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Cord Blood Bilirubin/Albumin Ratio As An Early Predictor For Neonatal Hyperbilirubinemia In Healthy Term Neonates

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ABSTRACT

Background

Neonatal jaundice is a common condition with implications for neonatal morbidity and mortality. Screening for hyperbilirubinemia before hospital discharge is crucial for early detection of at-risk newborns. Cord bilirubin and albumin can be valuable early screening indicators for neonatal hyperbilirubinemia. We aimed to evaluate the predictive value of cord blood bilirubin/albumin ratio in identifying healthy term neonates at risk for developing clinically significant neonatal hyperbilirubinemia and its associations with gender, birth weight and mode of delivery.

Materials and Methods

This hospital based prospective observational study was carried out on 120 term healthy neonates, ranging from 37 to 41 weeks of either gender with birth weight >2.5 kgs, without any significant illness or major congenital malformations. The neonates with conditions that could aggravate hyperbilirubinemia (sepsis, respiratory distress syndrome, asphyxia, diabetic mothers, delivered by instrumentation, cephalhematoma) or Rh-negative mother were excluded from the study. Cord blood bilirubin / albumin ratio was analyzed. All infants were monitored daily for jaundice by Kramer staging along with transcutaneous bilirubinometer until the 5th day of life. Infants who were suspected of having bilirubin levels exceeding the physiological limit on any day after birth underwent serum bilirubin measurement. If the serum bilirubin level fell within the interventional range, the babies were taken to the nursery for phototherapy or exchange transfusion. The cord bilirubin/albumin ratio was correlated with babies developing neonatal hyperbilirubinemia requiring either phototherapy or exchange transfusion.

Results

Cord blood bilirubin/albumin ratio cut off value ≥ 0.705 was found significant for predicting hyperbilirubinemia (p value <0.05) having sensitivity of 70.6%, specificity of 92.75 %, PPV 87.8%, and NPV 81.01%.

Conclusion

The present study highlights that the cord blood bilirubin/albumin ratio (a cost-effective and non-invasive test) can help us in identifying those newborns who are at risk of developing significant hyperbilirubinemia.

Keywords: Neonatal hyperbilirubinemia, cord bilirubin/albumin ratio, Phototherapy, jaundice

1. INTRODUCTION

Neonatal jaundice (NNJ) is a common condition seen in newborns worldwide(1,2) and one of the important contributors to neonatal morbidity and mortality.(3))Half of all term neonates and 80% of preterm newborns exhibit clinical jaundice.(5)Severe neonatal jaundice can damage the brain of healthy newborns and even cause neonatal death.(4)

A physiological increase in bilirubin causes indirect hyperbilirubinemia ,which usually manifests clinically, beyond 24 hours after delivery. This hyperbilirubinemia increases gradually with age and resolves gradually without intervention in most cases. However, if the bilirubin level exceeds the normal range, phototherapy or exchange transfusion may be required. Because acute encephalopathy and kernicterus/chronic encephalopathy can result from hyperbilirubinemia, it is crucial to identify newborns that are at risk for this condition.(6)

In birthing facilities with high delivery rate, physicians are compelled to discharge newborns early especially the otherwise healthy babies born by vaginal delivery due to familialand social pressures. This makes it crucial to identify the subset of these newborns, who are at increased risk of developing clinically significant neonatal hyperbilirubinemia hyperbilirubinemia defined as total serum bilirubin ≥ 95th percentile of the expected level for age, as per the available nomograms.(4) Many researchers have attempted to find simple markers for predicting neonatal hyperbilirubinemia and its progression, such as estimation of cord blood bilirubin (7,8), bilirubin estimation during 6 to 24 hours of age(7-12), pre-discharge hour specific bilirubin estimation(13) and transcutaneousbilirubin measurement. (14-17).

