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A STUDY OF UMBILICAL CORD BLOOD TOTAL BILIRUBIN TO ALBUMIN RATIO AS A SURROGATE MARKER FOR NEONATAL JAUNDICE

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ABSTRACT:

BACKGROUND: Neonatal jaundice is observed in 60% of healthy term neonates and about 80% of preterm neonates in the first week of life. Unconjugated jaundice affects the central nervous system and results in kernicterus which causes permanent neurological sequel. So, the importance of early prediction of neonatal jaundice has become important to identify the newborns who intend to develop jaundice.

AIM: To study the Cord Blood Bilirubin to Albumin Ratio as a surrogate marker for neonatal jaundice.

OBJECTIVE: To evaluate the predictive value of umbilical cord bilirubin to albumin ratio in identifying infants for subsequent jaundice.

METHODOLOGY: A prospective cross-sectional study was conducted over a period of 6 months in 63 term healthy neonates. Under aseptic conditions, umbilical Cord blood was collected after delivery of the newborn and analyzed for bilirubin and albumin levels and cord blood bilirubin to albumin ratio was measured. Measurement of serum bilirubin was done on the 3rd-5th day of life.

RESULT: Out of 63 newborns 28 were males and 35 were females. 26 newborns were born by LSCS and 37 by vaginal delivery. Our study showed a 24% incidence of neonatal jaundice. 15 out of 63 term neonates have developed jaundice. The cut-off point for CBB by ROC curve analysis was 1.88mg/dl with a sensitivity of 87% and specificity of 80%. The cut-off of 0.61 was observed for CBB/CBA ratio with 93% sensitivity and 90% specificity.

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CONCLUSION: Cord blood bilirubin and cord blood bilirubin to albumin ratio CBB/CBA are early predictors of neonatal jaundice but cord blood bilirubin to albumin ratio CBB/CBA ratio is a better surrogate marker to predict significant jaundice in healthy term neonates.
Keywords: Neonatal jaundice, Umbilical Cord blood, Cord Blood Bilirubin / Cord Blood Albumin CBB/CBA ratio.

INTRODUCTION:

The most common physical finding we observe during the first week of life is Neonatal jaundice. Neonatal Jaundice causes yellowish discoloration of the skin, sclera, and mucus membrane.[1]

Bilirubin is derived from haem after the destruction of senescent RBCs in the reticuloendothelial system. Bilirubin binds to albumin and is transported to the liver where it is conjugated and then excreted in urine and stool. Bilirubin from the fetus is removed by the placenta and after birth, the liver takes over the function of removing bilirubin. The rate of production of bilirubin in neonates is more because of increased red blood cell turnover which exceeds the capacity of the neonatal liver to conjugate the released bilirubin. This leads to indirect jaundice. Risk factors that cause increased indirect bilirubin in the neonate include prematurity, race, maternal age, maternal diabetes, ABO incompatibility, Rh isoimmunisation, polycythemia, and cephalohematoma, breastfeeding, and family history of a sibling who had physiological jaundice. [2]

Types of Jaundice in neonates include physiological jaundice which occurs on the 2nd to 3rd after birth and reaches peak levels between the 3rd to 5th day after birth, pathological jaundice occurs within 24hrs of birth, breast milk jaundice, and hemolytic jaundice including immune hemolytic (Rh factor incompatibility, ABO blood group incompatibility) and nonimmune hemolytic (Glucose-6-phosphate dehydrogenase (G6PD) deficiency, spherocytosis, sickle cell disease, alpha thalassemia). Bilirubin in plasma is transported by binding tightly but reversibly to serum albumin and the free bilirubin, the portion that is unbound can more readily cross the intact blood-brain barrier, so albumin level may predict the incidence of jaundice. [3]

Hypoalbuminemia, acidosis, low gestational age, and interference by drugs such as sulpha and some cephalosporins affect the binding of bilirubin to albumin.[4]

Neonatal Jaundice which is seen in 60% of term neonates and almost 80% of preterm neonates, is benign in nature and requires no intervention but 5-10% of them have clinically significant NH which mandates treatment in the form of phototherapy or exchange transfusion. Unconjugated jaundice enters the central nervous system which may result in kernicterus manifests as poor feeding, high-pitched cry, increased muscle tone, fever, seizures, auditory dysfunction, visual impairments, and permanent neurological sequelae.[5].

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Such conditions of neurotoxicity in newborn infants must be avoided by monitoring them to identify neonatal jaundice. It is possible to monitor newborns for neonatal jaundice if stayed in the hospital for 3 to 5 days.

