A Simpler Prediction Rule for Rebound Hyperbilirubinemia

Pearl W. Chang, MD,[a] Thomas B. Newman, MD, MPH[b,c,d]

abstract

OBJECTIVES: We previously reported a clinical prediction rule to estimate the probability of rebound hyperbilirubinemia using gestational age (GA), age at phototherapy initiation, and total serum bilirubin (TSB) relative to the treatment threshold at phototherapy termination. We investigated (1) how a simpler 2-variable model would perform and (2) the absolute rebound risk if phototherapy were stopped at 2 mg/dL below the threshold for treatment initiation.

METHODS: Subjects for this retrospective cohort study were infants born 2012–2014 at ≥35 weeks' gestation at 1 of 17 Kaiser Permanente hospitals who underwent inpatient phototherapy before age 14 days. TSB reaching the phototherapy threshold within 72 hours of phototherapy termination was considered rebound. We simplified by using the difference between the TSB level at the time of phototherapy termination and the treatment threshold at the time of phototherapy initiation as 1 predictor, and kept GA as the other predictor.

RESULTS: Of the 7048 infants treated with phototherapy, 4.6% had rebound hyperbilirubinemia. The area under the receiver operating characteristic curve was 0.876 (95% confidence interval, 0.854 to 0.899) for the 2-variable model versus 0.881 (95% confidence interval, 0.859 to 0.903) for the 3-variable model. The rebound probability after stopping phototherapy at 2 mg/dL below the starting threshold was 2.5% for infants ≥38 weeks' GA and 10.2% for infants <38 weeks' GA.

CONCLUSIONS: Rebound hyperbilirubinemia can be predicted by a simpler 2-variable model consisting of GA and the starting threshold–ending TSB difference. Infants <38 weeks' gestation may need longer phototherapy because of their higher rebound risk.

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Dr Chang conducted the statistical analysis and interpretation of data and drafted the initial manuscript; Dr Newman conceptualized and designed the study and guided the statistical analysis and interpretation of data; and both authors revised and reviewed the manuscript and approved the final manuscript as submitted.

DOI: https://doi.org/10.1542/peds.2018-3712

Accepted for publication Apr 16, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

WHAT'S KNOWN ON THIS SUBJECT: We previously reported a 3-variable clinical prediction rule that quantifies the risk of the bilirubin level rebounding to phototherapy levels after inpatient phototherapy.

WHAT THIS STUDY ADDS: We simplified the rule while maintaining excellent discrimination using as predictors only gestational age and the difference between the current bilirubin level and the treatment threshold at the time phototherapy was started.

To cite: Chang PW and Newman TB. A Simpler Prediction Rule for Rebound Hyperbilirubinemia. *Pediatrics.* 2019; 144(1):e20183712

Predicting rebound hyperbilirubinemia can help clinicians decide when to discontinue phototherapy for infants undergoing treatment of neonatal jaundice. We recently devised a 3-variable clinical prediction rule that quantifies the rebound risk after the first inpatient phototherapy according to an infant's gestational age (GA), age at phototherapy initiation, and total serum bilirubin (TSB) level relative to the American Academy of Pediatrics (AAP) phototherapy threshold at treatment termination.[1] An alternative approach is to discontinue phototherapy when the TSB is at least 2 mg/dL below the treatment threshold at the age of phototherapy initiation (M.J. Maisels, MB, BCh, DSc, personal communication, 2018). We sought to determine (1) if a 2-variable model, with just GA and the TSB relative to the threshold at phototherapy initiation, would perform as well as our previous 3-variable model and (2) the absolute risk of rebound if phototherapy were stopped as suggested.

