A Clinical Prediction Rule for Rebound Hyperbilirubinemia Following Inpatient Phototherapy

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abstract

OBJECTIVES: The American Academy of Pediatrics provides little guidance on when to discontinue phototherapy in newborns treated for hyperbilirubinemia. We sought to develop a prediction rule to estimate the probability of rebound hyperbilirubinemia after inpatient phototherapy.

METHODS: Subjects for this retrospective cohort study were infants born in 2012 to 2014 at ≥35 weeks' gestation at 16 Kaiser Permanente Northern California hospitals who received inpatient phototherapy before age 14 days. We defined rebound as the return of total serum bilirubin (TSB) to phototherapy threshold within 72 hours of phototherapy termination. We used stepwise logistic regression to select predictors of rebound hyperbilirubinemia and devised and validated a prediction score by using split sample validation.

RESULTS: Of the 7048 infants treated with inpatient phototherapy, 4.6% had rebound hyperbilirubinemia. Our prediction score consisted of 3 variables: gestational age <38 weeks (adjusted odds ratio [aOR] 4.7; 95% confidence interval [CI], 3.0–7.3), younger age at phototherapy initiation (aOR 0.51 per day; 95% CI, 0.38–0.68), and TSB relative to the treatment threshold at phototherapy termination (aOR 1.5 per mg/dL; 95% CI, 1.4–1.7). The model performed well with an area under the receiver operating characteristic curve of 0.89 (95% CI, 0.86–0.91) in the derivation data set and 0.88 (95% CI, 0.86–0.90) in the validation data set. Approximately 70% of infants had scores <20, which correspond to a <4% probability of rebound hyperbilirubinemia.

CONCLUSIONS: The risk of rebound hyperbilirubinemia can be quantified according to an infant's gestational age, age at phototherapy initiation, and TSB relative to the treatment threshold at phototherapy termination.

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WHAT'S KNOWN ON THIS SUBJECT: There are no standards and little evidence to support decisions about when to discontinue phototherapy in newborns being treated for hyperbilirubinemia.

WHAT THIS STUDY ADDS: We describe a model to quantify the risk of rebound hyperbilirubinemia. This model will enable clinicians to discontinue phototherapy when the risk of rebound hyperbilirubinemia reaches a suitably low level.

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Phototherapy is a widely used treatment of neonatal hyperbilirubinemia. The American Academy of Pediatrics (AAP) provides guidelines[1] for when to start phototherapy, but little guidance is available for when to discontinue phototherapy. A 1991 review recommended stopping birth hospital phototherapy after 2 consecutive total serum bilirubin (TSB) levels of <11 mg/dL.[2] Although the appendix to the AAP hyperbilirubinemia guideline states that phototherapy may be discontinued when the TSB level falls to <14 mg/dL in infants readmitted for phototherapy, no guidance is provided for when to stop birth hospitalization phototherapy. In contrast, the United Kingdom's National Institute for Health and Care Excellence guideline recommends stopping phototherapy ≥3 mg/dL below their treatment threshold, which could be a TSB as high as 17.5 mg/dL in a full-term infant.[3]

The main risk of discontinuing phototherapy too early is the potential for rebound hyperbilirubinemia, necessitating reinitiation of phototherapy and possible rehospitalization. Most previous studies of rebound hyperbilirubinemia examined rebound within a short time frame of ≤24 hours and varied in their definitions of "rebound" (returning to the bilirubin level at phototherapy termination[4–8] versus returning to treatment threshold[9,10]). In addition, these studies examined a limited number of risk factors, and sample sizes were modest.

In this study, we used a large data set from an integrated health care system to evaluate predictors of rebound hyperbilirubinemia in neonates after their first episode of inpatient phototherapy. We sought to create a clinical prediction rule to estimate the probability of rebound hyperbilirubinemia so that clinicians and parents can make more informed decisions about whether the benefit of earlier phototherapy discontinuation outweighs the risk of rebound hyperbilirubinemia.

