Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.59, No.5(2019). p. 244-51; doi: http://dx.doi.org/10.14238/pi59.5.2019.244-51

Original Article

Cord blood bilirubin, albumin, and bilirubin/albumin ratio for predicting subsequent neonatal hyperbilirubinemia

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Abstract

Background Early discharge of healthy term newborns after delivery has become a common practice, because of medical and social reasons, as well as economic constraints. Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of early discharge from the hospital. Since the dreaded complication of neonatal hyperbilirubinemia is kernicterus, an investigation which can predict the future onset of neonatal pathological jaundice is needed.

Objective To investigate the predictability of neonatal hyperbilirubinemia by using cord blood bilirubin, albumin and bilirubin/albumin ratio.

Methods This study was conducted on 300 healthy newborns. Umbilical cord blood was used to measure albumin and bilirubin. All infants were regularly followed up to 5th day of life. Neonates were divided into two groups: group A was consisted of neonates who developed jaundice which was in physiological range, while group B was consisted of neonates who developed neonatal hyperbilirubinemia (requiring phototherapy or other modality of treatment). Babies suspected to have bilirubin level which cross physiological limit on any day after birth were subjected to serum bilirubin measurement. Infants whose serum bilirubin level measurement revealed bilirubin levels crossing physiological values were sent to nursery for phototherapy.

Results The incidence of neonatal hyperbilirubinemia was 11%. Statistically significant correlations between cord blood bilirubin, albumin, and bilirubin/albumin ratio to the development of neonatal hyperbilirubinemia were observed. On ROC analysis, cut-off points to predict significant hyperbilirubinemia in newborn were cord blood bilirubin >3 mg/dL (sensitivity 60.61%, specificity 97.63%), albumin <2.4 mg/dL (sensitivity 78.79%, specificity 98.13%), cord blood bilirubin/albumin ratio >0.98 (sensitivity 78.79%, specificity 95.51%).

Conclusion Cord blood total bilirubin, albumin. and bilirubin/albumin ratio are excellent parameters to predict the occurrence of neonatal hyperbilirubinemia. However, cord blood albumin is better compared to cord blood bilirubin and bilirubin/ albumin ratio. **[Paediatr Indones. 2019;59:244-51; doi: http://dx.doi.org/10.14238/pi59.5.2019.244-51].**

Keywords: *cord blood bilirubin; cord blood albumin; cord blood bilirubin albumin ratio; significant hyperbilirubinemia*

Hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the newborn and a frequent reason for hospital readmission during the first week of life. Although generally benign, postnatal, transitional phenomenon, a few neonates develop marked potentially hazardous bilirubin levels that can pose a direct threat of serious brain injury.[1] Acute bilirubin encephalopathy (ABE) may ensue and evolve into kernicterus (chronic bilirubin encephalopathy), a permanent, disabling neurologic condition classically characterized by: (1) movement disorders of dystonia and/or choreoathetosis, (2) hearing loss caused by auditory neuropathy spectrum

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Submitted March 14, 2019. Accepted July 22, 2019.

disorders, and (3) oculomotor pareses.[1] The genesis of neonatal hyperbilirubinemia reflects the interplay of developmental red blood cell (RBC), hepatic, and gastrointestinal immaturities that result in an imbalance, favoring bilirubin production over hepatic enteric bilirubin clearance.[2]

Almost all newborn infants have serum or plasma total bilirubin (TB) level >1 mg/dL, in contrast to normal adults in whom the normal TB level is <1 mg/dL. Physiological jaundice usually appears on the 2nd to 3rd day, peaks between 3rd to 5th day of life.[3] Jaundice may appear at birth or may appear any time during neonatal period, depending upon the cause.[3] Since we know hyperbilirubinemia has deleterious effects like kernicterus, choreoathetoid cerebral palsy, hearing impairment, and cognitive impairment if not treated in time, thus meticulous screening of newborn is required to detect hyperbilirubinemia. Since bilirubin level typically peaks at 3rd to 5th day of life, healthy newborns should be followed regularly after discharge from hospital. Infants discharged before 72 hours should be seen within 2 days. Infants of lower gestational ages or having other risk factors should be seen earlier.[3] However, regular follow up is practically impossible in underdeveloped and developing nations because of poverty, low education, and cultural practices. Hence, an ability to predict neonatal hyperbilirubinemia becomes very important and life-saving in the context of a underdeveloped and developing country such as India, where costly investigations and regular follow-up are beyond the reach of the vast majority.

