RESEARCH PAPER

Bilirubin Nomogram for Prediction of Significant Hyperbilirubinemia in North Indian Neonates

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Objectives: (*i*) To construct hour-specific serum total bilirubin (STB) nomogram in neonates born at ≥35 weeks of gestation; (*ii*)To evaluate efficacy of pre-discharge bilirubin measurement in predicting hyperbilirubinemia needing treatment.

Design: Diagnostic test performance in a prospective cohort study.

Setting: Teaching hospital in Northern India.

Subjects: Healthy neonates with gestation ≥35 weeks or birth weight ≥2000 g.

Intervention: Serum total bilirubin was measured in all enrolled neonates at 24±6, 72-96 and 96-144 h of postnatal age and when indicated clinically. Neonates were followed up during hospital stay and after discharge till completion of 7th postnatal day.

Outcome: Key outcome was significant hyperbilirubinemia (SHB) defined as need of phototherapy based on modified American Academy of Pediatrics (AAP) guidelines. In neonates born at 38 or more weeks of gestation middle line and in neonates born at 37 or less completed weeks of gestation, lower line of phototherapy thresholds were used to initiate phototherapy. For construction of nomogram, STB values were clubbed in six-hour epochs (age ± 3 hours) for postnatal age up to 48 h and twelve-hour epochs (age ± 6 hours) for age beyond 48 h. Predictive ability of the nomogram was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio, by plotting receiver-operating characteristics (ROC) curve and calculating c-statistic.

Results: 997 neonates (birth weight: 2627 ± 536 g, gestation: 37.8±1.5 weeks) were enrolled, of which 931 completed followup. Among enrolled neonates 344 (34.5%) were low birth weight. Rate of exclusive breastfeeding during hospital stay was more than 80%. Bilirubin nomogram was constructed using 40th, 75th and 95th percentile values of hour-specific bilirubin. Pre-discharge STB of ≥95th percentile was assigned to be in high-risk zone, between 75th and 94th centile in upper-intermediate risk zone, between 40th and 74th centile in lower-intermediate risk zone and below 40th percentile in low-risk zone. Among 49 neonates with pre-discharge STB in high risk zone. 34 developed SHB (positive predictive value: 69.4%, sensitivity: 17.1%, positive likelihood ratio: 8.26). Among 342 neonates with pre-discharge STB in low risk zone, 32 developed PHB (negative predictive value: 90.6% and specificity: 42.5%, positive likelihood ratio: 0.37). Area under curve for this risk assessment strategy was 0.73.

Conclusion: Hour-specific bilirubin nomogram and STB measurement can be used for predicting subsequent need of phototherapy. Further studies are needed to validate performance of risk demarcation zones defined in this hour-specific bilirubin nomogram.

Key words: *Diagnostic test, Jaundice, Neonate, Outcome.*

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A significant proportion of neonates develop hyperbilirubinemia needing treatment ('significant' hyperbilirubinemia, SHB) during first week of life [1]. Decrease in duration of birth hospitalization has been temporally associated with increased incidence of bilirubin induced neurological damage [2]. Post-discharge home visits by health worker or hospital visits by family may detect SHB, but are not universally feasible or cost-effective. Therefore, before neonates are discharged from birth hospital those at risk of developing high bilirubin levels need to be identified [3] Pre-discharge objective assessment for risk of developing SHB is also important because of limited accuracy of visual assessment of extent of jaundice [4]. Risk stratification for SHB has been done by measuring bilirubin load (absolute levels or rate of rise of serum total bilirubin or transcutaneous bilirubin), bilirubin production (exhaled carbon monoxide) and identifying underlying clinical risk factors [5-7].

