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PERFORMANCE OF CORD BLOOD ALBUMIN AT BIRTH FOR PREDICTION OF SIGNIFICANT NEONATAL HYPERBILIRUBINEMIA

[1]*Dr. Zahoor Hussain Daraz, [2]Dr. Berkheez Shabir and [3]Dr. Rehana Afshan

[1]MBBS, MD (Paediatrics).
[2]MBBS, MS (Obstetrics & Gynaecology).
[3]MBBS, MD (Radiology & Imaging).

***Corresponding Author: Dr. Zahoor Hussain Daraz**
MBBS, MD (Paediatrics).

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ABSTRACT

TITLE "Performance of Cord Blood Albumin at Birth for Prediction of Significant Neonatal Hyperbilirubinemia". **Background:** Neonatal Jaundice is one of the commonest problems that occur in a newborn and most of the times it is physiological. However, a few (5-6%) become deeply jaundiced requiring immediate intervention. The cause of this significant hyperbilirubinemia has been attributed to many factors including a low concentration of bilirubin binding ligand Albumin. Henceforth Albumin in a critical concentration is of considerable importance in development of hyperbilirubinemia. Moreover, American Academy of Pediatrics recommends that newborn discharged within 48 hours should have a follow-up visit after 72 hours for any significant jaundice. The present study was therefore conducted to find out the cut off value of cord blood albumin at birth that can predict significant Neonatal Hyperbilirubinemia. **Objective:** To evaluate the performance of cord blood albumin at birth for prediction of significant Neonatal Hyperbilirubinemia with respect to sensitivity and specificity through receiver operator curve (ROC). **Method:** This prospective observational study was performed on 70 healthy term neonates. Relevant maternal history was taken. Neonates with low birth weight, perinatal asphyxia or septicemia were excluded. Cord blood was collected at birth and Cord Serum Albumin level (CSA) was measured. Study subjects were divided into 2 groups based on Cord Serum Albumin level. Neonates were assessed clinically every day. Total Serum Bilirubin (TSB) was measured during 72-96 hours of life. Total Serum Bilirubin (TSB) value ≥17mg/dl is considered significant Neonatal Hyperbilirubinemia (NH) requiring intervention like phototherapy (PT) or Exchange transfusion (ExT). Breast feeding was ensured and dehydration was excluded in each neonate. **Result:** Study population was divided into 02 groups based on Cord Serum Albumin (CSA) level at birth. Cord Serum Albumin level varied between 2.4g/dl to 4.5 g/dl. Mean Cord Serum Albumin level in Group-I was 2.58±0.12 and of group-II was 3.30±0.30 g/dl respectively and the difference among the 2 groups was significant; however, there was no significant difference between mean gestational age and mean birth weight of the 02 groups. (39.15weeks ±1.28 vs 39.09weeks ±0.15; 2877.6grams ±184.5 vs. 2850.5grams ±215.4. There was significant negative correlation seen between Cord Serum Albumin and Neonatal Hyperbilirubinemia (NH). Receiver operator curve (ROC) analysis was done and a cutoff point of 2.7 g/dL was determined with a sensitivity of 81.81%, specificity 96.6% for prediction of significant Neonatal Hyperbilirubinemia. **Conclusion:** Cord blood Albumin concentration at birth is a good predictor for significant hyperbilirubinemia and Cord Blood Albumin level of ≤2.7 g/dL has sensitivity of 81.81% and specificity of 96.5% in predicting Significant Neonatal Hyperbilirubinemia.

KEYWORDS: CSA, TSB.

INTRODUCTION

Jaundice is a visible manifestation in skin and sclera of elevated serum concentration of bilirubin. Neonatal Jaundice is one of the commonest problems that occur in a newborn and most of the times it is physiological in nature. In reality Physiological Jaundice takes place in approximately 60% of newborns, though it is unimportant in most.[1] however, a few (5-6%) have been observed to become deeply jaundiced requiring investigation and treatment & if not managed adequately, may result in death or survival with severe brain damage.[2] Hence, Significant Neonatal Hyperbilirubinemia is a cause of concern for parents as well as pediatricians.

