# Prediction of the development of neonatal hyperbilirubinemia by increased umbilical cord blood bilirubin

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## Abstract

In this prospective study the predictive value of the development of hyperbilirubinemia by increased umbilical cord blood bilirubin has been evalated. The project was completed in Level II NICU, paediatric department, KHS hospital, Sewagram.

A total of 200 healthy term neonates with gestation >37 weeks, in absence of significant illness or Rh hemolysis were included. Cord bilirubin was estimated by micromethod using calorimeterically using green filter with 540nm wavelength. Neonates were followed up clinically every 12 h till discharge and then after 72 h. total serum bilirubin(TSB) level was estimated again.

All infants were exclusively breastfed. Mean cord bilirubin was 2.38±0.51. Clinically detectable jaundice was present in 112 (56%) and hyperbilirubinemia occurred in 19 (9.5%) infants. Peak serum bilirubin of these 19 babies, at 83.21±5.27 hours of age was 18.3±0.82mg/dl. A cord bilirubin < 2mg/dl was present in 156 infants and only 2 (1.28%) neonates developed hyperbilirubinemia subsequently. In the remaining 44 neonates, with cord bilirubin >2mg/dl, subsequent hyperbilirubinemia developed in 17 (38.63%) (sensitivity 89.5%, specificity 85.1%, positive predictive value 38.6% and negative predictive value 98.7%.). No newborns had a serum total bilirubin level of ≥217 mg/dL in the first 72 hours of life. A mean cord serum bilirubin level of ≥2 mg/dL had the highest sensitivity (89.5%). At this critical cord serum bilirubin value, the negative predictive value was very high (98.7%) and the positive predictive value was fairly low (38.6%).

The use of the critical cord bilirubin level of 2 mg/dL in all healthy term newborn will pre-dict significant hyperbilirubinemia.

## Introduction

Neonatal hyperbilirubinemia is a cause of concern for the parents as well as for the pediatricians. Early discharge of healthy term newborns after delivery has become a com-mon practice because of medical and social reasons and economic constraints [1]. However, an association be-tween the decreased length of stay and the risk of readmission to the hospital has previously been shown [2], and it is significant that the most common cause for readmission during the early neonatal period is hyperbilirubinemia [3].

Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of earlier discharge from the hospital. Severe jaundice, and even kernicterus, can occur in some full-term healthy newborns discharged early with no apparent early findings of hemol-ysis [4]. The American Academy of Pediatrics recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaund ice and other problems [5]. This recommendation is not possible in our country due to limited follow up facilities in the community. The concept of prediction of jaundice offers an attractive option to pick up babies at risk of neo-natal hyperbilirubinemia.

A reliable, clinically evaluated method for estimation of the risk of bilirubin dependent brain damage is still lacking [6,7]. Physical exam is not a reliable measure of the serum bilirubins [8]. Under these circumstances it would be desirable to be able to predict the risk of jaundice, in order to implement early treatment and thereby minimize the risk of bilirubin dependent brain damage. The present study was conducted to evaluate the predictive value of cord bilirubin level for identifying term infants for subsequent hyperbilirubinemia.

## Subjects and Methods

This study was performed at the Department of Pediatrics of Kasturba medical college between November 2004 and April 2005. All healthy full-term newborns born at this hospital during this period were prospectively enrolled in the study.

### Inclusion criteria

1. gestation >37weeks
2. absence of significant illness requiring NICU admission
3. absence of major congenital malformations.

### Exclusion criteria

1. Newborn with blood group system of groups A, AB, B, and O or Rhesus blood factor incompatibility.
2. Glucose-6-phosphate dehydrogenase deficiency
3. Newborn who later developed significant illness requiring NICU admission

### Cord and Serum Bilirubin estimation

Cord bilirubin estimation was performed at birth, by a blinded observer. The total serum bilirubin was done after 72hours of birth. The cord and serum bilirubin estimation was done calorimeterically using green filter with 540nm wavelength (KLETTE) method.

### Follow up

In the days after birth the neonates were carefully observed for the development of jaundice. All infants were observed by the pediatric resident for atleast 5 days. The cord bilirubin value was unknown to the members of the departmental staff who observed the neonates. If clinical assessment of bilirubin level was more than 10 mg/dl by any observer, bilirubin estimation was repeated as above. Newborns with serum total bilirubin levels of ≥217 mg/dL after 24 hours of life were defined to have significant hyperbilirubinemia. In all cases, gender, birth weight, gestational age, delivery route, feeding pattern, Apgar scores, whether the mother had acquired any chronic diseases (hypertension, diabetes mellitus, etc) during gestation, and whether there were any siblings with neonatal jaundice and neonatal enclosed hemorrhage or abnormal weight loss were recorded. Informed consent was obtained from all parents of the new-borns enrolled in the study.