METHODS

Design, Subjects, and Human Subjects Committee Approval

We selected subjects for this retrospective cohort study from the population of 105 808 infants born at ≥35 weeks' gestational age at 16 Kaiser Permanente Northern California hospitals between January 1, 2012 and December 31, 2014. We included subjects who underwent their first inpatient phototherapy before age 14 days (n = 7202). We excluded infants (n = 126) who did not have ≥2 TSB levels before phototherapy termination (both not required to be after phototherapy initiation) and infants (n = 28) with a conjugated bilirubin level of ≥2 mg/dL before or during their first phototherapy admission. After these exclusions, the study cohort had 7048 infants.

This study was approved by the Kaiser Permanente Northern California Institutional Review Board and the University of California, San Francisco Committee on Human Research.

Predictor Variables

We derived all predictor variables from electronic data sources. We determined the number of formula feedings during phototherapy hospitalization from nursing flowsheets. For phototherapy start time, we used the time of the first order for phototherapy. We estimated the time of phototherapy termination by using[1] nursing flowsheet documentation of "discontinuation" of phototherapy (25% of cohort).[2] If no such documentation was available, we used the time stamp of the discontinuation order (41%).[3] If there was neither a nursing flowsheet nor order, we used the 1 hour before discharge time (34%).

TSB levels were measured via the Vitros BuBc Neonatal Bilirubin method (Ortho Clinical Diagnostics, Raritan, NJ); 75.0% of study infants were born after a significant recalibration of these instruments.[11] To estimate the coefficient of variation of TSB measurements across hospitals, we used a linear mixed effects regression with facility as a random effect to model the first TSB level as a function of facility of birth, age, and other covariates (adjusted R^2 = 0.69). At a mean first TSB of 8.9 mg/dL, the SD of the first TSB level across the 16 facilities was 0.327 mg/dL (coefficient of variation = 3.7%).

We subtracted the AAP phototherapy threshold from the last TSB before the start of phototherapy to obtain the relative TSB at phototherapy initiation. To estimate the TSB at the time of phototherapy discontinuation, we used the TSB level closest to phototherapy termination, if it was measured between 3 hours before and 1 hour after termination (24.6% of the cohort). If no TSB level was measured in this time window, we estimated a TSB at 3 hours before phototherapy termination by linear extrapolation using the last 2 TSB levels before termination. We then subtracted the AAP phototherapy threshold from the estimated TSB at termination to obtain the relative TSB at phototherapy termination.

We assumed infants were continued on home phototherapy after inpatient phototherapy if there was an order for a home unit during hospitalization, and we considered infants to have restarted on home phototherapy after discharge if there was an order for home equipment ≥1 calendar day before the day of our primary outcome (defined below) or within 2 calendar days of initial inpatient phototherapy termination.

Outcome Variables

Our primary outcome was rebound hyperbilirubinemia, defined as the return of TSB to or above the AAP phototherapy threshold within 72 hours of phototherapy termination. We chose 72 hours as a time frame that could be reasonably attributed to the same episode of hyperbilirubinemia. We anticipated that there were infants readmitted for inpatient phototherapy before reaching treatment threshold who would be censored by our definition of rebound hyperbilirubinemia. Therefore, we performed sensitivity analyses in which we included these infants in our primary outcome. In addition, we examined rebound of TSB to ≥1 and ≥2 mg/dL above phototherapy threshold within 72 hours of phototherapy termination as our secondary outcomes.

Statistical Analyses

We obtained bivariate and multivariate odds ratios (ORs) by logistic regression, with standard errors adjusted for clustering by hospital. We devised a clinical prediction rule and score by using a split sample approach, with a random one-half of the cohort used for derivation of the prediction rule and the other half for internal validation. To generate a parsimonious rule, we included variables if they were significant ($P < .01$) by using backward stepwise logistic regression. We confirmed these results by using best subsets variable selection.[12] To formulate the score, we summed the 3 highest ranked predictor variables, each multiplied by 10 times its logistic regression coefficient (to avoid decimals), and added 50 to the total (to avoid negative scores). Because the logistic coefficients are equal to the logarithms of the ORs, summing them is equivalent to multiplying their ORs. We assessed goodness of fit by using the Hosmer–Lemeshow test (10 groups) and discrimination by using area under the receiver operating characteristic (AUROC) curve. We performed analyses by using Stata version 14 (Stata Corp, College Station, TX).