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The concentration of bilirubin in peripheral blood is a function of age-specific rates of bilirubin production, metabolism, excretion and reabsorption. Therefore, interpretation of bilirubin level in a neonate is based on postnatal age. Hour-specific bilirubin nomogram developed by Bhutani, *et al.* [8] has demonstrated that

measurement of serum total bilirubin (STB) before discharge from birth hospital can help in identifying neonates who are at risk of having higher percentile values of STB during followup. Among various risk prediction methods pre-discharge measurement of STB has shown best discriminating ability among North American neonates [9-10]. However, due to genetically determined differences in bilirubin metabolism and dissimilarities in feeding practices clinical course of hyperbilirubinemia may vary in neonates belonging to different ethnicities or geographic locations. In addition, the previous nomogram was developed from a retrospective cohort in whom the information about outcome of significant hyperbilirubinemia was known for only one-fifth of study population [8]. Therefore, construction of hour-specific bilirubin nomogram in different neonatal populations is a prerequisite for using pre-discharge bilirubin measurement as a risk assessment strategy.

We planned this prospective cohort study to construct hour-specific serum total bilirubin nomogram in Indian neonates and to evaluate efficacy of pre-discharge bilirubin measurement in predicting hyperbilirubinemia needing treatment among term and late-preterm neonates.

METHODS

This prospective cohort study with evaluation of diagnostic test performance was conducted from February to June 2010 at a teaching hospital in northern India. Study protocol was approved by Ethics Committee of the hospital and written informed consent was obtained from parents. Healthy neonates with gestation ≥35 weeks or birth weight ≥2000 g were eligible for enrolment in the study. Due to logistic reasons, neonates completing 24 h of life on Sunday were not eligible for enrolment in the study. Neonates with major congenital malformation, admission in neonatal intensive care unit, positive direct Coombs' test (was done if mother blood group was Rhesus negative), phototherapy before first bilirubin measurement or inability to come for follow-up were excluded.

Study measurements and follow-up: Blood sample for first measurement of serum total bilirubin was withdrawn at the time of metabolic screening at 18-30 h of postnatal age. Capillary or peripheral venous blood was collected in pre-heparinized micro-capillaries. Blood was centrifuged immediately at 12000 rpm for 5 minutes and total bilirubin was measured with a spectrophotometer (NEO-BIL plus, das srl, Italy).

Neonates were followed up during hospital stay and after discharge till completion of 7th postnatal day. The timing of follow-up visit was decided based on age at discharge. Babies discharged before 48 h of age were called back between 72 and 96 h of age and babies discharged after 48 h of age at 96 to 120 h of age. In addition to first measurement of STB at the time of metabolic screening, two more STB measurements were performed in each neonate. After first measurement, decision to perform second and third STB measurements was based on clinical assessment. Clinical assessment of degree of jaundice was accompanied by transcutaneous bilirubin (TcB) measurement with a multi-wavelength transcutaneous bilimeter (BiliChek, coefficient of variation <5%). STB estimation was done if palms/soles were stained with icterus or TcB was >12 mg/dL or within 80% of age-specific phototherapy threshold. If not indicated clinically, second and third STB measurements were done at 72-96 h and 96-144 h of postnatal age, respectively. STB values after starting phototherapy were not included for construction of the nomogram.

Clinical and epidemiological risk factors which may influence risk of developing SHB were recorded. Following data were recorded: birthweight, gestation, gender, maternal education and religion, parity, antenatal complications, maternal ABO and Rh blood group, mode of delivery, type of anesthesia used during delivery and use of oxytocin infusion during labor. In addition, age at initiation of feeding, supplemental feeding (other than breast feeding or expressed breast milk) during and subsequent to first 24 h after birth and age at passage of first stool were also noted.

Outcome: Key outcome was significant hyperbilirubinemia (SHB) which was defined as need of phototherapy or exchange transfusion for treatment of hyperbilirubinemia. The decision to start phototherapy was made on the basis of the age of the baby in hours and STB levels, as per local adaptation of American Academy of Pediatrics (AAP) guidelines [3]. In neonates born at 38 or more weeks of gestation, medium-risk threshold, and in neonates born at 37 or less completed weeks of gestation, higher-risk threshold, was used to initiate phototherapy. Medium-risk threshold values in AAP guidelines are almost identical to 95th percentile values of Bhutani nomogram [3,8].