Early discharge of healthy, term newborns after delivery has become common practice, because of medical, social reasons and economic constrains.[4] Thus, the recognition, follow up, and early treatment of jaundice has become more difficult. Severe jaundice, and even kernicterus, can occur in some full-term, healthy newborns discharged early with no apparent early findings of haemolysis.[5]

This study aimed to investigate the predictability of neonatal hyperbilirubinemia by using cord blood bilirubin, albumin, and bilirubin/albumin ratio.

Methods

This prospective, hospital-based study was conducted in Department of Paediatrics and Neonatology, *World College of Medical Sciences* (WCMS) Haryana, India, from 17 January 2017 to 30 November 2018. A total of 300 newborn fulfil the predefined inclusion criteria delivered in our hospital were studied. Proper ethical and scientific clearance was taken from concerned hospital department. Proper informed consent was taken from parents after explaining to them the risks and benefits of neonatal jaundice, phototherapy, and blood sampling.

Inclusion criteria were gestational age 35 weeks and above (based on last menstrual period) and the absence of major congenital malformations. The exclusion criteria were presence of significant illness (i.e., sepsis, hypothyroidism), Rh incompatibility, ABO incompatibility, newborns with obvious life-threatening congenital malformation (tracheoesophageal fistula, anorectal malformation, and babies with conjugated hyperbilirubinemia).

All babies delivered in WCMS were examined and detailed antenatal and postnatal histories were taken. Blood was collected from umbilical cord blood from all neonates at birth. Maternal blood samples were simultaneously collected and sent for blood group testing, if it was not known prior. The infant cord blood sample was sent for blood group testing, as well as bilirubin and albumin measurement. All babies were examined every day up to 5th day of life by senior residents for clinical assessment of bilirubin as per Kramer's scale which states, "if on clinical examination we found jaundice in the face and neck only – total serum bilirubin (TSB) >5 mg/dL, jaundice on chest (up to umbilicus and back) – TSB between 5 and 10 mg/dL, jaundice from umbilicus to knees - TSB 10-15 mg/dL, and jaundice in palms and soles – TSB >15 mg/dL and by transcutaneous bilirubinometer for continuous 5 days." Grouping was done on the basis of physiological and neonatal hyperbilirubinemia (hyperbilirubinemia which required phototherapy). Babies whose bilirubin always remain within physiological limits on clinical examination, there bilirubin was checked by serum estimation method on 5th day thus, were included in Group A. Group B babies included those babies who had on both clinical and serum estimation method neonatal hyperbilirubinemia which required phototherapy or other modality of treatment (as per *American Academy of Pediatrician*/AAP nomogram for

hyperbilirubinemia management)[6] on any day from birth up to 5th day of life. Serum bilirubin of group B babies was checked on that very day when on clinical examination crossing of bilirubin level beyond physiological level was suspected.

Serum bilirubin was estimated by micro-bilirubin (Jendrassik & Grof method)[7] using venous blood taken in four microcapillaries and centrifuged at the rate of 10,000 rpm for 5 minutes. Bilirubin measurement was done spectrophotometrically, using beam method (55 nm wavelength) (micro la-300, *Merck*, The Netherlands). Bilimeter calibration was done daily using a labeteral solution.