RESULTS

Cohort Characteristics

Characteristics of the study cohort are shown in Table 1. The average gestational age was 38.0 ± 1.7 weeks. The mean postnatal age at phototherapy initiation was 2.3 (SD 1.3) days, and more than half of infants (61.9%) underwent their first inpatient phototherapy during the birth hospitalization. The TSB at phototherapy initiation was close to the AAP phototherapy threshold (mean difference 0.1 ± 2.0 mg/dL). The mean estimated TSB at phototherapy termination was 9.8 ± 2.7 mg/dL, which averaged 7.4 ± 3.1 mg/dL below the phototherapy threshold. Although ~75% of the TSB levels at phototherapy termination were extrapolated, the average difference between an infant's extrapolated value and his or her last measured TSB was 0.4 ± 1.1 mg/dL.

Predictors of Rebound Hyperbilirubinemia

Of the 7048 included infants, 324 (4.6%) met our definition of rebound hyperbilirubinemia (Table 1). The average age at the time of rebound hyperbilirubinemia was 3.3 ± 1.5 days. Thirty-four infants (0.5% of the cohort) were readmitted for inpatient phototherapy below the treatment threshold. There were 715 infants in the cohort (10.1%) who did not have a TSB measurement after inpatient phototherapy termination, and 462 infants in the cohort (6.6%) were later restarted on home phototherapy, of whom 34 infants (7.4%) met criteria for the primary outcome.

Table 2 shows the bivariate predictors and Table 3 shows the multivariate predictors of rebound hyperbilirubinemia. In adjusted analysis, lower gestational age was associated with higher odds of rebound hyperbilirubinemia, especially infants born at 35 to 37 weeks' gestation, for whom the OR was >10 compared with infants born at 40 weeks' gestation. In addition, the odds of rebound hyperbilirubinemia were higher for Asian infants and infants with a higher relative TSB at phototherapy termination.

The odds of rebound hyperbilirubinemia were lower in African American infants and infants at an older postnatal age at phototherapy initiation. Compared with infants with birth weights of 3000 to 3499 g, infants weighing <2500 g had lower odds of rebound hyperbilirubinemia. Furthermore, infants who received ≥4 formula feedings had lower odds of rebound hyperbilirubinemia, as did those who continued on home phototherapy after inpatient treatment (OR 0.62; 95% CI, 0.41–0.94) (Table 3).

Prediction Rule and Score

After stepwise selection, the prediction rule consisted of 3 predictors: gestational age, age at phototherapy initiation (as a continuous variable; OR 0.51; 95% CI, 0.38–0.68; logistic coefficient −0.68), and relative TSB at phototherapy termination (OR 1.5; 95% CI, 1.4–1.7; logistic coefficient 0.42). For ease of clinical use, we dichotomized gestational age at <38 weeks (OR 4.7; 95% CI, 3.0–7.3; logistic coefficient 1.5). Multiplying the logistic coefficients by 10 and adding 50, as previously described, resulted in the following equation for the score:

Score = 15 (if gestational age < 38 weeks) − 7 × (age in days at phototherapy initiation) − 4 × (AAP phototherapy threshold − TSB at phototherapy termination) + 50

For example, an infant born at 37 weeks' gestational age who was 2.5

TABLE 1 Cohort Characteristics ($N = 7048$)