The cause of this significant hyperbilirubinemia has been attributed to many factors including a higher circulating erythrocyte volume, a shorter erythrocyte life span, decreased uridine diphosphoglucuronosyl transferase (UDPGT) activity and low concentration of bilirubin binding ligand Albumin.[3]

Blood albumin in foetus is mostly derived from maternal circulation till baby's liver starts synthesis[4] and helps in transport of unconjugated bilirubin. It is considered as the major binding protein in the human neonate. Synthesis of albumin appears approximately at 7th-8th week in the human fetus. Albumin concentrations in a neonate can be as low as (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several months.[5] Lower normal limit for cord serum albumin in term babies is 2.8g/dl.[6] Low production of albumin will lower its transport and binding capacity. Bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the molar bilirubin- to- albumin (B: A) ratio is > 0.8. It is the free bilirubin which can cross the blood brain barrier. So Albumin level of a critical concentration is of immense importance in prevising the development of jaundice. Moreover, the absence of albumin renders bilirubin free to cross Blood Brain Barrier and cause brain damage.

Though neonatal hyperbilirubinemia is not a major cause of mortality in Bangladesh but its morbidity is significantly observed during neonatal period. It occurs in 5-10% of healthy term infants.[7] It is the most common cause of readmission after early hospital discharge.[8] Concern regarding jaundice has increased after reports of bilirubin induced brain damage came forth in healthy term infants even without hemolysis.[9]

Early discharge of healthy term infants after delivery has become a common practice because of social reasons and economic constrains.[10] however the association of decreased length of stay and the risk of readmission to hospital has previously been shown and it is significant that most common cause of readmission during early neonatal period is hyperbilirubinemia.[11]

Physiological jaundice is the most common type in neonates. There is a transient unconjugated hyperbilirubinemia in the neonatal period. In healthy term neonates, the unconjugated bilirubin rises usually at second and 3rd day of life and reaches peak level on 5th day of life and then decline gradually.[12] Jaundice persists no longer than one weak in term neonates.

Traditionally a distinction has been made between physiological jaundice and hyperbilirubinemia, which is either pathological in nature or severe enough to be considered for further evaluation and management. This latter entity is called "nonphysiologic", although no disease is identified as being causative or consequent.

Any serum bilirubin level exceeding 17mg/dl (291υmol/l) should be considered pathologic and warrants investigations for the cause and therapeutic intervention.[13]

Total serum bilirubin (TSB) in an infant discharged within 48hours of age generally shows an increasing trend and some of these infants later develop hyperbilirubinemia commonly occurring after 72 hours of age.

The American Academy of Pediatrics recommends that newborn discharged within 48 hours should have a follow-up visit after 72 hours for any significant jaundice and other problems.[14] What is concerning most to doctors is the early discharge of term neonates[15] whose follow up is missed. Thus recognition, follow up and early treatment of Jaundice has become more difficult as a result of earlier discharge from the hospital.[16]

However, as far as Bangladesh is concerned such recommendations as per American Academy of Pediatrics are not appropriate due to limited follow up facilities in the community. Therefore, it is difficult to predict which infant is at increased risk for significant and relatively late hyperbilirubinemia. And as such, there is obvious need to implement a follow up programme or to develop predictive guideline that will enable a physician to predict or to identify which of the early discharged newborns will develop significant hyperbilirubinemia.

MATERIALS AND METHODS

This was a Prospective observational study carried out in the Department of Neonatology & Department of Obstetrics & Gynaecology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2016 to August 2017 ($1^{1/2}$years).

Term healthy neonates with an average weight ≥2.5 kg and an APGAR score of >7 and without any complications (Perinatal Asphyxia, septicemia) were included in the study.

Data were collected using a structured questionnaire through relevant information from mother; physical findings of neonates at birth and during follow up of 5 days. Exclusive breast feeding was ensured to avoid any dehydration and laboratory investigation results were recorded.

