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Predischarge Risk Factors for Predicting Significant Hyperbilirubinemia in Term and Near-term Infants

Kishore Kumar R[1]*, Chandrasekaran M[2], Mahindre A[1] and Harish B[1]

[1]*Neonatal Intensive Care Unit, Cloudnine Hospitals, Bangalore, India*
[2]*Neonatology Department, Cloudnine Hospital, Chennai, India*

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***Corresponding author:** Kishore Kumar R, Neonatal Intensive Care Unit, Cloudnine Hospital, 1533, 9th Main, 3rd Block Jayanagar, Bangalore, India, 560011, Tel: 0091-990-015-5001; Fax: 0091-804-020-2233; E-mail: drkishore@cloudninecare.com*

Abstract

Aim: Our objective was to compare the predictive ability of predischarge serum total bilirubin (STB) and clinical factors for significant hyperbilirubinemia (SHB) in newborn to see if we can improve the prediction of the hyperbilirubinemia.

Methods: We conducted a prospective cohort study, recruiting healthy newborn infants of > 35 weeks gestation, in a tertiary hospital in south India. The risk factors for SHB were identified and serum bilirubin was performed between 36-48 hours of age before discharge. SHB was defined as a bilirubin level that exceeded or was within 1 mg/dL (17μmol/L) of the hour-specific phototherapy treatment threshold recommended in the American Academy of Pediatrics (AAP) clinical practice guideline on the management of neonatal hyperbilirubinemia. SPSS 21 was used for statistical analysis.

Results: Of 605 infants, 486 infants were included in final analysis, among which 72 babies (14%) 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 predictive ability of predischarge STB is higher than that of percentage of weight loss and GA. The predictive accuracy of predischarge (< 48 hours) STB level was similar to that of percentage of weight loss (AUC = 0.83, 95 % CI 0.78–0.88). However, the prediction model that combined multiple clinical risk factors (predischarge STB, GA and percentage of weight loss) had the best accuracy for predicting SHB.

Conclusions: Predischarge serum total bilirubin, when combined with specific clinical factors (gestational age and percentage of weight loss), best predicts development of significant hyperbilirubinemia.

Keywords: Predischarge bilirubin; Risk factors

Abbreviations: STB: Serum Total Bilirubin; SHB: Significant Hyperbilirubinemia.

Introduction

Hyperbilirubinemia is a common problem in newborns with an incidence of around 70% [1]. Approximately 9% of them can develop significant hyperbilirubinemia (SHB) needing treatment during the first week of life [2]. Newborns without screening could be exposed to the risk of developing SHB and, if untreated, could develop acute bilirubin encephalopathy, sensorineural hearing loss and bilirubin induced neurological damage (known as Kernicterus).

American Academy of Pediatrics (AAP) [2] recommends all newborns (> 35 weeks gestation) should be assessed before discharge using clinical risk factors and/or bilirubin measurement for the risk of developing SHB. The guideline stresses the need to plot the serum bilirubin levels using the hour specific nomogram designed by Bhutani, et al [3] and segregating them into various risk zones as a guide for intervention. In United Kingdom, post-discharge home visits by community midwife helps in detecting significant hyperbilirubinemia. However, this is neither feasible nor cost effective in Indian or Australian setting. National neonatology forum (NNF) in India recommends pre-discharge assessment for all newborns to prevent SHB in the form of thorough clinical assessment and, a biochemical screening, if feasible [4]. Nevertheless more studies are needed to confirm the best method of bilirubin measurement (transcutaneous or serum total bilirubin) for predischarge assessment in Indian newborns [4].

The combination 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 [7] studied 464 infants and recommended a risk score (consisting of TcB, gestation at birth and parity status) which predicts SHB. Another study in late preterm infants concluded that TcB predicts later jaundice better than clinical risk factors [8]. Pathak, et al [9] showed that hour-specific bilirubin nomogram and STB could be used for predicting subsequent need of phototherapy. When measured early in the life (at 18-24 hours after birth), STB, using a cut-off value of > 3.99 mg/dl, could also predict later SHB [10]. However, there have been no studies on pre-discharge cut-off value of STB in Indian infants and also none explored the combination of STB and clinical risk factors for predischarge assessment in term newborns.

