

ORIGINAL ARTICLE

Diagnostic Accuracy of Cord Blood Bilirubin in Predicting Neonatal Hyperbilirubinemia, Taking Neonatal Hyperbilirubinemia within One Week of Birth as Gold Standard

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ABSTRACT

Objective: To determine the diagnostic accuracy of cord blood bilirubin in predicting neonatal hyperbilirubinemia, taking neonatal hyperbilirubinemia within one week of birth as the gold standard.

Study Design: Across-sectional study.

Place and Duration of Study: The Study was conducted at the Department of Pediatric Medicine, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan from 7th September 2020 to 6th March 2021.

Methods: A total of 366 term neonates of both genders were included. Neonates with congenital hypothyroidism, neonatal hepatitis, biliary atresia, and sepsis were excluded. After getting informed consent from parents, a cord blood sample was taken and sent to the institutional laboratory for measuring total bilirubin levels, and neonatal hyperbilirubinemia (yes/no) was noted. All neonates were followed by the researcher for one week and neonatal hyperbilirubinemia was noted.

Results: The study yielded 193 true positive and 14 false positive cases, along with 7 false negative and 152 true negative cases, with a statistically significant p -value of 0.0001. Overall, the diagnostic accuracy of cord blood bilirubin in predicting neonatal hyperbilirubinemia, using neonatal hyperbilirubinemia within one week of birth as the gold standard, was found to be 96.50% for sensitivity, 91.57% for specificity, 93.24% for positive predictive value, 95.60% for negative predictive value, and 94.26% for diagnostic accuracy.

Conclusion: This study has shown that cord blood bilirubin has a rather good diagnostic accuracy for predicting newborn hyperbilirubinemia.

Keywords: Bilirubin, Cord Blood, Neonatal Hyperbilirubinemia, Sensitivity.

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Introduction

Jaundice, a yellow coloring of the skin and sclera of the eyes, is a disease that affects a lot of newborns during their initial period of life i.e., 1st week. It occurs 60% of the time in term newborns and 80% of the time in preterm infants.¹ Raised levels of bilirubin are very dangerous for the newborn as bilirubin can deposit in brain tissue leading to permanent brain damage. The magnitude of this problem needs early identification and prompt management of neonatal jaundice to save newborns from lifelong disability.² In many cases, there is no apparent physiological

cause for the condition. However, sometimes it can be attributed to pathological factors such as the destruction of red blood cells, liver disease, infection, hypothyroidism, or metabolic issues.³ Bilirubin levels can be higher than 34 mol/l or 2 mg/dL without indicating jaundice. However, when bilirubin levels exceed 308 mol/L or 18 mg/dL in healthy infants from the first day of birth, or when the bilirubin levels rise rapidly, jaundice lasts for more than two weeks, or the infant shows signs of illness, it is a matter of concern. It is advised to conduct additional investigations in cases where there are alarming findings to identify the underlying reason.⁴

Jaundice in infants is a frequent issue. Kernicterus may develop in neonates with neonatal hyperbilirubinemia (NH), even if they are otherwise healthy. If age-appropriate hyperbilirubinemia is quickly recognized and well-treated, this can be avoided with ease.⁵ Babies can have a checkup to determine the degree of their bilirubinemia before they leave the hospital. Identifying infants who are at risk of developing high levels of bilirubin during the first week of life can be aided by this.⁶ Which of these neonates will experience substantial hyperbilirubinemia (Total Serum Bilirubin 15mg/dl) is difficult to predict. 3% of normal-term newborns often have significant hyperbilirubinemia.^{7,8}

Non-invasive, most affordable, and feasible investigation at delivery is an estimation of umbilical cord blood bilirubin (UCB). It might be simply included in the widespread practice of regular umbilical cord blood biochemical examination, which is now popular. The potential usefulness of UCB estimates in predicting eventual hyperbilirubinemia has been examined in several earlier investigations.^{9,10} The outcomes have been inconsistent, and according to the assessment by the UK's National Institute for Health and Care Excellence (NICE), it is an unreliable risk indicator.¹¹ About 21.59% of infants are affected by neonatal

hyperbilirubinemia and cord blood bilirubin has a sensitivity of 71.4% and specificity of 65.6% in diagnosing this condition.¹² In another study, it was found that cord blood bilirubin can predict infant hyperbilirubinemia with a sensitivity of 100.0% and specificity of 98.17%.¹³ In predicting newborn hyperbilirubinemia, a local investigation found that the sensitivity and specificity were 87.0% and 98.0%, respectively.¹⁴