Data were recorded, properly validated, then checked for errors and then analysed using *Windows SPSS 21* software. Appropriate univariate and bivariate analyses were done with student's T-test for continuous variables (age), and two-tailed Fisher's exact or Chi-square (X^2) tests for categorical variables. Sensitivity, specificity, as well as positive and negative predictive values of different cut-off points of cord blood serum bilirubin were derived. Results with P values <0.05 were considered statistically significant.

This study aimed to investigate the predictability of neonatal hyperbilirubinemia by using cord blood bilirubin, albumin and bilirubin/albumin ratio.

Results

All the 300 newborn were exclusively breastfed, 169 (56.33%) were males. Cord blood bilirubin, serum bilirubin, and cord blood bilirubin/albumin ratio were not signficantly different between males and females (**Table 1**).

Gestational age of two hundred eighteen (72.67%) infants were >37 weeks and 82 (27.67%) 35-37 weeks. Mean cord blood bilirubin, albumin, bilirubin/albumin ratio, and serum bilirubin estimated up to 5th day were not significantly different between the two gestational age categories. Similarly, birth weight and mode of delivery comparison of cord blood bilirubin, albumin, bilirubin/albumin ratio, and serum bilirubin estimated up to the 5th day were also not significantly different (**Table 1**).

A total of 267 (89%) (group A) developed jaundice in physiological range, so went home without treatment. The mean total albumin, bilirubin, and bilirubin/albumin ratio in cord blood were 2.63 (SD 0.26) mg/dL, 2.574 (SD 0.57) mg/dL, and 0.91 (SD 0.14) mg/dL, respectively. Mean serum bilirubin on day 5 of group A was 10.5 (SD 2.1) mg/dL (**Table 2**). No significant differences were revealed within group A subjects when their cord blood parameters (albumin, bilirubin & bilirubin albumin

Table 1. Distribution of subjects by sex, gestational age, birth weight, and mode of delivery

Characteristics	(N=300)	Mean cord blood bilirubin (SD)	Mean cord blood albumin (SD)	Mean cord blood bilirubin/albumin ratio (SD)	Mean bilirubin while monitoring up to 5th day of life (SD)	P value
Sex, n (%)						
Male	169 (56.33)	2.6 (0.8)	2.4 (0.7)	0.96 (0.24)	1.39 (2.4)	0.89[1] 0.90[2]
Female	131 (43.67)	2.5 (0.4)	2.1 (0.8)	0.82 (0.27)	12.9 (1.8)	0.86[3]
Gestational age, n (%)						
35-37 weeks	82 (27.67)	2.4 (1.4)	1.4 (1.1)	0.67 (0.17)	13.2 (2.2)	0.95[1]
>37 weeks	218 (72.67)	2.7 (0.8)	2.9 (0.6)	0.95 (0.24)	13.7 (2.2)	0.68[2] 0.76[3]
Mode of delivery, n (%)						
Vaginal	198 (66)	2.9 (1.3)	2.7 (1.2)	0.86 (0.34	11.9 (2.0)	0.78[1]
Lower segment caesarean section (LSCS)	102 (34)	2.6 (0.8)	2.1 (0.7)	0.79 (0.41)	12.9 (2.4)	0.64[2] 0.78[3]
Birth weight, n (%)						
1.5-2.5 kg	98 (32.67)	2.5 (1.9)	2.4 (1.7)	0.78 (0.56)	14.21 (1.4)	0.999[1]
2.6-3.5 kg	152 (50.67)	2.9 (1.4)	2.8 (1.6)	0.89 (0.7)	12.3 (1.7)	0.84[2]
>3.5 kg	50 (16.67)	2.87 (0.4)	1.9 (0.7)	0.85 (0.75)	12.5 (2.8)	0.57[3]

[1]=P value for cord blood bilirubin association with characteristics
[2]=P value for cord blood albumin association with characteristics
[3]=P value for cord blood bilirubin/albumin ratio association with characteristics

ratio) were compared with bilirubin on 5th day of their life (**Table 2**).