## Statistical Analysis

Statistical data were analyzed with the independent sample t test and the descriptive analysis and $\chi^2$ tests. Sensitivity, specificity, negative and positive predictive values and likelihood ratio of the test were calculated. The

critical cord bilirubin level having the highest sensi-tivity was determined with the receiver operating characteristic (ROC) curve analysis.

## Results

200 eligible neonates were enrolled. The baseline data of 200 neonates is shown in Table 1. All neonates were exclusively breastfed. Clinically detectable jaundice was present in 112 (56%) neonates. Study outcome, as defined by total serum bilirubin of >17mg/dl after 72hours, occurred in 19 ( 9.5 %) neonates. Peak serum bilirubin of these 19 babies, at 83.21±5.27 hours of age was 18.3±0.82mg/dl. All neonates required phototherapy and none required exchange transfusion.

**Table 1:** Baseline characteristics of subject (n = 200)

| Characterstics | Number (% ) |
|---|---|
| **Maternal** | |
| **Type of delivery** | |
| Cesarean | 66 (33%) |
| Normal Vaginal delivery | 134 (77%) |
| **Parity** | |
| 1 | 96 (48%) |
| 2 | 68 (34%) |
| 3 | 25 (12.50%) |
| 4 | 11 (5.50%) |
| Oxytocin use | 38 (19%) |
| Pregnancy induced hyperten-sion | 22 (11%) |
| Meconium | 12 (06%) |
| Gestational diabetes | 04 (02%) |
| H/o neonatal jaundice in pre-vious sibling | 02 (01%) |
| Premature rupture of the membranes | 08 (04%) |
| **Blood Group** | |
| A+ve | 40 (20%) |
| B+ve | 124 (62%) |
| AB+ve | 26 (13%) |
| 0+ve | 10 (05%) |
| **Neonatal** | |

| | |
|---|---|
| Birth weight | 2555±442* |
| Gestations | 38.9±2.07* |
| Males | 82 (41%) |

(* = mean±standard deviation)

**Table 2:** Relationship between cord bilirubin and serum bilirubin after 72hrs

| Cord bilirubin | Neonates with serum bilirubin >17mg/dl (n=19) | Neonates with serum bilirubin <17mg/dl (n=181) |
|---|---|---|
| >2mg/dl (n=44) | 17 | 27 |
| <2mg/dl (n=156) | 2 | 154 |

The relationship of cord bilirubin and serum bilirubin after 72hrs is shown in Table 2. The probability that an neonates with cord bilirubin higher than 2mg/dl would later become hyperbilirubinemia (Positive Predictive Values) was 38.6% (24.7, 54.5). The negative predictive values, the probability of nonhyperbilirubinemia given a cord bilirubin lower or equal to 2mg/dl was 98.7% (95.0, 99.8). If a child become hyperbilirubinemic, the probabil-ity that the cord bilirubin was higher than 2mg/dl was 89.5% (65.6,98.2) (Sensitivity). Given a non-hyperbiliru-binemia child, the probability that the cord bilirubin was lower or equal to 2 mg/dl was 85.1% (78.9,89.8) (Specificity). No newborns had a serum total bilirubin level of ≥217 mg/dL in the first 72 hours of life. 19 of 200 newborns (9.50%) had serum total bilirubin levels of ≥17 mg/dL after 72 hours of life.

There were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight, delivery route, meconium, oxytocin used, PIHin mother, feeding pattern, hemoglobin level and haemotocrit level (Table 3). There were no significant differences between the cases who had cord bilirubin level <2mg/dl and >2mg/dl with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight, delivery route, meconium, oxytocin used, PIH in mother, feeding pattern, hemoglobin level and haemotocrit level (Table 4).

