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Prediction of Development of Neonatal Jaundice by Cord Blood Bilirubin and Albumin

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Abstract:

Background: Neonatal jaundice is a common cause of early postnatal readmission and contributes to both financial and socio-economic burden. In resource-constrained nations, where the patient-to-resource-constrained-bed ratio is very high, early prediction of hyperbilirubinaemia will help in early discharge, prevent re-hospitalization, and reduce the duration of hospital stay. This study aims to estimate the cord blood bilirubin (CBB) and albumin (CBA) levels for future prediction of neonatal jaundice among deliveries at Bhagat Phool Singh Government Medical College for Women (BPS GMC (W)).

Methods: A prospective study was conducted among 384 randomly selected neonates delivered at BPS GMC (W). Socio-demographic data were recorded, and cord blood samples were collected at birth for bilirubin and albumin estimation. Neonates were followed for 10 days to assess the development of clinical jaundice.

Result: Incidence of neonatal jaundice was 21.4% with 10 days of follow-up. 94.8% neonates developed jaundice with CBB level ≥ 2mg/dL, proving it statistically significant. Additionally, 62.7% of neonates with serum albumin < 3 g/dL developed jaundice. Cord blood Bilirubin-to-Albumin ratio proved a good indicator, as area under the curve is 0.933 with sensitivity and specificity of 68.30% and 99.0% respectively at a cut-off level of 0.61.

Conclusion: Cord blood bilirubin and bilirubin-to-albumin ratio may help identify neonates at higher risk of subsequent jaundice and may assist in prioritizing follow-up in resource-limited settings. A bilirubin-to-albumin ratio ≥ 0.61 was found to be a highly specific predictor.

Keywords: cord albumin, cord bilirubin, neonatal jaundice

Introduction

Hyperbilirubinemia is one of the most common causes of readmission during the early neonatal period in developing nations. Hyperbilirubinemia develops on days 2-4 of life in 50% of term and 80% of preterm neonates. Severe hyperbilirubinemia can occur without apparent reason in some healthy neonates and may develop kernicterus.[1, 2] In modern clinical practice, healthy term neonates are allowed to early discharge because of advantages including prevention of nosocomial infections, high patient-to-bed ratio, lower cost, and some social reasons like early naming ceremony. The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 48-72 hours.[3] In developing nations, the value of follow-up visits is questionable as mothers do not return due to long travel distances and financial burden.[4] Neonatal jaundice is one of the common reasons for readmission in the early neonatal period, which causes a financial and socio-economic burden on families. In resource-constrained nations, where the patient-to-bed ratio is very high, early prediction of hyperbilirubinaemia will help in early discharge, prevent re-hospitalization, and reduce the duration of hospital stay of babies and mothers.[2] Neonatal jaundice can be treated easily by phototherapy when detected early in the course of illness, which prevents the development of chronic bilirubin encephalopathy (kernicterus) associated with poor outcome, as it may lead to neurological handicap and early death of affected infants even after treatment.[5]

Currently, we don't have a highly reliable and specific investigation to detect jaundice up to 100% at birth, but we can follow neonates with high bilirubin and low albumin values.[6] Also, the bilirubin-to-albumin ratio proved highly useful.[7] Moreover, testing is easy and reports come within hours without delays. So, the concept of predicting the development of jaundice via bilirubin testing is helpful before bilirubin levels reach a critical limit. Cord blood bilirubin (CBB) and cord blood albumin (CBA) are important predictors for neonatal jaundice. Very few studies have been conducted in India, and our study aimed to use cord blood bilirubin and albumin for the prediction of subsequent development of neonatal jaundice so that dreaded complications like kernicterus can be prevented.

Method

Study setting: The present study was conducted among the neonates delivered in the labour room of the Department of Obstetrics and Gynaecology at Bhagat Phool Singh Government Medical College for Women (BPS GMC(W)), Khanpur Kalan, Sonepat, between 30/12/2023 and 30/07/2024.