In this prospective cohort study, we 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). We planned this study to evaluate the following: 1) We tested the predictive accuracy of the following: (a) a predischarge STB (obtained at age 36 to 48 hours), (b) individual clinical risk factors, and (c) a combination of the multiple clinical risk factors and predischarge STB. 2) We also hypothesized that a STB level (a cut-off level) before discharge is a good predictor for later SHB. 3) We also evaluated the effectiveness of an hour-specific bilirubin nomogram in predicting SHB in Indian infants.

Material and Methods

This prospective cohort study was conducted from March 2011 to August 2011 in a tertiary care hospital in south India, which caters around 2600 deliveries per year.

Inclusion and Exclusion Criteria

Newborns were enrolled for the study if they were managed exclusively with the mother in the ward and if they were more than 35 weeks' Gestation age (GA). Newborns who were admitted to the intensive care nursery for any acute illness, with blood group incompatibility, with major congenital anomalies, and those who received > 48 hours of intravenous antibiotics for presumed sepsis were excluded from the study.

Study Protocol

Our hospital has adopted universal serum bilirubin (STB) screening at age 36-48 hours along with newborn screening program for all newborn infants. All infants were assessed for weight loss before discharge from the unit. Infants who were discharged from the hospital before 36 hours of age were called to obtain a STB, weight measurement and newborn screening test within next 24 hours of discharge. Venous sampling was used to collect the blood sample. All study infants were followed up during the hospital stay and after discharge until the end of first week of age. Infants whose STB measurement exceeded the 75th percentile on an hour-specific bilirubin nomogram [2] were called within 48 hours to recheck for hyperbilirubinemia. All other infants were also called back in within 48–72 hours of discharge to have clinical assessment. Decisions to obtain additional bilirubin measurements and to initiate phototherapy after discharge were made by the primary care physicians on the basis of clinical assessment. The hospital review board approved the study protocol. Informed consent was obtained from parents of all infants in the study.

Predictor Variables

Predischarge STB and clinical risk factors for hyperbilirubinemia were used as the predictor variables. Predischarge bilirubin was measured at age 36-48 hours. We used the hour-specific bilirubin nomogram to convert the predischarge bilirubin values into risk 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 who had more than one bilirubin value obtained before 48 hours of age, we selected the highest risk zone value to serve as the predictor value. If the predischarge bilirubin also met our criteria for significant hyperbilirubinemia, then that bilirubin served as both a predictor and an outcome value (in which case the predictor predicted the outcome perfectly). A research assistant collected maternal, infant, and delivery characteristics from the admission chart.

Outcome Variable

Significant hyperbilirubinemia (SHB) needing phototherapy was used as outcome measure. SHB was defined as a bilirubin level that exceeded or was within 1 mg/dL (17 μmol/L) of the hour-specific phototherapy treatment threshold recommended in the AAP's clinical practice guideline on the management of neonatal hyperbilirubinemia [2]. The decision to start phototherapy was made on the basis of the infant's age and STB levels, as per AAP guidelines [2]. We followed the AAP guideline in using specific risk factors for bilirubin neurotoxicity to decide which phototherapy treatment threshold curve to use in determining whether a study infant's bilirubin exceeded the threshold.

Statistical Analysis

Statistical analyses were performed using SPSS 21. Continuous data with normal distribution was analyzed by Student t-test and non-normally distributed data by Mann–Whitney U test are used to compare means, and chi square or. categorical data was analyzed by chi-square or Fisher exact test are used to compare proportions. A *p value* of < 0.05 was considered significant. Multiple logistic regression analysis was used to evaluate 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 considered were GA, sex, birth weight, percentage of weight loss, parity, mode of delivery and maternal diabetes. Model effect sizes were compared in terms of the receiver-operating area under the curve (AUC), which is equivalent to the c-statistic. The predictive values of a cut-off value of STB were calculated after analyzing the data in the two-by-two table. All tests were two-sided and z performed at the 0.05 significance level. 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. Three logistic regression models were developed to predict the outcome of significant hyperbilirubinemia: (1) a model that included predischarge bilirubin (STB) alone; (2) a model that included clinical risk factors; and (3) a model that combined the multiple clinical risk factors and STB.

Results

Six hundred and five infants were born during the study period; 63 infants were excluded from the study according to exclusion criteria, 542 infants were enrolled for the study in which 53 infants (9%) were lost to follow-up, three infants were positive for G6PD deficiency. Hence, 486 infants were included in the final analysis (Figure 1). SHB was observed in 72 (14.8%) infants. Mean birth weight was 3029 grams (SD 0.43) and mean gestational age was 38.4 (SD 1.23). Median age of the infants, at which blood sample was taken, was 42 hours (IQR: 36, 48). All 486 infants returned for follow up evaluation between four and six days of age. Breastfeeding was initiated in all infants according to hospital policy; however, supplemental feeds may have been introduced in small number of infants (around 10%) after first few days of age. Selected maternal, perinatal and infant characteristics of this cohort 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).