There is a felt need for simple, low cost tools to identify neonates who are at risk for clinically significantneonatal hyperbilirubinemia in otherwise healthy term neonates, so that their parents can be counselled accordingly and these neonates can be closely followed up to institute timely management to prevent complications of hyperbilirubinemia.

If we have a way to identify neonates who are at risk for hyperbilirubinemia, we can shorten hospital stays and lower readmission rates. Phototherapy can be started early in this group of babies which is more effective, simple and cheap and can avoid neurological complications. (18)

The present study was planned to study the utility of cord blood bilirubin/albumin ratio for predicting the subsequent development of clinically significant neonatal hyperbilirubinemia in newborns at our institute. This is likely to contribute to early recognition of neonatal jaundice thereby reduce morbidity and mortality of neonates due to it.

2. MATERIALS AND METHODS

This is a prospective observational study that included 120 term healthy neonates born in Sharda Hospital, from August 2022 to July 2023. All neonates born full term (gestational age ranging from 37 to less than 42 completed weeks) of either gender with birth weight more than 2500 grams without any significant illness or major congenital malformations were assessed for eligibility. The neonates with conditions that could aggravate hyperbilirubinemia (sepsis, respiratory distress syndrome, asphyxia, diabetic mothers, or delivered by instrumentation) or neonate born to Rh negative mother were excluded from the study. The babies who were discharged early and/or who could not followed up for at least 5 days were also excluded from this study. An approval from the Institutional Ethics Committee was obtained before initiating this study.

Prior to their participation, informed consent was obtained from the parents of the newborns. Detailed history was obtained from the parents of the recruited babies including antenatal and perinatal history, history about maternal illness, maternal drug use, and fever. Additionally, mother's blood group was also noted.

Cord blood samples (3 ml) were collected in plain vials from all newborns enrolled in the study.

Soon after birth, a thorough clinical examination of the neonate was conducted, which encompassed vital signs, anthropometric measurements, and assessment for the presence of major congenital malformations or cephalhematoma. Systemic examination was also performed, including cardiac, abdominal, chest, and neurological evaluation to loof for any other abnormality.

Following the delivery of the newborn, the umbilical cord was clamped at two points and cut after 1 minute. After identifying a suitable puncture site, the umbilical cord was cleaned, and a sterile syringe was used to puncture the umbilical vein. Approximately 3 ml of blood was withdrawn from the umbilical vein and then transferred into a plain vacutainer for biochemical analysis. Bilirubin was analyzed by Colorimetric Diazo method using fully automated analysis Vitros (5600), and diazotized sulphanilic acid reaction using in vitro diagnostic (Ortho clinical diagnostics, New Jersey, USA). Albumin was analyzed using fully automated bromocresol green dye binding technique using in vitro diagnostic (Ortho clinical diagnostics, New Jersey, USA).

All infants were regularly monitored for jaundice until the 5th day of life. The clinical assessment of bilirubin levels was performed according to Kramer's scale, which provides guidelines for identifying the severity of jaundice based on specific regions of the body affected. For instance, if jaundice was observed only in the face and neck, the total serum bilirubin (TSB) level was determined to be around 5 mg/dL. If jaundice was present on the chest up to the umbilicus and back, the TSB level was between 5 and 10 mg/dL. When jaundice extended from the umbilicus to the knees, the TSB level was found to be 10-15 mg/dL. Moreover, if jaundice was visible in the palms and soles of the feet, the TSB level exceeded >15 mg/dL.

Additionally, transcutaneous bilirubinometer readings were taken using the Dräger JM-105 for five consecutive days. This involved placing the instrument on the baby's sternum to estimate the transcutaneous bilirubin (TCB) levels following the method recommended by the manufacturer.

Infants who were suspected of having bilirubin levels exceeding the physiological limit on any day after birth, as assessed either by Kramer's criteria or transcutaneous bilirubin nomograms (19), underwent serum bilirubin measurement using 2 ml blood sample collected in a plain vacutainer, as per the standard protocol followed in our neonatal unit. If the serum bilirubin level fell within the interventional range, the babies were taken to the nursery for phototherapy or exchange transfusion, as deemed necessary.