Statistical analysis: In a prospective study significant hyperbilirubinemia was observed in 10% of neonates born at ≥35 weeks of gestation [5]. For investigating a diagnostic test with sensitivity of at least 95% (confidence interval 5%) and alpha value of 0.05, we needed to enrol about 1000 subjects [11].

Data were analyzed using Stata 9 (StataCorp, College Station, TX, USA). For construction of nomogram, STB

values were clubbed in six-hour epochs (age±3 hours) for postnatal age up to 48 h and twelve-hour epochs (age±6 hours) for age beyond 48 h. Data for each epoch was examined for symmetry. The 5th, 10th, 25th, 40th, 75th, 90th and 95th percentile values were calculated for each epoch. Microsoft Excel (Microsoft Corporation, Richmond, US) was used to plot the hour-specific bilirubin nomogram. Smoothened nomogram depicting 40th, 75th and 95th percentile was plotted using cubic spine modeling with GAMLSS package for R statistical software. After smoothening 36.5% cases were below 40th percentile line, 77.8% cases were below 75th percentile line and 95.1% cases were below 95th percentile line. Predictive ability of the nomogram was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio, by plotting receiver-operating characteristics (ROC) curve and calculating c-statistic.

RESULTS

During the study period, a total of 1255 neonates were born of which 1090 were eligible for enrolment. Among these, 93 were excluded for different reasons (***Fig.* 1**). A total of 997 neonates were enrolled in the study. Mean ± SD value for birthweight was 2627±536 g and for gestation age was 37.8±1.5 weeks (median and IQR: 38 and 37-39) (***Web Table* I**). Most of study infants were born after uncomplicated antenatal course and had uneventful transition to extrauterine life. More than 80% of neonates were breastfed exclusively during the hospital stay.

Construction of bilirubin nomogram: First measurement of bilirubin was performed at 23.3±6.3 h of age and mean STB was 7.0±2.0 mg/dL. Twenty nine (2.9%) neonates needed phototherapy based on first measurement of bilirubin. In these neonates phototherapy was started at 27±5.6 h of age with STB levels of 12.3±2.0 mg/dL. Sixty-six (6.6%) neonates were lost to follow-up after discharge from study hospital. First bilirubin value in these neonates was comparable to neonates who never developed SHB (6.5±1.9 *vs* 6.7±1.7 mg/dL, *P*=0.54) and was significantly lower than those who developed SHB (6.5±1.9 *vs* 8.5±2.2 mg/dL, *P*< 0.001).

For construction of nomogram and assessing distribution of STB values, the postnatal age was divided into six-hour epochs for postnatal age up to 48 h and twelve-hour epochs for age beyond 48 h. The STB at each of the epochs except at 42 h was observed to be symmetrically distributed (***Fig.* 2**). Distribution of STB values at 42 h was observed to be positively skewed and these values were not used for construction of the nomogram.

