

Predicting the Need for Phototherapy After Discharge

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abstract

BACKGROUND AND OBJECTIVES: Bilirubin screening before discharge is performed to identify neonates at risk for future hyperbilirubinemia. The American Academy of Pediatrics recommends using a graph of bilirubin levels by age (the Bhutani Nomogram) to guide follow-up and a different graph to determine phototherapy recommendations. Our objective was to evaluate predictive models that incorporate the difference between the last total serum bilirubin (TSB) before discharge and the American Academy of Pediatrics phototherapy threshold (Δ -TSB) to predict a postdischarge TSB above the phototherapy threshold by using a single graph.

METHODS: We studied 148 162 infants born at ≥ 35 weeks' gestation at 11 Kaiser Permanente Northern California facilities from 2012 to 2017 whose TSB did not exceed phototherapy levels and who did not receive phototherapy during the birth hospitalization. We compared 3 logistic models (Δ -TSB; Δ -TSB-Plus, which included additional variables; and the Bhutani Nomogram) by using the area under the receiver operating characteristic curve (AUC) in a 20% validation subset.

RESULTS: A total of 2623 infants (1.8%) exceeded the phototherapy threshold postdischarge. The predicted probability of exceeding the phototherapy threshold after discharge ranged from 56% for a pre-discharge Δ -TSB 0 to 1 mg/dL below the threshold to 0.008% for Δ -TSB > 7 mg/dL below the threshold. Discrimination was better for the Δ -TSB model (AUC 0.93) and the Δ -TSB-Plus model (AUC 0.95) than for the Bhutani Nomogram (AUC 0.88).

CONCLUSIONS: The use of Δ -TSB models had excellent ability to predict postdischarge TSB above phototherapy thresholds and may be simpler to use than the Bhutani Nomogram.



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WHAT'S KNOWN ON THIS SUBJECT: The American Academy of Pediatrics recommends using a graph of pre-discharge total serum bilirubin (TSB) levels by age (the Bhutani Nomogram) to aid in determining timing of follow-up and a different graph to determine phototherapy recommendations.

WHAT THIS STUDY ADDS: The Δ -TSB, the difference between the appropriate phototherapy threshold and the pre-discharge TSB, improves the prediction of subsequent hyperbilirubinemia, exceeding the phototherapy threshold and allows use of a single graph to determine follow-up and phototherapy recommendations.

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BACKGROUND

Jaundice affects 50% to 80% of term and late preterm infants.^{1,2} In the absence of risk factors, jaundice usually does not require treatment, reaching peak levels at 4 to 7 days after birth. However, when bilirubin reaches extremely high levels, it can penetrate the blood-brain barrier, resulting in neurotoxicity. The possibility that newborns will develop bilirubin levels that put them at risk for neurotoxicity drives recommendations for testing, follow-up and treatment.³⁻⁶ Some experts have advocated universal bilirubin screening before discharge to identify infants at risk for severe hyperbilirubinemia.^{4,7}

The 2004 American Academy of Pediatrics (AAP) hyperbilirubinemia guidelines³ and a 2009 update with clarifications⁴ recommend using a graph of bilirubin levels by age (sometimes called the Bhutani Nomogram)⁸ to determine appropriate follow-up. The Bhutani Nomogram classifies infants into 4 risk zones for developing clinically significant hyperbilirubinemia, which was defined as a total serum bilirubin (TSB) level \geq 95th percentile in the first week after birth. The risk zones are based on a study of 2840 healthy, term and late preterm, predominantly white (43%) or African American (41%) Pennsylvania newborns born from 1993 to 1997. The Bhutani Nomogram's ability to predict subsequent hyperbilirubinemia was used in the 2009 update to provide specific recommendations for timing of follow-up and subsequent bilirubin tests. However, the Bhutani Nomogram is a different graph from the ones providing phototherapy thresholds, which has sometimes led to confusion and its "high risk" line being used to make phototherapy decisions. The ability to plot (or have the electronic medical record plot) the bilirubin on a single graph should save time and reduce confusion.

