A New Hour-Specific Serum Bilirubin Nomogram for Neonates ≥35 Weeks of Gestation

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Objective To develop a statistically rigorous, hour-specific bilirubin nomogram for newborns based on a very large data set; and use it prospectively as a replacement for the 1999 Bhutani nomogram.

Study design This was a retrospective analysis of first total serum bilirubin (TSB) measurements from 15 years of universal bilirubin screening during birth hospitalizations at 20 Intermountain Healthcare hospitals. Hour-specific TSB values were assembled into a nomogram by percentile, and subgroups were compared.

Results The information obtained included robust data in the first 12 hours after birth (which was not included in the 1999 nomogram), general agreement with the 1999 nomogram for values in the first 60 hours, but higher 75th and 95th percentile TSB values thereafter in the new version, no difference in TSB between male and female infants, higher TSB values among earlier gestation neonates ($35^{0/7}$-$36^{6/7}$ weeks vs ≥37 weeks, $P < .0001$), and lower TSB values in neonates of Black race ($P < .0001$) and higher values in neonates of Asian race ($P < .001$).

Conclusions An updated and more informative Bhutani neonatal bilirubin nomogram, based on 140 times the number of subjects included the 1999 version, is now in place in our health care system. *(J Pediatr 2021;236:28-33)*.

Evaluating for hyperbilirubinemia is an integral part of newborn care.[1,2] In 1999, Bhutani, Johnson, and Sivieri published an hour-specific bilirubin nomogram constructed from prehospital discharge total serum bilirubin (TSB) values of 2840 neonates who had negative direct antiglobulin tests (DAT).[3] After defining hour-specific percentiles for TSB in newborns ≥35 weeks of gestation, the publication reported the ability of hour-specific predischarge serum bilirubin percentiles to predict subsequent hyperbilirubinemia. The prognostic value of hour-specific predischarge serum bilirubin percentiles was upheld in subsequent publications by the same group.[4,5] Therefore, the 1999 Bhutani et al publication was central to developing the 2004 and the 2009 American Academy of Pediatrics (AAP) clinical guidelines for managing hyperbilirubinemia in the newborn infant ≥35 weeks.[6,7]

The 1999 Bhutani nomogram was widely used and impactful, in part because no other hour-specific serum bilirubin nomogram existed. Despite this, it was limited by a small sample size, and the data were not sufficiently robust to stratify by sex, or specific gestational ages between 35 and 40 weeks, or race. In addition, later publications recognized biases in the Bhutani study design. Specifically, the nomogram data were generated only from newborns who had at least 1 outpatient follow-up TSB (2976/13 003). Because obtaining an outpatient TSB was at the discretion of the outpatient clinician, this was likely a biased sample.[8,9]

Since 2004, the Intermountain Healthcare hospitals have mandated 1 or more TSB determinations on each neonate during the birth hospitalization, with a report to the responsible clinician, including suggestions for management.[10] We used data from this program to recreate the Bhutani nomogram. To do this we excluded TSB values of neonates with a positive DAT, and (in keeping with our Intermountain Healthcare neonatal reference interval guidelines)[11] we also excluded TSB values from neonates with an eventual diagnosis of the hemolytic disorders hereditary spherocytosis and glucose-6-phosphatase dehydrogenase (G6PD) deficiency.[12,13]

In this report, we present an hour-specific bilirubin nomogram based on first predischarge serum bilirubin of 397 395 newborn infants, including analysis of the effect of sex, gestational age, and race.