Prevalence of neonatal hyperbilirubinemia (babies who required phototherapy or other treatment modality) in our study was 33 (11%) (group B). Group B mean cord blood albumin, bilirubin, and bilirubin/albumin ratio were 2.28 (SD 0.32) mg/dL, 3.136 (SD 0.33) mg/dL, and 1.4 (SD 0.35), respectively, and mean serum bilirubin when measured up to the 5th day of life was 16.2 (SD 1.6) mg/dL. Statistical analysis revealed significant correlations of all three parameters with subsequent neonatal hyperbilirubinemia (**Table 2**).

All data collected was analysed for cut-off values in receiver-operating characteristic (ROC) curves. For cord blood albumin, area under curve (AUC) was 0.901, cut-off point of <2.4 mg/dL, good statistical significance with sensitivity of 78.79%, specificity 98.13%, positive likelihood ratio 42.07, negative likelihood ratio 0.22, positive predictive value 83.9, and negative predictive value 97.4, for predicting subsequent neonatal hyperbilirubinemia (P<0.001) (**Table 3** and **Figure 1**).

There was a significant correlation between cord blood bilirubin and development of subsequent neonatal hyperbilirubinemia, with AUC 0.766 (P<0.001) for a cut-off point of >3 mg/dL, which had sensitivity of 60.61%, specificity 97.63%, positive likelihood ratio 23.31, negative likelihood ratio 0.4, positive predicative value 74.1, and negative predictive value 95.2 (**Table 4** and **Figure 2**).

Similarly, cord blood bilirubin/albumin ratio has significant correlation with subsequent development of neonatal hyperbilirubinemia with AUC of 0.896 (P<0.001) at cut-off value of 0.98 with sensitivity of 78.79%, specificity of 95.51%, positive likelihood ratio 17.53, negative likelihood ratio of 0.22, positive predicative value of 68.41, and negative predictive value of 97.3 (**Table 5** and **Figure 3**).

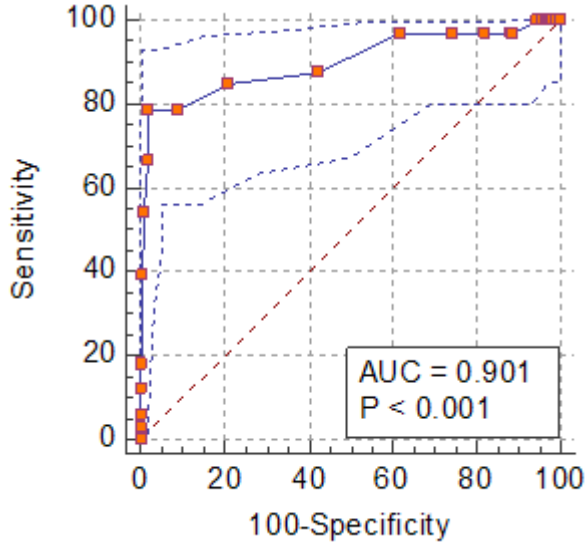

Figure 1. ROC curve for mean cord blood albumin

Table 2. Mean cord blood albumin, bilirubin, bilirubin/albumin ratio, and bilirubin up to 5th day of life

Group	n(%)	Mean cord blood albumin in mg/dL (SD)	Mean cord blood bilirubin in mg/dL (SD)	Cord blood bilirubin/albumin ratio (SD)	Mean bilirubin during monitoring in mg/dL (SD)	P value
A	267 (89)	2.63 (0.26)	2.574 (0.57)	0.91 (0.14)	10.5 (2.1) [on 5th day]	0.097[1] 0.67[2] 0.7[3]
B	33 (11)	2.28 (0.32)	3.136 (0.33)	1.4 (0.35)	16.2 (1.6) [up to 5th day]	0.0001[1] 0.000[2] 0.003[3]

[1]=P value for association of cord blood albumin with future predictability of hyperbilirubinemia
[2]=P value for association of cord blood bilirubin with future predictability of hyperbilirubinemia
[3]=P value for association of cord blood bilirubin/albumin ratio with future predictability of hyperbilirubinemia