The 2004 AAP phototherapy thresholds differ on the basis of risk factors such as gestational age and iso-immune hemolytic disease,³ but they were not available at the time the Bhutani Nomogram was created. The probability that a subsequent TSB level will be above the phototherapy threshold and when that may occur is more relevant for determining timing of follow-up TSB testing than the probability of exceeding the 95th percentile.

Our objective was to develop predictive models that incorporate the difference between the last TSB before discharge and the phototherapy threshold (Δ -TSB) to predict a postdischarge TSB above the phototherapy threshold and compare their discrimination to the Bhutani Nomogram.

METHODS

Study Design and Population and Human Subjects Approval

We performed a retrospective cohort study that included infants born at \geq 35 weeks' gestational age at Kaiser Permanente, Northern California (KPNC) facilities from July 1, 2012, through December 31, 2017. We included 11 facilities that were employing universal screening with TSB levels (not transcutaneous bilirubin levels) before discharge. We excluded vaginal deliveries with infant length of stays \geq 72 hours and cesarean deliveries with infant length of stays \geq 120 hours because of the likelihood of additional medical conditions. Infants with direct hyperbilirubinemia, defined as a direct bilirubin \geq 50% of the TSB and a direct bilirubin \geq 2.5 mg/d, were also excluded because these infants are also excluded from the AAP guideline.³

The KPNC Institutional Review Board approved the study (CN-17-3051_01).

Bilirubin Measurements

From existing KPNC laboratory databases, we obtained all TSB levels from an infant's first month after birth using previously described methods.⁹ Infants had a TSB measured before discharge or earlier if clinically indicated. Subsequent TSB testing was done at the discretion of the treating clinicians. TSB was determined by using either the dry chemistry method (51%) with the Vitros Fusion 5.1 or Vitros 250 analyzer (Ortho Clinical Diagnostics, Raritan, NJ) after recalibration of testing instruments in May 2012,¹⁰ or with the diazo (wet) chemistry method (49%) using the AU680 clinical chemistry analyzer (Beckman Coulter, Inc, Brea, CA).

Predictors and Models

We used the infant's last TSB measurement before hospital discharge (predischarge TSB) to calculate the Δ -TSB, defined as how far (in mg/dL) the predischarge TSB was below the appropriate AAP phototherapy threshold. Because AAP phototherapy thresholds are lower for newborns with positive direct antiglobulin test (DAT) results and lower gestational age, comparing the TSB to the AAP phototherapy threshold incorporates both gestational age and the DAT result into the model. Each infant was assigned to the appropriate 2004 AAP neurotoxicity risk group on the basis of gestational age and DAT result, as previously described.¹¹

Our simple model used the Δ -TSB, categorized into 8 groups in 1 mg/dL increments, from 0 to 1 mg/dL to 7 or more mg/dL below the phototherapy threshold. We also developed a Δ -TSB-Plus model that incorporated the Δ -TSB variable, TSB rate of rise (ROR), gestational age, timing of TSB measurement after birth, and inpatient feeding. Variables were chosen on the basis of availability in the electronic record and previous work.¹²⁻¹⁵ The ROR was defined as

the change in TSB (mg/dL) from the previous TSB measurement divided by the time in hours between the 2 TSB measurements if they were at least 3 hours apart. If there were no previous TSB measurements, ROR was calculated by using an estimated TSB at birth of 1.7 mg/dL.^{16,17}

Inpatient feeding was categorized as exclusive breast milk feeding, mixed breast milk and formula feeding, or exclusive formula feeding on the basis of nursing flowsheets documenting feeding. For comparison, we developed a model based on the Bhutani Nomogram by assigning each predischarge TSB a Bhutani risk zone (high, high-intermediate, low intermediate, or low).⁸

TSB measurements obtained 12 to 120 hours after birth were used in the models. We excluded newborns from predictive modeling if their predischarge TSB was obtained after phototherapy or after crossing the AAP phototherapy threshold. We determined inpatient phototherapy start time from nursing flowsheets or, if unavailable, the time of the phototherapy order. All home phototherapy units are provided through KPNC, and delivery time is recorded in the KPNC durable medical equipment database.