**Table 3:** Characterstics of cases who did and who did not develop significant hyperbilirubinemia (>17mg/dl) after 72 hours of life.

| Characterstics | Serum bilirubin (<17mg/dl) after 72 hours of life | Serum bilirubin (≥17mg/dl) after 72 hours of life | P value |
|---|---|---|---|
| Males/ Females | 74 / 107 | 8 / 11 | 0.323 |
| Gestational Age | 39.7±2.12* | 39.9±1.68* | 0.690 |
| Birth Weight | 2568±449.9* | 2543±428.5* | 0.817 |
| **Delivery route** | | | |
| Normal | 123 | 11 | 0.527 |
| Caesarean | 58 | 8 | 0.374 |

| | | | |
|---|---|---|---|
| Meconium | 9 | 3 | 0.167 |
| Oxytocin used | 32 | 6 | 0.245 |
| PIH in mother | 17 | 5 | 0.06 |
| Cord haemoglobin | 14.7±2.43* | 16.7±3.96* | 0.158 |
| Cord haemotocrit | 45.4±6.49* | 49.1±4.86* | 0.016 |
| Cord bilirubin | 1.76±0.36* | 2.58±0.46* | 0.000 |

(p value <0.05 is significant; *= mean±standard deviation)

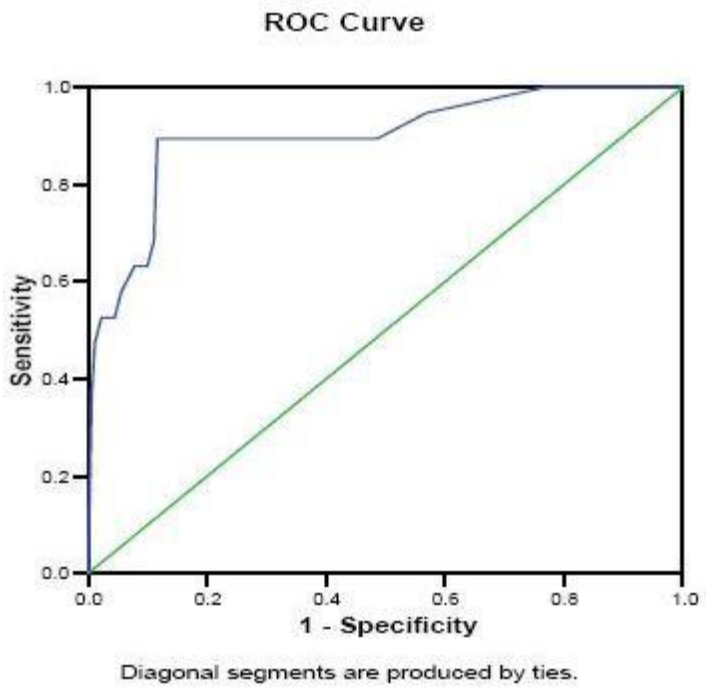
With Receiver operating characterstic (ROC) analysis, a mean cord bilirubin level of ≥22 mg/dL was determined to have the highest sensitivity (89.5%) to predict the newborns who would develop significant hyperbilirubinemia (Fig.1). At this critical mean cord bilirubin level, the negative predictive value was very high (98.7%) and the positive predictive value was fairly low (38.6%). Of the 44 newborns who had a cord bilirubin level of ≥22 mg/dL, 17 (38.63%) developed significant hyperbilirubinemia after 72 hours of life, whereas only 2 of the 156 newborns (1.28%) who had a cord bilirubin level of <2 mg/dL on the first day developed significant hyperbilirubinemia (Table 2). Of the 156 newborns, who had a cord serum bilirubin level of <2 mg/dL, 2 developed significant hyperbilirubinemia, but none of these cases had peak bilirubin levels of >20 mg/dL. In contrast, of the 17 cases who developed significant hyperbilirubinemia among the 44 newborns with a cord serum bilirubin level of ≥22mg/dL, and these cases received phototherapy treatment, but none of these cases required exchange transfusion.

**Table 4:** Characterstics of cases who had a cord bilirubin level of <2mg/dl and >2mg/dl

| Characterstics | Cord bilirubin <2mg/dl | Cord bilirubin >2mg/dl | P value |
|---|---|---|---|
| Males / Females | 66 / 90 | 16 / 28 | 0.478 |
| Gestational Age | 38.9±2.15* | 39.2±1.66* | 0.392 |
| Birth Weight | 2591±445.4* | 2574±418.4* | 0.821 |
| **Delivery route** | | | |
| Normal | 108 | 26 | 0.206 |
| Caesarean | 48 | 18 | 0.204 |
| Meconium | 8 | 4 | 0.536 |
| Oxytocin used | 32 | 6 | 0.304 |
| PIH in mother | 13 | 9 | 0.045 |
| Cord haemoglobin | 14.9±2.79* | 14.8±2.16* | 0.826 |
| Cord haemotocrit | 45.8±6.06* | 45.9±7.72* | 0.927 |
| Cord bilirubin | 1.64±0.20* | 2.54±0.33* | 0.000 |

(p value <0.05 is significant; *= mean±standard deviation)

Fig. 1. The ROC analysis of the various cord bilirubin levels predicting the development of subsequent significant hyperbilirubinemia.