Table 3. Area under the curve for cord blood albumin (CBA)

Test result variable: cord blood albumin				Associated criterion					
AUC	Std. error	Asymptomatic sig.	Asymptomatic 95%CI	2.4 mg/dL					
				Sensitivity	Specificity	Positive LR	Negative LR	PPV	NPV
0.901	0.37	0.000	0.828 to 0.975	78.79%	98.13%	42.07	0.22	83.9	97.4

LR=likelihood ratio; PPV=positive predictive value; NPV=negative predictive value

Table 4. Area under the curve for cord blood bilirubin (CBB)

Test result variable: cord blood bilirubin				Associated criterion					
AUC	Std. error	Asymptomatic sig.	Asymptomatic 95%CI	3 mg/dL					
				Sensitivity	Specificity	Positive LR	Negative LR	PPV	NPV
0.766	0.055	0.000	0.658 to 0.874	60.61%	97.63%	23.12	0.40	74.1	95.2

LR=likelihood ratio; PPV=positive predictive value; NPV=negative predictive value

Table 5. Area under the curve for cord blood bilirubin/albumin ratio (BAR)

Test result variable: cord blood bilirubin/albumin ratio				Associated criterion					
AUC	Std. error	Asymptomatic sig.	Asymptomatic 95%CI	0.98					
				Sensitivity	Specificity	Positive LR	Negative LR	PPV	NPV
0.896	0.0392	0.000	0.856 to 0.928	78.79%	95.51%	17.53	0.22	68.4	97.3

LR=likelihood ratio; PPV=positive predictive value; NPV=negative predictive value

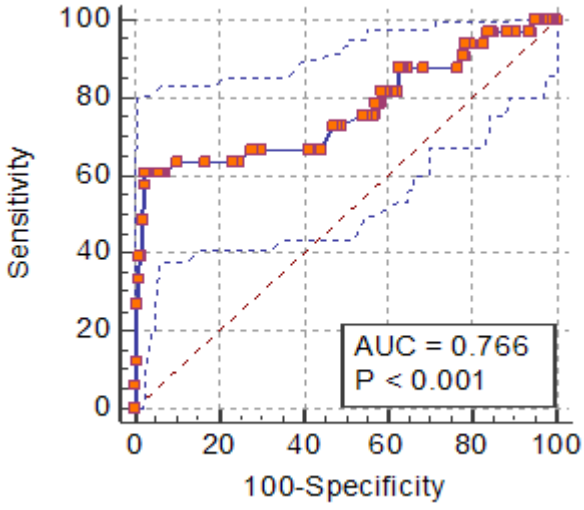

Figure 2. ROC curve for mean cord bilirubin

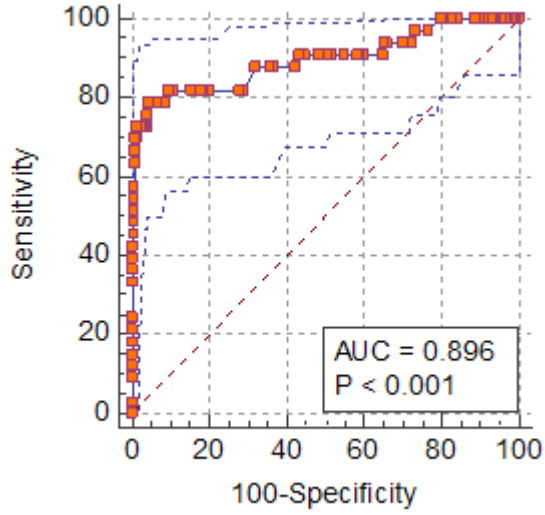

Figure 3. ROC curve for mean cord blood bilirubin/

Table 6. ROC curve statistics of parameters.

