Correlation of cord blood albumin values with neonatal jaundice in health new-borns: a prospective observational study

Jehangir Allam Bhat*, Roshan Ara

Department of Paediatrics, Kurji Holy Family Hospital, Patna, Bihar, India

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*Correspondence:
Dr. Jehangir Allam Bhat,
E-mail: ajaalam333@gmail.com

ABSTRACT

Background: The objective of the present study was to investigate the predictability of pathological jaundice on cord blood albumin values.

Methods: It was a prospective observation study conducted in Kurji holy family hospital on 289 healthy new-borns. Babies were divided into two groups. Group A who developed physiological jaundice and group B who developed pathological jaundice. Cord blood albumin was estimated in all new-born who were then followed up-to 5th day of life. Babies who developed jaundice requiring treatment were admitted in NICU for phototherapy. Rest where checked regularly up-to 5th day of life and value recorded on 5th day by estimation of serum albumin.

Results: Incidence of pathological hyperalbuminemia in present study was 11.2%. There was statistically significant correlation between cord blood albumin and development of pathological jaundice. Gender, age, mode of delivery and birth weight has no correlation with cord albumin and the subsequent development of jaundice. Cord blood albumin <3.5mg/dl when compared with subsequent development of jaundice has high specificity (83.92%) and negative predictive value (87.35%). Cord blood value of >2.5mg/dl has high sensitivity (97.06%), specificity (99.22%), Positive predictive value (94.29%) and negative predictive value (99.61%) in predicting future development of pathological jaundice.

Conclusions: The 87.35% negative predictive value in the present study suggests that in healthy term babies (Cord blood albumin ≤3.5mg/dl) cord serum albumin can help to identify those new-borns who are unlikely to require further evaluation and intervention. These new-borns can be discharged with assurance to parents. Babies with CBA level <2.5mg/dl should be followed more frequently. Thus, this study concludes that cord blood total albumin levels reliably predict the occurrence of pathological hyperalbuminemia.

Keywords: Cord blood serum albumin, Pathological Jaundice, Phototherapy, Physiological jaundice

INTRODUCTION

Hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the newborn and is a frequent reason for hospital readmission during the first week of life. Although generally a 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) the movement disorders of dystonia and/or choreoathetosis, (2) hearing loss caused by auditory neuropathy spectrum disorders, and (3) oculomotor pareses.3 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.

Almost all newborn infants have a serum or plasma total bilirubin (TB) level >1mg/dL in contrast to normal adults in whom the normal TB level is <1mg/dL. Physiological jaundice usually appears on the 2nd-3rd day, peaking between the 5th and 7th days of life. Jaundice may appear at birth or may appear any time during neonatal period depending upon the cause.

Since authors know hyperbilirubinemia has a deleterious effect like kernicterus, chore athetoid cerebral palsy, hearing impairment and cognitive impairment if not treated at the time. So meticulous screening of newborn is required to detect hyperbilirubinemia. Since the peak bilirubin level typically occurs at 72 to 96 hours, after healthy newborns are discharged from their birth hospital, follow-up is essential. Infants discharged before 72 hours should be seen within the next 2 days. Infants at lower gestational ages or who have other risk factors should be seen earlier. This is practically impossible in underdeveloped and even in developing nations because of poverty, low education, cultural practice. Here comes the role of prediction of neonatal hyperbilirubinemia.

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

METHODS

This prospective hospital-based study was conducted in Department of Pediatrics and Neonatology, Kurji Holy Family Hospital, Patna Bihar from 17 January 2016 to 30 December 2018. A total of 289 new-born, fulfilling the predefined inclusion criteria, delivered in our hospital were studied.

Proper ethical and scientific clearance was taken from concerned hospital department. Proper consent was taken from parents of babies after explaining the risks and benefits of neonatal jaundice, phototherapy and blood sampling.

Inclusion criteria

- Gestational age 35 weeks and above. (based on last Menstrual period)
- The absence of major congenital malformations
- Residing at Patna or nearby whose parents agree to come for follow up.

Exclusion criteria

- Presence of significant illness, (i.e. sepsis & hypothyroidism)
- Rh incompatibility
- ABO incompatibility
- Newborns with obvious life-threatening congenital malformation (trachea-esophageal fistula (TOF), anorectal malformation)
- Babies with conjugated hyperbilirubinemia.

Statistical analysis

Data analysis was carried out using Microsoft excel sheet. In case of quantitative data, mean and standard deviation, as well as range (minimum and maximum value), is computed. Sensitivity, specificity, positive and negative predictive value of different cut-points of cord blood serum bilirubin were derived. For determining the significance of each test p-value of <0.05 was used.