METHODS

Study Cohort

Our retrospective cohort consisted of 7048 newborns born in Kaiser Permanente Northern California hospitals between 2012 and 2014 at ≥35 weeks' GA who underwent their first inpatient phototherapy before age 14 days. We excluded infants who did not have at least 2 TSB levels before phototherapy termination and infants with a conjugated bilirubin level of ≥2 mg/dL before or during their first phototherapy admission. Details of the cohort have been previously described.[1] In brief, 39.6% of the infants were <38 weeks' GA, and 14.5% had positive direct antiglobulin test (DAT) results. Phototherapy was initiated at a mean age of 2.3 (SD 1.3) days and terminated at a mean age of 3.6 (SD 1.3) days. The mean TSB level at phototherapy termination was 9.8 (SD 2.7) mg/dL. Approximately 90% of infants had a TSB measurement after inpatient phototherapy termination. There was an order for home phototherapy equipment during the hospitalization for 4.4% of infants, who were thus assumed to have continued on home phototherapy after inpatient treatment. An additional 6.6% of infants had an order for home equipment after hospitalization and were thus assumed to have restarted on home phototherapy after discharge.

Predictor and Outcome Variables

All of the variables were derived from electronic data sources.[1] We used the time of the first order for phototherapy as the time of phototherapy initiation. 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%); and (3) if there was neither a nursing flowsheet nor order, we used the 1 hour before discharge time (34%). To estimate the TSB level at the time of phototherapy termination, we used the TSB level closest to the time of phototherapy discontinuation if 1 was measured between 3 hours before and 1 hour after treatment 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. As previously reported, the average difference between an infant's extrapolated TSB value and his or her last measured TSB was 0.4 (SD 1.1) mg/dL. For this analysis, we subtracted the estimated TSB at phototherapy termination (ending TSB) from the AAP treatment threshold at phototherapy initiation (starting threshold) and used this difference and the GA (dichotomized at <38 weeks) to form a 2-variable model. Rebound hyperbilirubinemia was defined as the TSB reaching or exceeding the hour-specific AAP phototherapy threshold within 72 hours of discontinuing phototherapy, as in our previous report. In our study cohort, 4.6% of infants had rebound hyperbilirubinemia.

Statistical Analyses

To derive and validate this 2-variable prediction rule, we used the same random-split samples previously used to derive the 3-variable prediction rule. As before,[1] we summed the variables multiplied by 10 times their logistic regression coefficients to formulate a prediction score. Because the logistic coefficients are equal to the logarithm of the odds ratios, summing them is equivalent to multiplying their odds ratios. We assessed model fit in the validation data set with a calibration plot and the Hosmer-Lemeshow test (10 groups), and we assessed discrimination with the area under the receiver operating characteristic (AUROC) curve. We performed analyses using Stata 14.2 (Stata Corp, College Station, TX).

RESULTS

Of the 7048 infants, the mean difference between the starting threshold and ending TSB was 4.4 (SD 3.5) mg/dL. The logistic coefficients from the derivation data set were 1.55 (95% confidence interval [CI], 1.02 to 2.08) for GA <38 weeks and −0.43 per mg/dL (95% CI, −0.52 to −0.34) for the starting threshold–ending TSB difference. The equation for the score is thus:

$$\text{Score} = 15.5\ (\text{if GA} < 38\ \text{weeks}) - 4.3 \times (\text{starting threshold} - \text{ending TSB})$$