Parameters	AUC	SE	95% CI
CBA	0.901	0.0378	0.862 to 0.932
CBB	0.766	0.0559	0.714 to 0.813
BAR	0.896	0.0392	0.856 to 0.928

CBA=cord blood albumin; CBB=cord blood bilirubin; BAR=bilirubin albumin ratio; AUC=area under curve

The AUC values for predictive ability of cord blood albumin, bilirubin, and bilirubin/albumin ratio for subsequent neonatal hyperbilirubinemia were: CBA (0.901) > BAR (0.896) > CBB (0.766) (**Table 6**). Statistical analysis revealed significant differences between CBB~BAR (P=0.003) and CBA~CBB (P=0.0297). However, CBA~BAR AUCs were not significantly different (P=0.9032) (**Table 7** and **Figure 4**).

Discussion

Jaundice is a common entity in newborn which requires attention in the first few days after birth. Most jaundice which develops in newborn is in physiological range, except small fraction which need intervention like phototherapy, exchange transfusion, or other new modalities of treatment. Although about 8-10% are affected, as shown in our study with 11%, timely diagnosis and immediate treatment is essential to prevent the devasting effects of kernicterus, which can lead to mental retardation, choreoathetoid type of cerebral palsy, or hearing defects. These side effects have dramatically decreased in last decade because of public awareness educational programs. But there

Table 7. Pairwise comparison of ROC curves

Group comparison	Difference between areas	Standard error	95%CI	Z statistic	P value
CBA~CBB	0.135	0.0620	0.0133 to 0.257	2.174	0.0297
CBA~BAR	0.00499	0.0411	-0.0755 to 0.0855	0.122	0.9032
CBB~BAR	0.130	0.0360	0.0594 to 0.200	3.612	0.0003

CBA=cord blood albumin; CBB=cord blood bilirubin; BAR=bilirubin albumin ratio

remains a small fraction of newborn who fall prey to the devasting side effects of neonatal hyperbilirubinemia, especially in developing countries, because of poor follow up, limited resources, and most importantly parental emotional attachment. Some parents do not want their child to experience pain, even from a single needle prick. Keeping in view all these factors, the objective of this research was framed to determine the cut-off values for cord blood bilirubin, albumin, and bilirubin/albumin ratio, with hope that such values could be used to predict development of subsequent neonatal hyperbilirubinemia. We also compared these three parameters to determine which one is better.

The prevalence of significant hyperbilirubinemia in our study was 11%. Similarly, Awasthi *et al.*[8] reported 12.80%, Randev *et al.*[9] reported 12.00%, and Dhanwadkar *et al.*[10] reported 11.4%. In our study, there were no significant relationships between neonatal hyperbilirubinemia and cord blood bilirubin, albumin, and bilirubin/albumin ratio, with regards to gender, gestational age, birth weight, or mode of delivery. Similar findings were noted by Awasthi *et al.*[8] and Alpay *et al.*[11]

In our study, mean cord blood albumin of babies who developed neonatal hyperbilirubinemia which required treatment was 2.28 (SD 0.32) mg/dL, similar to the finding of Aiyappa *et al.*[12] On ROC curve analysis, the cord blood albumin cut-off point to predict subsequent neonatal hyperbilirubinemia was <2.4 mg/dL. Pahuja *et al.*[13] noted that the predictive value of cord albumin for development of neonatal hyperbilirubinemia was 75%, which implied a fair predictive value of the criteria, with 61.3% sensitivity and 76.8% specificity, and was in agreement with our study. Thakur P *et al.*[14] found 4% incidence of neonatal hyperbilirubinemia at cord blood albumin level cut-off of <2 mg/dL, with specificity of 98.23%. Also, Mahmoud Alalfy *et al.*[15] noted the highest sensitivity (83.3%) was for cord bilirubin cut-off value 1.8 8mg/dL, with PPV 72.9%, which means that 83.3% of patients can be predicted to have the disease (true positives), but 16.7% of cases with the disease will go undetected (false negatives).

