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ORIGINAL RESEARCH

Evaluating the prognostic significance of cord blood bilirubin and albumin for substantial newborn hyperbilirubinemia: Prospective research from India

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ABSTRACT

Introduction-Hyperbilirubinemia is a common medical condition in neonates. It becomes problematic when bilirubin levels go to abnormally high levels and result in neurological problems. The present study was conducted to evaluate the prognostic significance of cord blood bilirubin and albumin for substantial newborn hyperbilirubinemia.

Material and methods-Over the course of a year, the prospective observational study was carried out in the department of pediatrics among 108 healthy term neonates. They were monitored daily for jaundice symptoms until they were five days or until they were released from the hospital. According to Kramer's rule, venous blood was sent for bilirubin measurement if clinical icterus was found within 72 hours of birth or at any time after. A p-value of less than 0.05 was deemed statistically significant.

Results-Hyperbilirubinemia was detected in 23.18% of the 108 individuals in the current investigation. There were more male patients (60%) than female patients (40%). Bilirubin levels were over 2.5 mg/dL in 42.3% of cases, below 2.5 mg/dL in 17.1% of cases, and above 2 mg/dL in 32.6% of cases and below 2 mg/dL in 15.2% of cases. With a p-value of less than 0.001, the correlation between the UCB cut-off of 2.5 mg/dL and the UCB cut-off of 2 mg/dL to predict neonatal hyperbilirubinemia was highly statistically significant.77.2% of patients had albumin levels above 3.2 and 9.3% had albumin levels below 3.2, while 51.1% of patients had albumin levels above 3 and 3.2% had albumin levels below 3. With both albumin cut-offs of 3 and 3.2, there was a statistically significant connection between albumin and neonatal hyperbilirubinemia (p-value <0.001). Sensitivity and specificity of UCB was greater than UCA.

Conclusion-Neonatal hyperbilirubinemia can be predicted well by both UCB and UCA, However UCB is a stronger predictor than UCA.

Keywords- Cord blood albumin, Neonates, Prediction tool, Umbilical cord bilirubin

INTRODUCTION

Hyperbilirubinemia is a common physiological phenomenon in neonates. By days 2 to 4, it impacts 60–70% of term infants and 80% of preterm infants [1]. The mean bilirubin values in cord blood range from 1.4 to 1.9 mg/dL [2,3]. Newborns produce bilirubin everyday at an approximate rate of 6 to 8 mg per kilogramme. On the third or fourth day of life, the average total blood bilirubin level generally reaches a peak of 5 to 6 mg per dL and gradually normalises within 1 to 2 weeks.[4,5] In babies with multiple risk factors, a severe variant of physiologic jaundice may occur, resulting in total blood bilirubin levels reaching 17 mg/dL.[6] The primary causes of hyperbilirubinemia in neonates are reduced red blood cell (RBC) survival, enhanced enterohepatic circulation, and a transient deficit in bilirubin conjugation [1]. If neglected, hyperbilirubinemia may

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advance to kernicterus, a clinical condition associated with seizures, neurological impairments, and potential mortality [7, 8].

In this context, it is essential to possess a sensitive and cost-effective prognostic marker for hyperbilirubinemia in newborns.[9] Total blood bilirubin levels typically range from 1 to 3 mg/dl at birth, peak between 5 to 15 days, and subsequently decrease by 3 weeks.[10]

Numerous prior research have suggested that cord blood bilirubin may serve as a non-invasive and rapid biochemical diagnostic for predicting neonatal hyperbilirubinemia.[11-13]

Recently, cord blood albumin has been investigated as a marker for the same purpose. Albumin binds to unconjugated bilirubin and facilitates its transit. This subsequently diminishes bilirubin toxicity in tissues by competing for bilirubin binding sites.[14] Reduced albumin synthesis will diminish its transport and binding capacity, hence facilitating the early identification of at-risk infants to prevent issues related to neonatal jaundice. [9]

Nonetheless, there is a deficiency of clinical research regarding the accuracy of these approaches as predictors of hyperbilirubinemia, particularly in Indian contexts. Hence the present study was conducted to evaluate the prognostic significance of cord blood bilirubin and albumin for substantial newborn hyperbilirubinemia.