Characteristic	*n*	%
Gestational age, wk, mean (SD)	38 (1.7)	
<38 wk	2791	39.6
Birth wt, g, mean (SD)	3237 (577)	
Male sex	3830	54.3
Infant race and ethnicity		
White	2106	29.9
Asian	2357	33.4
Hispanic	1607	22.8
African American	356	5.1
Other	453	6.4
Unknown	169	2.4
DAT		
Positive	1019	14.5
Negative	3340	47.4
Not done	2689	38.2
Feeding during phototherapy hospitalization		
Breast milk only	2051	29.1
1–3 formula feedings	994	14.1
4–10 formula feedings	2605	37.0
≥11 formula feedings	1107	15.7
Unknown	291	4.1
Phototherapy during birth hospitalization	4364	61.9
Initiation of phototherapy		
Age, d, mean (SD)	2.3 (1.3)	—
Relative TSB, mg/dL, mean (SD)	0.1 (2.0)	—
Termination of phototherapy		
Age, d, mean (SD)	3.6 (1.3)	—
Estimated TSB, mg/dL, mean (SD)	9.8 (2.7)	—
Estimated relative TSB, mg/dL		
<−13	197	2.8
−13 to <−10	1153	16.4
−10 to <−7	2677	38.0
−7 to <−4	2114	30.0
−4 to <0	839	11.9
≥0	68	1.0
Home phototherapy order		
During inpatient phototherapy	310	4.4
After inpatient phototherapy termination	462	6.6
Rebound hyperbilirubinemia within 72 h	324	4.6
≥0 to <1 above AAP phototherapy threshold	159	2.3
≥1 to <2 above AAP phototherapy threshold	86	1.2
≥2 above AAP phototherapy threshold	79	1.1
Recurrent inpatient phototherapy below threshold	34	0.5

—, not applicable.

days (60 hours) old at phototherapy initiation and whose TSB was 6 mg/dL below the treatment threshold at phototherapy termination (eg, TSB 11.5 mg/dL at 96 hours) would have a score of 15 − (7 × 2.5) − (4 × 6) + 50 = 23.5, whereas a score for the same baby at ≥38 weeks' gestation would be 15 fewer, or 8.5.

The discrimination and fit of the predictive model using the generated score were excellent. In the derivation data set ($n = 3518$), the Hosmer–Lemeshow χ^2 (8 degrees of freedom) was 7.7 ($P = .47$) and the AUROC was 0.887 (95% CI, 0.864–0.910). The validation data set ($n = 3530$) had a similar AUROC (0.881) and 95% CI (0.859–0.903) (Fig 1). With the best subsets variable selection, the best model by Bayesian information criterion consisted of the same 3 predictors. The best model by Akaike's information criterion consisted of the same 3 predictors plus formula use and race and ethnicity. With a 5-variable model, the AUROC minimal improved to 0.895 in the derivation sample. Therefore, we elected to include only the original 3 variables in our prediction rule.

We also performed sensitivity analyses with inclusion of gestational age as a categorical variable in the predictive model, which minimally affected the AUROC (0.891 as a categorical versus 0.887 as a dichotomous variable). Inclusion of the 34 infants who underwent recurrent phototherapy below treatment threshold did not alter the predictors selected by stepwise regression or the equation or have a marked effect on the Hosmer–Lemeshow goodness of fit ($P = .22$) and AUROC (0.877) in the derivation data set. In the subset of infants with measured TSB at phototherapy termination ($n = 1737$), AUROC was slightly higher at 0.901 (95% CI, 0.871–0.930). For our secondary outcome of TSB rebound to ≥1 mg/dL above treatment threshold, application of the above score gave an AUROC of 0.888 (95% CI, 0.866–0.909), and for TSB rebound to ≥2 mg/dL above treatment threshold, the AUROC was 0.901 (95% CI, 0.869–0.932).

The probability of rebound hyperbilirubinemia was <10% with a prediction score of <30 (87% of the derivation group, 86% of the validation group) and <4% with a prediction score of <20 (71% of the derivation group, 69% of the validation group) (Table 4 and Fig 2). There were 3023 infants who had ≥2 measured TSBs after the start of phototherapy. Of these infants, 1025 (34%) had a score of <20 at the penultimate TSB measurement and were continued on inpatient phototherapy for another average 23 ± 9 hours.