Methods

The study protocol was approved by the Intermountain Healthcare Institutional Review Board. The Board granted a waiver from individual parental consent

AAP	American Academy of Pediatrics
DAT	Direct antiglobulin tests
G6PD	Glucose-6-phosphatase dehydrogenase
TSB	Total serum bilirubin

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The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2021.05.039

because this was a deidentified, retrospective, data-only study with appropriate privacy protection. The data set for this study was obtained from the Intermountain Healthcare Enterprise Data Warehouse, which houses clinical data from all hospitals within the Intermountain Healthcare system. All births ≥35 weeks of gestation from January 1, 2004 to through October 31, 2018 from all hospitals in the health care system, with at least at least 1 serum bilirubin, were included. Starting in 2004, all Intermountain Healthcare hospitals protocolized obtaining at least 1 TSB on all newborns prior to discharge from the birth hospital.[10] The protocol did not specify a time or a time range for the first bilirubin sample. Therefore, in cases of prolonged hospitalization for maternal indications (eg, cesarean delivery), the allowable time frame to obtain a TSB was longer. The Intermountain Healthcare guidelines that were utilized during the study period required that all newborns receive follow-up within 24-48 hours.

Data for the first TSB were obtained from each newborn, as well as all subsequent TSB values, as was the delivery hospital, delivery date, gestational age at birth, sex assigned at birth, race as identified by mother, and date/time the blood sample was obtained. We excluded TSB values of neonates with a positive DAT, and those from neonates with an eventual diagnosis of the hemolytic disorders hereditary spherocytosis and G6PD deficiency. If either of these diagnoses appeared as a "problem" or a "diagnosis" in the electronic medical record during any encounter up through the time of our analysis, that patient was excluded from the nomogram dataset.

We evaluated multiple methods to estimate percentile curves for the nomogram including traditional quantile regression, Bayesian quantile regression, and estimation of percentiles within each epoch using a normal distribution. We found that a method similar to that used by Bhutani et al in 1999 provided the best fit of the data.[3] Specifically, we divided the data into epochs based on postnatal age in hours and data availability, with an effort to ensure at least 300 data points within each epoch. Subsequently, we estimated the 40th, 75th, and 95th percentiles within each epoch with no normality assumption. We then fit cubic spline functions to these percentiles using the method described by Chambers and Hastie.[14] For bilirubin values in neonates born $\geq 35^{0/7}$ weeks of gestation, data were placed into 1 hour epochs (times rounded to the nearest hour) for the first 72 hours of life; in six hour epochs (time ± 3 hours) until 108 hours of life; and in 12 hour epochs (time ± 6 hours) until 144 hours of life. For subgroups analyses, we used a similar method but with wider epochs when fewer data points were available.

As part of a secondary aim for this project, we randomly selected 100 neonates from each of the following four TSB strata; (1) <40th percentile line, (2) 40th to the 75th percentile line, (3) 75th to the 95th percentile line, and (4) over the 95th percentile line. Similar to the 1999 nomogram report,[3] each of the 400 was reviewed to determine the proportion of neonates that subsequently had a TSB exceeding the 95th percentile. Absolute risk values with 95% CIs were estimated.

We determined the statistical significance of differences between subgroup TSB percentile estimates using the permutation test developed by Fisher[15] and Pitman.[16] Statistical analysis was done in the R language and environment for statistical computing (R Foundation). Code used for modeling is available by email request from the corresponding author.

Results

First-obtained TSB values were assembled from 421 267 neonates (consort diagram, **Figure 1** [available at www.jpeds.com]). Of these, 407 842 were born at a gestational age $\geq 35^{0/7}$ weeks. Values from neonates with a positive DAT (n = 10 405), known hereditary spherocytosis (n = 45) or known G6PD deficiency (n = 4) were excluded from the data set. Seven neonates had hereditary spherocytosis plus a positive DAT. These exclusions resulted in 397 395 TSB values for primary analysis and nomogram construction.

The gestational age at birth, sex, and race of the neonates in the data set are shown in **Table I**. The numbers of TSB values, at various time points after birth that we used to construct the nomogram are displayed in **Table II** (available at www.jpeds.com). The number of values for each epoch was, at minimum, 50 for 133-144 hours of life; and at maximum 31 527 for 24 hours.

The percentile curves generated from the data are shown in **Figure 2**. We had sufficient data in the set to estimate the 40th, 75th, and 95th percentiles at all time points from birth to 144 postnatal hours.