MATERIAL AND METHODS

The prospective observational study was carried out in the department of paediatrics over a duration of one year. Ethical approval was obtained from the institutional ethical committee of the allied medical college and hospital prior to the initiation of the investigation.

A total of 108healthy term newborns were selected for the study based on the following inclusion and exclusion criteria:

Inclusion criteria: Term neonates with a gestational age exceeding 37 weeks of either sex, born via normal vaginal delivery or caesarean section, with a birth weight of at least 2 kg and Apgar score of 7 or above at one minute of life.

Exclusion criteria: Preterm infants, infants with ABO and Rh incompatibility, twin delivery, neonates delivered with emergency LSCS, those with an Apgar score of less than 7 at one minute of life, infants delivered instrumentally, neonates with sepsis, respiratory distress, and significant congenital defects.

Informed consent was obtained from parents or guardians following a comprehensive explanation of the study's method. A pertinent prenatal history was obtained through maternal interviews or antenatal records. Subsequent to the infant's birth, the umbilical chord was clamped on two occasions. Two millilitres of cord blood were collected into two separate vials; one vial was dispatched for analysis of the infant's blood type, while the other was utilised to assess albumin and bilirubin concentrations.

The colourimetric diazo method was utilised in a semi-automated assay to assess cord bilirubin levels. The semi-automated bromocresol green method was employed to assess umbilical cord albumin. An analysis of the infant's blood type was also dispatched. Consequently, the rhesus factor, blood group, total cord bilirubin, and cord albumin levels of the neonates were assessed.

The neonates were monitored daily for the onset of jaundice over a period of five days or until their discharge, whichever occurred first. A peripheral venous blood sample for bilirubin testing was obtained after 72 hours. If Kramer's rule suggests clinical icterus at any stage, venous blood must be drawn and submitted for bilirubin assessment. The National Neonatology Forum of India (NNF) clinical practice guidelines stipulate that bilirubin levels over 13 mg/dL on day 2 or equal to or greater than 17 mg/dL on day 3 necessitate phototherapy. The risk of hyperbilirubinemia was assessed using cord bilirubin cutoff values of 2 mg/dL and 2.5 mg/dL, with corresponding BAR values of 0.59 and 0.69.

The analysis was conducted using SPSS version 25.0. Qualitative data were presented as numbers and percentages, whereas quantitative data were represented as mean ± standard deviation (SD). The statistical data were evaluated using the t-test, Chi-square test, and Pearson's correlation. A p-value of ≤ 0.05 was deemed statistically significant.

RESULTS

Hyperbilirubinemia was detected in 23.18% of the 108 individuals in the current investigation as shown in graph.