DISCUSSION

We used a large cohort to examine predictors of rebound hyperbilirubinemia, defined

as returning to phototherapy treatment threshold within 72 hours of termination of an infant's first inpatient phototherapy. We found that rebound hyperbilirubinemia can be predicted well from the infant's gestational age, age at phototherapy initiation, and relative TSB at phototherapy termination.

In our study cohort, 4.6% (324 out of 7048) had rebound hyperbilirubinemia and 0.5% (34 out of 7048) were readmitted for inpatient phototherapy below treatment threshold. This is lower than what Barak et al[10] found in their randomized controlled trial, in which 19% of infants needed reinitiation of phototherapy for a TSB level that returned to AAP phototherapy thresholds 24 hours after treatment termination. However, phototherapy in that study was discontinued at an average of 1.7 mg/dL or 4.1 mg/dL below treatment threshold (depending on the randomization group), much higher TSB levels at termination than the average in this study. In contrast, in the Bansal et al[9] study, 7.3% of 232 infants who had a postphototherapy TSB returned to phototherapy threshold within 24 ± 6 hours of treatment termination, although that study included infants born at <35 weeks' gestation.

We found that 3 of the best predictors of rebound hyperbilirubinemia were an infant's gestational age, age at phototherapy initiation, and TSB level at phototherapy termination relative to the AAP treatment threshold. Gestational age is a well-established risk factor for neonatal jaundice[1] and was also found to be a risk factor for rebound hyperbilirubinemia and recurrent phototherapy in previous studies.[8,9] Previous studies have also found postnatal age to be a risk factor for recurrent phototherapy.

TABLE 2 Bivariate Predictors of Rebound Hyperbilirubinemia

Variable	*N* Total	*N* Rebound	% Rebound	OR	95% CI	*P*
Sex						.43
Female	3218	142	4.4	Reference		
Male	3830	182	4.8	1.08	0.89–1.31	—
Gestational age, wk						<.001
35	643	28	4.4	1.90	1.30–2.78	—
36	834	59	7.1	3.18	1.82–5.57	—
37	1314	120	9.1	4.20	2.63–6.71	—
38	1152	34	3.0	1.27	0.88–1.84	—
39	1615	50	3.1	1.34	0.97–1.84	—
40	1070	25	2.3	Reference		
41	420	8	1.9	0.81	0.39–1.69	—
Birth wt, g						.002
<2000	131	1	0.8	0.15	0.03–0.69	—
2000–2499	554	16	2.9	0.60	0.36–0.98	—
2500–2999	1674	92	5.5	1.17	0.90–1.51	—
3000–3499	2446	116	4.7	Reference		
3500–3999	1620	74	4.6	0.96	0.69–1.34	—
4000–4499	490	19	3.9	0.81	0.39–1.69	—
≥4500	132	6	4.5	0.96	0.38–2.41	—
Infant race and ethnicity						<.001
White	2106	82	3.9	Reference		
Asian	2357	137	5.8	1.52	1.13–2.05	—
Hispanic	1607	75	4.7	1.21	0.77–1.90	—
African American	356	13	3.7	0.94	0.56–1.56	—
Other	453	8	1.8	0.69	0.33–1.45	—
DAT						<.001
Negative	3340	135	4.0	Reference		
Positive	1019	91	8.9	2.33	1.76–3.08	—
Not done	2689	98	3.6	0.90	0.64–1.25	—
Feeding during phototherapy hospitalization						<.001
Breast milk only	2051	131	6.4	Reference		
1–3 formula feedings	994	46	4.6	0.71	0.47–1.07	—
4–10 formula feedings	2605	91	3.5	0.53	0.43–0.66	—
≥11 formula feedings	1107	37	3.3	0.51	0.32–0.80	—
Age at phototherapy initiation, per day	—	—	—	0.47	0.39–0.56	<.001
Age at phototherapy termination, per day	—	—	—	0.46	0.35–0.60	<.001
Relative TSB at phototherapy termination, per mg/dL	—	—	—	1.55	1.41–1.70	<.001
Home phototherapy at discharge						<.001
No	6738	290	4.3	Reference		
Yes	310	34	11.0	2.74	1.84–4.08	—
Born before BuBc recalibration						.17
No	5273	253	4.8	Reference		
Yes	1775	71	4.0	0.83	0.63–1.08	—

—, not applicable.

