International Journal of Contemporary Pediatrics
Mehta N et al. Int J Contemp Pediatr. 2019 Mar;6(2):315-319
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20190526

Original Research Article

Predischarge risk factors for predicting significant hyperbilirubinemia in term of infants

Nirali Mehta[1]*, R. G. Bhatt[2], Hetal Vora[3], Divya Reddy[3]

[1]Pharma-Stats, Ahmedabad, Gujarat, India
[2]Department of Statistics, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India
[3]Department of Pediatrics, Shardaben General Hospital, Smt. NHL Medical College, Ahmedabad, Gujarat, India

Received: 28 January 2019
Accepted: 05 February 2019

***Correspondence:**
Mrs. Nirali Mehta,
E-mail: niralimehta008@gmail.com

ABSTRACT

Background: The objective of the study to compare the predictive ability of predischarge serum total bilirubin (STB) and clinical factors for significant hyperbilirubinemia (SHB) in newborn to observe the prediction of the hyperbilirubinemia.
Methods: In the prospective study, enlist of healthy newborn infants with >35 weeks gestation, in a tertiary hospital in western India. The serum bilirubin between 36-48 hours of age and risk factors for SHB were identified before discharge. SHB was distinct as a bilirubin level that exceed or was within 1mg/dL (17µmol/L) of the hour-specific phototherapy conduct threshold recommended by American Academy of Pediatrics (AAP) guideline on the management of neonatal hyperbilirubinemia.
Results: Of 505 infants, 380 infants were included in final analysis, among which 70 babies (22.5%) developed SHB. On univariate analysis STB, gestational age (GA) and percentage of weight loss were found to be predictive of SHB. On multiple logistic regressions, the prognostic ability of predischarge STB is higher than that of percentage of weight loss and GA. The predictive accurateness of predischarge (<48 hours) STB level was comparable to that of percentage of weight loss (AUC=0.88, 95% CI 0.84-0.93). However, the prediction model that combined multiple risk factors such as predischarge STB, GA and percentage of weight loss have the best accuracy for predicting SHB.
Conclusions: Combination of specific clinical factors (gestational age and percentage of weight loss) with predischarge serum total bilirubin described best predicts development of considerable hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Predischarge bilirubin, Significant hyperbilirubinemia

INTRODUCTION

The incidence of Hyperbilirubinemia is a general problem in newborns of around 70%.[1] Approximately 9% of them can enlarge significant hyperbilirubinemia (SHB) required treatment during the first week of life.[2] Newborns without viewing could be uncovered to the risk of developing SHB and, if untreated, could extend to acute bilirubin encephalopathy, sensorineural hearing loss and bilirubin induced neurological damage which known as Kernicterus. American Academy of Pediatrics (AAP) recommends all newborns (>35 weeks gestation) should be reviewed before discharge using clinical risk factors and/or bilirubin dimension for the risk of developing SHB. The guideline stresses the need to plot the serum bilirubin levels with the hour specific nomogram considered by Bhutani, et al and separate out them into various risk zones as a guide for interference.[3] In United Kingdom, post-discharge home visits by community midwife helps in noticed significant hyperbilirubinemia.

However, this is neither practicable nor cost effective in Indian setting. National neonatology forum (NNF) in India recommends pre-discharge assessment for all newborns to avoid SHB in the form of thorough clinical assessment and, a biochemical screening, if possible.[4] Nevertheless more studies are desirable to substantiate the best method of bilirubin measurement (transcutaneous or serum total bilirubin) for predischarge assessment in Indian newborns.[4] The arrangement of using serum total bilirubin (STB) or transcutaneous bilirubin (TcB) with clinical risk factors has been suggested for predischarge risk assessment.[5,6] Chawla, et al studied 464 infants and recommended a risk score (consisting of TcB, gestation at birth and parity status) which predicts SHB.[7] Another study in late preterm infants concluded that TcB predicts later jaundice better than experimental factors.[8] Pathak, et al also showed that STB and hour-specific bilirubin nomogram could be used for forecast subsequent require of phototherapy.[9] When considered early in the life (at 18-24 hours after birth), STB, using a cut-off value of >3.99mg/dl, could also predict later SHB.[10] However, none of the studies on pre-discharge cut-off value of STB in Indian infants and also none of discovered the combination of STB and clinical risk factors for predischarge assessment in term newborns.