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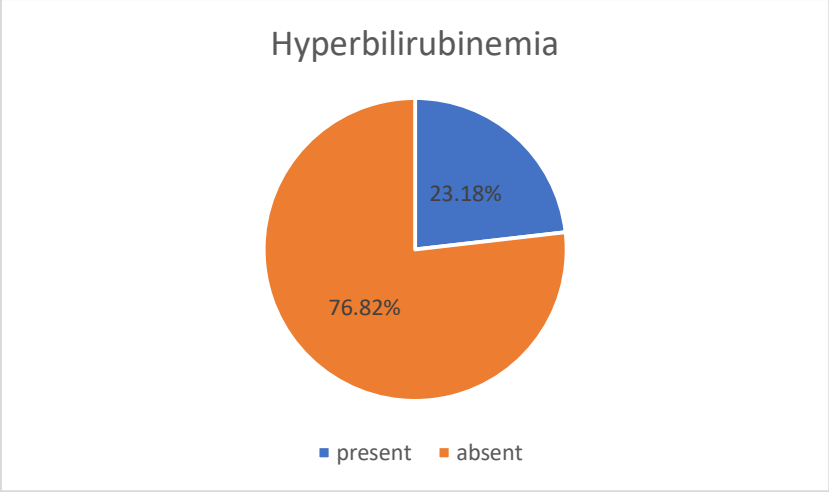
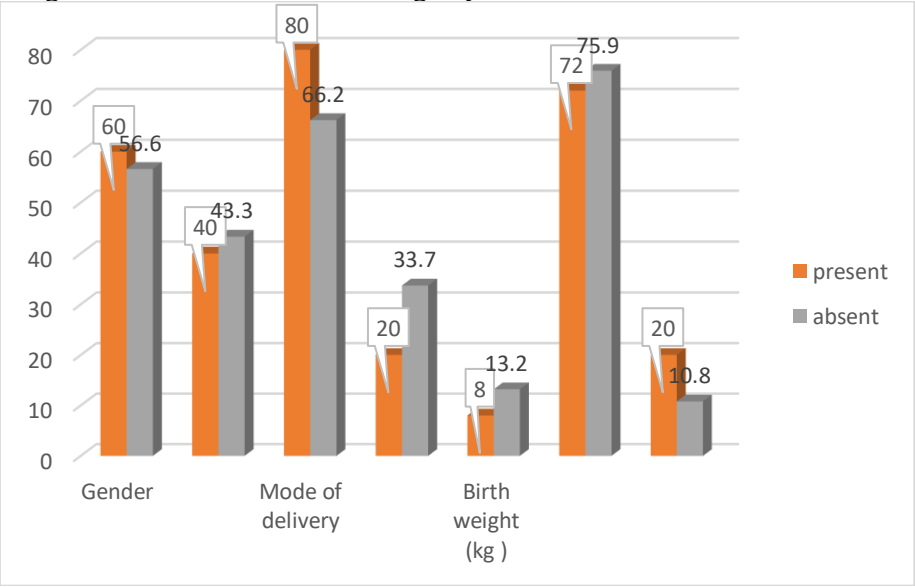


There were more male patients (60%) than female patients (40%). Vaginal birth was the most prevalent method (80%). Of the patients born, 8% weighed between 2 and 2.5 kg, 72% weighed between 2.5 and 3.5 kg, and 20% weighed more than 3.5 kg. The baseline features of patients with and without newborn hyperbilirubinemia did not differ statistically significantly as shown in table 1, graph 2.

Table 1 showing baseline characteristics of two groups

Variable		Hyperbilirubinemia		P value
		Present N=25	Absent N=83	
Gender	Male	15 (60)	47 (56.6)	0.134
	Female	10 (40)	36 (43.3)	
Mode of delivery	Vaginal	20 (80)	55 (66.2)	0.168
	C section	5 (20)	28 (33.7)	
Birth weight (kg)	2-2.5	2 (8)	11 (13.2)	0.342
	2.5-3.5	18 (72)	63 (75.9)	
	>3.5	5 (20)	9 (10.8)	

Graph: 2 showing baseline characteristics of two groups



In patients with hyperbilirubinemia, bilirubin levels were over 2.5 mg/dL in 42.3% of cases, below 2.5 mg/dL in 17.1% of cases, and above 2 mg/dL in 32.6% of cases and below 2 mg/dL in 15.2% of cases. With a p-value of less than 0.001, the correlation between the UCB cut-off of 2.5 mg/dL and the UCB cut-off of 2 mg/dL to predict neonatal hyperbilirubinemia was highly statistically significantas shown in table 2, graph 3.