All babies delivered in KHFH were examined and a detailed antenatal and postnatal history was taken. Cases were selected if they fulfilled all the criteria set out above. Informed consent was taken from the parents and blood was collected from cord blood at birth.

Blood sample of the mother was simultaneously collected and sent for blood grouping if it was not known from before. The cord blood sample of the infant was sent for grouping and albumin estimation and then all babies were examined by senior registrars and experts for clinical assessment of bilirubin as per Kramer’s scale (Figure 1) and by transcutaneous bilirubinometer for continuous 5 days.

**Figure 1: Modified Kramer’s scale.**

Babies were divided into two groups: Group A developing jaundice within physiological range and Group B developing jaundice which needs treatment (pathological jaundice). Babies suspected of having high bilirubin were cross checked by serum bilirubin level and admitted for treatment if needed as per AAP nomogram for hyperbilirubinemia management. Remaining babies were checked for serum bilirubin on 5th day of life.
**Bilirubin estimation**

The Serum Bilirubin was estimated by micro-bilirubin (Jendrassik and Grof method) for that venous blood is taken in four microcapillaries and centrifuged at the rate of 10000 rpm for 5 minutes. Bilirubin estimation is done spectrophotometrically using beam method (55nm wavelength) (micro la-300, Merck, Netherland). Calibration of bilimeter is done daily using labeteral solution.

**RESULTS**

Out of 300 new-borns enrolled, 11 could not be included in the study because of refusal of consent, drop in follow up, Rh/ABO incompatibility and admission in NICU because of cause other than hyperbilirubinemia. All new born were exclusively breast fed. A total of 289 subjects were followed up for the first five days of life with clinical assessment and laboratory investigations. Of the enrolled subjects, 169 (58.48%) were males and 120 (41.52%) were female with mean cord blood albumin and serum bilirubin during evaluation up to 5 days of (2.6±0.8 and 13.9±2.4) and (2.5±0.4 and 12.9±1.8) respectively with P value of 0.89 thus, no statistical significance (Table 1). 208 (71.19%) were babies >37 weeks of age and 81 (28.03%) were 35-37weeks babies. Gestational age included in study has no statistically significant effect when comparison between cord blood albumin and serum bilirubin when estimated up to 5th day (Table 1) (P value 0.95) as revealed by present study in which out of total 34 babies who developed pathological jaundice meriting intervention wherein 35-37 weeks age and rest 25 weeks of age group >37 weeks with no statistical significance. Similarly birth weight and mode of delivery comparison of cord blood albumin and serum bilirubin when estimated up to 5th day has no statistical significance with P value of 0.78 and 0.999 respectively as depicted in Table 1. A total of 255 (84.5%) (Group A) developed jaundice which was in physiological range so went home without any treatment. The mean±SD serum total albumin in cord blood, and on day 5 of the babies in this group were 3.3±0.8mg/dl and 11.9±2.4mg/dl respectively (Table 2). Statistical correlation revealed no significance with P value of 0.087.

Total 34 (Group B) (11.76%) infants developed hyperbilirubinemia up to 5th day with mean albumin of 2.4mg/dl with standard deviation of 0.4mg/dl and mean serum bilirubin when estimated up to 5th day of life of 16.7mg/dl with standard deviation of 1.8. Statistical correlation between these two was strong with p value of 0.0001 (Table 2).

Table 3 illustrates babies having cord blood albumin of >3mg/dl where compared with their serum bilirubin which was recorded up to their 5th day of life. Sensitivity 8.82 % (CI-1.86% to 23.68%) and specificity of 83.92% (CI- 78.83% to 88.21%) with positive predictive value and negative predictive value of 6.82% (2.34% to 18.26%) and 87.35 % (85.99% to 88.59%) respectively.

**Table 1:** Distribution of the enrolled new-born’s according to gender, gestational age, birth weight and mode of delivery.

| Characteristics | Number | %     | Cord blood albumin Mean±SD | Bilirubin during monitoring up to 5th day of life Mean±SD | P value |
|-----------------|--------|-------|----------------------------|----------------------------------------------------------|--------|
| Gender          |        |       |                            |                                                          |        |
| Male            | 169    | 58.48 | 2.6±0.8                    | 13.9±2.4                                                 | 0.89   |
| female          | 120    | 41.52 | 2.5±0.4                    | 12.9±1.8                                                 |        |
| Gestational age |        |       |                            |                                                          |        |
| >37weeks        | 208    | 71.19 | 2.7±0.8                    | 13.7±2.2                                                 | 0.95   |
| 35-37weeks      | 81     | 28.03 | 2.4±1.4                    | 13.2±2.2                                                 |        |
| Mode of delivery|        |       |                            |                                                          |        |
| vaginal         | 188    | 65.05 | 2.9±1.3                    | 11.9±2.0                                                 | 0.78   |
| LSCA            | 101    | 34.94 | 2.6±0.8                    | 12.9±2.4                                                 |        |
| Birth weight    |        |       |                            |                                                          |        |
| 1.5-2.5         | 98     | 33.91 | 2.5±1.9                    | 14.2±1.4                                                 | 0.999  |
| 2.6-3.5         | 146    | 50.52 | 2.9±1.4                    | 12.3±1.7                                                 |        |
| >3.5            | 45     | 15.57 | 2.87±0.4                   | 12.5±2.8                                                 |        |