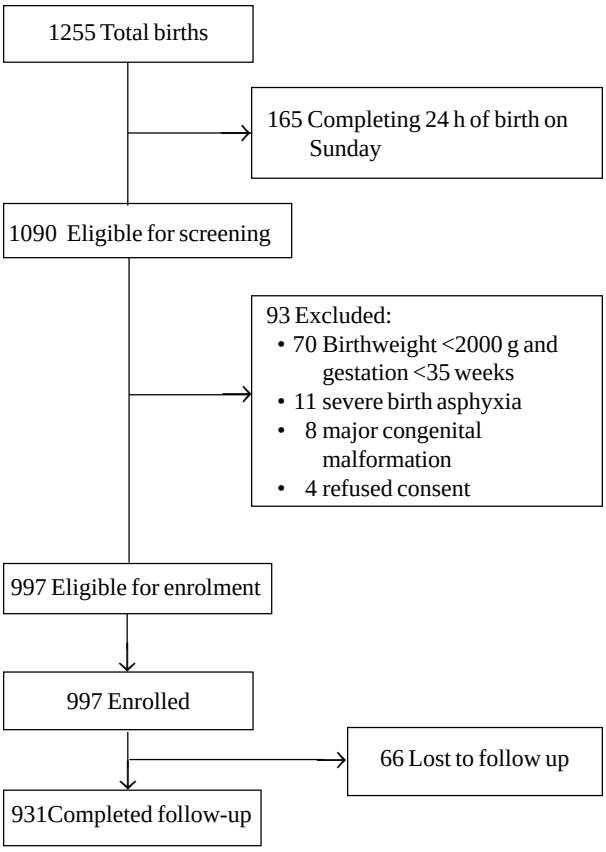

FIG. 1 *Study flow.*

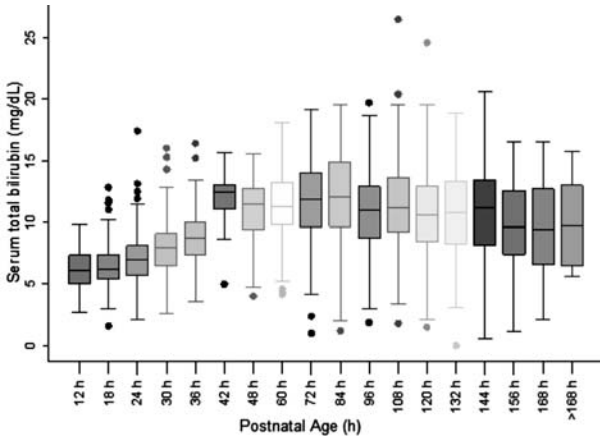

FIG. 2 *Box-whisker plot showing distribution of serum total bilirubin.*

The 5th, 10th, 25th, 40th, 75th, 90th and 95th percentile values for each epoch were calculated. Age-specific serum bilirubin nomogram was drawn with 40th, 75th and 95th percentile values at advancing postnatal age (***Fig.* 3**).

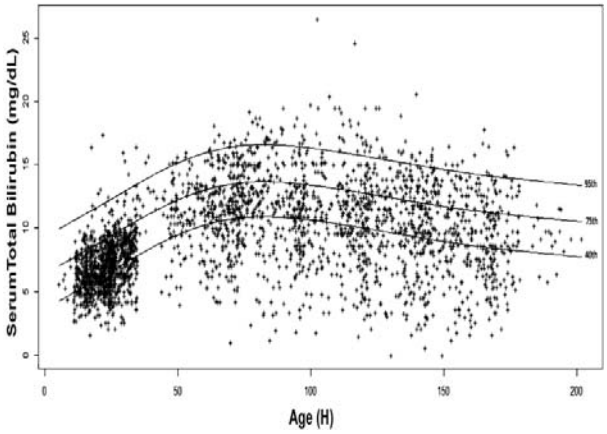

FIG. 3 *Bilirubin nomogram - hour-specific serum total bilirubin depicted as 40th, 75th and 95th percentiles.*

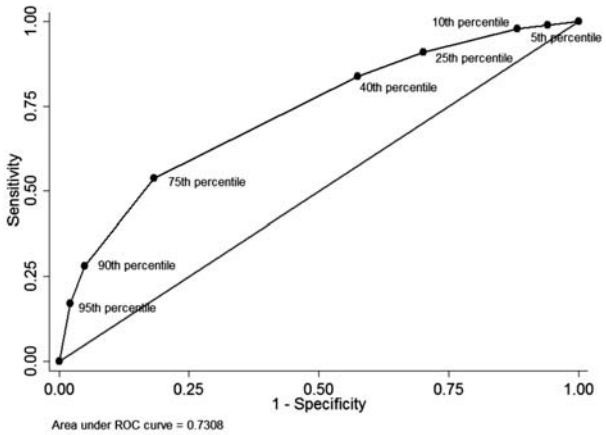

FIG. 4 *The ROC curve for diagnostic ability of different percentile cut-offs of pre-discharge serum total bilirubin.*