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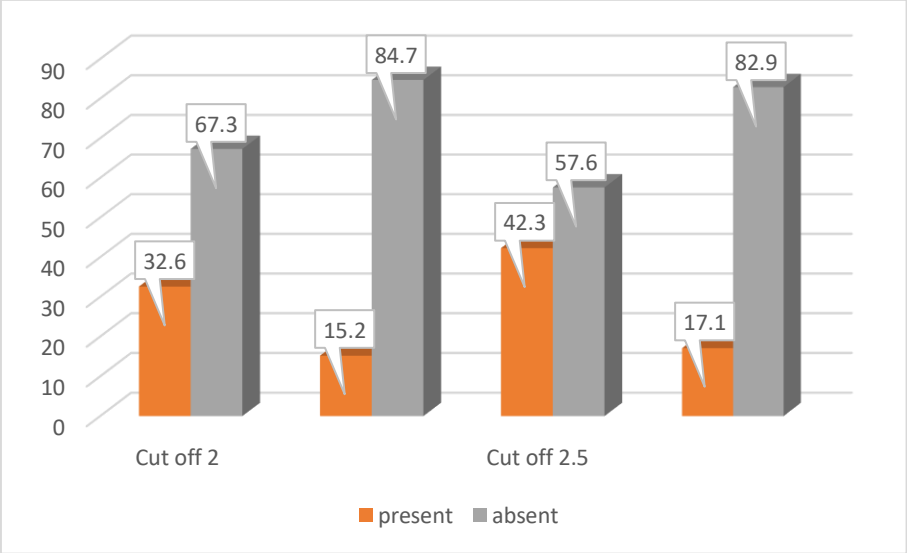
Table: 2 showing association between cut-off cord bilirubin 2 mg/dL and 2.5 mg/dL and neonatal hyperbilirubinemia

Cut off values	Umbilical cord bilirubin (mg/dL)	Hyperbilirubinemia		Total	P value
		Present	Absent		
Cut off 2	>2	16 (32.6)	33 (67.3)	49	<0.001
	<2	9 (15.2)	50 (84.7)	59	
Cut off 2.5	>2.5	11 (42.3)	15 (57.6)	26	<0.001
	<2.5	14 (17.1)	68 (82.9)	82	

Graph: 3 showing association between cut-off cord bilirubin 2 mg/dL and 2.5 mg/dL and neonatal hyperbilirubinemia

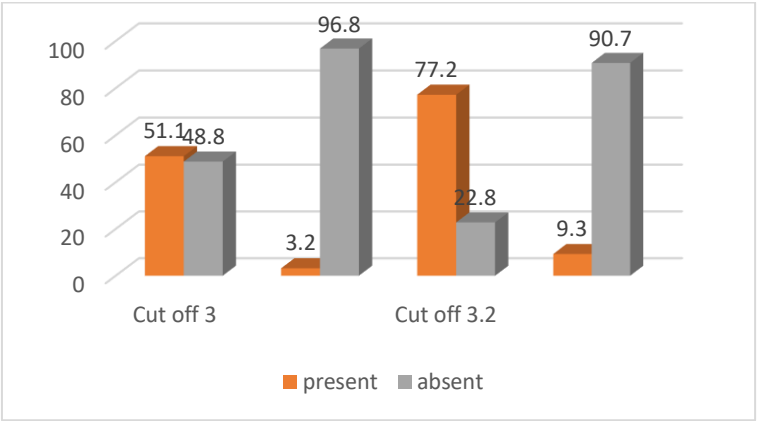


In hyperbilirubinemia, 77.2% of patients had albumin levels above 3.2 and 9.3% had albumin levels below 3.2, while 51.1% of patients had albumin levels above 3 and 3.2% had albumin levels below 3. With both albumin cut-offs of 3 and 3.2, there was a statistically significant connection between albumin and neonatal hyperbilirubinemia (p-value <0.001)as shown in table 3, graph 4.