There must be more study on this as I could only find a few papers on it while browsing the literature. The existing literature has also produced a mixed bag of findings. All of this was taken into consideration when I designed this study. The findings of my study will be a valuable addition to the body of literature, and if the diagnostic accuracy of the study is found to be high, we can offer these specific patients a straightforward method for early prediction of neonatal hyperbilirubinemia that can be used regularly in our general practice for early consultation and management of the condition to lower the morbidity and mortality of these specific patients. Our study is to determine the diagnostic accuracy of cord blood bilirubin in predicting neonatal hyperbilirubinemia, taking neonatal hyperbilirubinemia within one week of birth as the gold standard.

Methods

The descriptive, cross-sectional study was done at the Department of Pediatric Medicine, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan from 7th September 2020 to 6th March 2021 after taking approval from the ethical review committee of the hospital vide reference no IRB letter no. ERB/2019/088 held on December 09, 2019. A total sample size of 366 cases was needed to reach statistical significance at the 95% confidence level, with the estimated prevalence of newborn hyperbilirubinemia set at 21.59% and the required precision set at 10% for a sensitivity of 71.4% and 5.5% for a specificity of 65.6% using cord blood bilirubin.¹² Non-probability sampling technique was used for enrollment of cases.

Sample Selection

Inclusion Criteria: The inclusion criteria were all term neonates (gestational age ≥ 37 weeks as

assessed on LMP) delivered at the obstetrics and gynecology department, both genders, birth weight more than or equal to 2.5 kilograms, and Apgar score of 6 or more.,

Exclusion Criteria:

The exclusion criteria catered to the neonates with congenital hypothyroidism [elevated level of serum TSH >4.94 mIU/mL), decreased T4 < 63.06 nmol/L) and decreased T3 < 0.44 nmol/L]; neonates with hepatitis or biliary atresia (direct hyperbilirubinemia) or sepsis [neonate with fever $>38.5^{\circ}\text{C}$, heart rate >140 beats/min, respiratory rate >30 breaths/min and positive blood culture (>105 organism/HPF)]. Also excluded were the cases with Rh incompatibility (the blood group of RH mother and fetus is different) and ABO incompatibility (the neonate has either A or B blood group while the mother has O blood group).

Data Collection Procedure

Upon receiving approval from the IERC, a total of 366 neonates delivered at the Department of Obstetrics & Gynecology were selected based on the inclusion criteria. Following the acquisition of informed consent from the parents, cord blood samples were obtained from the institutional laboratory to measure total serum bilirubin levels. The presence or absence of neonatal hyperbilirubinemia was noted as per the operational definitions. All neonates were followed by the researcher for one week and neonatal hyperbilirubinemia was noted. All this data including the demographic data (gestational age, gender, place of living, mother education status (educated/uneducated), mode of delivery (SVD/Cesarean), bilirubin levels, and neonatal hyperbilirubinemia on cord blood bilirubin) were recorded on a specific author's designed proforma.

Data Analysis Procedure

SPSS v25.0 was used to examine the data that was collected. Calculations were made for the means and standard deviations of gestational age, newborn weight, Apgar score, and bilirubin levels. The frequency and percentage of gender, location of residence (rural/urban), mother's educational level (educated/uneducated), delivery method (SVD/Cesarean), and newborn hyperbilirubinemia on cord blood bilirubin (yes/no) were determined. Neonatal hyperbilirubinemia was assessed within

one week of delivery to determine the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of UCB in predicting neonatal hyperbilirubinemia. Stratification was used to control the effect of modifiers such as gestational age, gender, birth weight, Apgar score, place of residence (rural/urban), mother's educational level (educated/uneducated), and delivery method (SVD/Cesarean). Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated after stratification.