Predictive ability of pre-discharge STB: Overall, 199 (20%) neonates developed SHB (received phototherapy). First bilirubin value was used to predict subsequent need of treatment for hyper-bilirubinemia. If more than two values were obtained in first 48 h after birth, higher percentile value was used for prediction purpose.

Among neonates who had pre-discharge STB measurement and completed follow-up (*n*=928), in 49 (5.3%) neonates pre-discharge STB was more than 95th percentile of age-specific distribution (***Table* I**). Of these 34 neonates subsequently needed phototherapy (positive predictive value: 69.4%, sensitivity: 17.1%). In 342 (36.8%) neonates pre-discharge STB was less than 40th percentile of age-specific distribution. Of these, 310 neonates did not need subsequent treatment for hyperbilirubinemia (negative predictive value: 90.6% and specificity: 42.5%). Positive predictive value of 75th percentile cut-off was 44.8% and negative predictive value was 86.2%. The ROC curve as shown in ***Fig.* 4** illustrates the diagnostic performance of each percentile-cutoff with area under curve (c-statistic) being 0.73.

Likelihood ratio (LR) is a better tool of measuring diagnostic test performance as the ratio is unaffected by change in background prevalence of the outcome. LR of positive test (LR+, likelihood of test positive in diseased/ likelihood of test positive in non-diseased) was calculated for each risk demarcation zone. Pre-discharge STB of ≥95th percentile was assigned to be in high-risk zone, between 75th and 94th centile in upper-intermediate risk zone, between 40th and 74th centile in lower-intermediate risk zone and below 40th percentile in low-risk zone. Among 49 neonates in high-risk zone 34 developed SHB; therefore, positive LR for STB in high-risk zone was 8.26 (***Table* II**). Among 190 neonates in upper-intermediate risk zone, 73 developed SHB; therefore, positive LR for STB in this risk zone was 2.30. Similarly, positive LR for STB in lower-intermediate risk zone was 0.76 and for low-risk zone was 0.37.

TABLE I PREDICTIVE CHARACTERISTICS OF PERCENTILE VALUES AS RISK DEMARCATORS FOR SUBSEQUENT NEED OF TREATMENT FOR HYPERBILIRUBINEMIA

Pre-discharge serum total bilirubin		*Outcome*		*Test performance*			
Percentile	*Number(n=928)*	*SHB+*	*SHB-*	*PPV*	*NPV*	*Sensitivity*	*Specificity*
Above 95th percentile	49	34	15	69.4	81.2	17.1	97.9
Below 95th percentile	879	165	714				
Above 75th percentile	239	107	132	44.8	86.2	53.8	81.9
Below 75th percentile	689	92	597				
Above 40th percentile	586	167	419	28.5	90.6	83.9	42.5
Below 40th percentile	342	32	310				

SHB: significant hyperbilirubinemia, PPV: positive predictive value, NPV: negative predictive value.

TABLE II PREDICTIVE ABILITY OF PRE-DISCHARGE SERUM TOTAL BILIRUBIN FOR SUBSEQUENT SIGNIFICANT HYPERBILIRUBINEMIA (NEED OF PHOTOTHERAPY)

Pre-discharge serum total bilirubin		*Outcome*			*Test performance*		
Pre-discharge cumulative risk zone	*Percentile*	*Total*	*SHB+*	*SHB-*	*P:A ratio*	*Probability of disease*	*LR+*
High-risk	≥95th	49	34	15	7:3	7/10	8.26
Upper-intermediate	75th to 94th	190	73	117	2:3	2/5	2.30
Lower-intermediate	40th to 74th	347	60	287	1:5	1/6	0.76
Low-risk	<40th	342	32	310	1:10	1/11	0.37
		928	199	729	1:4	1/5	

SHB: significant hyperbilirubinemia; P:A ratio: Presence of outcome : Absence of outcome.