Variable	Significant Hyperbilirubinemia (n=72)	No Significant Hyperbilirubinemia (n=414)	*p value*
Maternal Gestational			
Diabetes	3 (4)	23 (5)	0.78
Prim parity	55 (76)	267 (65)	0.24
Mode of Delivery			
NVD	40 (55)	113 (27)	0.001
LSCS	18 (25)	253 (61)	0.002
Instrumental	14 (20)	48 (11)	0.16
Gestational Age at Birth (weeks)			
35–37	15 (21)	14 (3)	0.01
37–40	52 (72)	202 (49)	0.03
≥ 40	5 (7)	198 (48)	0.02
Birth Weight (kg)			
Less than 2.5	12 (17)	39 (9)	0.36
2.5–3.5	55 (76)	320 (77)	0.8
≥ 3.5	5 (7)	55 (13)	0.1
Male gender	35 (48)	200 (48)	0.9
Percentage Of Weight Loss			
Less than 2.5%	2 (3)	76 (19)	0.04
2.5–5%	5 (7)	193 (46)	0.002
More than 5%	65 (90)	145 (35)	0.001

Table 1: Select Maternal, perinatal and neonatal characteristics of the study cohort with and without significant hyperbilirubinemia. All values are represented as numbers (percentages).

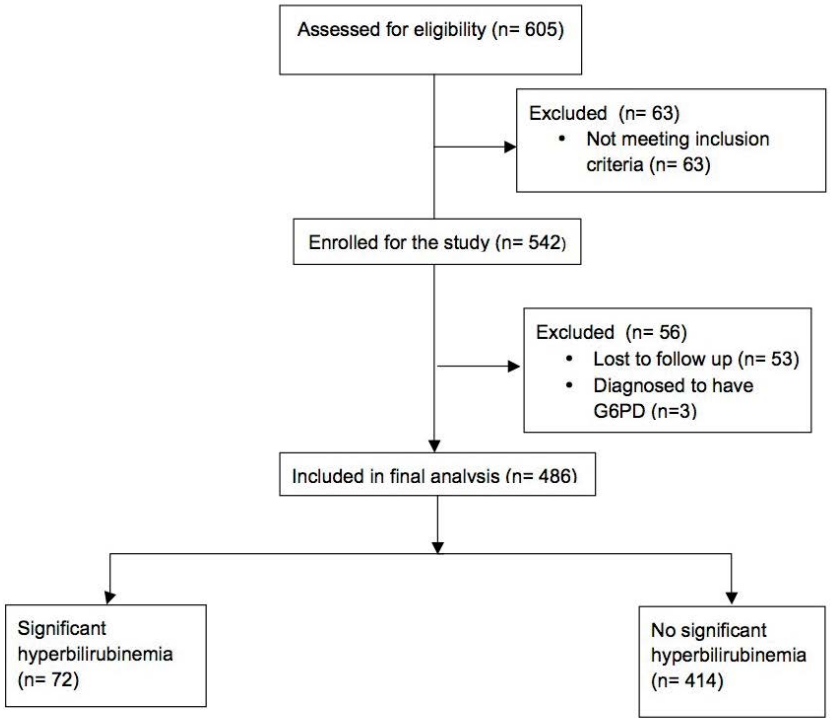

Figure 1: Flow chart indicating enrollment and outcome.

The Predictive Ability of Risk Factors for Phototherapy

On univariate analysis, three risk factors including 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. Based on these three risk factors, we built a multivariate logistic regression model to predict significant hyperbilirubinemia.

The clinical variables collectively added significant information to a model that was based on bilirubin alone and also to the individual factor alone. The predictive ability for predischarge STB (or 2.1, *p 0.001*) was higher than percentage of weight loss (or 1.58, *p 0.001*) and GA (or 0.53, *p 0.001*) (Table 2). Furthermore, this predictive accuracy was confirmed by ROC curve (Figure 2) with highest predictive ability for predischarge STB with AUC = 0.84 (95% CI 0.79-0.88), 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 = 0.89 (95% CI 0.84–0.93).