Maisels et al[13] found that a second course of phototherapy occurred more commonly in infants who received phototherapy during their birth hospitalization than infants readmitted for phototherapy, and Kaplan et al[8] found that age <72 hours at phototherapy initiation was a risk factor for rebound, although rebound in that study was defined as rising above the TSB level at phototherapy termination. Most previous studies have not examined TSB level as a risk factor

TABLE 3 Multivariate Predictors of Rebound Hyperbilirubinemia

Variable	OR	95% CI	*P*
Male sex	1.19	0.95–1.49	.124
Gestational age, wk			<.001
35	10.63	5.48–20.62	—
36	11.39	6.51–19.92	—
37	11.68	6.95–19.64	—
38	2.70	1.88–3.89	—
39	1.91	1.34–2.74	—
40	Reference		
41	0.76	0.34–1.70	—
Birth wt, g			<.001
<2000	0.12	0.04–0.37	—
2000–2499	0.33	0.19–0.56	—
2500–2999	0.83	0.57–1.20	—
3000–3499	Reference		
3500–3999	1.40	0.99–1.97	—
4000–4499	1.43	0.63–3.25	—
≥4500	1.74	0.60–5.01	—
Infant race and ethnicity			<.001
White	Reference		
Asian	1.62	1.11–2.36	—
Hispanic	1.02	0.67–1.54	—
African American	0.46	0.26–0.81	—
Other	0.53	0.25–1.12	—
DAT			.34
Negative	Reference		
Positive	1.37	0.90–2.07	—
Not done	0.86	0.59–1.27	—
Feeding during phototherapy hospitalization			.001
Breast milk only	Reference		
1–3 formula feedings	0.92	0.62–1.36	—
4–10 formula feedings	0.63	0.48–0.83	—
≥11 formula feedings	0.43	0.27–0.68	—
Age at phototherapy initiation, per day	0.38	0.33–0.44	<.001
Age at phototherapy termination, per day	1.15	0.83–1.57	.40
Relative TSB at phototherapy termination, per mg/dL	1.48	1.32–1.66	<.001
Home phototherapy at discharge	0.62	0.41–0.94	.02

—, not applicable.

for rebound hyperbilirubinemia. In the aforementioned Bansal et al[9] trial, there was no significant difference in the occurrence of repeat phototherapy between infants randomly assigned to discontinue phototherapy at a TSB of ≥1 mg/dL versus ≥3 mg/dL below the AAP phototherapy threshold (5 out of 25 vs 5 out of 27, respectively, *P* = .58), but the trial was small, consisting of 52 infants born at >36 weeks' gestation.

Additional significant predictors of rebound hyperbilirubinemia were formula feeding during the phototherapy hospitalization and continuing on home phototherapy after discharge. A higher number of formula feeds was associated with lower odds of rebound hyperbilirubinemia. Interestingly, the OR for 4 to 10 formula feedings (0.63) was similar to that for continuation on home phototherapy (OR = 0.62) and for a 1mg/dL decrease in relative TSB at phototherapy termination (OR = 0.68). These results suggest that a clinician aiming to reduce the risk of rebound hyperbilirubinemia further could consider supplementing with formula, discharging an infant with home phototherapy (if available), or lowering the relative TSB by an additional 1 mg/dL at phototherapy termination with similar efficacy.