In the study, authors assessed the usefulness of STB measurement at age 36 to 48 hours (predischarge) in combination with clinical factors for predicting SHB in term and near-term newborns (>35 weeks gestation). Authors have designed the study to assess the following: 1) predictive accuracy of the predischarge STB (obtained at age 36 to 48 hours), individual clinical risk factors, and a mixture of the numerous clinical risk factors and predischarge STB. 2) STB level (a cut-off level) before discharge is a good predictor for later SHB. 3) The effectiveness of hour-specific bilirubin nomogram in predicting SHB in infants.

METHODS

This prospective study was conducted from March 2017 to August 2018 in a tertiary care Civil Hospital Ahmedabad, which caters around 3600 deliveries per year.

Inclusion criteria

- Newborns were enrolled for the study if they were managing entirely with the mother in the ward and if they were more than 35 weeks' gestation age (GA).

Exclusion criteria

- Newborns who were admitted to the intensive care nursery for any acute illness, with blood group incompatibility, with major congenital anomalies, and those who conventional >48 hours of intravenous antibiotics for alleged sepsis were excluded from the study.

Present hospital has accepted universal serum bilirubin (STB) screening at age 36-48 hours beside with newborn screening program for all newborn infants. All infants were assessing for weight loss before discharge from the unit. Infants who were discharged from the hospital earlier than 36 hours of age were called to acquire a STB, weight measurement and newborn screening test within subsequently 24 hours of discharge. Venous case was used to collect the blood sample. All study infants were followed up throughout the hospital stay and after discharge awaiting the end of first week of age. Every additional infants were also calling back in within 48-72 hours of discharge to have clinical assessment. Decision to obtain supplementary bilirubin measurements and to initiate phototherapy after discharge was made by the primary care physicians on the source of clinical assessment. The hospital review board approved the study protocol. Authors obtained informed consent from parents of all infants in the present study.

Predictor variables

Clinical risk factors and predischarge STB for hyperbilirubinemia were used as interpreter variables. Predischarge bilirubin was deliberated at age 36-48 hours. The hour-specific bilirubin nomogram to convert the predischarge bilirubin values into danger zones (zone A: low, 0-40th percentile; zone B: low-intermediate, 41st to 75th percentile; zone C: intermediate-high, 76th to 95th percentile; and zone D: high, >95th percentile). For newborns that had more than one bilirubin value obtained before 48 hours of age, authors selected the highest risk zone value to hand out as the predictor value. If the predischarge bilirubins also convene present criteria for significant hyperbilirubinemia, then that bilirubin served as both a predictor and an outcome value. The collection of characteristics of maternal, infant, and delivery carried out from the admission chart.

Outcome variable

Significant hyperbilirubinemia (SHB) requiring phototherapy was used as outcome assessment. SHB was defined as bilirubin levels that surpass or was within 1mg/dL (17µmol/L) of the hour-specific phototherapy treatment threshold recommended in the AAP's clinical practice guideline on the management of neonatal hyperbilirubinemia. The choice to start phototherapy was made on the basis of the infant’s age and STB levels, as per AAP guidelines. The AAP guideline is using for specific risk factors such as bilirubin neurotoxicity to make a decision which phototherapy action doorstep curve to use in determining whether a study infant's bilirubin exceeded the threshold.

Statistical analysis

Statistical analysis was performed by using SPSS 22.0. Student t-test was analyzed for continuous data with normal distribution and Mann-Whitney U test for non-

normally distributed data used to compare means, and chi square or unconditional data was analyzed by chi-square or Fisher exact test are used to compare proportions.

A $p<0.05$ was measured significant. Multiple logistic regression analysis for the predictive value of bilirubin measurements and clinical factors for hyperbilirubinemia, with phototherapy use (as none of them needed exchange transfusion) as the outcome. Clinical variables measured such as GA, sex, birth weight, percentage of weight loss, parity, mode of delivery and maternal diabetes. Model consequence sizes were compared in terms of the receiver-operating area under the curve (AUC), which is equivalent to the c-statistic. The prognostic values of a cut-off value of STB were planned after analyzing the data in the two-by-two table. Confidence intervals were computed at the 95% level.

The association between individual risk factors (predictors) and the outcome of interest was estimated first using univariate analysis. The clinical factors, which were significantly associated with the outcome, were only included in the multiple logistic regression model.