Type of study: Prospective study.

Sample size: Taking the proportion of neonatal jaundice as 50% in neonates with cord blood bilirubin ≥2mg/dL from a previous study, at 95% confidence interval, 5% absolute precision, the calculated sample size is 384 neonates.[8]

Cut-offs: Cut off for serum bilirubin ≥2mg/dL, serum albumin ≤ 3g/dL, and bilirubin-to-albumin ratio ≥0.61were taken for consideration of hyperbilirubinemia.

Neonatal jaundice was defined as clinically apparent jaundice identified during follow-up and confirmed by serum bilirubin assessment as per departmental paediatric protocol.

Sampling technique: Systematic random sampling was done. Every third delivered neonate was selected for participation in the study.

Study population: Neonates delivered at BPS GMC (W) Khanpur Kalan Sonepat during the study period.

Inclusion criteria:

- Healthy neonates delivered at BPS GMC (W) Khanpur Kalan Sonepat during the study period
- Parents of neonates consenting for participation in the study.

Exclusion criteria:

- Neonates with significant illnesses such as neonatal sepsis, birth asphyxia, respiratory distress syndrome, meconium aspiration syndrome, or any who are critically ill or haemodynamically unstable.
- Neonates with major congenital anomaly.

Data collection: For all 384 neonates, data were collected on a semi-structured proforma after taking informed consent from the parents of the neonates. They were informed that their personal details would not be disclosed and efforts were made to conceal their identities. Detailed history was taken with full emphasis on both antenatal and perinatal history (maternal illness, drugs, fever with rash) and relevant birth history.

For blood sample collection, permission from the Department of Obstetrics and Gynaecology was taken. After delivery of the newborn, the umbilical cord was double clamped and cut at the placental end. As soon as the neonate was removed from the operative field, the cord blood sample was taken after clamping the cord with a sterile cord clamp at the neonatal end by puncturing the cord with a 5 mL syringe at a suitable point after taking proper aseptic measures. During the whole procedure, the umbilical cord was held in a slanting manner for ease of sample collection. The collected blood sample was stored in a red vacutainer away from light to prevent

degradation. The vacutainers were sent to the biochemistry laboratory of the institute for estimation of serum albumin and serum bilirubin by the spectrophotometer technique. Hemolysed samples were excluded from testing.

All the neonates were followed for 10 days for the development of clinical jaundice and the neonates who developed jaundice were treated as per the current protocol in the Department of Paediatrics, BPS GMC (W) Khanpur Kalan Sonepat.

Ethical consideration: The Institutional Ethics Committee, BPS GMC (W) approved the research vide letter number- BPSGMCW/RC993/IEC/23.

Statistical analysis: All the collected data were entered in an Excel spreadsheet and analysed using SPSS version 28. We calculated the mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. Chi-square test was applied for determining any association between neonatal jaundice and high cord blood bilirubin, albumin, and other factors associated with it. Sensitivity, specificity, and Area Under Curve (AUC) in the ROC curve were calculated. A p-value less than 0.05 was considered statistically significant.

Result

The present study was conducted among the 384 neonates delivered in the labour room, and they were followed for 10 days. Out of 384 neonates, 82 developed clinical jaundice within 10 days, so the incidence of neonatal jaundice was 21.4%.

Neonatal jaundice was slightly higher in female neonates than in males, but the difference was not statistically significant. The study showed that the mean birth weight of neonates with jaundice was 2.77±0.39 kg, which was less than the mean birth weight of neonates without jaundice, but it was not found to be statistically significant. The study showed that among the breastfed neonates, only 19.6% neonates developed jaundice, whereas 32.1% developed jaundice who were not breastfed timely, which was statistically significant. Nearly half of neonates developed jaundice who were given pre-lacteal feed while less than 1/5th of neonates developed jaundice who were not given pre-lacteal feed which was found statistically significant **(Table 1).**