Although the OR for a positive direct antiglobulin test (DAT) was significant in unadjusted analyses, the adjusted OR was only 1.37 (95% CI, 0.90–2.07), probably because a positive DAT moves a baby to a higher risk group, with a lower phototherapy threshold. This change in turn reduces the difference between the last measured TSB and the threshold. Thus, the effect of the DAT is captured by the difference between the last TSB and the phototherapy threshold.

In our cohort, 34% of infants may have been able to discontinue inpatient phototherapy a day earlier with <4% risk of rebound hyperbilirubinemia. The decision to discontinue phototherapy is based on balancing the risks and costs of prolonging treatment against the benefit of reducing the risk of rebound hyperbilirubinemia. Hospitalization is burdensome for families, and phototherapy can disrupt breastfeeding and infant bonding. In addition, there is emerging evidence that phototherapy may have potential associations with melanocytic nevi[14] and infantile cancer, especially acute myeloid leukemia.[15,16] Our prediction score quantifies the probability of rebound hyperbilirubinemia to help physicians and parents decide, based on their level of acceptable risk for rebound hyperbilirubinemia, when to discontinue phototherapy. For example, consider a 37-week gestational age infant who starts phototherapy at 4 days of age. Discontinuing phototherapy at a

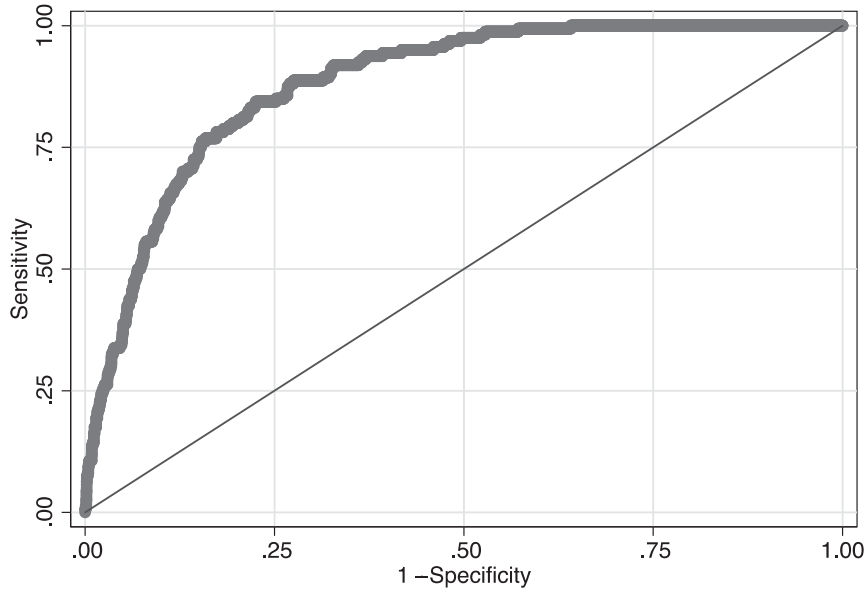

FIGURE 1
Receiver operating characteristic curve of the prediction score in the validation data set. Area under receiver operating characteristic curve = 0.8808.