Out of 72 infants who developed SHB, 66 infants had predischarge STB of 10 mg/dl or higher. Furthermore, all the LBW infants, whose predischarge STB of 10 mg/dl or higher, developed SHB. The sensitivity and specificity of STB at 10 mg/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 2.5 kg) infants and 86% for LBW infants with more than 5% weight loss (Table 3). None of the LBW infants developed significant hyperbilirubinemia if predischarge STB is below 10 mg/dl.

We also evaluated the hour specific bilirubin nomogram in our

Risk factors	Odds Ratio (95% CI)	*p Value*	AUC (95% CI)	*p Value*
Predischarge TSB	2.1 (1.72–2.64)	0.001	0.84 (0.79–0.88)	0.001
Percentage of Weight Loss (PWL)	1.58 (1.38–1.77)	0.001	0.83 (0.78–0.88)	0.001
Gestational Age (GA)	0.53 (0.38–0.66)	0.001	0.71 (0.64–0.77)	0.001
Combined Clinical Risk Factors (GA, PWL and TSB)	0.89 (0.84–0.93)			0.001

Table 2: The predictive ability of predischarge serum bilirubin (STB) and selected clinical risk factors for subsequent use of phototherapy. Odds ratio was obtained by stepwise logistic regression (forward LR) with phototherapy as outcome. AUC is calculated using ROC curve for different models. 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).

Study population (N)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
All infants (486)	92%	66%	32%	99%
All LBW infants (51)	100%	82%	65%	100%
All LBW Infants With > 5% Weight Loss (25)	100%	85%	86%	100%

Table 3: Predictive values of predischarge STB of 10 mg/dl in study infants. LBW–Low Birth Weight.

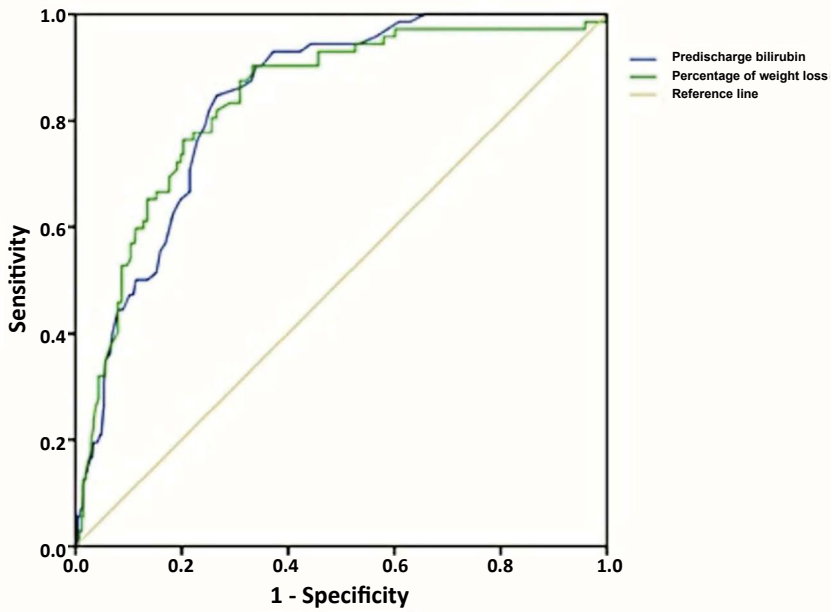

Figure 2: ROC curve of predischarge serum bilirubin and percentage of weight loss in predicting significant hyperbilirubinemia (outcome).

Risk Zone	Total Number of Infants	Number of Infants Needed Phototherapy in Our Study (%)	Number of Infants Needed Phototherapy in Bhutani, et al [3] Study
Zone A (< 40th percentile)	107	0%	0%
Zone B (41st–75th percentile)	215	4%	2%
Zone C (76th–95th percentile)	125	26%	13%
Zone D (> 95th percentile)	39	77%	40%

Table 4: Comparison of predischarge bilirubin as per risk zone (based on hour specific bilirubin nomogram) with the study by Bhutani et al [3].

study. Infants who had their predischarge STB in high-risk zone (> 95%) in hour specific bilirubin nomogram, majority (77%) of them developed significant hyperbilirubinemia (Table 4). For those infants, whose predischarge bilirubin in the low-risk zone, none of them developed significant hyperbilirubinemia.

Discussion

In our prospective study, predischarge STB and the combination of clinical risk factors were able to predict significant hyperbilirubinemia in term and near term infants. Our study has suggested that clinical risk factors (GA and weight loss) had good predictive accuracy, similar to that of the predischarge STB. In our study, we have shown that predischarge STB is an independent predictor of significant hyperbilirubinemia later. This is consistent with previous studies reported in the literature [6,9,11].