## Discussion

Jaundice in newborn is quite common affecting nearly 60% of term and 80% of preterm neonates during first week of life [9]. Higher cord bilirubin level levels among infants who later become jaundiced compared to cord bilirubin levels in non-jaundiced infants indicate that mechanisms of importance for the subsequent jaundice are already active in late fetal life. Nearly all fetal bilirubin is unconjugated, due to a limited ability of the fetal liver to conjugate bilirubin. In plasma, unconjugated bilirubin is tightly bound to albumin, which is the dominant bilirubin binding protein in plasma. Under normal circumstances no bilirubin deposition in fetal tissue takes place. Unconjugated bilirubin is rapidly transferred to the maternal circulation by the placenta, whereas only small quantities of conjugated bilirubin cross the placenta. Thus bilirubin produced by the fetus is excreted by the mother, who presumably has a large reserve capacity for bilirubin excretion, and only minor differences in maternal bilirubin concentrations can be expected [10]. Raised cord blood bilirubin in ABO or non-ABO situation indicates ongoing in utero hemolysis. These babies are more likely to develop hyperbiliru-binemia. A cord bilirubin level >2.5mg/dl predicts devel-opment of pathological jaundice (defined as bilirubin >13mg/dl) with sensitivity of 71% and specificity of 96% [11].

Alpay et al observed that a serum bilirubin >6mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >17mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97.9%. No cases with TSB of <6mg/dl in the first 24 hours required phototherapy treatment value of measuring cord bilirubin concentration in ABO-incompatibility has been investigated by Riesenberg et al [13] who found that all infant with cord bilirubin level s higher than 68mumol/l, developed severe jaundice. The study done by Seidman et al found that the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dL at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was 5 mg/dL at 24 hours of life [14]. The maternal and umbilical cord bilirubin concentration at delivery, a yellow skin colour on the first post-natal day, an increase in the yellow skin colour during the first 24 h or postnatal life, and carbon monoxide excre-tion are all associated with the later development of neo-natal jaundice in the healthy, mature newborn infant [15]. The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin, and the incidence of breastfeeding. In our study group, there were no significant differences between the cases who did and the cases who did not develop significant hyper-bilirubinemia with respect to these factors (such as hemo-globin level, haematocrit level, gender, delivery route, birth weight and gestational age) that may be associated with the risk of hyperbilirubinemia.

Rosenfeld J reported that infants with cord bilirubin levels less than 2.0 mg/dL have only a 4 percent chance of developing hyperbilirubinemia and a 1.4 percent chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dL, the infant has a 25 percent chance of developing subsequent hyperbili-rubinemia Rataj J et al reported that if cord bilirubin was under 1 mg% the jaundice occurred in 2.4% newborns, where as 89% of the infants with cord bilirubin above 2.5 mg% became jaundiced [17]. Knudsen A found that if cord bilirubin was below 20 mumol/l, 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 40 mumol/l. Furthermore, 57% of jaundiced in-fants with cord bilirubin above 40 mumol/l required phototherapy, but only 9% if cord bilirubin was 40 mumol/l or lower (p less than 0.003) [18].

In our study, the cord bilirubin level of >2 mg/dL had the highest sensitivity (89.5%), and this critical bilirubin level had a very high (98.7%) negative predictive value and fairly low (38.6%) positive predictive value. According to our findings, a critical cutoff level of cord bilirubin was 2 mg/dL predicted 90% of the newborns who developed jaundice. However, the cord bilirubin level of <2 mg/dL did not completely exclude the development of signifi-cant hyperbilirubinemia; only 2.05% of the newborns with cord bilirubin levels of <2mg/dL developed jaundice. A 98.7% negative predictive value in the present study suggests that measurement of cord serum bilirubin can help in identify those newborns who are unlikely to require further evaluation and intervention.

So, we conclude that the use of the critical cord bilirubin level of 2 mg/dL in all healthy term newborns will predict significant hyperbilirubinemia.

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