Infants were excluded from analyses if they received “subthreshold” phototherapy (phototherapy before a TSB measurement that was above the AAP phototherapy threshold). Such infants may or may not have crossed phototherapy thresholds if they had not been treated with phototherapy, so their outcome is unknown. Excluding them can create bias because their exclusion is not random: they have a higher-than-average risk of developing a subsequent TSB above the phototherapy threshold. To address this, we used inverse probability weighting to make up for the loss of these observations.¹⁸ We created models for the probability (P) of receiving subthreshold phototherapy

and then weighted all remaining observations by $1/(1-P)$. Thus, subjects whose covariates (TSB, gestational age, etc) put them at highest risk of subthreshold phototherapy (but who did not receive it) would have the highest values of P , and therefore would receive more weight in the analysis, to make up for excluding similar subjects who did receive subthreshold phototherapy.

Outcomes

We defined the outcome as a subsequent TSB above the 2004 AAP phototherapy threshold. We assessed the outcome in 3 time periods in relation to the predischarge TSB: within 24 hours, within 48 hours, or up to age 30 days. Linear interpolations were used, when necessary, to estimate the time that the TSB crossed the phototherapy thresholds.

Statistical Analysis

Analyses were performed by using Stata 16.0 (Stata Corp, College Station, TX). We randomly split the data set into estimation (80%) and validation (20%) data sets. We developed logistic models with the estimation data set. Discrimination was assessed in the validation data set by using the area under the receiver operating characteristic curve (AUC). We compared discrimination between models using Stata’s “roccomp” command.¹⁹ We assessed performance of the models in the entire validation data set as well as in subgroups defined by age at predischarge TSB, gestational age, and DAT result.

RESULTS

During the study period, 164 007 infants ≥ 35 weeks’ gestational age were born in facilities employing universal TSB screening, of whom 163 930 had at least 1 TSB sent before discharge. Exclusions consisted of 9800 infants due to

prolonged hospitalization, 4 for significant direct hyperbilirubinemia, 476 with the only predischarge TSB before 12 hours of age, and 2438 who received phototherapy or had a TSB above the AAP threshold before discharge. We also excluded 3050 infants who, after discharge, received phototherapy before having a TSB above the AAP threshold. The final cohort included 148 162 infants. The group was diverse in its racial and ethnic distribution, with exclusive breastfeeding in 73% of the infants during the birth hospitalization (Table 1). Subsequent readmission for phototherapy was uncommon (1.2%).

Follow-up TSB testing was performed in 59 038 (40%) infants. A total of 2623 infants (1.8%) exceeded the phototherapy threshold postdischarge. As expected, the odds of a subsequent TSB above the AAP phototherapy threshold increased dramatically with Δ -TSB levels. Odds ratios obtained from multiple logistic regression for the lowest versus highest-risk predischarge Δ -TSB level categories varied by a factor of >2000 for both the Δ -TSB model and the Bhutani model (Table 2).

Odds ratios for the Δ -TSB-Plus model show that lower gestational age was associated with higher risk of the outcome, although a monotonic “dose response” between lower gestational age and risk was not seen (Supplemental Table 4). Exclusive formula feeding was associated with lower predicted risk of a subsequent TSB above the phototherapy threshold, whereas mixed (breast milk and formula) was associated with higher risk compared with exclusive breast milk feeding (Supplemental Table 4).

All 3 models had good discrimination in the validation data set with the Δ -TSB-Plus model having the highest AUC (Fig 1). The discrimination of the models was also similar in subgroups defined by age, gestational age, and

TABLE 1 Infant Characteristics

Characteristic	n (%)
Total infants	148 162
Male sex	75 139 (50.7)
Race or ethnicity	
Asian American	27 408 (18.5)
African American	10 708 (7.2)
Hispanic	26 096 (17.6)
Non-Hispanic white	59 834 (40.4)
Other	24 116 (16.3)
Cesarean delivery	38 378 (25.9)
Small for gestational age, <10th percentile ^a	8055 (5.4)
Large for gestational age, >90th percentile ^a	10 991 (7.4)
Gestational age, wk	
35	1489 (1.0)
36	3946 (2.7)
37	11 237 (7.6)
38	25 150 (17.0)
39	51 409 (34.7)
40	36 987 (25.0)
≥41	17 944 (12.1)
Positive DAT result	3851 (2.6)
Negative DAT result	71 230 (48.1)
DAT not done	73 081 (49.3)
Inpatient feeding	
Exclusive breast milk	108 633 (73.3)
Breast milk and formula	35 443 (23.9)
Exclusive formula	4086 (2.8)
Phototherapy type	
Home phototherapy	1420 (1.0)
Readmission phototherapy	1716 (1.2)