The data was collected in a predesigned, pretested proforma and tabulated in Microsoft Excel version 2017 (Microsoft Corporation) New York, USA. Results were analyzed using Microsoft Excel and statistical package for social sciences (IBM SPSS statistics for windows, Version 23, Armonk, NY: IBM Corp). Qualitative data was expressed as number and percentage and quantitative data was expressed as mean ± SD. T test, chi-square test and ANOVA were used to find the significance of study parameters on categorical scale between two or more groups. Diagnostic statistics such as Sensitivity, Specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained for prediction potential of Cord Serum albumin, bilirubin and bilirubin-albumin ratio as an indicator for neonatal hyperbilirubinemia. Receiver operating characteristic (ROC) curve was constructed with area under curve analysis performed to detect best cut-off value of cord blood albumin, cord blood bilirubin and cord bilirubin/albumin ratio for detection of positive cases. For statistical significance, p value of less than 0.05 was considered statistically significant.

3. RESULT

During the study period, a total of 143 neonates were screened as shown in study flowchart in **Fig. 1**, and finally, 120 neonates were recruited. Demographic profile of the study population is presented in **Table 1**. Out of total 120 term healthy neonates, majority of newborns 69 (57.5%) did not require phototherapy (no clinically significant neonatal jaundice) and only 51(42.5%) neonates had clinical jaundice requiring phototherapy. Socio-demographic and obstetric data differences between non jaundiced and jaundiced cases presented in **Table 2**. Comparison of cord blood bilirubin/albumin ratio between jaundiced and non-jaundiced subjects is summarized in **Table 3**.
Discriminatory power of cord bilirubin/albumin ratio (AUC 0.85; 95%CI: 0.77 to 0.92) was excellent. Cord bilirubin/albumin ratio was the significant predictor of neonatal jaundice at cut off point of 0.705 with Diagnostic accuracy of 83.33% of predicting neonatal jaundice.

Of those neonates who developed jaundice, 70.6% (56.17-82.51) of newborns had cord bilirubin/albumin ratio ≥0.705. If cord bilirubin /albumin ratio ≥ 0.705, then there was 87.8% (73.8-95.92) probability of neonatal jaundice and if cord bilirubin/ albumin ratio<0.705 then 81.01% (70.62-88.97)) chances of no neonatal jaundice. Among newborns that did not have jaundice, 92.75% (83.89-97.61) of newborns had cord bilirubin/albumin ratio<0.705 is summarized in **Table 4, figure 2.**

Correlation between Cord B/A ratio and clinical jaundice by Kramer's criteria, bilirubin by TcB and Serum bilirubin requiring phototherapy were also done which showed Positive correlationwas observed between Cord B/A ratio and its association with clinical jaundice by Kramer's criteria among the jaundiced (0.73±0.17) and non jaundiced (0.56±0.16). (P value=<0.001) which is statistically significant.

Positive correlation was observed between Cord B/A ratio and its association with clinical jaundice by TcB among the jaundiced (0.77±0.17) and non jaundiced (0.55±0.14), (p value=<0.001) which is statistically significant. **Table 5**