This study showed that 69.4% neonates born to mothers with urinary tract infections (UTI) developed neonatal jaundice. One-fourth of neonates developed neonatal jaundice whose mother consumed certain drugs during pregnancy. About 15% of neonates developed jaundice whose mothers didn't consume iron and folate tablets during pregnancy. Although it was not significant. Nearly four-fifths of infants of diabetic mothers developed jaundice, which was statistically insignificant. Similarly, two-thirds of neonates of hypertensive mothers develop neonatal jaundice. One -third

of neonates developed jaundice whose mothers had thyroid disorders, which was not significant as compared to only 20.9% neonates of healthy mothers. ABO-Rh incompatibility was present more in neonates with jaundice, which was statistically significant **(Table 2)**.

Table 1. Distribution of neonatal characteristics among the study population

Neonatal Characteristics		Neonatal Jaundice		P value
		Yes (%)	No (%)	
Sex of neonate	Male	40 (20.7)	153 (79.3)	0.762
	Female	42 (22)	149 (78)	
Birth weight of the neonate	<2.5Kg	14 (19.7)	57 (80.3)	0.709
	≥2.5Kg	68 (21.7)	245(78.3)	
	Mean Weight	2.77 ± 0.39	2.8 ± 0.38	0.815
Early initiation breastfeeding	Done	65 (19.6)	266 (80.4)	**0.040**
	Not done	17 (32.1)	36 (67.9)	
Pre- lacteal feed to neonates	Given	18 (47.4)	20 (52.6)	**<0.001**
	Not given	64 (18.5)	282 (81.5)	

Table 2. Association of maternal factors with neonatal jaundice (n=384).

Maternal Factors		Neonatal Jaundice		P value
		Yes (%)	No (%)	
Urinary tract infection	Present	75 (69.5)	33 (30.5)	0.530
	Absent	7 (2.6)	269 (97.4)	
Drugs intake for any disease	Present	11 (24.4)	34 (75.6)	0.590
	Absent	71 (20.9)	268 (79.1)	
IFA tablets course completion in pregnancy	Present	8 (15.4)	258 (77.7)	0.259
	Absent	74 (22.3)	44 (84.6)	
Anemia in pregnancy	Present	59 (40.13)	88 (59.87)	0.847
	Absent	23 (9.7)	214 (90.3)	
Gestational diabetes mellitus	Present	78 (73.5)	28 (26.5)	0.202
	Absent	4 (1.43)	274 (98.57)	
Hypertension	Present	76(67.2)	37 (32.8)	0.209
	Absent	6 (2.2)	265 (97.8)	
Thyroid disorders	Present	6 (30)	14 (70)	0.333
	Absent	76 (20.9)	288 (79.1)	
ABO-Rh incompatibility	Present	20 (87)	3 (13)	**<0.001**
	Absent	62 (17.2)	299 (82.8)	
Gestational age of pregnant mothers	≤37weeks	79 (21.8)	284 (78.2)	0.416
	>37weeks	3 (14.3)	18 (85.7)	

The study showed that 94.8% neonates with jaundice had raised bilirubin levels. Only 5.2% neonates with bilirubin levels > 2 mg/dL had not developed neonatal jaundice. The difference was statistically significant. The data in the table indicated that 62.7% of neonates with cord albumin below 3g/dL developed neonatal jaundice, while only 13.8% of neonates with albumin values higher than 3g/dL developed jaundice, which was statistically significant. In the present study population, the mean cord blood albumin level among neonates who developed jaundice was 3.00 ± 0.99 g/dL, compared to 3.83 ± 0.69 g/dL among those who did not develop jaundice. The study showed that 94.6% of neonates with a bilirubin-to-albumin ratio greater than 0.61 developed jaundice, whereas only 8% neonates with a bilirubin-to albumin ratio below 0.61 developed jaundice. This difference was statistically significant. Similarly, the mean bilirubin-to-albumin ratio in neonates with jaundice was 1.62, whereas levels in neonates without jaundice were 0.24 **(Table 3)**.