^a Fenton Curve.²⁰

DAT positivity (Fig 2). In all subgroups, the Δ -TSB-Plus model had the highest discrimination and the Δ -TSB model the next highest. The Bhutani model, although it still had good discrimination, showed the lowest discrimination. AUCs and 95% confidence intervals are shown in Supplemental Table 5. The models all had good discrimination using an outcome of a TSB above the AAP threshold in 24 or 48 hours (Supplemental Table 6).

We calculated the predicted probabilities of having a subsequent TSB postdischarge above the phototherapy threshold in 24 hours, in 48 hours, or by 30 days for each Δ -TSB category and Bhutani risk zone, using inverse probability weighting to account for informative censoring (Table 2). The predicted probability is useful in determining the timing or need for subsequent follow-ups bilirubin checks. For

example, if using the Δ -TSB model, a pre-discharge TSB 2.5 mg/dL below the AAP threshold (Δ -TSB -2 to -3) would indicate that the probability of a subsequent TSB above the AAP threshold in the next 24 hours was 6%, in the next 48 hours was 13%, and ever was 16%.

Whereas the Bhutani and Δ -TSB model generally agree on their classification of the lowest- and highest-risk individuals, the models differ substantially between those extremes. For example, ~20% of newborns have a last pre-discharge TSB in the Bhutani high-intermediate risk zone. The 2009 update with clarifications recommends follow-up within 48 hours for all such infants. However, 44% of these infants had a Δ -TSB between -4 and -5 mg/dL. In these infants, the risk of a subsequent TSB above the AAP threshold was only 1.6% (Table 3),

suggesting that follow-up within 48 hours might not be needed.

DISCUSSION

In this study of an ethnically diverse population of >150 000 Northern California newborns, we found that comparing the pre-discharge TSB to the phototherapy threshold allowed simultaneous determination of the need for phototherapy and accurate estimation of the risk of subsequent clinically significant hyperbilirubinemia. We confirmed that the risk stratification suggested by Bhutani et al⁸ and incorporated into the 2004 AAP guideline³ and 2009 update⁴ performed well. However, using only the Δ -TSB improved predictions, with the best results when Δ -TSB was used with additional variables.

This study builds on previous studies that have used early bilirubin levels to predict subsequent hyperbilirubinemia. Bilirubin measurements at 1 to 2 days of age have performed well (AUC ~0.8–0.9) in some studies^{21–25} and somewhat less well (AUC 0.7–0.8) in others.^{26,27} Prediction is improved with the addition of clinical risk factors, especially gestational age.^{12–15}

The current study offers improvements to many of these previous studies. First, unlike the Bhutani Nomogram, the Δ -TSB incorporates both gestational age and iso-immune hemolytic disease into assessment of risk by comparing the TSB to differential treatment thresholds according to the AAP neurotoxicity risk group.

Second, the study uses a more relevant outcome than many other prediction models: TSB levels exceeding AAP phototherapy thresholds. In the original study, Bhutani et al⁸ used exceeding the 95th percentile for postnatal age in the study population as the outcome. Although this considers age at testing, it does not account for differences in

TABLE 2 Bhutani and Δ -TSB Model Odds Ratios and Predicted Probabilities for Predischarge Bilirubin