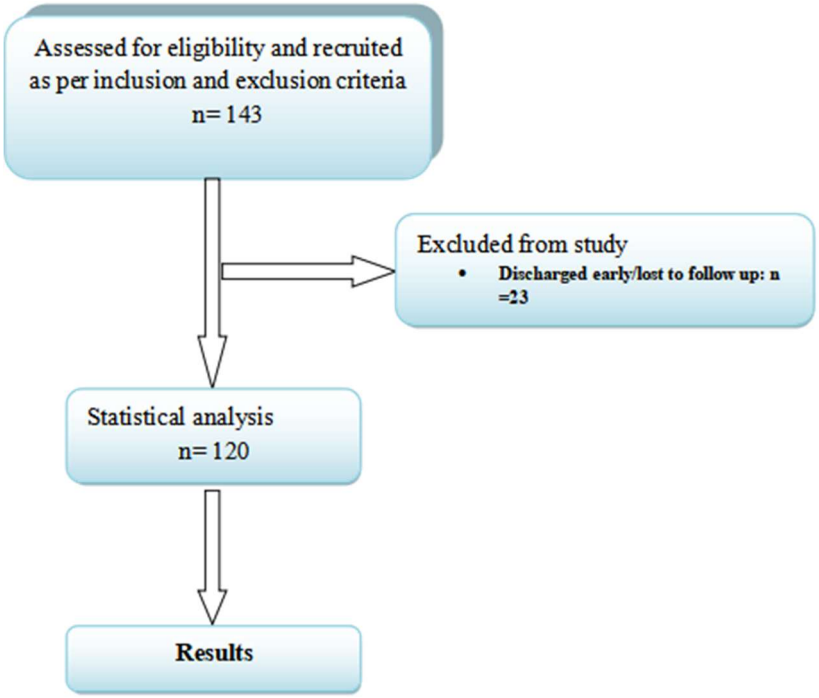

Figure:-1 Study flow chart

Variable	**Number of patient (%)**	
Gender	**Frequency**	**Percentage**
Male	58	48.3
Female	62	51.7
Gestational age(weeks)		
37 weeks to 38 weeks + 6 days	67	55.83
39 weeks to 40 weeks + 6 days	51	42.5
≥ 41 weeks	2	1.7
Birth weight(grams)		
2500-2999	73	60.8
3000-3499	40	33.3
3500-3999	7	5.8
Mode of delivery		
Normal vaginal delivery	46	38.3
Lower segment cesarean section	74	61.7

Table 1: Demographic profile of the study population

		Non-Jaundiced **(n=69)**	Jaundiced **(n=51)**	P-value
Gestational Age/weeks		40.1±2.1	38.12±2.21	0.09
Gender	Male	35 (50.7%)	23 (45.1%)	0.54
	Female	34 (49.3%)	28 (54.9%)	
Mode of Delivery	NVD	25 (36.2%)	21 (41.2%)	0.70
	LSCS	44 (63.8%)	30 (58.8%)	

Birth Weight (Mean ± SD)		2991.59±343.54	2915.92±273.56	0.23
Parity (Mean ± SD)		1.96±1.04	1.96±0.89	0.69
Exclusive Breastfeeding	Yes	62 (89.9%)	27 (52.9%)	<0.001
	No	7 (10.1%)	24 (47.1%)	

Table 2:- Socio-demographic and obstetric data differences between non jaundiced and jaundiced Cases.

	Mean ± SD		
	Non-Jaundiced	**Jaundiced**	P-value
Cord Blood Bilirubin (mg/dl)	2.04±0.64	2.76±0.69	**<0.001**
Cord Blood Albumin (g/dl)	3.81±0.59	3.67±0.57	0.84
Cord Blood Bilirubin/Albumin ratio	0.53±0.14	0.75±0.16	**<0.001**

Table:-3 Comparison of cord blood bilirubin, albumin and ratio between jaundiced and non-jaundiced subjects

Neonatal jaundice	**Cord blood bilirubin/albumin ratio**
Area under the ROC curve (AUC)	0.85
Standard Error	0.03
95% Confidence interval	0.77-0.92
P value	<0.001
Cut off	0.705
Sensitivity(95% CI)	70.6% (56.17-82.51)
Specificity(95% CI)	92.75% (83.89-97.61)
PPV(95% CI)	87.8% (73.8-95.92)
NPV(95% CI)	81.01% (70.62-88.97)
Diagnostic accuracy	83.33% (75.44-89.51)

Table 4:- Utility of Cord blood bilirubin/albumin ratio for predicting neonatal hyperbilirubinemia.

