Original Research Article

Race specific nomograms: time for change?

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ABSTRACT

Background: Hyperbilirubinemia is a common problem in neonates. Because of the genetic differences in bilirubin metabolism, an hour specific nomogram is better in each geographical location. No studies in South India for creation and validation of a nomogram for significant hyperbilirubinemia. The aim of this study was to create and validate a bilirubin nomogram in South Indian infants.

Methods: A prospective cross-sectional study. The data was collected in 2 parts, over 18 months (264 infants) and 20 months (450 infants) respectively. Babies with established direct hyperbilirubinemia, polycythemia, hypothyroidism, culture proven sepsis, major congenital anomalies and jaundice on day 1 of life were excluded. For all babies, cord bilirubin (for first set of infants), total serum bilirubin values were sent at 24 hours of life and at the time of discharge. An hour specific nomogram was created with 834 bilirubin values (first set of data). The predictive ability of this nomogram and Bhutani nomogram were tested and compared using 972 total serum bilirubin values (second set of data)

Results: A nomogram was created with serum bilirubin values from the first set of infants and validated it with the serum bilirubin values from the second set of infants. Bhutani nomogram was also validated. Comparing with Bhutani nomogram, our nomogram was better in predicting significant hyperbilirubinemia in our population.

Conclusions: Discharging neonates without risk assessment for severe hyperbilirubinemia may be dangerous. A nomogram generated and validated with our data is an accurate tool for predicting significant hyperbilirubinemia in our population.

Keywords: Nomogram, Phototherapy, Significant hyperbilirubinemia, Serum bilirubin

INTRODUCTION

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates.¹ Physiological jaundice, in term babies, peaks to 6-8 mg/dl by 3-5 days of age with the maximum level of 12 mg/dl and then falls.

In premature babies, the peak may be 10-12 mg/dl on the fifth day of life, probably rising to >15 mg/dl.² Although bilirubin may have a physiological role as an antioxidant, elevations of unconjugated bilirubin are potentially neurotoxic. Kernicterus, which occurs due to severe

hyperbilirubinemia, is the most easily preventable cause of neonatal mortality and brain death. With the increasing demand for shorter length of hospital stay for babies after delivery, there is an increased risk of unrecognised or delayed hyperbilirubinemia resulting in an increase in the incidence of babies affected with kernicterus.⁴

Wang ML et al suggested that the addition of clinical risk factors, such as gestational age (GA), can significantly increase the predictive accuracy of the pre-discharge bilirubin.⁵ Gupta P showed that out of 193 babies who came for follow up, neonatal jaundice was the most

frequent problem seen in 105 (54.4%) and the most common cause of rehospitalisation in 8.3%.⁶

Bhutani et al proposed a nomogram for designation of risk in 2840 well newborns at 36 weeks gestational age with birth weight of 2000 g or 35 weeks gestational age and birth weight of 2500 g based on the hour-specific serum bilirubin values.⁷ It is also known that the demographics of the study population do not represent Indian population.⁸

A nomogram was developed in a sample of 625 healthy late preterm and term Indian neonates.⁹ The predictive accuracy of the nomogram, performed lower than previous studies. The sensitivity for the 75th percentile only reached 86.1% with 11 false negative results, and the 50th percentile had 1 false negative (sensitivity 98.7%). Only when the 25th percentile was chosen as the risk predictor for significant hyperbilirubinemia, defined as the 2004 AAP TSB thresholds for phototherapy, were all false negatives avoided.

Because of the differences in bilirubin metabolism determined genetically and also with the feeding practices followed in the different ethnicities or race, an hour specific nomogram is better in each geographical location. There are no studies done in South India for creation and validation of a nomogram for detecting significant hyperbilirubinemia either with serum bilirubin or with transcutaneous bilirubin measurements. The aim of this study was to create a bilirubin nomogram in South Indian infants and validating this nomogram for the study population.

METHODS

A prospective cross-sectional study was done at a Tertiary Care Hospital, Level II NICU in South India (Pondicherry Institute of Medical Sciences, Pondicherry). The data was collected in 2 parts: first set of data was collected over a period of 18 months (October 2012 to April 2014) from 264 infants. Second set of data was collected during the period of November 2014 to June 2016 from 450 babies.