Results

Mean gestational age was 38.56 ± 1.23 weeks as shown in Table 1. Among 366 patients, 210 (57.38%) and 156 (42.62%) were males and females respectively with a ratio of 1.3:1 (Figure 1).

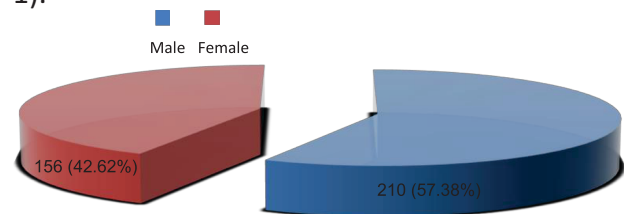


Fig 1: Distribution of patients according to Gender (n=366).

The mean birth weight was 3.24 ± 0.50 kg (Table 1). The mean Apgar score was 7.86 ± 1.16 (Table 1). The distribution of patients according to place of living, mode of delivery, and education is shown in Table 1. Table 2 shows that out of the total sample, 193 were correctly identified as positive by cord blood bilirubin (True Positive), while 14 were incorrectly identified as positive (False Positive), and 7 were incorrectly identified as negative (False Negative), and 152 were correctly identified as negative (True Negative), with a statistically significant p -value of 0.0001. The diagnostic accuracy of cord blood bilirubin in predicting neonatal hyperbilirubinemia, using neonatal hyperbilirubinemia within one week of birth as the gold standard, was found to be 96.50% for sensitivity, 91.57% for specificity, 93.24% for positive predictive value, 95.60% for negative predictive value, and 94.26% for overall diagnostic accuracy.

Table 1: Distribution of patients

		No. of Patients	% age	Mean ± SD
Gestational Age (weeks)	37-39	269	73.50	38.56 ± 1.23 weeks
	≥39	97	26.50	
Birth weight (kg)	≤3.5	253	69.13	3.24 ± 0.50 kg
	>3.5	113	30.87	
Apgar score	6-8	235	64.21	7.86 ± 1.16
	9-10	131	35.79	
Place of living	Rural	182	49.73	
	Urban	184	50.27	
Mode of delivery	Vaginal	172	46.99	
	Cesarean	194	53.01	
Education	Uneducated	102	27.87	
	Educated	264	72.13	

Table 2: The accuracy of predicting neo natal hyperbilirubinemia using cord blood bilirubin, with neonatal hyperbilirubinemia within one week of birth as the gold standard

	Positive result on within a week of birth	Negative result within a week of birth	P-value	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Diagnostic Accuracy
Positive result on cord blood bilirubin	193 (TP)*	14 (FP)***						
Negative result on cord blood bilirubin	07 (FN)**	152 (TN)***	0.0001	96.5	91.57	93.24	95.6	94.26

True Positive (TP), False Positive (FP), False Negative (FN), True Negative (TN)

Table 3 displays the stratification of diagnostic accuracy in relation to gestational age and gender, while Table 4 shows the stratification of diagnostic accuracy based on birth weight, APGAR score, and mode of delivery. Place of living stratification and diagnostic accuracy with respect to education is shown in Table 5.

Discussion

Jaundice, or newborn hyperbilirubinemia (NNH), is the most common medically treatable baby illness.¹⁵ Approximately 60% of term and 80% of preterm neonates have neonatal hyperbilirubinemia in the first week.¹⁶ In the first week of life, all newborns have unconjugated blood bilirubin levels above 30 mol/L (1.8 mg/dL), according to the AAP.¹⁷ Many newborns are discharged soon after delivery for

medical, social, and financial reasons. NNH eventually causes readmission. According to the AAP, newborns released from the hospital within 48 hours should be scheduled for a follow-up to check for severe jaundice and other concerns.¹⁷ This plan is not always practical due to a lack of community-based follow-up services in our nation.