RESULTS

Five hundred and five infants were born during the study period; 63 infants were excluded from the study according to exclusion criteria, 442 infants were enrolled for the study in which 125 infants (9%) were lost to follow-up, three infants were positive for G6PD deficiency. Hence, 380 infants were included in the final analysis. SHB was observed in 70 (22.5%) infants. Mean birth weight was 2896 grams (SD 0.43) and mean gestational age was 38.2 (SD 1.22). Median age of the infants was 42 hours (IQR: 36, 48). All 380 infants returned for follow up evaluation between four and six days of age. Breastfeeding was commencing in all infants according to hospital guiding; however, supplemental feeds may have been introduced in small number of infants (around 10%) after first few days of age. Demographic characteristics of maternal, perinatal and infant are mentioned in Table 1. Clinical factors such as normal vaginal delivery, lower gestational age (35–37 weeks) and weight loss (more than 5%) were significantly associated with infants who needed phototherapy (Table 1).

Table 1: Select maternal, perinatal and neonatal characteristics of the study cohort with and without significant hyperbilirubinemia; all values are represented as numbers.

Variable	Significant hyperbilirubinemia (n=70)	No significant hyperbilirubinemia (n=310)	P value
Maternal gestational			
Diabetes	2 (2.8%)	21 (6.7%)	0.214
Prim Parity	51(72.8%)	198(63.8%)	0.153
Mode of delivery			
NCD	38 (54.2%)	110 (35.4%)	0.001
LSCS	18 (25.7%)	153(49.3%)	0.001
Instrumental	14 (20%)	47(15.1%)	0.319
Gestational age at birth (week)			
35-37	15 (21.4%)	12(3.8%)	0.01
37-40	51 (72.8%)	152 (49%)	0.01
>40	4 (5.7%)	146 (47.1%)	0.01
Birth weight (kg)			
<2.5	12 (17.1%)	27 (8.7%)	0.035
2.5-3.5	54 (77.1%)	245 (79.03%)	0.726
>3.5	4 (5.7%)	38(12.2%)	0.114
Percentage of weight loss			
<2.5%	2 (2.8%)	55 (17.7%)	0.001
2.5-3.5%	5 (7.1%)	142 (45.8%)	0.0001
>3.5%	63 (90%)	113 (36.4%)	0.0001

The predictive ability of risk factors for phototherapy

With the help of univariate analysis, there were three risk factors such as predischarge STB, GA, and percentage of weight loss were highly predictive of SHB. However, mother's parity, sex of the baby, mode of delivery was not significantly associated with development of significant hyperbilirubinemia. Depending of these three risk factors, authors built a multivariate logistic regression model to predict significant hyperbilirubinemia. The clinical variables cooperatively added significant in sequence to a model that was based

on bilirubin alone and also to the individual factor alone. The predictive ability for predischarge STB (or 2.3, p 0.001) was higher than percentage of weight loss (or 1.56, p 0.001) and GA (or 0.52, p 0.001) (Table 2). Furthermore, this predictive accuracy was confirmed by ROC curve with highest predictive ability for predischarge STB with AUC=0.83 (95% CI 0.79-0.89), followed by percentage of weight loss and gestational age (Table 2). However, on combining all three factors, the predictive ability raised even higher with AUC=0.88 (95% CI 0.84-0.93).

Table 2: The predictive ability of predischarge serum bilirubin (STB) and selected clinical risk factors for subsequent use of phototherapy.

Risk factors	Odds ratio (95% CI)	P value	AUC (95% of CI)	P value
Predischarge TSB	2.3 (1.68-2.62)	0.001	0.83 (0.79-0.89)	0.001
Percentage of weight loss	1.56 (1.36-1.76)	0.001	0.84 (0.76-0.86)	0.001
Gestational age	0.52 (0.36-0.64)	0.001	0.68 (0.61-0.76)	0.001
Combined clinical risk factors (GA, PWL, and TSB)	0.88(0.84-0.93)			0.001

Sequence of building predictive models are: 1) predischarge STB alone, 2) Percentage of weight loss (PWL) alone, 3) Gestational age (GA) alone, and 4) the combination of all three above mentioned factors (predischarge STB, GA and PWL).

Table 3: Predictive values of predischarge STB of 10mg/dl in study infants.

Study population	Sensitivity	Specificity	Positive prediction value	Negative predictive value
All infants	92%	66%	32%	99%
All LBW infants	100%	81%	65%	100%
All LBW infants with >5% weight loss	100%	84%	86%	100%

Out of 70 infants who developed SHB, 66 infants had predischarge STB of 10mg/dl or higher. Moreover, SHB was developed if all the LBW infants, whose predischarge STB of 10mg/dl or higher. The sensitivity and specificity of STB at 10mg/dl for all study infants to predict SHB were 92% and 66% respectively (Table 3). The positive predictive values were 32% for all infants, 65% for all LBW (less than 2.5kg) infants and 86% for LBW infants with more than 5% weight loss (Table 3).