DISCUSSION

Pre-discharge risk assessment for subsequent development of SHB is recommended as a potential strategy to reduce the incidence of bilirubin induced neurological damage or kernicterus. In this prospective cohort study we have constructed hour-specific serum bilirubin nomogram in a subset of north Indian neonates and have evaluated the efficacy of risk demarcation by pre-discharge STB measurement in predicting subsequent need of phototherapy (SHB). Baseline incidence of SHB was high in our study cohort with 2 out of 10 neonates developing SHB. Location of pre-discharge STB in two higher risk zones significantly increased the risk of subsequent SHB with 7 out of 10 neonates in high risk zone developing SHB (positive LR=8.26) and 4 out of 10 neonates in higher-intermediate risk zone developing SHB (positive LR=2.3). Location of pre-discharge STB in low risk zone significantly decreased the risk of subsequent SHB with 1 out of 10 neonates developing SHB (positive LR=0.37). However, as negative predictive value of low risk cut-off was only 90%, location in low-risk zone was not able to rule-out the possibility of subsequent SHB.

Bhutani, *et al*. [8] showed in a large cohort that neonates with pre-discharge STB in high- and high-intermediate risk zones are more likely to have SHB during followup. The authors constructed percentile charts of serum bilirubin level at different postnatal ages in near-term and term neonates. They found that 6.1% of neonates had pre-discharge serum bilirubin >95th percentile; 32.1% of these infants showed hyperbilirubinemia subsequently. In comparison to hour-specific nomogram by Bhutani, *et al*. [8], percentile values of STB in this study are higher by up to 2 mg/dL till 84-108 h of postnatal age. Neonates of north Indian origin have been observed to reach higher values of bilirubin and have higher incidence of hyperbilirubinemia [5]. Mean STB of 7.0±2.0 mg/dL observed in this study is between 75th and 95th percentile of Bhutani nomogram. Similarly Agarwal, *et al*. [5] reported a mean STB of 5.9±1.8 mg/dL at 24 h of postnatal age which is close to 75th percentile value of Bhutani nomogram. Higher proportion of preterm or low birth weight neonates and higher rate of exclusive breastfeeding in our study may be the factors contributing to increased STB values and increased incidence of SHB. In addition, our decision to use middle instead of upper line of AAP phototherapy thresholds even in low-risk neonates also increased the incidence of SHB. Beyond 108 h of postnatal age, percentile values of STB in this study are lower than corresponding values in the Bhutani nomogram. Inclusion of STB values from neonates who were selectively followed up on clinician judgement for construction of nomogram may have resulted in use of higher STB levels for plotting the Bhutani nomogram, therefore diminishing latter's generalizability [12]. In the present study, as follow-up was completed irrespective of severity of hyperbilirubinemia, the nomogram peaks on 4th and 5th day of postnatal age with natural decline at end of the first week.

In a prospective cohort study, Agarwal, *et al*. measured STB at 24±6 h of age in 220 neonates born at ≥35 weeks of gestation for prediction of hyperbilirubinemia [5]. Absence of STB >6 mg/dL at 24±6 h of age virtually ruled out the possibility of subsequent SHB (likelihood ratio of negative test 0.07) within 5 days of birth. However, selective measurement of outcome in only those neonates who during followup had 'clinical' bilirubin level of >10 mg/dL introduced verification bias in the study. In another Indian study, a cut-off of 3.99 mg/dL at 18-24 h was found to have sensitivity and specificity of 67% each for prediction of subsequent bilirubin level >15 mg/dL [13]. However, complete follow-up was present only in infants who stayed in the hospital either for neonatal illness or some maternal reason, such as cesarean section. More than 50% of infants, who were healthy and thus discharged early, were not followed up. A study from Turkey presented hour-