	Frequency (%)	Odds Ratio ^a (95% CI)	Predicted Probability of Exceeding Phototherapy Threshold ^b		
			Within 24 h, %	Within 48 h, %	Ever (<30 d), %
Bhutani risk group					
High	3758(2.5)	82.99 (71.35–96.53)	20	29	31
High-intermediate	31 007 (20.9)	12.01 (10.45–13.79)	2	5	6
Low intermediate	58 397 (39.4)	Reference	0.03	0.2	0.5
Low	55 000 (37.1)	0.04 (0.02–0.08)	n/a	0.004	0.02
Δ-TSB (mg/dL below the AAP phototherapy threshold)					
0 to –1	611(0.4)	120.44 (96.78–149.89)	49	55	56
<–1 to –2	2240 (1.5)	51.35 (43.94–60.01)	24	34	36
<–2 to –3	5911 (4.0)	16.69 (14.44–19.29)	6	13	16
<–3 to –4	14 078 (9.5)	4.58 (3.95–5.31)	0.4	3	5
<–4 to –5	30 355 (20.5)	Reference	n/a	0.4	1.1
<–5 to –6	38 612 (26.1)	0.14 (0.1–0.19)	n/a	0.03	0.2
<–6 to –7	26 102 (17.6)	0.03 (0.01–0.06)	n/a	n/a	0.03
<–7	30 253(20.4)	0.007 (0.002–0.029)	n/a	0.008	0.008

CI, confidence interval; n/a, predicted probabilities could not be calculated for infants in these categories because none of the infants has a TSB exceeding the AAP threshold in the specified time frames.

^a Odds ratios for exceeding AAP phototherapy thresholds before age 30 d.

^b Adjusted by using inverse probability weighting to account for censoring due to subthreshold phototherapy (see text).

the significance of a high TSB level at different gestational ages and in those with and without isoimmunization. In other studies, researchers have targeted an outcome of a TSB level exceeding a specific threshold (eg, 17 mg/dL).^{12,21,23,28} The disadvantage of such a single threshold is that it has different clinical significance for different newborns. A TSB of 17 mg/

dL in a low-risk ≥ 38 -week and ≥ 5 -day-old infant is well below the 2004 AAP phototherapy threshold (21 mg/dL), whereas, for a 37-week, 60-hour-old infant with a positive DAT result, it would be significantly above the threshold (12.2 mg/dL). An approach using an outcome related to the AAP thresholds has previously been used by Varvarigou et al²⁹ and Keren et

al,¹³ who used TSB within 1 mg/dL of thresholds.

Third, our models predict not only the overall risk of a subsequent TSB above the AAP threshold but also the risk of that outcome in the next 24 and 48 hours. This is helpful in determining the timing of follow-up to avoid both unnecessarily frequent follow-up and missing infants at high risk. A specific risk threshold can be set, and decisions for follow-up can be based on that risk threshold. In the original Bhutani et al study,⁸ the risk of a subsequent TSB above the 95th percentile for the high-intermediate zone was 12.9%. Therefore, a reasonable threshold may be 10%. Using the Δ -TSB model (Table 2), a follow-up TSB would be recommended in the next 24 hours for a Δ -TSB 0 to –2 mg/dL because the probability of TSB exceeding the AAP phototherapy threshold in the next 24 hours is 49% with a predischarge Δ -TSB of 0 to –1 mg/dL or 24% if the Δ -TSB is <–1 to –2 mg/dL. If the Δ TSB is <–2 to –3 mg/dL, a follow-up TSB could be deferred for 48 hours (avoiding testing at 24 hours) because the probability of exceeding the AAP threshold in the subsequent 24 hours