**Table 2:** Mean±SD of albumin levels in cord blood and bilirubin at 5th day blood of neonates and their association.

| Group | Number | %     | Cord blood albumin Mean±SD | Bilirubin during monitoring up to 5th day of life Mean±SD | P value |
|-------|--------|-------|----------------------------|----------------------------------------------------------|--------|
| A     | 255    | 88.24 | 3.3±0.8                    | 11.9±2.4                                                 | 0.087  |
| B     | 34     | 11.76 | 2.4±0.4                    | 16.7±1.8                                                 | 0.0001 |

Group A: Physiological hyperalbuminemia. Group B: Pathological hyperalbuminemia
Neonates having cord blood albumin level in the range of 2.5-3 when compared with their serum bilirubin recorded up to 5\textsuperscript{th} day of life were having sensitivity, specificity, Positive predictive value and negative predictive value of 66.67\% (49.03\% to 81.44\%), 92.94\% (89.07\% to 95.76\%), 57.14\% (44.67\% to 68.77\%), and 95.18\% (92.55\% to 96.91\%) respectively. Similarly, cord blood albumin of <2.5mg/dl has sensitivity, specificity Positive predictive value and negative predictive value of 97.06\% (84.67\% to 99.93\%), 99.22\% (97.21\% to 99.91\%), 94.29\% (80.56\% to 98.50\%), 99.61 \% (97.36\% to 99.94\%) (Table 3).

### DISCUSSION

Jaundice is a common entity which needs attention up to some days of birth. Most of the jaundice which develops in newborn is in physiological range except small fraction who need intervention like phototherapy, exchange transfusion or new modalities of treatment. Although their fraction is low usually in the range of 8-10 \%, as proved in present study with 11.2\%. But timely diagnosis and immediate treatment is very essential because it could have devastating effect on their future life because of kernicterus, which lead to mental retardation, chore athetoid type of cerebral palsy or hearing defect. Since percentage of these side effects have dramatically decreased in last decade because of public awareness educational programs. But, still there is small fraction of new-born who fall prey to the devastating side effects of neonatal hyperalbuminemia especially in developing country because of poor follow up, limited resources and most important parental emotional attachment, who did not want their child to get hurt even from a single needle prick. Keeping in view all these factors, the objective of this research was framed. Present study presumption was that a low serum albumin level at birth would also predict a high peak later in life.

Incidence of pathological hyperalbuminemia in present study was 11.2mg/dl. This is in accordance to studies conducted by other authors like was12.80\% in a study by Awasthi S et al, 12.00\% as per a study by Randev S et al,11.4\% in a study by Dhanwadkar et al.

In present study there was no relation between cord blood albumin and bilirubin monitored up to 5\textsuperscript{th} days of life when gender, gestational age, birth weight and mode of delivery was compared. Similar findings were noted by Awasthi S et al and Alpay F et al.

Incidence of pathological hyperalbuminemia was11.2 \% in present study which is supported by research conducted by Knupfer M et al and Awasthi et al, who derived incidence of 10.6 and 12.8 \% respectively.

In present study mean cord blood albumin of those babies who developed pathological jaundice was 2.4±0.4 (Mean±SD). This finding was in accordance of the research Aiyappa GKC et al, investigated the predictability of umbilical cord blood albumin concentration on subsequent hyperalbuminemia. Utilizing a cut-off point of albumin of 2.8 mg/dl, the sensitivity of cord albumin to detect hyperbilirubinemia in newborn was determined and found to be 71.8\%, while specificity was 65.1\%. The positive predictive value was found to be 38.9\% and the negative predictive value was found to be 88.2\%. The accuracy rate was 67.3\%. Reshad M et al, showed similar association. He stated in term newborn group,19 (61.2\%) newborns with CSA < 2.8g/dL developed neonatal hyperbilirubinemia. 13 (32.3\%) newborns had CSA level between 2.9-3.3g/dL, and only 2 (6.5\%) of the newborns with CSA level ≥3.4g/dL developed significant neonatal hyperbilirubinemia. Pahuja M et al, in their had noted that predictive value of cord albumin for development of neonatal hyperbilirubinemia was 75\% which implies a