Table 3. Association of cord blood bilirubin & albumin levels with neonatal jaundice (n=384).

	Variables	Neonatal Jaundice		P value
		Yes (%)	No (%)	
Cord blood bilirubin	≤ 2 mg/dL	27 (8.3)	299 (91.7)	**<0.001**
	> 2 mg/dL	55 (94.8)	3 (5.2)	
	Mean Total bilirubin (mg/dL) ± SD	4.10 ± 2.71	0.80 ± 0.45	**<0.001**
Albumin levels	≤ 3 g/dL	37 (62.7)	22 (37.3)	**<0.001**
	> 3 g/dL	45(13.8)	280 (86.2)	
	Mean Serum Albumin (g/dL) ± SD	3.00 ± 0.99	3.83 ± 0.69	**<0.001**
Bilirubin-to-Albumin ratio	≤ 0.61	26 (8)	299 (92)	**<0.001**
	> 0.61	56 (94.6)	3 (5.4)	
	Mean Bilirubin-to-albumin ratio ± SD	1.62 ± 0.24	0.24 ± 0.2	**<0.001**

Sensitivity and specificity of cord blood bilirubin at a cutoff level of 2 mg/dL was 67.06% and 99%, respectively. Although the specificity of serum albumin at the cut-off level of 3 mg/dL was 92.72% but sensitivity at the same level was found to be only 45.12% **(Table 4)**.

Figure 1 shows that cord blood Bilirubin-to-Albumin ratio also proves a good indicator as the area under the ROC curve is 0.933 with sensitivity and specificity of 68.30% and 99.0%, respectively, at a cut-off level of 0.61 **(Table 4)**.

Table 4. Sensitivity, specificity, and AUC of cord blood bilirubin and albumin

Variables		Neonatal Jaundice Yes (%)	Neonatal Jaundice No (%)	Sensitivity/ Specificity	AUC	P value
Cord blood bilirubin	> 2 mg/dL	55 (94.8)	3 (5.2)	67.07% / 99.0%	0.911	**<0.001**
	≤ 2 mg/dL	27 (8.3)	299 (91.7)			
Albumin levels	≤ 3 g/dL	37 (62.7)	22 (37.3)	45.12% / 92.72%	0.757	**<0.001**
	> 3 g/dL	45(13.8)	280 (86.2)			
Bilirubin-to-Albumin ratio	> 0.61	56 (94.6)	3 (5.4)	68.30% / 99.0%	0.933	**<0.001**
	≤ 0.61	26 (8)	299 (92)			

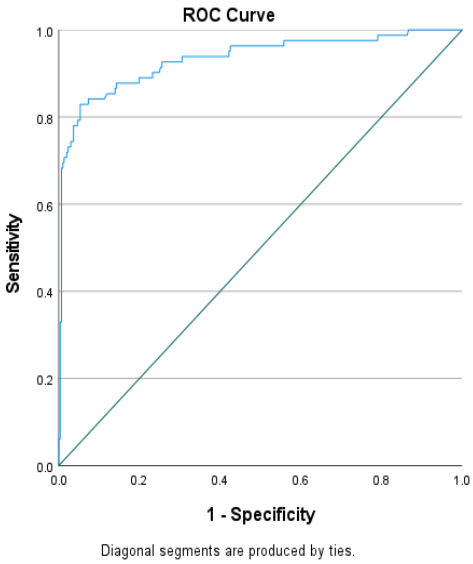

Figure 1. ROC Curve showing cord blood bilirubin-to-albumin ratio sensitivity and specificity in detecting hyperbilirubinemia

Discussion

Neonatal jaundice is the most commonly reported cause for readmission during the early neonatal period. The need for early prediction of hyperbilirubinemia in early-discharged newborns from the hospital is therefore important.