Four ml of cord blood was collected from all the newborns under study through the placental end of the umbilical cord at birth. Two ml was poured in a plain test tube for serum albumin estimation, 1ml in a plain test tube for blood grouping & Rh typing & direct antiglobin test and remaining 1ml in an EDTA coated test tube for complete blood picture. At 72- 96 hours after birth, 2ml of venous blood was collected from superficial vein after proper aseptic care for serum bilirubin estimation. All infants were followed up clinically everyday till their discharge for any development of jaundice and its severity. Furthermore, the parents of those subjects who got an early discharge were asked to come for follow-up at 72 hours or early if they find their babies icteric. Study population was divided into 2 groups based on cord blood albumin level.

Group-I: Newborns with Cord Blood Albumin level of ≤2.8g/dL and Group-II: Newborns with Cord Blood Albumin level of >2.8g/dL.

Data collected were analyzed using SPSS 20.0 software with the help of Fischer's exact test, unpaired t-test and ROC (Receiver operative characteristic curve) analysis. Written informed consent was obtained from all parents and guardians of the patients under study.

RESULTS

Eighty-eight healthy term new born babies were enrolled in the study. Of them, 11 newborns were withdrawn by their parents on the day of follow up, 07 newborns didn't comply with the follow up schedule or they developed sepsis and needed neonatal intensive care (NICU) admission and were excluded from the study and hence dropout rate was 20%.

A total of 70 neonates were followed up for the first 72-96 hours of life clinically and with laboratory investigations. Notably all the neonates were ensured exclusive breast feeding and dehydration was excluded.

In the present study out of 70 enrolled babies 42 were male and 28 were female. The male to female ratio was 1.5:1. Study population was divided into 2 groups based on Cord Blood albumin level. Group-I had CBA ≤2.8g/dL and Group-II had CBA of >2.8g/dL. Mean birth weight of the study subjects in Group-I was 2877.6±184.5 grams and mean birth weight of study subjects in Group-II was 2850.5±215.4 grams, there was no significant difference between the mean weights of 2 groups. (Table-III).

Mean gestational age of neonates in Group-I was 39.15±1.28 weeks and mean gestational age of neonates in Group-II was 39.09±0.15 (Table-III) and there was no significant difference between the 2 groups in terms of gestational age.

However, there was significant difference found between 2 groups in terms of mean albumin levels with a p-value of <0.05. (Table III) 2.58±0.12 vs 3.30±0.30 (g/dL).

Out of 42 male neonates, 06 (14.2%) developed significant hyperbilirubinemia while out of 28 female neonates, 05 (17.8%) newborns developed hyperbilirubinemia. This difference was not found significant statistically (p >0.05) (Table II).

Forty-nine neonates were delivered by Lower uterine caesarian section (LUCS) and 7 (14.2%) developed hyperbilirubinemia, 17 neonates were delivered by Normal vaginal delivery (NVD) out of which 4 (23.5%) developed hyperbilirubinemia but statistically the difference was not significant (*P*-value = 0.616) (Table II).

The majority of the cases that is (9/11) who develop significant hyperbilirubinemia belong to Group-I (81.8%) and from Group- II only 2 out of 59 (3.382%) developed significant Hyperbilirubinemia and there was a significant relationship between these categorical variables with *p*-value of <0.001). (Table-IV).

Group-I has lower mean albumin level than the group-II and hyperbilirubinemia was found to be the highest in Group-I. Overall, there was a significant negative correlation found between hyperbilirubinemia and albumin level in the study population. (Table-III and Figure-I).

For the prediction of significant Neonatal Hyperbilirubinemia, the cut off value of cord serum albumin of ≤2.7 g/dL was chosen, on the basis of receiver operating characteristics (ROC) curve analysis. (Fig-II) In the present study the cord serum albumin level of ≤2.7 g/dL having the sensitivity 81.82%, specificity 93.22%, positive predictive value 69.23% and negative predictive value 96.49% in the prediction of the neonatal hyperbilirubinemia was determined. (P <0.001*) (Fig-II and Table V).

Clinical characteristics of all those study subjects who developed significant Hyperbilirubinemia irrespective of Cord Blood Albumin level has been depicted in Table-VI.

Table 1: Baseline clinical characteristics of study population (n=70).

Parameter	Mean ± SD	Range
Cord serum albumin (g/dl)	3.1± 0.395	(2.4 – 4.5)
Weight (Grams)	2855.6±209.0	(2500-3250)
Gestational age (Weeks)	39.1±1.6	(37-41)

Table II: Distribution of significant Neonatal Hyperbilirubinemia according to gender and mode of delivery n=70.

