirubin value of 1.65 mg/dL had a sensitivity of 66.7% and a specificity of 53.9%. An area under the curve of 74.5% was observed for cord bilirubin levels above 2 mg/dL. The most useful cut-off point for serum bilirubin levels in cord blood was found to be more than 1.6 mg/dL, except for one baby who had no risk factors but developed jaundice at 48 hours. The low-risk group of babies were those with a cord bilirubin level of <1.4 mg/dL, and they did not develop significant jaundice at 48 hours of life. This proposal may help ensure safer early discharge for these newborns.

Taksande A et al., found that cord serum bilirubin values >2 mg/dL have a sensitivity of 89.5%, specificity of 85%, negative predictive value of 98.7%, and positive predictive value of 38.8%, which is similar to the findings of the present study [16]. In a similar study by Kumaran U et al., it was suggested that healthy term babies with cord bilirubin <2 mg/dL can be discharged early with assurance to parents [17]. Hamdi N et al., also observed that the optimum cutoff level for predicting neonatal jaundice using umbilical cord blood bilirubin was 2.0 mg/dL, and hyperbilirubinemia requiring intervention can be predicted with 96.25% clinical sensitivity when the level is above 2 mg/dL [14].

In the present study, the female-to-male ratio of newborns who developed significant hyperbilirubinemia was 1.05:1. When considering babies who underwent phototherapy, the female-to-male ratio was 0.9:1. The prevalence of hyperbilirubinemia was higher in females compared to males, but this difference was not found to be statistically significant, which is consistent with studies by Bernaldo AJ and Segre CA, and Newman TB et al., [18,19]. Babies who underwent a trial of labor or were delivered by normal vaginal delivery had a higher chance of requiring phototherapy, which indirectly suggests a relationship between oxytocin and hyperbilirubinemia [20].

Cord blood bilirubin can be used as a non-invasive test to predict which babies will develop neonatal hyperbilirubinemia. Combining cord blood bilirubin with risk factors provides better accuracy than relying solely on biochemical values.

Limitation(s)

Parameters like umbilical cord albumin and bilirubin albumin ratio were not measured and preterm infants were not included in the study.

CONCLUSION(S)

This study found a statistically significant correlation between cord blood bilirubin and serum bilirubin at 48 hours. The mean cord blood bilirubin level in this study was 1.6 mg/dL, and babies with cord blood bilirubin levels above 1.6 mg/dL had a higher chance of requiring phototherapy. When considering various maternal and neonatal factors, male babies had a higher chance of developing early neonatal hyperbilirubinemia that required treatment. Neonates who underwent a trial of labor or were delivered by normal vaginal delivery had a higher chance of requiring phototherapy, suggesting a possible relationship between oxytocin and hyperbilirubinemia. When comparing maternal and baby's blood groups, babies with ABO incompatibility or Rh incompatibility had a higher chance of requiring phototherapy.

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PARTICULARS OF CONTRIBUTORS:
1. Consultant Paediatrician, Department of Paediatrics and Neonatology, Dr. Kamakshi Memorial Hospitals, Chennai, Tamil Nadu, India.
2. Professor, Department of Paediatrics and Neonatology, Dr. SMCSI Medical College, Trivandrum, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Aparna Gilbert,
2/60, 9th Street, Raghava Nagar, Madipakkam, Chennai, Tamil Nadu, India.
E-mail: aparnagilbert@gmail.com

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