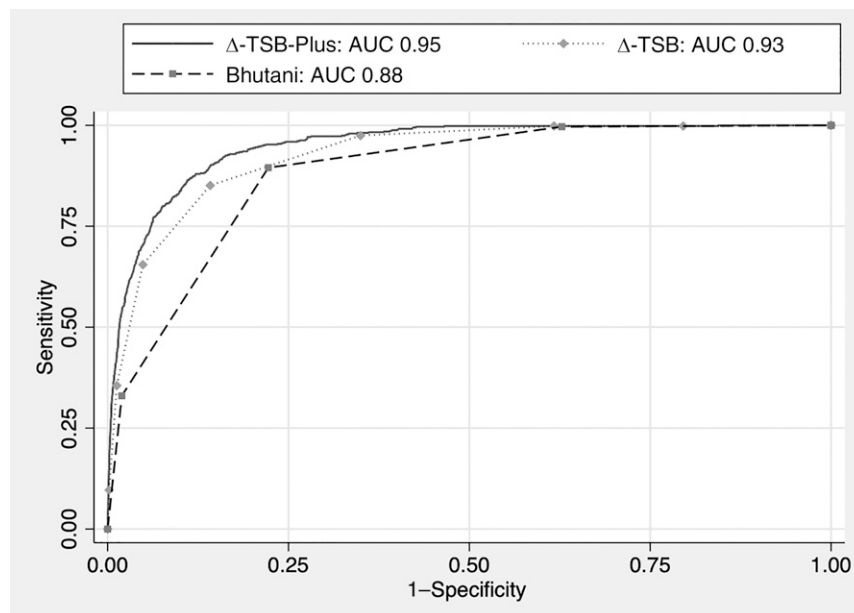


FIGURE 1 Receiver operating characteristic curves for Bhutani, Δ -TSB, and Δ -TSB-Plus models for exceeding AAP phototherapy thresholds before age 30 days.

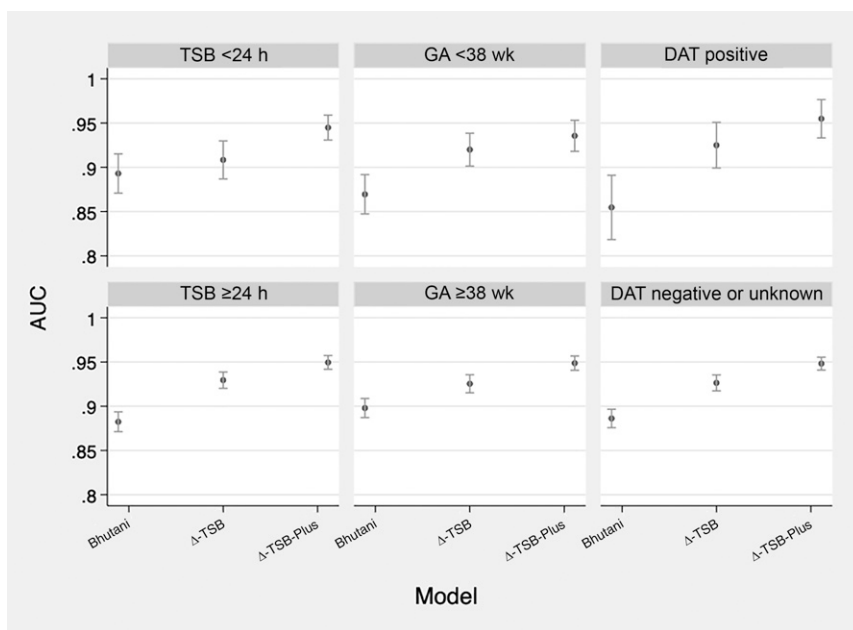


FIGURE 2 AUC and 95% confidence interval for exceeding AAP phototherapy thresholds before age 30 days by model and subgroup. GA, gestational age.

is only 6% but increases to 13% at 48 hours. For a Δ -TSB < -3 mg/dL, clinical follow-up alone could be recommended because the probability of ever exceeding the AAP threshold is $\leq 5\%$. Clinicians may choose a different risk threshold but basing follow-up on risk should enable more evidence-based clinical decision-making.

Last, the simplicity of the Δ -TSB model is a strength. By subtracting the appropriate age-specific phototherapy threshold from the

current TSB, we were able to combine information about the infant's age, gestational age, and DAT positivity with the TSB result to improve the predictive accuracy of a single number. This means that only 1 graph (the one with phototherapy thresholds) needs to be consulted to determine if the TSB is above the threshold, to categorize the infant's risk, and to help guide the timing of follow-up, eliminating a source of confusion from the 2004 AAP guideline. As risk prediction algorithms move away from requiring

data input by users toward receiving input from electronic medical records, more complex and accurate algorithms become more feasible. Incorporation into an electronic record is feasible for our complex model because all its inputs are available from the KPNC electronic medical record.