NNH requires quick and proper care to prevent neurological disorders including bilirubin-induced encephalopathy.¹⁸ Preventing serious effects requires timely diagnosis and effective treatment. Recently, several attempts have been made to identify neonates at risk of neonatal jaundice. Clinical examinations are often used to identify jaundice; however, they cannot accurately estimate serum bilirubin. Thus, other approaches to

Table 3: Classifying the accuracy of diagnosis according to gestational age and gender

		Positive result within week of birth	Negative result within week of birth	P-value	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Diagnostic Accuracy
Gestational Age 37-39 Weeks (n=269)	Positive result on cord blood bilirubin	139 (TP)	14 (FP)	0.001	95.21	88.62	90.85	93.97	92.19
	Negative result on cord blood bilirubin	07 (FN)	109 (TN)						
Gestational Age 40-41 Weeks (n=97)	Positive result on cord blood bilirubin	54 (TP)	00 (FP)	0.001	100	100	100	100	100
	Negative result on cord blood bilirubin	00 (FN)	43 (TN)						
Male Gender (n=210)	Positive result on cord blood bilirubin	119 (TP)	08 (FP)	0.001	100	91.21	93.7	100	96.19
	Negative result on cord blood bilirubin	00 (FN)	83 (TN)						
Female Gender (n=156)	Positive result on cord blood bilirubin	74 (TP)	06 (FP)	0.001	91.36	92	92.5	90.79	91.67
	Negative result on cord blood bilirubin	07 (FN)	69 (TN)						

predicting considerable jaundice may reduce hospital stays for healthy neonates and identify future NNH.

Some reliable ways to identify jaundiced babies after birth. There are numerous ways to identify and treat newborn hyperbilirubinemia. These include universal clinical assessment of jaundice risk factors, universal follow-up within 1-2 days of early release, routine predischarge blood bilirubin, and transcutaneous, and umbilical cord bilirubin concentration at delivery.¹⁹ Estimating cord bilirubin levels after delivery is the most frequent method since it is cheap, practical, easy, and may indicate hyperbilirubinemia later. Being able to predict jaundice would help implement safe, inexpensive, and quick treatment and reduce the risk of bilirubin-dependent neurological disorders.

The gold standard for newborn hyperbilirubinemia prediction was one week after birth, hence this study

measured UCB's diagnostic precision. I found 193 True Positives, 14 False Positives, 7 False Negatives, and 152 True Negatives ($p=0.0001$). Umbilical cord bilirubin (UCB) had a sensitivity of 96.50%, specificity of 91.57%, positive predictive value of 93.24%, negative predictive value of 95.60%, and diagnostic accuracy of 94.26% for neonatal hyperbilirubinemia with a gold standard of one week. Newborn hyperbilirubinemia was frequent (21.59%) and cord blood bilirubin had a sensitivity and specificity of 71.4% and 65.6%, respectively, in predicting it.¹² Cord blood bilirubin may predict infant hyperbilirubinemia with a sensitivity of 100.0% and specificity of 98.17%, according to another research.¹³

Khairy et al. reported that cord blood bilirubin levels over 2 mg/dL had 89.5% sensitivity, 85% specificity, 98.7% negative predictive value, and 38.8% positive predictive value.¹⁹ Another research by Nahar et al.

Table 4: Stratification of the precision of diagnosis based on birth weight, APGAR score, and mode of delivery

Birth Weight ≤3.5 Kg (n=253)	Positive result on cord blood bilirubin	141 (TP)	09 (FP)	0.001	100	91.96	94	100	96.44
	Negative result on cord blood bilirubin	00 (FN)	103 (TN)						
Birth Weight >3.5 Kg (n=113)	Positive result on cord blood bilirubin	52 (TP)	05 (FP)	0.001	88.14	90.74	91.23	87.5	89.38
	Negative result on cord blood bilirubin	07 (FN)	49 (TN)						
APGAR score 6 - 8 (n=235)	Positive result on cord blood bilirubin	123 (TP)	09 (FP)	0.001	100	91.96	93.18	100	96.17
	Negative result on cord blood bilirubin	00 (FN)	103 (TN)						
APGAR score 9 - 10 (n=131)	Positive result on cord blood bilirubin	70 (TP)	05 (FP)	0.001	90.91	90.74	93.33	87.5	90.84
	Negative result on cord blood bilirubin	07 (FN)	49 (TN)						
SVD (n=172)	Positive result on cord blood bilirubin	93 (TP)	01 (FP)	0.001	100	98.73	98.94	100	99.42
	Negative result on cord blood bilirubin	00 (FN)	78 (TN)						
Cesarean Delivery (n=194)	Positive result on cord blood bilirubin	100 (TP)	13 (FP)	0.001	93.46	85.06	88.5	91.36	89.69
	Negative result on cord blood bilirubin	07 (FN)	74 (TN)						