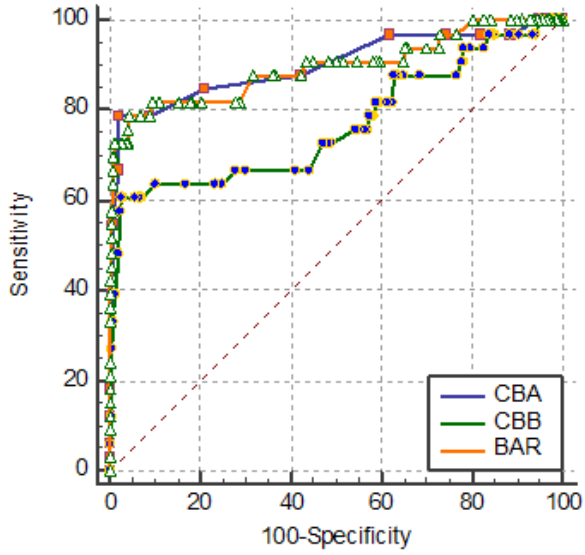

Figure 4. Comparison of ROC curves of cord blood albumin (CBA), cord blood bilirubin (CBB), and bilirubin albumin ratio (BAR)

The mean cord blood bilirubin of newborn who developed neonatal hyperbilirubinemia was 3.136 (SD 0.33) mg/dL, which was same as shown by a previous study that reported a mean value of 3.2 (SD 0.8) mg/dL.[16] The ROC curve analysis cord blood bilirubin cut-off point was > 3.0 mg/dL, with sensitivity 60.61%, specificity 97.63%, positive likelihood ratio 23.31, negative likelihood ratio 0.4, PPV 74.1, and NPV 95.2. Similarly, Taksande *et al.*[17] noted the cut-off value of 2.0 mg/dL, with sensitivity 89.5% and NPV 98.7%. However, at the cut off value of 2.0 mg/dL, 53% sensitivity was observed by Bernaldo and Segre[16] and at 2.5 mg/dL, 71% sensitivity and 96% specificity were noted by Agarwal *et al.*[18] In addition, another previous study noted that cord blood bilirubin level of 3 mg/dL (51.3 micromol/L) was not a useful predictor of neonatal jaundice.[19] Venkatamurthy *et al.*[20] found that at cord blood bilirubin level ≥2.1

mg/dL, sensitivity was 100%, specificity 61.04%, PPV 25%, and NPV 100%.

The ROC curve analysis of the bilirubin/albumin ratio in cord blood revealed that, cut-off point of >0.98 was predictive with good accuracy of development of subsequent neonatal hyperbilirubinemia. Similarly, a previous study reported a cord blood bilirubin/albumin ratio cut-off of 0.82, as obtained by ROC curve, and with 88.9% sensitivity, 85.7% specificity, PPV 94.1%, and NPV 75% for predicting neonatal hyperbilirubinemia in a high-risk group.[15] Ramteke *et al.*[21] derived a 0.89 cut-off point of cord bilirubin/albumin ratio, and suggested that 95.5% of patients will likely develop future neonatal NNH if their ratio is above 0.89.

On comparing the ROC curves of the three parameters, there were significant differences between CBA and CBB, as well as BAR and CBB, which indicated better predictability of CBA and BAR for the development of subsequent jaundice. However, the comparison of BAR and CBA revealed no significant difference in the two parameters, as P value was greater than 0.05. However, keeping in view other statistical figures like AUC, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, PPV, and NPV, the CBA as the single parameter would be more useful to predict subsequent significant neonatal hyperbilirubinemia.

In conclusion, there is significant correlation between development of neonatal hyperbilirubinemia and cord blood serum bilirubin, albumin, and bilirubin/albumin ratio. Cord blood albumin has the best predictive value, followed by bilirubin/albumin ratio and cord blood bilirubin in predicting development of subsequent neonatal hyperbilirubinemia.

Conflict of Interest

None declared.

Acknowledgements

We are highly thankful to our Paediatric Department and its faculty who devoted their precious time to guide us while conducting this study.

Funding Acknowledgment

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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