The Hosmer-Lemeshow χ^2 (8 degrees of freedom) was 9.21

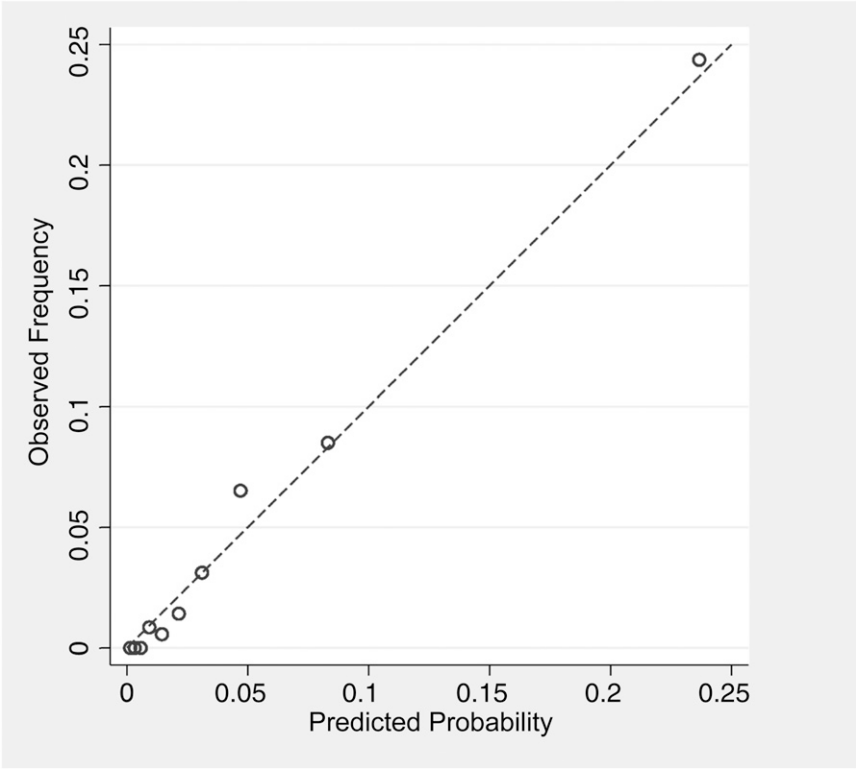

FIGURE 1
Calibration curve of the 2-variable prediction rule. Each point represents 1 decile of predicted probability of rebound.

(P = .33) in the validation data set (n = 3530). Figure 1 shows the calibration curve on the validation data set. The discrimination of this 2-variable model was similar to that of the 3-variable model. In the derivation data set (n = 3518), the AUROC of the 2-variable model was 0.877 (95% CI, 0.856 to 0.899) compared with 0.887 (95% CI, 0.864 to 0.910) in the 3-variable model. In the validation data set, the AUROC was 0.876 (95% CI, 0.854 to 0.899) compared with 0.881 (95% CI, 0.859 to 0.903). In the subset of infants with a measured TSB at phototherapy termination (n = 1737), the AUROC was slightly higher at 0.901 (95% CI, 0.874 to 0.927).

The score can be translated into a predicted probability of rebound hyperbilirubinemia by consulting Fig 2. Alternatively, the following equation can be programmed into a spreadsheet, mobile application, or Web site.

$$\text{Predicted probability of rebound} = 1/(1 + \exp(-(0.097 * \text{score} - 2.84)))$$

The mean difference of an infant's predicted probability of rebound hyperbilirubinemia using the 2 different models was 0% (SD 4.6%). Stopping phototherapy at 2 mg/dL below the starting threshold gave a rebound probability of 2.5% for infants ≥38 weeks' gestation and 10.2% for infants <38 weeks' gestation. For infants <38 weeks' gestation, phototherapy would need to be stopped at 5.5 mg/dL below the starting threshold to have a rebound probability (2.6%) similar to that of infants ≥38 weeks' GA who stopped phototherapy at 2 mg/dL below the starting threshold.

DISCUSSION

We originally evaluated 10 variables (including race and ethnicity, DAT status, and formula and home phototherapy use) and by backward logistic regression devised a 3-variable clinical prediction rule that estimates the probability of rebound hyperbilirubinemia for an individual infant. That rule was based on (1) GA, (2) age at phototherapy initiation, and (3) TSB relative to the treatment threshold at phototherapy termination.[1]

Here, using the same large infant cohort, we turned the previous 3-variable model into a 2-variable model by using the difference between the starting threshold and ending TSB as 1 predictor, effectively combining the age at initiation with the relative TSB at termination. We kept GA as the other predictor. The AUROC of this simpler model was excellent and only minimally lower than that of the 3-variable model. Similarly, the calibration is excellent. The worst point on the calibration plot is when the predicted risk of rebound is ∼5% and the observed risk was 7%, a small absolute difference (Fig 1). However, calibration should be assessed in additional populations.