Variables	Significant Hyperbilirubinemia No (n=59) No / (%)	Significant Hyperbilirubinemia Yes (n =11) No/ (%)	*P*-value
Gender			
Male	36 (61.0%)	6 (54.5%)	0.688^{ns}
Female	23 (39.0%)	5 (45.5%)	
Mode of delivery			
CS	42 (71.2%)	7 (63.6%)	0.616^{ns}
NVD	17 (28.8%)	4 (36.4%)	

Data were expressed as frequency and percentage and analyzed by Fischer Exact test, ns= Not significant.

Table III: Clinical characteristics of study groups with comparison of the mean GSA (Gestational age), MBW (Mean Birth Weight) and MCSA (Mean Cord Serum Albumin.

Parameters	Group I (n=13)	Group II (n=57)	*P*-value
Gestational age (weeks) Mean ± SD	39.15±1.28	39.09±0.15	> 0.05
Birth weight (grams) Mean ± SD	2877.6±184.5	2850.5±215.4	> 0.05
Cord Serum Albumin (g/dl) Mean ± SD	2.58±0.12	3.30±0.30	<0.001

Group I = Cord blood albumin ≤2.8gm/dl)
Group II = Cord blood albumin >2.8gm/dl
Significance between 2 groups was derived using t-test.

Table IV: Significant Hyperbilirubinemia in study subjects among both groups.

Cord Albumin	Significant Hyperbilirubinemia Yes	No	Total	RR	*P*-Value
Group I					
≤2.8gm/dL	9 (69.2%)	4 (30.8%)	13		
				19.73	
Group II				(4.82-80.72)	<0.001
>2.8gm/dL	2 (3.5%)	55 (95.6%	57		
Total	13 (100.0%)	57 (100.0%)	70		

Data were expressed as frequency and percentage and analyzed by Fischer-Exact test.

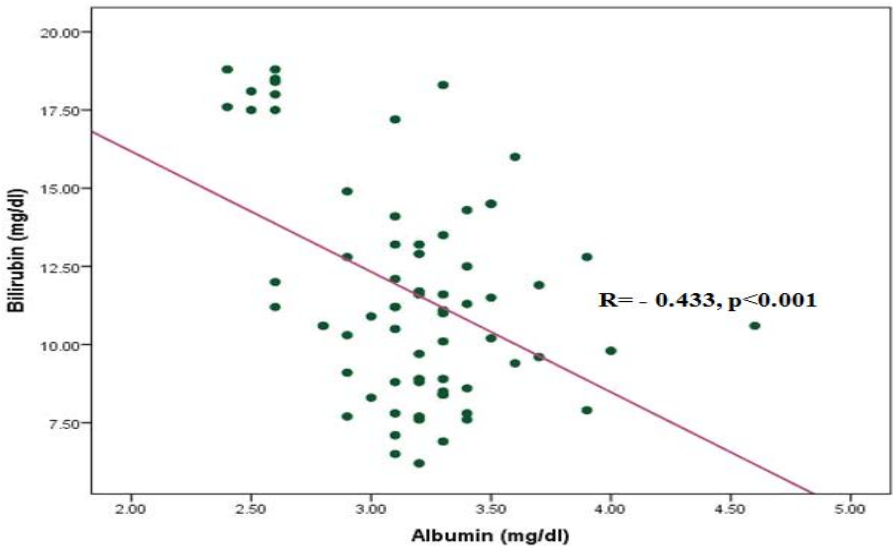

Fig. I: Correlation between bilirubin and albumin.