found that cord bilirubin levels below 2.5 mg/dL predicted newborn hyperbilirubinemia with 77% sensitivity, 98.6% specificity, and 96% negative predictive value.²⁰ A local investigation predicted newborn hyperbilirubinemia with 87.0% sensitivity and 98.0% specificity.¹⁴ Calkins et al. and Jones et al. reported that UCB concentrations are relevant and predictive for newborns at risk for hemolytic diseases related to hyperbilirubinemia.^{21,22} In this cohort, UCB may help

predict severe hyperbilirubinemia and phototherapy, Calkins concluded. Blood type O women's arterial umbilical cord bilirubin predicts neonatal jaundice, according to Jones et al. and Chary et al. found that cord blood bilirubin levels above 2.0 mg/dl identified neonates at risk of substantial hyperbilirubinemia with 94.12% sensitivity and 90.91% specificity.^{22,23} Krishnan et al. discovered that cord blood bilirubin levels are the best predictor of pathological hyperbilirubinemia,

Table 5: Stratification of diagnostic accuracy with respect to living style and education

Rural Living (n=182)	Positive result on cord blood bilirubin	98 (TP)	07 (FP)	0.001	93.33	90.91	93.33	90.91	92.31
	Negative result on cord blood bilirubin	07 (FN)	70 (TN)						
Urban Living (n=184)	Positive result on cord blood bilirubin	95 (TP)	07 (FP)	0.001	100	92.13	93.14	100	96.2
	Negative result on cord blood bilirubin	00 (FN)	82 (TN)						
Un-Education (n=102)	Positive result on cord blood bilirubin	76 (TP)	05 (FP)	0.001	91.57	73.68	93.83	66.67	88.24
	Negative result on cord blood bilirubin	07 (FN)	14 (TN)						
Educated (n=264)	Positive result on cord blood bilirubin	117 (TP)	09 (FP)	0.001	100	93.88	92.86	100	96.59
	Negative result on cord blood bilirubin	00 (FN)	138 (TN)						

and newborns with levels above 1.8 mg/dl are more likely to develop it.²⁴

Ahire et al. found that a cord blood serum bilirubin level of 3 mg/dL predicted hyperbilirubinemia with 100% sensitivity, 98.17% specificity, 66.67% positive predictive value, and 100% negative predictive value.¹³ Kumaran et al. found that neonates with UCB ≥ 2 mg/dl should be closely observed on the fifth day, preferably in a hospital or outpatient facility.¹¹ Pathological hyperbilirubinemia and cord blood total bilirubin are linked, according to Pradhan et al.¹⁰ They found 84.1% sensitivity and 88.5% specificity for cord bilirubin below 2.5 mg/dl. 98.0% of this variable's predictions were positive, 45.1% negative.¹⁰ Rostami et al. studied 643 term infants. The study found that 92.4% of neonates with UCB under 3 mg/dl did not develop harmful hyperbilirubinemia. Compared to the current analysis, the study showed lower sensitivity (18.4%), PPV (24.6%), greater specificity (92.4%), and NPV (89.4%) along with *P*-value 0.04. Unlike the studies described, the new

study demonstrated better sensitivity, PPV, and a cut-off point of 3. However, the research done by Rostami et al. employed a cut-off value of 2 mg/dl and found 59.2% sensitivity and 48.1% specificity, identical to the current study.²⁵

Conclusion

The findings of this study suggest that cord blood bilirubin is an effective method for predicting newborn hyperbilirubinemia. Therefore, we recommend that this simple and non-invasive method be routinely used in general practice for early prediction of neonatal hyperbilirubinemia, which can facilitate early consultation and management of the condition, and potentially reduce future morbidity and mortality of affected patients.

Authors Contribution

- MM:** Idea conception and data collection
- DA:** Data analysis, results and interpretation
- DH:** Study designing
- HK:** Manuscript writing and proof reading

AA: Data analysis, results and interpretation

ZAA: Manuscript writing and proof reading

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