Due to social, medical, and economical reasons, healthy term neonates are discharged early after delivery. As a result, neonatal jaundice is the most common cause of readmission.[6]

Prevention of kernicterus, aggressive management, unnecessary expenditures, maternal anxiety, and decrease in the length of stay in hospital is avoided by early prediction and identification of NH.[7]

Because of poverty, low education, and cultural practices, regular follow-up is almost impossible in developing and underdeveloped nations. So, the prediction of NH is vital and lifesaving in developing countries like India where most of them can't follow the protocol of regular follow-up of neonates and spend on costly investigations and treatments.[8]

The bilirubin albumin ratio (BAR) is a surrogate parameter for free bilirubin and an interesting additional parameter in the management of NNH. The bilirubin albumin ratio serves as a sensible marker of bilirubin binding to albumin until the albumin binding reserve or bilirubin which is unbound can be clinically measured with accuracy and precision. [9]

The aim of this study is to evaluate the cord blood bilirubin to albumin ratio as a predictor of neonatal jaundice.

MATERIAL AND METHODS:

This Prospective cross-sectional study was conducted among 63 healthy term neonates over a period of 6 months during 2020- 2021 at Niloufer Children Hospital after taking clearance from the Institutional ethical committee. After explaining in the local language about nature of the study in detail informed consent was taken from the parents of recruited neonates.

Inclusion criteria: Newborns with gestational age ≥37 weeks, irrespective of gender, birth weight > 1800gms, born by LSCS or vaginal delivery, with APGAR score greater than 7 at 1 min and 5 min.

Exclusion criteria: Preterm infants (gestational age <37 weeks), Newborns with ABO blood group, and Rh incompatibility. Newborns with significant illnesses such as neonatal sepsis, birth asphyxia, respiratory distress syndrome, meconium aspiration syndrome, and gross congenital malformations, are critically ill or hemodynamically unstable. Neonates with antenatal risk factors like Gestational Diabetes, preeclampsia, malaria, maternal fever, and chorioamnionitis.

METHODOLOGY:

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Detailed antenatal, perinatal and postnatal history was collected from the mother and case sheets. Under aseptic conditions umbilical cord blood was collected after delivery of the newborn, 3ml of cord blood was collected into 2 vacutainers -one plain vacutainer and another EDTA vacutainer. A serum sample from a plain vacutainer was analyzed for bilirubin and albumin levels in an autoanalyzer (BECKMAN COULTER-AU 5800 SERIES). EDTA vacutainer was sent for ABO blood grouping and Rh typing. Cord blood Serum was analyzed for total bilirubin and albumin. After that total bilirubin to albumin ratio was calculated. Examination of 63 babies was done after 72hrs of age clinically and with total serum bilirubin estimation.

The data was entered into an EXCEL sheet and analyzed in SPSS software. Results were expressed as Mean ± SD. A P-value less than 0.05 was statistically significant. Receiver Operating Characteristic (ROC) curve was created and Area Under Curve analysis was done to detect the best cut-off value of cord blood bilirubin and cord blood bilirubin to albumin ratio. Sensitivity and specificity of Cord Blood Bilirubin (CBB) and (CBB/CBA) Cord Blood total Bilirubin to Albumin ratio (CBB/CBA) was calculated.

RESULTS:

Table 1: Distribution of study population according to variables.

Gender	**Number of cases**	**Percentages**
Male	28	44.44%
Female	35	55.56%
Mode of delivery		
Normal Vaginal Delivery	37	58.7%
Lower Segment Caesarean Section	26	41.2%

Out of 63 newborns, 28 were males and 35 were females. 26 newborns were born by LSCS and 37 by vaginal delivery. Our study showed a 24% incidence of neonatal jaundice. 15 out of 63 term neonates have developed jaundice.

Table-2: Other parameters of the study are mentioned

Parameters	**Mean ± SD**
Birth Weight	(2.49 ± 0.34)
Gestational Age – Weeks	(38.39 ± 1.14)

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CBB (mg/dl)	(1.84 ± 0.59)
CBA (g/dl)	(3.52 ± 0.65)
CBB/CBA Ratio	(0.54 ± 0.26)
Serum Bilirubin (3rd to 5th day)	(11.89 ± 4.31)

With cord blood bilirubin levels more than 2mg/dl, 13 developed significant hyperbilirubinemia that is greater than or equal to 15mg/dl and 2 neonates had below 2mg/dl. we classified neonates into 2 groups based on cord blood albumin levels of less than 2.9g/dl and more than 2.9g/dl.13 out of 63 neonates had cord blood albumin CBA levels ≤ 2.9 g/dl and 50 neonates had cord blood albumin levels ≥ 2.9.

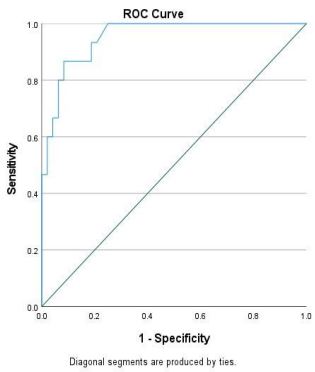
8 out of 15 neonates who developed significant hyperbilirubinemia had cord albumin levels < 2.9g/dl and 7 had >2.9 g/dl. A significant positive correlation of 0.803 was observed between CBB and Serum bilirubin levels on the 3rd day of birth with p <0.05 and a Significant negative correlation of -0.340 was observed between CBA and serum bilirubin levels at 3rd day with p <0.05.