specific bilirubin nomogram in neonates with a gestational age between 35 and 37 weeks. STB value more than 95th percentile had a high positive predictive value for subsequent development of SHB [14]. However, STB value less than 30th percentile had a negative predictive value of about 90%. Two large retrospective studies have reported excellent predictive ability of early/pre-discharge measurement of STB with area under curve (AUC) of 0.83 [15,16]. In our study, discriminating ability of 40th and 75th percentile values was lower than those previously reported [15,16]. This shifted the ROC curve in our study towards the diagonal line resulting in decreased discriminating ability (AUC= 0.73). High baseline incidence of SHB in Turkish (25.3%) and our study (20%) may explain the inability of low percentile values to rule-out the development of subsequent SHB, thereby limiting the utility of pre-discharge STB measurement.

An alternative risk assessment strategy for prediction of subsequent SHB is evaluation of clinical risk factors. Gestation at birth, history of jaundice needing treatment in previous sibling, oxytocin infusion, instrumental delivery, birth trauma and inadequate feeding have been implicated as risk factors of SHB [15,17,18]. However, discriminating ability of clinical risk model has been reported to be lower than that of early STB measurement [15]. Newman, *et al*. [16] reported improved discriminating ability when a clinical risk instrument was combined with early STB measurement [16]. Due to significant proportion of low birth weight and preterm neonates in our cohort, we speculate that combination of these objectively measurable clinical risk factors with early STB measurement would generate a risk model with improved discriminating ability.

External applicability of observations made in the study may be influenced by relatively high incidence of hyperbilirubinemia in the study cohort because of use of lower bilirubin thresholds for starting phototherapy. In contrast to developed countries, kernicterus has been reported at lower levels of peak bilirubin in India, which indicates that Indian neonates may develop bilirubin-induced neurological damage at lower peak serum bilirubin levels [19,20]. In addition, about one-third neonates born in India are of low birthweight. Owing to these reasons, the National Neonatology Forum of India in its guidelines suggests use of lower thresholds for starting phototherapy, especially in areas with higher incidence of glucose-6-phosphate dehydrogenase deficiency [21-22].

Strengths of our study include prospective study design, large sample size, more than 90% follow-up rate and absence of verification bias. We could not ascertain occurrence of outcome in about 7% of enrolled neonates. However, as early STB and demographic characteristics in these lost-to-follow-up neonates were similar to those who never developed SHB, hour-specific nomogram and risk assessment instrument are unlikely to be affected. We did not use high performance liquid chromatography (HPLC) which is the 'gold-standard' method for measurement of bilirubin. We measured bilirubin by a more commonly used bedside method of spectrophotometry. The bilimeter used in our study had low coefficient of variation and it was calibrated before each use.

We recommend that as neonates with pre-discharge STB in high or high-intermediate risk zone have high probability of developing SHB early and frequent follow-up should be ensured. In settings where close follow-up is not feasible, delaying discharge from hospital till bilirubin falls to lower risk zones may be considered. Neonates with pre-discharge STB in lower-intermediate or low risk zones can be discharged as per local policy. However, adequate follow-up should be ensured as subsequent development of SHB cannot be ruled out.

In conclusion, despite fair discriminating ability, the higher level of follow-up in our study increases the confidence in the ability of pre-discharge STB to predict SHB in Indian infants. Further studies are needed to validate performance of risk demarcation zones defined in this hour-specific bilirubin nomogram.

Contributors: DC: conceptualized and designed the study; UP and SK: collected data; DC: analyzed data; UP: drafted the paper with critical inputs from DC, SK and SJ. All authors approve final version of manuscript for submission.
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