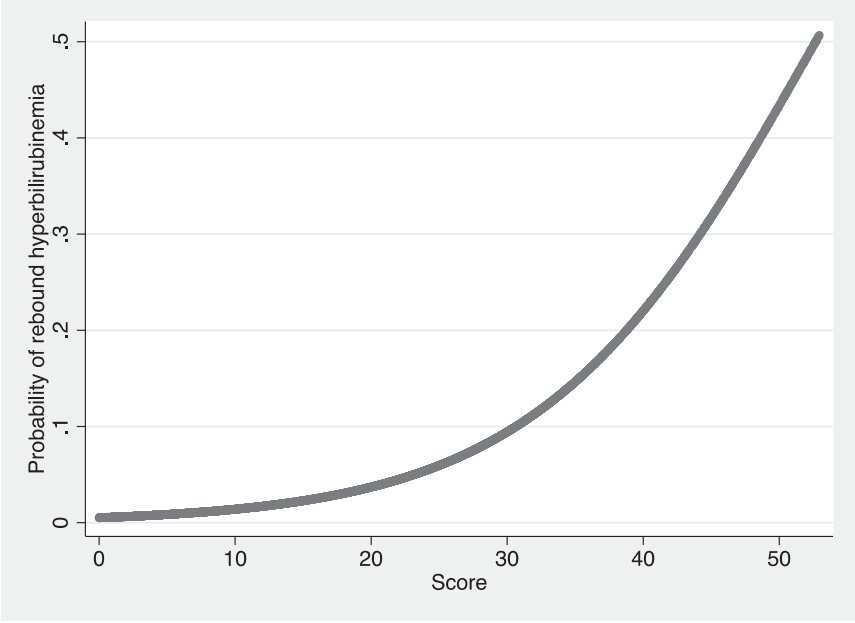

FIGURE 2
Probability of rebound hyperbilirubinemia by score. Score = 15 (if gestational age <38 weeks) − 7 × (age in days at phototherapy initiation) − 4 × (AAP phototherapy threshold − TSB at phototherapy termination) + 50.

TSB of 5 mg/dL below treatment threshold gives a score of 17 and an estimated 2.8% probability of rebound hyperbilirubinemia. In comparison, the probability of rebound would increase to 6.0% at a TSB of 3 mg/dL below and 12.3% at a TSB of 1 mg/dL below treatment threshold. In infants for whom follow-up TSB testing is difficult or readmission for hyperbilirubinemia presents a greater hardship, it may make sense to continue phototherapy longer. On the other hand, a 10% or 15% risk may be acceptable for a reliable family close to an infant care center.

This study has limitations. One of our key predictor variables, the TSB at time of phototherapy termination, was estimated by extrapolation for the majority of our subjects, which presumably worsened the discrimination of the prediction rule. However, we envision clinicians using the rule to decide whether to

continue phototherapy each time a TSB result becomes available. Thus, they will know the TSB at the time of phototherapy termination and will not need to extrapolate. In the subset of subjects in whom the TSB at time of phototherapy termination was known rather than extrapolated, the AUROC for the clinical prediction rule was 0.90.

Additionally, we based our variable for home phototherapy on equipment orders, and therefore we did not know precisely whether and when home phototherapy was used. There may have been infants whose TSB returned to treatment threshold within 72 hours who did not have a TSB measurement until later. Given this limitation and the use of home phototherapy, the risk of rebound hyperbilirubinemia may be underestimated in our study, which may not be generalizable to infants for whom home phototherapy is not an option. We also only examined rebound hyperbilirubinemia after infants' first inpatient phototherapy, and rebound risks may be different after subsequent phototherapy. Finally, we were not able to externally validate our prediction rule, a consideration for future research.

TABLE 4 Risk of Rebound Hyperbilirubinemia by Score

	Infants With Rebound Hyperbilirubinemia			
	Derivation Group (N = 3518)		Validation Group (N = 3530)	
Prediction Score	*N*	%	*N*	%
≤9	6/1792	0.3	5/1723	0.3
10–19	20/707	2.8	13/708	1.8
20–29	27/568	4.8	38/617	6.1
30–39	56/303	18.5	55/316	17.4
40–49	36/109	33.0	32/124	25.8
≥50	19/39	48.7	17/42	40.5

CONCLUSIONS

Rebound hyperbilirubinemia can be predicted with excellent discrimination by an infant's gestational age, age at initiation of phototherapy, and relative TSB at phototherapy termination. With a prediction score of <20, phototherapy can be discontinued with <4% probability of rebound. Clinical implementation of this prediction rule via a Web-based calculator or integration into electronic medical records could help guide decisions about when to discontinue phototherapy.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
aOR: adjusted odds ratio
AUROC: area under the receiver operating characteristic curve
CI: confidence interval
DAT: direct antiglobulin test
OR: odds ratio
TSB: total serum bilirubin

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