Table-3: Incidence of pathological hyperbilirubinemia in relation to CBB levels

	Cord Blood Bilirubin≥ 2	**Cord Blood Albumin≤ 2.9**
Serum bilirubin ≥ 15mg/dl	13(86.67)	8(53.33)
Serum bilirubin ≤15mg/dl	2(13.33)	7(46.67)

Fig. 1. ROC curve denoting sensitivity and specificity for A) cord blood bilirubin (CBB), and B) CBB/CBA ratio for the prediction of development of Neonatal hyperbilirubinemia

A.



B.

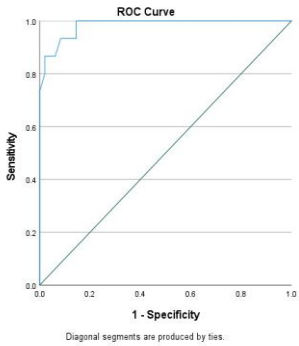


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Table-4: Variable in receiver operating curve in the present study

	AUC	95% Confident Interval Predictor		Cut of Value	Sensitivity (%)	Specificity (%)
		Lower Bound	Upper Bound			
CBB	0.953	0.904	0.956	1.88	87	80
CBB/CBA Ratio	0.983	0.958	0.987	0.61	93	90

The cut-off point for CBB by ROC curve analysis was 1.88mg/dl with a sensitivity of 87% and specificity of 80%. The cut-off of 0.61 was observed for CBB/CBA ratio with 93% sensitivity and 90% specificity. The Area Under Curve (AUC) of CBB/CBA ratio by ROC analysis is 0.983 which is higher than the 0.953 of CBB. By this, we infer that CBB/CBA ratio has higher sensitivity and specificity compared to CBB.

DISCUSSION:

Considering the neurological morbidities of high bilirubin toxicity in neonates, it is extremely important to identify the neonates at risk of developing neonatal jaundice. In our study with 63 neonates, we observed a 24% incidence of neonatal jaundice, which is slightly higher than 19.84% which was reported in [6] and [10]. Some studies which are similar to our study showed a lower incidence of 10.7% [11], and 12.80% [12] though some studies showed a high incidence that showed variation from 34% to54.3% [13] [14]. The change in different studies may be because of racial, and ethnic variations and due to different inclusion or exclusion criteria used in other studies.

In our study, the relationship was insignificant between neonatal jaundice and cord blood bilirubin, and bilirubin/albumin ratio, with regards to gender, gestational age, birth weight, or mode of delivery. This coincided with Awasthi et al. [12] and Alpay et al. [15]

In our study, the cut-off Cord Blood Bilirubin CBB level (1.88 mg/dl) with Receiver Operating Characteristic (ROC) curve analysis was similar to (1.90 mg/dl) Indra Kumar et al. [10] and lower than that of previous studies by Knudsen et al. [16], Sun et al. [17], Ahire et al. [18] which conveyed the cut-off of 2.3mg/dl and the 3.0 mg/dl respectively.

The ROC curve analysis on the Cord Blood Bilirubin / Cord Blood Albumin CBB/CBA ratio revealed a cut-off point of 0.61 mg/dl with a sensitivity of 93% and specificity of 90% which is similar to that in the study by Khairy MA at al. [7] where ROC curve analysis of Cord Blood Bilirubin CBB/ Cord Blood Albumin CBB/CBA ratio revealed that a cut off value > 0.61 mg/dl had a good predictive value with a sensitivity of 100.0%, specificity of 88.4%, and other studies showed cut- off point 0.78 [19], 0.98 [20]. The differences in bilirubin estimation methods and sample size may cause such variation in the cut-off value. A 0.89

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cut-off point of cord blood bilirubin/albumin ratio with a sensitivity of 95.65% and specificity of 95.57% was demonstrated by Ramteke et al. [21]

In our study with Receiver Operating Characteristic (ROC) curve, the cut-off of Cord Blood Bilirubin CBB 1.88mg/dl demonstrated 87% sensitivity and 80% specificity and the cut-off of Cord Blood Bilirubin CBB/ Cord Blood Albumin CBA Ratio 0.61 demonstrated 93% sensitivity and 90% specificity.

Based on the above discussion we infer that Cord Blood Bilirubin CBB/ Cord Blood Albumin CBA Ratio is a better surrogate marker for the prediction of neonatal jaundice. Hence, we recommend the estimation of Cord Blood Bilirubin CBB/ Cord Blood Albumin CBA Ratio in all healthy term neonates to plan to follow up of neonates and prevent readmission due to neonatal jaundice.

CONCLUSION:

Cord blood bilirubin and cord blood bilirubin to albumin ratio CBB/CBA are early predictors of neonatal jaundice but cord blood bilirubin to albumin ratio CBB/CBA ratio is a better surrogate marker to predict significant jaundice in healthy term neonates. The limitation of the study is the small sample size. Research on a large scale should be done for more clarification on the predictive value of cord blood bilirubin to albumin ratio for early prediction of neonatal jaundice.

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