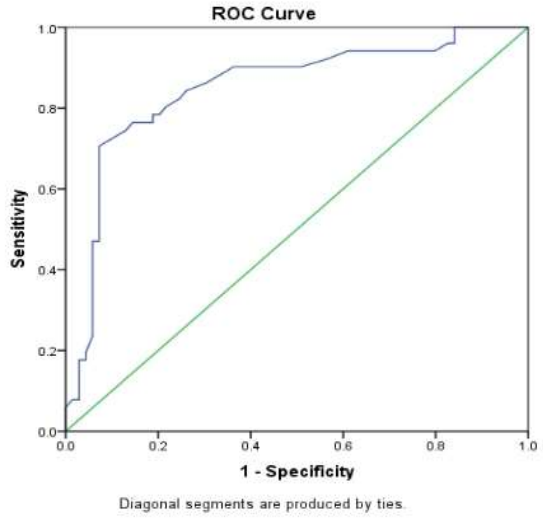

Figure 2: Receiver operating characteristic curve of Cord bilirubin/albumin ratio for predicting neonatal jaundice.

		CSB/A Ratio Mean ± SD	P value
Jaundice by Kramer's Criteria	Jaundiced	0.73±0.17	<0.001
	Non-Jaundiced	0.56±0.16	
TcB	Jaundiced	0.77±0.17	<0.001

Table 5: Agreement between Cord B/A ratio and clinical jaundice by Kramer's criteria, bilirubin by TcB and Serum bilirubin requiring phototherapy

4. DISCUSSION

Early detection of jaundice is crucial for identifying babies at risk of neonatal hyperbilirubinemia, given the serious neurological complications associated with bilirubin toxicity. So there is a felt need for a marker which can be reliably used to predict clinically significant jaundice in a neonate.

In our study we observed 42.5% incidence of neonatal jaundice, which is similar to **Alalfy M et al**[20], who reported a similar incidence of 56%. However some similar studies done by **T Rehna et al**[21] 24%, **Sharma I et al**[22] 19.8% , **M.A. Khairy et al**[23] 16% , **Nidhi Gupta et al**[24] 11.2 % , reported a lower incidence. These differences may be due to different racial and ethnic variations or different set of inclusion or exclusion criteria considered in various studies.

The ROC curve analysis on the Cord Blood Bilirubin / Cord Blood Albumin ratio revealed a cut-off of 0.705 with sensitivity of 70.6%, specificity of 92.75%, PPV of 87.8% and negative predictive value (NPV) of 81.01% while the cut-off point for CBB/CBA ratio obtained in other studies for prediction of hyperbilirubinaemia was 0.86 in a study by **M.A. Khairy et al**[23] and 0.719 in a study by **Sharma I et al**[22]. This variation in cut-off values may be due to the differences in sample size and estimation methods of bilirubin in other studies.

The use of CBB and CBA in the form of a ratio provides us with a new parameter which is more sensitive and specific than CBB or CBA alone. Thus, CBB/CBA ratio is a better predictor for development of neonatal hyperbilirubinemia with high sensitivity, NPV, PPV and specificity when compared with CBB and CBA alone.

Strengths of our study were unbiased enrolment, large sample size, and use of transcutaneous bilirubinometry for jaundice screening, which gave us a more uniform approach and removed interobserver bias.

In this study, only healthy full-term neonates with a birth weight of more than 2.5 kg were included. The research was conducted within a single hospital and was time-bound. Since only inborn neonates were included, it is not a community-based study. Notably, neonates with ABO incompatibility were not excluded from the study. The authors emphasize the need for further research that should be community-based and involve a larger sample size.

DISCLOSURE

The authors declare no conflict of interest

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee, School of Medical Science and Research, Sharda University, Greater Noida (U.P).

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