Exclusion criteria

Babies with established direct hyperbilirubinemia or hemolytic anemia, polycythemia requiring partial exchange, proven hypothyroidism, culture proven sepsis, major congenital anomalies, any known gastrointestinal malformations (from antenatal scans) and all babies who received phototherapy before 24 hours.

Parameters studied were cord blood total bilirubin (first set of infants), 24 hours total serum bilirubin, mother and baby's blood group, haemolytic work up, when required, which included complete blood count, peripheral smear, reticulocyte count, direct coomb's test, total and direct serum bilirubin

The study protocol was approved by institutional ethics committee. Written informed consent was obtained from the mothers of all infants who were included in the study, for using their baby's de-identified data. Gestational age of the mother was determined by dating scan if available or according to the first day of the mother's last menstrual period or as decided by treating obstetrician. As per hospital policy, blood grouping and typing was also done for all babies and their mothers.

Cord blood was taken for bilirubin values for all infants who were enrolled for first set of data. If there was a setting for haemolysis, haemolytic work up that included complete blood count, peripheral smear, reticulocyte count, direct coomb's test was also done. If the babies had any evidence of haemolysis (Rhesus haemolytic disease, a positive direct coomb's test, reticulocytosis or a peripheral smear compatible with haemolysis) they were excluded from the study. All babies received Vitamin K 1 mg intramuscularly immediately after birth. No prophylactic intervention for hyperbilirubinemia was employed. For all babies who were enrolled in the study, cord bilirubin (for first set of infants), total serum bilirubin values were sent at 24 hours of life and at the time of discharge. In between total serum bilirubin levels were sent if the baby was found icteric clinically according to Kramer's scale. 1 ml of venous blood for serum bilirubin was collected under strict aseptic precautions after the mother was explained about the procedure. The samples were taken immediately to the biochemistry laboratory and measured. Serum bilirubin measurements were measured in a colorimetric method in the INTEGRA 400 machine. The bilirubin levels are plotted in the Bhutani's nomogram according to the gestational age and a risk zone is assigned accordingly. Further action is done according to Bhutani's nomogram and/or using bilitool.

The definition of significant hyperbilirubinemia for the new-borns in the study was made on the basis of American Academy of Pediatrics guidelines.¹⁰

All newborns with significant hyperbilirubinemia were started on phototherapy. Pre-phototherapy bilirubin levels were considered for analysis for babies who underwent phototherapy. Serum bilirubin values after the initiation of phototherapy were excluded from analysis but were documented and recorded. Sunlight exposure was always constant throughout the study period.

In all cases maternal factors like gestational age, gravidae, mode of delivery were documented. Baby details like birth weight, gender and growth were documented. The babies who had significant hyperbilirubinemia which requires phototherapy was also documented.

The data was entered in Epi-info and analysed in SPSS version 20 software. Statistical analysis was performed

using student's *t*-test for continuous predictors and chi-square test for categorical data.

Creation of study nomogram

Total serum bilirubin percentiles for each designed time were calculated and these data were used to design an hour specific nomogram with the bilirubin values of 264 infants (first set of data). 40th, 75th and 95th percentile values were calculated from the bilirubin values for cord, 24 hours, 48 hours, 72 hours and 96 hours respectively. The sensitivity, specificity, positive predictive value, negative predictive value was calculated for the 40th, 75th and 95th percentile of the nomogram.

Validation of study nomogram

The predictive ability of this nomogram was tested using the total serum bilirubin values, data from 450 babies (second set of data). These values were plotted in the nomogram we created and tested the predictive ability was tested. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the 40th, 75th and 95th percentile of the nomogram. Receiver operating characteristic (ROC) curve analysis was performed with SPSS version 20.0, which was used

to assess the predictive ability of the bilirubin nomogram and was then compared with Bhutani nomogram.