In the present study, cord blood bilirubin and albumin were examined as a tool to predict subsequent neonatal jaundice. In our study, a total of 384 subjects were studied and followed for 10 days; among them, 82 neonates (21.4%) developed jaundice. Incidence was similar to a study done in Nigeria by Chime et al., stating the development of neonatal jaundice in 21% in males and 12% of females.[9] A study done by Rafi et al. in India showed the incidence of neonatal hyperbilirubinaemia 14% (42/300), considering a cut-off of cord bilirubin levels >2mg/dL.[10] Another similar study by Narang et al. showed 14.56% (551/3791) prevalence of neonatal jaundice.[11]

Our study demonstrates that the sex of neonates was not strongly associated with neonatal jaundice, as both sexes were equally affected. The findings were similar to a study done by Rafi et al. in Andhra Pradesh.[10]

Our study revealed that early initiation of breastfeeding is protective for neonates. Among the breastfed neonates, only one-fifth develop jaundice, whereas 1/3rd develop jaundice who were not breastfed timely, which is statistically significant. Similar results were concluded by Bertini et al.[12] The reason behind developing jaundice can be starvation and dehydration in late breastfed neonates, and such practices also put them at high risk of bilirubin encephalopathy.

Pre-lacteal feeding significantly increases the incidence of development of jaundice, while timely breastfeeding reduces the risk of developing jaundice. Nearly half of neonates developed jaundice who were given pre-lacteal feed due to any cause developed jaundice, while less than 1/5th of normal neonates develop jaundice. The reason can be increased infections via pre-lacteal food and utensils. According to Nguyen et al., pre-lacteal feeding and early formula feeding before hospital discharge are associated with higher risks of infection and hospital admission in Vietnamese infants.[13] Support for exclusive breastfeeding should be provided to mothers to avoid the adverse consequences of giving formula milk and pre-lacteal foods.

Our study showed that neonates of mothers with UTI were at high risk of developing jaundice as compared to neonates of healthy mothers. A study by Bilgin et al. found presence of maternal urinary tract infection may contribute to increased infections in the neonatal period.[14] Neonates born to mothers with UTI had a high risk of getting infection while delivering, causing increased hemolysis. It is important to diagnose a UTI in neonates in the perinatal period.

In the present study, 40.13% neonates of anemic mothers developed jaundice. This showed that anemic mothers had a high risk of having anemic neonates. Similar results by Bham et al. state that the overall frequency of newborns with hyperbilirubinemia was 50.6%, and there was a potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice, suggesting the need to exercise early intervention in pregnant mothers who were at high risk of newborn jaundice.[15]

Our study showed that 67% neonates of hypertensive mothers developed neonatal jaundice. Whereas only 2.2% of neonates of healthy mothers developed subsequent jaundice, which is not statistically significant. However, a study by Boskabadi H et al. states that maternal risk factors for neonatal jaundice with hypertension as most common cause, with 11.85% of prevalence rate.[16] Higher values in our study might be

because of a greater number of referral cases at the only available tertiary care institute in a rural area nearby.

Our study showed that premature birth had 21.8% prevalence of neonatal jaundice, whereas only 14.3% of term neonates developed statistically significant jaundice. Similar results were concluded by Sayed et al. in a study done in Iran.[17] The reason might be a lack of sucking reflex in premature babies, and usually, they are artificially fed for the initial days. Also, there is a replacement of fetal hemoglobin to adult haemoglobin after birth, causing some rise in bilirubin levels, causing stress on the underdeveloped liver to metabolize haemoglobin. But the majority of term neonates (85.7%) remain normal as enzymes for bilirubin metabolism start to function properly. The incidence of ABO Rh incompatibility in our study was 23, out of which 87% neonates developed jaundice, which was statistically significant. ABO-Rh incompatibility causes excessive hemolysis due to the presence of antibodies against neonatal blood cells, causing severe jaundice.