Our study also has important limitations. One, shared with the original work by Bhutani et al,⁸ is that our apparent predictive accuracy may be inflated by differential verification bias.³⁰ Differential verification bias (also called double gold standard bias³¹) occurs when >1 gold standard exists for a diagnostic or predictive test and the gold standard used is partly dependent on the test result. In this case, the gold standard is a follow-up TSB level exceeding the phototherapy threshold, and infants in whom no such TSB was observed are assumed not to have had the outcome. However, how closely infants are followed and their likelihood of having additional TSB tests depend on the index TSB test: if the first TSB level puts the infant at low risk, the likelihood of any future TSB tests is lower. Thus, there may be some infants who would have been noted to have crossed phototherapy thresholds if they had additional TSB tests, but who did not receive them because their initial TSB was reassuring. We do not believe that this differential verification bias is

TABLE 3 Comparison of Bhutani and Δ -TSB Categories for PredischARGE TSB and Percentage of Infants Within Each Category With a Subsequent TSB Ever Exceeding AAP Phototherapy Threshold

Δ -TSB, mg/dL	Bhutani							
	Low		Low Intermediate		High-Intermediate		High	
	n (% ^a)	% With Outcome	n (% ^a)	% With Outcome	n (% ^a)	% With Outcome	n (% ^a)	% With Outcome
0 to -1	—	—	5 (<0.01)	40.0	127 (0.1)	49.0	479 (0.3)	55.0
<-1 to -2	—	—	34 (0.02)	32.0	948 (0.6)	31.0	1258 (0.8)	36.0
<-2 to -3	1 (<0.01)	0.0	545 (0.4)	7.9	3904 (2.6)	14.00	1461 (1.0)	19.0
<-3 to -4	34 (0.02)	0.0	1849 (1.2)	3.0	11 635 (7.9)	4.8	560 (0.4)	7.5
<-4 to -5	535 (0.4)	0.6	16 204 (10.9)	0.8	13 616 (9.2)	1.6	—	—
<-5 to -6	5053 (3.4)	0.0	32 782 (22.1)	0.2	777 (0.5)	0.4	—	—
<-6 to -7	19 153 (12.9)	0.0	6949 (4.7)	0.0	—	—	—	—
<-7	30 224 (20.4)	0.0	29 (0.02)	0.0	—	—	—	—

—, not applicable.

^a Percentage of total study population.

a serious problem for the current study. In KPNC, all newborns are followed closely after discharge, so it is likely that those significantly jaundiced at follow-up would have a TSB level measured even if the predischarge TSB was low. In addition, because the goal of phototherapy is to prevent exchange transfusions and kernicterus, if neither of these outcomes occurred, having missed an infant with a TSB above phototherapy thresholds is unlikely to have caused the infant any harm.

For infants who received phototherapy before crossing phototherapy thresholds, we used inverse probability weighting to reduce bias that would arise from either dropping them from the analysis or assuming they did or did not develop the outcome.¹⁸

Inverse probability weighting gives increased weight to patients in the study sample who (based on their distance from the treatment threshold and other covariates) resemble those who received subthreshold phototherapy, thus making up for the censoring of those who received subthreshold phototherapy. The effect of inverse weighting was to slightly increase predicted risks.

CONCLUSIONS

Δ -TSB models can be used to accurately predict postdischarge hyperbilirubinemia exceeding AAP phototherapy thresholds. The Δ -TSB combines information about the infant's age, gestational age, and DAT positivity. The Δ -TSB is simpler to use than the Bhutani because only the AAP phototherapy

thresholds are needed to guide follow-up, not another graph. The probability of exceeding the AAP phototherapy curve in the subsequent 24 hours, 48 hours, and ever after the predischarge TSB can be useful in determining need for and timing of follow-up TSB testing.

ABBREVIATIONS

AAP: American Academy of Pediatrics
AUC: area under the receiver operating characteristic curve
DAT: direct antiglobulin test
KPNC: Kaiser Permanente, Northern California
ROR: rate of rise
TSB: total serum bilirubin

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