Validation of Bhutani nomogram

The predictive ability of Bhutani nomogram was tested using the total serum bilirubin values from 450 babies were taken (second set of data). The serum bilirubin levels were plotted on the Bhutani nomogram and validated for the population using Receiver Operating Characteristic (ROC) curve separately. The sensitivity, specificity, positive predictive value, negative predictive value was calculated for the 40th, 75th and 95th percentile of the nomogram using the study data.

RESULTS

This was a prospective cohort study done in two-time periods: first set of data (834 values from 264 infants) was collected from October 2012 to April 2014 and second set of data (972 values from 450 infants) from November 2014 to June 2016 at Pondicherry Institute of Medical Science, a tertiary care hospital with level II neonatal intensive care. Baseline characteristics of both sets of infants are given in Table 1.

Table 1: Demographic characteristics of the study population.

Study population	First set N = 264		Second set N = 450	
Characteristics	Number	Percentage	Number	Percentage
Gender				
Male	152	57.5	413	91.7
Female	112	42.5	37	8.3
Weight				
<2000g	15	5.6	11	2.4
2000-2499g	42	15.9	40	8.8
2500-2999g	105	39.8	167	37.2
3000g-3499g	84	31.8	187	41.6
>3500g	18	6.9	45	10
Mode of delivery				
Normal vaginal delivery	169	64	293	65.1
Instrumental delivery	18	6.8	23	5.1
Caesarean delivery	77	29.2	134	29.8
Gestational age				
34-36 ⁶ weeks	72	27.2	39	8.6
37-39 ⁶ weeks	162	61.4	355	78.8
>40 weeks	30	11.4	56	12.6
Growth				
Small for gestational age	69	26.1	52	11.5
Approximate for gestational age	187	70.8	396	88
Large for gestational age	8	3.1	2	0.5
Significant hyperbilirubinemia				
Yes	83	31.4	54	12
No	181	68.6	396	88

For the first set of data, 76.6% (23/30) of babies who had significant hyperbilirubinemia at 24 hours were near terms. There was no statistically significant difference between the two groups in the mean serum bilirubin values at 24, 48, 72 and 96 hours. Considering the babies who had significant hyperbilirubinemia developed at 24 hours and >72 hours, there was statistically significant difference between two groups (p value = 0.002 and 0.00001 respectively).

This nomogram for predicting significant hyperbilirubinemia was generated using serum bilirubin measurements of first set of infants.

Figure 1: Nomogram made from present study bilirubin levels (mg/dl).

None of the babies had significant birth asphyxia, delayed passage of meconium, cephalohematoma or bruising. This institution is baby friendly, and initiation of breast feeding occurred almost always within one hour of birth in cases and controls.

Figure 2: Validation of study nomogram with second set of data. Prediction of significant hyperbilirubinemia at 24 hours.

The babies included in final analysis were all exclusively breastfed, any baby requiring further care for excessive weight loss (>10% of birth weight) would be admitted in NICU and excluded from study.

We have created a nomogram with cord blood, 24 hours, 48, 72 and 96 hours serum bilirubin measurements from first set of infants (Figure 1) and validated it with the serum bilirubin values from the second set of infants. The area under the curve in ROC curve at 24 hours, 48 hours, 72 hours and 96 hours are 0.939, 0.967, 0.993 and 0.958 respectively (Figure 2, 3, 4 and 5).

The area under ROC curve from validation of Bhutani nomogram with our population at 24 hours, 48 hours, 72 hours and 96 hours are 0.967, 0.939, 0.702 and 0.727 respectively (Figure 6).

Figure 3: Validation of study nomogram with second set of data. Prediction of significant hyperbilirubinemia at 48 hours.

Figure 4: Validation of study nomogram with second set of data. Prediction of significant hyperbilirubinemia at 72 hours.

Figure 5: Validation of study nomogram with second set of data. Prediction of significant hyperbilirubinemia at 96 hours.

Figure 6: Validation of Bhutani nomogram with study data. Prediction of significant hyperbilirubinemia at 24 hours, 48 hours.

Hence comparing with Bhutani nomogram, our nomogram was better in predicting significant hyperbilirubinemia in our population even though predictability of both nomograms was accurate (Table 2).