We have also shown that the clinical risk factors such as GA and loss of birth weight in percentage are very good predictors of SHB. Studies have shown that predischarge STB with GA could be a good predictor for SHB [6,11]. Similar to the previous studies [5,12], we 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 distinct risk categories. We also noted that risk-assessment strategies that combined multiple clinical risk factors have better accuracy to the one that relies on the predischarge bilirubin value alone.

We have also shown that, when measured between 36 and 48 hours of age, STB cut-off value of 10 mg/dl in the study infants has good predictive value for developing SHB later. These predictive values were particularly high for LBW infants, and for those who lost more than 5% of birth weight. In one study, it has been shown that the cut-off value of < 6 mg/dl at 24 + 6 hours of age could be a safe guide to discharge infants [13]. In another study, it has been shown that newborn infants who were subsequently treated with phototherapy had a higher serum bilirubin level even within 18 to 24 hours of birth [10]. However, our study is the first one to present a cut-off value with good predictive values around usual discharge time of 36–48 hours (median age 44 hours). Further studies are needed to validate this cut-off value in larger sample size.

Our analysis, based on hour specific bilirubin nomogram, suggests a clear plan for the treatment with phototherapy (table 4). Our study validates the results from previous study by Pathak, et al, based on hour specific nomogram on newborns from north India [9]. When compared to previous study by Bhutani, et al [3], we noted that the percentage of infants developing significant hyperbilirubinemia were much higher when STB level was in high risk zone (40% vs. 77%). Infants in the 'zone A' risk category can be followed clinically, assuming the physical examination and history do not change dramatically to warrant a bilirubin measurement. Infants in the 'zone B' risk category can also be managed expectantly, but the threshold for performing a follow-up bilirubin may be a little lower than for the 'zone A' risk group. Finally, the infants who are categorized as 'zone C' risk, may warrant, a bilirubin in 48 hours, or in cases of 'zone D', delayed discharge from the birth hospitalization.

The strengths of our study include prospective study design, good follow up rate (90%) and the first to report a cut-off STB value during discharge time. We also demonstrated that because we combined we could avoid unnecessary prick and pain to all babies as STB was done with routine newborn screening program, the number of times the babies are subjected to blood tests are reduced. Our study has some limitations. Our sample size could have been more, which would have allowed us to detect other risk assessment strategies including the use of combination of gestational age and percentage of weight loss. However, it is an ongoing study and maybe we will be able to predict this combination in post term babies after the adequate data in near future. In addition, use of GA as one of the clinical risk factors for prediction introduces bias, as AAP threshold for treatment is lower for earlier GA infants.

Conclusion

Our study shows that strategies that use either clinical risk factors or predischarge bilirubin values to assess the risk of significant hyperbilirubinemia have similar predictive accuracy, although larger studies are needed to prospectively validate the accuracy and reliability of specific clinical risk factor prediction rules. The most accurate risk-assessment strategy incorporates information about gestational age and percentage of weight loss. In future, risk-assessment strategies using clinical risk factors for predicting significant hyperbilirubinemia and exploring cut-off values should be validated on larger sample size. The implementation of these strategies should be considered in order to reduce risk of significant hyperbilirubinemia especially in countries like Australia where the distance health care is a challenge. This process will also be cost-effective and minimally invasive.

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):297-316.
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. Guruprasad GCD, Aggarwal S, Narang A, DeorariA. Management of Neonatal Hyperbilirubinemia. nnfpublication.org/guidelines/articles, 2012.
5. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. Arch Pediatr Adolesc 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):477-482.e1. doi: 10.1016/j.jpeds.2012.08.022.
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. doi: 10.1007/s12098-011-0409-x.
8. Lavanya KR, Jaiswal A, 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 > or =35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124(4):1193-8. doi: 10.1542/peds.2009-0329.
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. doi: 10.1542/peds.2006-3499.
13. Agarwal R, Kaushal M, Aggarwal R, Paul VK, Deorari AK. Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian Pediatr. 2002;39(8):724-30.

***Corresponding author:** Kishore Kumar R, Neonatal Intensive Care Unit, Cloudnine Hospital, 1533, 9th Main, 3rd Block Jayanagar, Bangalore, India, 560011, Tel: 0091-990-015-5001; Fax: 0091-804-020-2233; E-mail: drkishore@cloudninecare.com

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