The rebound probability predicted by the 2-variable model may differ from that of the 3-variable model by up to ∼5%, more noticeably for infants <38 weeks' GA. Possible scenarios include the 2-variable model's estimates being lower for those who start phototherapy younger and have relatively short treatment durations and higher for those who stay on phototherapy longer. For example, if a DAT-negative infant of 37 weeks' gestation starts phototherapy at 24 hours of age and stops at 48 hours of age at an ending TSB of 7.9 (2 mg/dL below the starting threshold), then the predicted

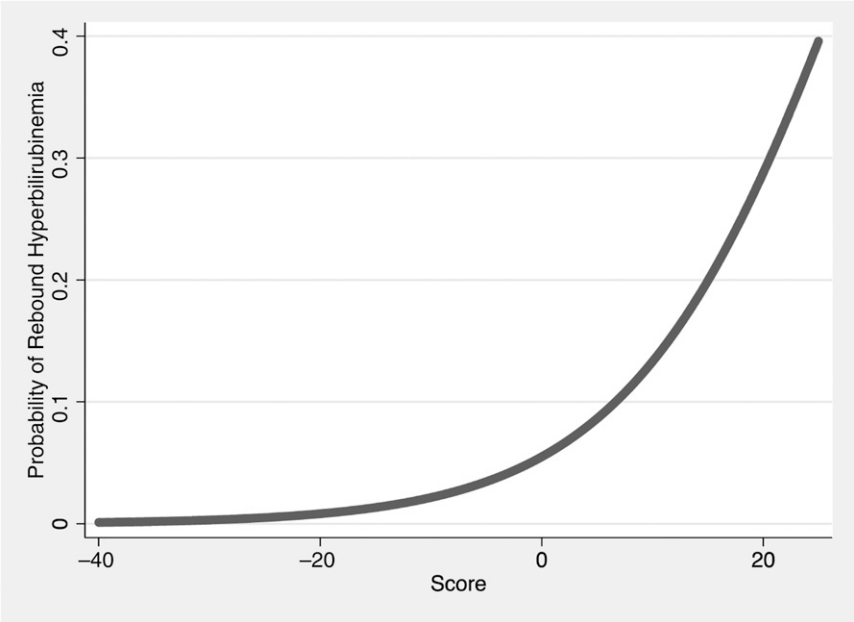

FIGURE 2
Probability of rebound hyperbilirubinemia by score. Score = 15.5 (if GA <38 weeks) − 4.3 × (AAP phototherapy threshold at initiation − TSB at phototherapy termination).

rebound probability would be ∼10.2% on the basis of the new model compared with 15% on the basis of the previous model.

If phototherapy were discontinued at 2 mg/dL below the threshold for treatment initiation, the predicted probability of rebound is 2.5% for infants ≥38 weeks' gestation but 10.2% for infants <38 weeks' gestation. Lower GA has been well established as a risk factor for both hyperbilirubinemia and rebound hyperbilirubinemia.[2–4] In most previous studies of rebound hyperbilirubinemia, phototherapy was stopped when the TSB decreased below a fixed threshold or at the physicians' discretion.[2,3,5,6]

A randomized controlled trial from Israel compared discontinuing phototherapy at 3 vs 1 mg/dL below the threshold for phototherapy initiation. They reported no significant difference in the occurrence of rebound hyperbilirubinemia within ∼24 hours.[7] However, 19% of infants in that study had rebound, which is higher than estimated by our prediction rule. The trial, however, had a small sample size (n = 52), and 15% of the infants had glucose-6-phosphate dehydrogenase (G6PD) deficiency.[7] The prevalence of G6PD deficiency in our population is unknown but likely lower.[8,9] G6PD deficiency is a known cause of hemolysis and severe hyperbilirubinemia[10,11] but has not been well characterized in rebound hyperbilirubinemia.

As before, this 2-variable prediction rule has several limitations.[1,12] Notably, it does not capture the rebound risk after the second episode of inpatient phototherapy, and because almost 97% of the cohort started treatment before age 5 days, it does not capture the rebound probability of older infants. The prediction rule also has not yet been externally validated.

CONCLUSIONS

Rebound hyperbilirubinemia after inpatient phototherapy can be predicted by a simple 2-variable model consisting of GA and the difference between the starting treatment threshold and the ending TSB level. For infants <38 weeks' GA, it may be prudent to continue phototherapy longer because of their higher risk of rebound hyperbilirubinemia.

ABBREVIATIONS

AAP: American Academy of Pediatrics
AUROC: area under the receiver operating characteristic
CI: confidence interval
DAT: direct antiglobulin test
GA: gestational age
G6PD: glucose-6-phosphate dehydrogenase
TSB: total serum bilirubin

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2019;144;
DOI: 10.1542/peds.2018-3712 originally published online June 13, 2019;

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