Table 2: Comparison between the predictive ability of Bhutani versus study nomogram (comparison of area under the curve (AUC)).

	Our nomogram	Bhutani nomogram
24 hours	0.939	0.967
48 hours	0.967	0.939
72 hours	0.993	0.702
96 hours	0.958	0.728

Figure 7: Validation of Bhutani nomogram with study data. Prediction of significant hyperbilirubinemia at 72 hours, 96 hours.

DISCUSSION

Jaundice in the newborn is a common cause for prolonged stay in hospital as well as hospital readmission during the first two weeks of life. Early discharge is making the management of jaundice quite difficult, since it is one of the cause for hospital readmission.^{11,12}

Hence in 2004, American Academy of Pediatrics recommended all newborn infants be assessed before discharge for the risk of developing significant hyperbilirubinemia subsequently.¹³

This study was a prospective case control study, which was done in the Department of Pediatrics, Pondicherry Institute of Medical Sciences, Pondicherry. The aim of the study was to create a nomogram for the prediction of significant hyperbilirubinemia and validating this nomogram for the study population from serum bilirubin measurements.

Although the patients are from different socioeconomic status, most of the baseline characteristics are similar. There was no statistical significant difference between the two groups with respect to maternal age, antenatal complications, gravidae and mode of delivery.

Many studies suggest that preterm/near term babies are at higher risk for developing significant hyperbilirubinemia.¹¹⁻¹⁶ In this study, the incidence of significant hyperbilirubinemia was more in near term/pre

term infants when compared to term infants at 24 hours and at 72 hours and later.

Bhutani and colleagues created a nomogram and demonstrated the relationship of total serum bilirubin values plotted on an hour specific nomogram and the later risk of significant hyperbilirubinemia.⁷ This nomogram was designed to help identify the newborns who are at low, intermediate or high risk for reaching bilirubin levels above the 95th percentile in the first week of life. There are multiple critiques about this nomogram. One study highlighted the false negative results reported with this nomogram. They also mentioned that, the patient in low risk and low intermediate risk as per Bhutani nomogram developed significant hyperbilirubinemia later.¹⁷ The different performances of Bhutani nomogram was explained by racial difference, genetic and environmental factors which play a role or because of the presence of clinical risk factors. There were many other flaws with Bhutani nomogram like follow up was not performed in more than 75% of the study population and they validated the nomogram in the same sample of patients from which the nomogram was created. Bhutani nomogram could not perform well in all settings if there is significant difference between the population. In this study we tried to validate Bhutani nomogram in our population.

We plotted total serum bilirubin measurements of our study population on Bhutani hour specific nomogram and found that it was useful in predicting significant hyperbilirubinemia. 24 hours serum bilirubin values were more accurate in predicting significant hyperbilirubinemia compared with other values. But in the study done by Sarici U, they found that 6th hour serum total bilirubin value has more predictive ability for the development of significant hyperbilirubinemia in near term babies.

We have developed an hour specific percentile based nomogram using serial measurements of TSB which includes cord blood, 24 hours, 48 hours, 72 hours and 96 hours from first set of our study population (264). We prospectively validated the predictive ability to identify the risk of significant hyperbilirubinemia in second set of infants (450 infants). Even though the sample size was small, we tried to eliminate one major criticism of Bhutani nomogram.⁸

Costantino et al in their study developed and validated their nomogram in a large neonatal population of Rome.⁴ Similarly there is nomogram developed and validated for the Chinese, Hispanic and Mongolian population.¹⁸⁻²¹ There has been paucity of similar studies in India except one done in North India.²¹

All these studies concluded that the nomograms created for that population will be able to predict significant hyperbilirubinemia in their population more accurately.

CONCLUSION

Discharging neonates without risk assessment for severe hyperbilirubinemia may be dangerous. A nomogram generated and validated with our data proved to be an accurate tool for predicting significant hyperbilirubinemia in our population.

Recommendations

A local nomogram for predicting significant hyperbilirubinemia is ideal. Bhutani nomogram may be used if locally created nomograms are not available.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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