Table: 3showing association between cut-off cord bilirubin 3 and 3.2g/dL and neonatal hyperbilirubinemia

Cut off values	Umbilical cord albumin (g/dL)	Hyperbilirubinemia		Total	P value
		Present	Absent		
Cut off 3	>3	23 (51.1)	22 (48.8)	45	<0.001
	<3	2 (3.2)	61 (96.8)	63	
Cut off 3.2	>3.2	17 (77.2)	5(22.8)	22	<0.001
	<3.2	8 (9.3)	78 (90.7)	86	

Graph: 4 showing association between cut-off cord bilirubin 3 and 3.2g/dL and neonatal hyperbilirubinemia



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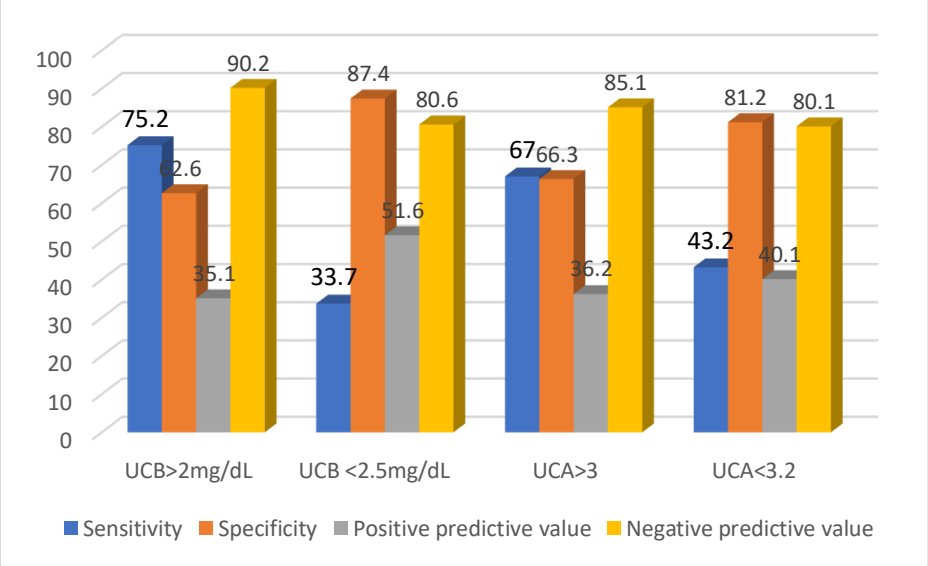
In predicting the risk of neonatal hyperbilirubinemia, UCB 2 mg/dL had the following sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV): 75.2%, 62.6%, 35.1%, and 90.2%, respectively. With a cut-off of UCB >2.5 mg/dL, the sensitivity, specificity, PPV, and NPV are 33.7%, 87.4%, 51.6%, and 80.6%, respectively. Sensitivity, specificity, PPV, and NPV were 67%, 66.3%, 36.2%, and 85.1%, respectively, with a cut-off value of UCA at 3. Sensitivity, specificity, PPV, and NPV for cut-off UCA 3.2 were 43.2%, 81.2%, 40.1%, and 80.1%, respectivelyas shown in table 4, graph 5.

Table 4 showing Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

Variable	Sensitivity	Specificity	Positive predictive value	Negative predictive value
UCB>2mg/dL	75.2	62.6	35.1	90.2
UCB <2.5mg/dL	33.7	87.4	51.6	80.6
UCA>3	67	66.3	36.2	85.1
UCA<3.2	43.2	81.2	40.1	80.1

Graph: 5 showing Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)



DISCUSSION

Neonatal hyperbilirubinemia requires prompt and suitable treatment regardless of its physiological or pathological origins.[16] Untreated physiological neonatal jaundice often resolves spontaneously as the liver matures in most neonates.[17,18] In contrast, pathological jaundice, particularly in cases of hemolytic conditions such as Rh and ABO incompatibility, minor blood group incompatibility, or G6PD deficiency, can result in hyperbilirubinemia that reaches toxic levels capable of causing brain damage.[19] Bilirubin infiltrates the brain as either free (unbound) bilirubin or bilirubin bound to albumin when the blood-brain barrier is compromised, as seen in severe metabolic acidosis, asphyxia, and prematurity, primarily damaging neuronal cells and subsequently affecting astrocytes, oligodendrocytes, and microglia.[20]

The present prospective observational study was carried out in the NICU and postnatal wards among 108 neonates over a duration of one year to evaluate the prognostic significance of cord blood bilirubin and albumin for substantial newborn hyperbilirubinemia. In our study there was predominance of male patients over female. The predominant mode of delivery was vaginal. Maximum patients had a birth weight between 2.5 and 3.5 kg. There was no statistically significant variations in birth weight, sex of the infant, or mode of delivery between infants who developed hyperbilirubinemia and those who did not.