ROC Curve

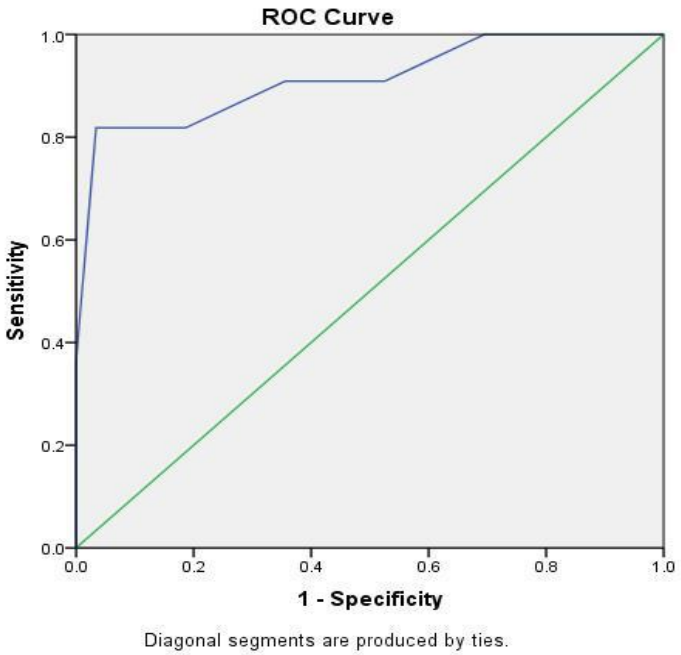

Figure II: ROC (Receiver operating characteristic curve) analysis at various Albumin levels in cord blood for prediction of Subsequent-Hyperbilirubinemia.

Area under the Curve

Test Result Variable (s): Albumin (g/dl)

			Asymptotic 95% Confidence	
		Asymptotic	Interval	
Area	Std. Error	Sig.	Lower Bound	Upper Bound
0.912	0.057	0.000	0.801	1.000

Table V: Coordinates of the ROC Curve showing cut-off values at different albumin levels.

Coordinates of the Curve

Test Result Variable(s): Albumin (mg/dl)

Cut-off Values	Sensitivity	1 - Specificity
1.4000	0.000	0.000
2.4500	0.182	0.000
2.5500	0.364	0.000
2.7000	**0.818**	**0.034**
2.8500	0.818	0.068
2.9500	0.818	0.153
3.0500	0.818	0.186
3.1500	0.909	0.356
3.2500	0.909	0.525
3.3500	1.000	0.695
3.4500	1.000	0.797
3.5500	1.000	0.864
3.6500	1.000	0.898
3.8000	1.000	0.932
3.9500	1.000	0.966
4.3000	1.000	0.983
5.6000	1.000	1.000

Cut off value = 2.70, Sensitivity = 81.8%, Specificity = 96.6%.

Table VI: General characteristic features of those 13 study subjects who developed significant Hyperbilirubinemia out of total study population. (n=70).

Serial	Sex	Gestational age (weeks)	Birth weight (grams)	Cord Serum Albumin(g/dl)	Serum Bilirubin
1.	F	38	2800	2.6	18.8
2	F	40	2810	2.4	18.7
3	M	40	3200	2.6	18.5
4	F	37	2800	2.6	18.3
5	M	39	2780	2.7	18.1
6	F	38	2910	2.5	18
7	M	41	3000	2.6	17.6
8	F	40	3100	2.4	17.5
9	M	40	3000	2.6	17.5
10	F	39	2850	2.5	17.5
11	M	38	2900	2.5	17.2
12	F	39	3200	3.6	17.5
13	M	37	2850	2.9	17.8

DISCUSSION

This prospective observational study was conducted to see the performance of Cord blood albumin in predicting significant Neonatal Hyperbilirubinemia. Regarding length of stay in the hospital after birth, debates continue to pass on without a proper conclusion. Bravemann *et al.*, (1997)[16] associated readmissions in hospitals with early discharge and community attitude; hence a benefitting follow up schedule for community is a priority. By determining performance of albumin in prediction of significant hyperbilirubinemia one could easily frame a follow up schedule with confidence and accuracy.

In this study, a total of 88 new born babies were enrolled. Of them, 11 newborns were withdrawn by their parents on the day of follow up, 07 newborns were excluded from the study due to NICU admission for sepsis.