### Table 3: Statistics of values of various cord blood albumin levels in predicting the development of significant hyperalbuminemia.

| Statistics                          | >3 Value | 2.5-3 Value | <2.5 Value |
|-------------------------------------|----------|-------------|-----------|
| Sensitivity                         | 8.82\%   | 66.67\%     | 97.06\%   |
| Specificity                         | 83.92\%  | 92.94\%     | 99.22\%   |
| Likelihood Ratio                    | 0.55     | 5.72        | 124.24    |
| Positive Predictive Value           | 1.09     | 0.23        | 0.03      |
| Negative Predictive Value           | 11.76\%  | 8.82\%      | 11.72\%   |
| Disease prevalence                  | 8.29\%   | 8.82\%      | 11.72\%   |
| Positive Predictive Value           | 6.82\%   | 44.67\%     | 94.29\%   |
| Negative Predictive Value           | 87.35\%  | 92.55\%     | 99.61\%   |

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fair predictive value of the criteria with 61.3% sensitive and 76.8% specific and is in correlation with the present study, present study revealed at cord blood albumin level of >3mg/dl, sensitivity 8.82% and specificity of 83.92% with positive predictive value and negative predictive value of 6.82% and 87.35 % respectively.13 Thus, at cord blood >3.5mg/dl probability of not developing hyperalbuminemia is 83.92%. This finding was supported by Thakur P et al, who found 4% incidence of NNH at cord blood albumin level of <2mg/dl with specificity of 98.23%.14 Alalfy M et al noted the highest sensitivity (83.3%) was for cut off value of cord bilirubin (1.88mg/dl)with PPV 72.9%, which mean that authors can predict 83.3% of patients with the disease (true positives) but 16.7% of cases with the disease go undetected (false negatives); whilst the highest specificity (84.8%) was for cut off value of cord bilirubin albumin(-0.6)with NPV 74.1%,which mean that authors can correctly report 84.8% of patients without the disease as test negative (true negatives) but 15.2% patients without the disease are incorrectly identified as test positive (false positives).15 Other findings which authors extracted from present study were sensitivity, specificity, positive predictive value and negative predictive value at cord blood serum albumin level of <2.5,2.5-3mg/dl and >3mg/dl and other studies which support this are shown in Table 4. As illustrated in Table 4, present study predicts with high probability, at serum albumin level <2.5mg/dl chances of developing pathological neonatal hyperalbuminemia are very high. Thus, these new-borns must be meticulously checked on follow up. Cord blood albumin level of 2.5-3 also showed good specificity but due to decreased sensitivity, these new born can be categorized into intermediate risk and babies having cord blood albumin >3mg/dl. So, present study can classify new-born into three risk categories as per cord blood serum albumin.

Cord blood albumin (mg/dl): Risk category

- <2.5mg/dl: High risk
- 2.5-3mg/dl: Intermediate
- >3mg/dl: Low risk.

**Table 4: Studies on the predictive ability of cord blood albumin level and the neonatal hyperalbuminemia.**

| Studies       | Cut off CA (mg/dl) | Cut off NNH (mg/dl) | SNV  | SPV  | PPV  | NPV  |
|---------------|--------------------|---------------------|------|------|------|------|
| Present study | <2.5               | <12                 | 8.82%| 83.92%| 6.82%| 87.35%|
|               | 2.5-3              | 14.5-15.6           | 66.67%| 92.94%| 57.14%| 95.18%|
|               | >3                 | >16                 | 97.06%| 99.22%| 94.29%| 99.61%|
| Aiyappa GKC et al11 | <2.8            | 15.9               | 71.8%| 65.1%| 38.9%| 67.3%|
| Thakur P et al14 | ≤2.5              | <15                 | 73.54%| 56.45%| 63.18%| 67.74%|
|               | >2.5              | >15                 | 81.40%| 63.40%| 69.3%| 77.10%|
| Alalfy M et al15 | 2.75              | >16                 | 64.3%| 81.8%| 81.8%| 80%|

**CONCLUSION**

The study concludes with result that there is significant correlation between cord blood serum albumin and development of neonatal jaundice. Cord blood albumin can be used to categorise neonates into risk group. Neonates with serum albumin >3mg/dl have low risk for neonatal hyperalbuminemia, thus can be kept in low priority as compared to neonates with cord blood serum albumin <2.5mg/dl.

Neonates with cord blood albumin level <2.5mg/dl should be followed more frequently to reduce morbidity and mortality due to neonatal hyperalbuminemia.

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