The prevalence of newborn hyperbilirubinemia was 23.18%. This aligned with the study of Satrya R et al, which reported that 24% of patients exhibited hyperbilirubinemia [21]. Research indicates a higher prevalence of 34%, alongside lower incidences of 12.8% and 10.6% [22-24]. Multiple factors may contribute to the disparity. The study has been conducted in many racial and geographic circumstances. The diazo method and the enzymatic method with bilirubin oxidase are two distinct techniques for estimating bilirubin levels. Zeitoun AA et al's study included high-risk and near-term babies, which increased the incidence of hyperbilirubinemia [24].

The correlation between the UCB cut-off of 2 mg/dL and the UCB cut-off of 2.5 mg/dL for predicting

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neonatal hyperbilirubinemia was highly statistically significant, with a p-value of <0.001. Research by Kara L. et al. indicates that newborns who had phototherapy exhibited elevated bilirubin levels in their umbilical cord blood relative to those who did not receive the treatment. They concluded that bilirubin from umbilical cord blood may predict the probability of severe hyperbilirubinemia and the need for phototherapy [25]. A recent study at this center indicates that umbilical cord bilirubin (UCB) can predict neonatal hyperbilirubinemia, so it is advised that all babies undergo UCB estimation [26].

In hyperbilirubinemia, 77.2% of patients had albumin levels beyond 3.2, while 9.3% had values below 3.2. Additionally, 51.1% of patients had albumin levels surpassing 3, while 3.2% had levels beneath 3. Both albumin cut-offs of 3 and 3.2 demonstrated a statistically significant association with neonatal hyperbilirubinemia (p-value <0.001). A study conducted by Suchanda Sahu et al. demonstrated the prediction of substantial hyperbilirubinemia using the measurement of cord blood albumin. 82% of neonates with cord blood albumin levels below 2.8 g/dl developed hyperbilirubinemia. The current study concludes that cord serum albumin levels of ≤ 2.6 gm/dl may serve as an early indicator of neonatal hyperbilirubinemia. Cord serum bilirubin, being more sensitive than cord serum albumin, is more useful in identifying infants who have substantial newborn hyperbilirubinaemia when compared to one another.[27]

Sensitivity and specificity of cord bilirubin was higher than cord albumin as found in our study. The findings contradicted an Indian study by Aiyappa et al., which reported analogous results and concluded that cord blood albumin levels below 2.8 gm/dl are linked to an increased chance of developing clinical icterus.[28] Grover et al in a research including 200 infants, 24 neonates (12%) developed hyperbilirubinemia. The average first day total serum bilirubin (TSB) value among newborns who later developed hyperbilirubinemia was 7.716 mg/dl, in contrast to 5.154 mg/dl as those who did not. The difference was substantial (p=0.000).

Receiver operating characteristic (ROC) curve analysis identified a threshold of 6.4 mg/dl (first day total serum bilirubin) as optimal for predicting subsequent hyperbilirubinemia, demonstrating a sensitivity of 87.5%, specificity of 80.11%, positive predictive value of 37.5%, and negative predictive value of 97.92%.[29]

CONCLUSION

This study demonstrates that both UCB and UCA are potentially effective screening methods for identifying neonatal hyperbilirubinemia. UCB had a higher specificity of 2.5 mg/dL and superior sensitivity of 2 mg/dL compared to UCA, rendering it a more precise predictor of the development of infant hyperbilirubinemia. Consequently, UCB outperformed UCA in both sensitivity and specificity regarding the identification of hyperbilirubinemia.

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