The present study showed that 94.8% neonates with jaundice had raised cord blood bilirubin levels >2 mg/dL, which was statistically significant. A cord blood bilirubin level cut off at 2mg/dL has a good specificity of 99% and sensitivity of about 67%. Nahar et al. showed that cord bilirubin >2.5 mg/dL has a sensitivity 77% and a specificity 98.6% in predicting neonatal hyperbilirubinemia.[18] Pradhan et al. showed that cord bilirubin level >2.5 mg/dL has a sensitivity of 84.1%, specificity of 88.5%.[19] The slight differences may be due to different cut-off levels for cord bilirubin levels.

In the present study, a low albumin value below 3g/dL was found in 62.7% among the neonates who developed jaundice, which was similar to a study done by Assam et al., who stated that 60 out of 100 neonates with cord albumin <2.8g/dL developed significant jaundice within a five-day follow-up.[7] From this study, cord blood albumin level was demonstrated as having good specificity of 92.7%, although it has a low sensitivity of only 45%, which was less than studies conducted by Nahar Z et al. and Pradhan et al.[19]

Bilirubin-to-albumin ratio was calculated for association with the development of jaundice, which turned out to be a good indicator. A ratio higher than 0.61 was among 95% neonates who developed jaundice. Bilirubin-to-albumin ratio proved to be a good indicator with a sensitivity of about 68% along with a specificity of 99% to reduce damage of kernicterus, as detection can be done at an early stage before central nervous system (CNS) complications arise.

Strength:

- Minimally invasive procedure with highly useful results.
- Random sampling greatly removed chances of bias.

- All samples being tested at a single laboratory reduced the chances of variations in results.

Limitations: This study has certain limitations. It was conducted at a single tertiary care center, which may limit generalizability to other healthcare settings. The proportion of preterm neonates in the study population was relatively high due to the referral nature of the institute, which may have influenced the observed incidence of jaundice. Important confounding factors such as oxytocin administration during labor, cephalhematoma, and complications during delivery were not assessed and may have affected the occurrence of neonatal jaundice. In addition, subgroup analyses for maternal conditions such as gestational diabetes and hypertension may have been underpowered due to small sample sizes in those categories.

Recommendation: Frequent outreach sessions should be organized to improve knowledge of the community and make them understand the need for prompt reporting. Community awareness regarding early signs of neonatal jaundice should be improved through counseling during antenatal and postnatal care. Exclusive breastfeeding and timely initiation of feeding should be encouraged. Neonates identified as high-risk based on cord blood parameters may be considered for closer follow-up after discharge. Larger multicenter studies are recommended before establishing standardized risk-based discharge policies. Mothers should be encouraged to breastfeed exclusively, frequently at least 8 times a day, without giving top feeds, glucose, water, etc. Mothers should be informed to consult a doctor if their baby shows yellowing discoloration, excessive cry or irritated behaviour so that dreaded complications can be prevented.

Clinical significance: Neonatal jaundice is a common cause of readmission in the early neonatal period, due to which there is an emotional and socio-economic burden on families. Testing cord blood bilirubin and albumin is a very simple, easy, and non-invasive method to predict the development of subsequent neonatal jaundice. Also, it will help in providing a knowledge source for upcoming clinicians.

Conclusion

The present study suggests that cord blood bilirubin and bilirubin-to-albumin ratio are useful predictors for identifying neonates at increased risk of developing neonatal jaundice. Cord blood albumin alone showed lower sensitivity and therefore may not be suitable as an independent screening test, though it may provide supportive value when combined with bilirubin. Neonates with elevated cord blood bilirubin (>2 mg/dL) and bilirubin-to-albumin ratio (>0.61) may require closer postnatal follow-up for early detection of jaundice. Further multicenter studies with larger and more diverse populations are required before these findings can be applied to broader clinical protocols or discharge policies.

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Conflict of Interest

There is no conflict of interest

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