DISCUSSION

In present prospective study, predischarge STB and the mixture of clinical risk factors were competent to forecast significant hyperbilirubinemia in term and near term infants. The has found that clinical risk factors (GA and weight loss) had good predictive accurateness, similar to that of the predischarge STB. Moreover, the predischarge STB is an independent predictor of significant hyperbilirubinemia afterward. This is consistent with previous studies reported in the literature.[6,9,11]

The clinical risk factors such as GA and loss of birth weight in percentage are very good predictors of SHB found in the present study. Studies have suggested that predischarge STB with GA could be a superior predictor for SHB.[6,11] Similar to the preceding studies, authors also showed that, after the predischarge STB, GA was the strongest predictor of SHB and could be used in combination with the predischarge risk zone to stratify infants into separate risk categories.[5,12] Authors also noted that risk-assessment strategies that combined multiple clinical risk factors have better precision to the one that communicate on the predischarge bilirubin value only.

In addition, the measurement between 36 and 48 hours of age, STB cut-off value of 10mg/dl in the study infants has good predictive value for rising SHB later. These predictive values were especially high for LBW infants, and for those who misplaced more than 5% of birth weight. In one study, it has been found that the cut-off value of <6mg/dl at 24+6 hours of age could be a protected guide to discharge infants.[13] In another study, it has been exposed that newborn infants who were later treated with phototherapy had a higher serum bilirubin level even contained by 18 to 24 hours of delivery.[10] However, present study is the first one to present a cut-off value with good predictive values around customary discharge time of 36-48 hours (median age 44 hours). Additional studies are needed to authenticate this cut-off value in larger sample size.

The potency of present study includes good follow up rate (90%) and the first to report a cut-off STB value throughout discharge time.

Some limitation of present study described as present sample size could have been more, which would have permitted us to detect other risk appraisal strategies

including the use of combination of gestational age and percentage of weight loss. In addition, use of GA as one of the clinical risk factors for prediction bring in bias, as AAP threshold for treatment is lower for earlier GA infants.

CONCLUSION

The clinical risk factors and predischarge bilirubin values are powerful strategies to review the risk of significant hyperbilirubinemia have similar prognostic accuracy, even though larger studies are needed to prospectively authenticate the accuracy and dependability of specific clinical risk factor prediction rules. The most accurate risk-assessment policy incorporates in sequence regarding gestational age and percentage of weight loss. The completion of these strategies should be considered in order to reduce risk of significant hyperbilirubinemia especially in developed countries where the distance health care is confronted.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004;114(1):e130-53.
2. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297.
3. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103(1):6-14.
4. Kishore Kumar R, Chandrasekaran M, Mahindre A, Harish B. Predischarge risk factors for predicting significant hyperbilirubinemia in term and near-term infants. J Ped Moth Care. 2016;1(2):107.
5. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. Arch Pediatr Adolescent Med. 2005;159(2):113-9.
6. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr. 2013;162(3):477-82.
7. Chawla D, Jain S, Dhir S, Rani S. Risk assessment strategy for prediction of pathological hyperbilirubinemia in neonates. Indian J Pediatr. 2012;79(2):198-201.
8. Lavanya KR, Jaiswal S, Reddy P, Murki S. Predictors of significant jaundice in late preterm infants. Indian Pediatr. 2012;49(9):717-20.
9. Pathak U, Chawla D, Kaur S, Jain S. Bilirubin nomogram for prediction of significant hyperbilirubinemia in north Indian neonates. Indian Pediatr. 2013;50(4):383-9.
10. Awasthi S, Rehman H. Early prediction of neonatal hyperbilirubinemia. Indian J Pediatr. 1998;65(1):131-9.
11. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant≥ 35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124(4):1193-8.
12. Keren R, Luan X, Friedman S, Saddlemire S, Cnaan A, Bhutani VK. A comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. Pediatrics. 2008;121(1):e170-9.
13. Agarwal R, Kaushal M, Aggarwal R, Paul VK, Deorari AK. Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian Pediatrics. 2002;39(8):724-30.

Cite this article as: Mehta N, Bhatt RG, Vora H, Reddy D. Predischarge risk factors for predicting significant hyperbilirubinemia in term of infants. Int J Contemp Pediatr 2019;6:315-9.