Incidence of hyperbilirubinemia varies from 8.3% to 14.8%.[17] In the present study 70 subjects all of them term healthy babies were followed up till 72-96 hours of life for significant hyperbilirubinemia. And during the follow-up period 11 of 70 (15.7%) developed significant hyperbilirubinemia (≥17mg/dl) which correlates well with other studies. Similar incidence of (14.5%) was observed by Narang *et al.*, (1997).[18] The incidence is relatively higher compared to observations of Singhal *et al.*, (1992) who found 5.9% neonates developed significant jaundice and this could be probably due to our smaller sample size.[19]

In this study male female ratio was 1.5:1 however the difference was found insignificant in relation with significant hyperbilirubinemia. Similarly, Taksande *et al.*, (2005) a study on 200 neonates with 82 males and 118 females found no relation between the sex of the neonate and the neonatal hyperbilirubinemia.[20] Another study done by Venkatamurthy *et al.*, (2011) on 174 neonates, 98 were male and 76 were female and the relation between gender and Hyperbilirubinemia was found insignificant with a *p*-value of 0.899.[21]

In the umbilical cord blood samples, applying the critical value of 2.8g/dl for albumin, study population were divided into 2 groups and 9 neonates out of 11 from Group-I developed significant hyperbilirubinemia having Albumin level less than 2.8g/dl. In the same text Trivedi *et al.*, (2013) studied 605 neonates and 205 developed hyperbilirubinemia and he concluded that majority of the infants who require phototherapy had cord albumin level lower than 2.8 g/dL.[22] This finding was similar to our study.

Suchanda *et al.*, (2011) in a study of 40 neonates found that 80% neonates with cord albumin ≤2.8 g/dl developed significant icterus requiring phototherapy and this finding matches with our study where in Group-I, 88% neonates developed significant jaundice requiring intervention and all neonates had albumin ≤2.8 g/dL.[23]

Meena K (2011) study of 40 neonates divided study population into 2 groups based on Albumin level and found 80% neonates of Group-I with albumin ≤2.8g/dL developed significant jaundice. In the present study under Group-I with albumin≤2.8g/dL, 09 babies out of 11 developed significant hyperbilirubinemia that matches with the above study.[24]

In this study ROC analysis reveals the sensitivity of cord albumin at 2.7g/dL to be 81.81%, specificity of 96.3% in determining the predictability of significant hyperbilirubinemia. The positive and negative predictive value was found to be 69.23% and 96.49% respectively at the same cord serum albumin level.

Pahuja M *et al.*, (2016) in their study had noted that positive predictive value of cord albumin for development of neonatal hyperbilirubinemia was 75% which implies a fair predictive value of the criteria with

61.3% sensitivity and 76.8% specificity and is slightly lower than the present study.[25]

Sahu *et al.,* (2011), showed that 70% newborns who developed significant Neonatal hyperbilirubinemia had cord albumin level <2.8 g/dL, 30% newborn had cord albumin level 2.9-3.3 g/dL. These findings match with this study where we found babies with albumin <2.7g/dL developed significant hyperbilirubinemia.[26]

In a recent study kumar *et al.,* (2016), found a significant correlation between Cord serum albumin level and neonatal hyperbilirubinemia. They concluded that cord serum albumin level of ≤2.8 g/dL is a good risk indicator in predicting the neonatal hyperbilirubinemia at birth. In the present study we also found a significant correlation between albumin level and bilirubin level.[27]

Aiyappa K (2017), in a study of 165 neonates found the sensitivity and specificity of cord albumin at ≤2.8g/dL to be 71.8% and 65.1% respectively in detecting significant neonatal hyperbilirubinemia, the percentage is marginally less than our results however support well the fact that less albumin is related with development of more significant jaundice as determined by our study.[28]

CONCLUSION

Cord blood Albumin concentration at birth is a good predictor for significant hyperbilirubinemia and Cord Blood Albumin level of ≤2.7 g/dL has sensitivity of 81.81% and specificity of 96.5% in prediction of significant neonatal hyperbilirubinemia.

Recommendation

Cord blood albumin level at birth helps to track down high risk neonates by predicting the possibility of development of neonatal hyperbilirubinemia. A value less than 2.7 g/dL has been found to be associated with significant hyperbilirubinemia needing intervention. Hence routine determination of cord blood Albumin at birth can be implemented.

Limitations of the study

1. Sample size was small.
2. Study was conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU) only, a tertiary care hospital and does not represent the whole community of Bangladesh.

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