For comparison (and with permission), we superimposed the 1999 Bhutani curves[3] on our new curves (**Figure 3**). Comparisons between the 2 sets of curves reveal; (1) The 1999 curves did not have values between birth and 12 hours, but the new curves do. (2) The 1999 curves have temporary troughs around 24 hours of life and peak/plateau between 96 and 120 hours of life. The new curves have no troughs and plateau around 144 hours of life. (3) The 1999 and new curves estimate similar TSB values between 36 and 60 hours of life. However, between 60 and 144 hours, the new curves estimate higher upper quartile TSB values. For example, at 120 hours the 95th percentile estimate from the 1999 curve is 17.6 mg/dL and from the new curve is 20.1 mg/dL ($P < .0001$). Similarly, the estimated value for the 75th percentile at 120 hours on the 1999 curve is 15.8 mg/dL and from the new curve is 16.5 mg/dL ($P < .0001$). The 40th percentile values from the 1999, and new curves are similar. The possible effect of racial make-up of the 1999 vs new nomogram populations on the 75th and 95th percentile TSB levels is addressed below.

Curves for the 4 subgroup analyses are shown in **Figure 4**. Regarding gestational age (panel A), starting at 36-48 hours, the younger gestational age neonates ($35^{0/7}$-$36^{6/7}$ weeks) had significantly higher 40th, 75th, and 95th percentile TSB values than did the more mature neonates (≥37 weeks;

Table I. The number of TSB values we used to construct the new bilirubin nomogram is shown, according to the subsets of gestational age at birth, sex, and maternally declared race/ethnicity

Gestational age at birth (wk)		Sex		Race/ethnicity	
≥40	94 272 (23.7%)	Male	204 017 (51.3%)	White	323 906 (81.5%)
39 $^{0/7}$-39 $^{6/7}$	161 070 (40.5%)	Female	193 378 (48.7%)	Unknown or Undeclared	38 527 (9.7%)
38 $^{0/7}$-38 $^{6/7}$	77 955 (19.6%)			Hispanic	55 742 (14.0%)
37 $^{0/7}$-37 $^{6/7}$	39 556 (10.0%)			Asian	5866 (1.5%)
36 $^{0/7}$-36 $^{6/7}$	16 779 (4.2%)			Hawaiian or Pacific Islander	4409 (1.1%)
35 $^{0/7}$-35 $^{6/7}$	7763 (1.9%)			Black	2868 (0.7%)
				American Indian or Alaska Native	1885 (0.5%)

For the race/ethnicity column, the sum of the percentages exceeds 100% because some subjects are counted in multiple categories, according to mother's medical record.

$P < .0001$). The magnitude of this difference is constant through 96 hours of life. After 96 hours, the data available for earlier gestation groups is sparse, thus, the comparison is truncated. Regarding sex (panel B), we observed no significant differences in TSB percentiles between male and female neonates. Regarding race (panel C), after 36 hours the 40th, 75th, and 95th percentile TSB values for Black neonates are approximately 1 mg/dL lower than their peers. Panel D shows that TSB values for Asian neonates are approximately 1 mg/dL higher than their peers. After 52 hours, the data for these 2 race-based populations became too sparse for estimation.

Of the 400 charts sampled for follow-up review, follow-up TSB measurements until downtrending was observed were available on 93.3% (373/400). Of the 200 who had an initial TSB below the 75th percentile, only 2 had a subsequent TSB above the 95th percentile (absolute risk 1.0%; 95% CI 0.2%-3.9%). Only 1 of the 2 was readmitted to the hospital for phototherapy. The blood smear of that neonate showed microspherocytes and schistocytes but no precise diagnosis was made. The newborn was discharged on day of life 10 with a downtrending TSB. The patient had a normal neurologic examination at 2 months of age at a health supervision appointment.

Discussion

The principal aim of a neonatal bilirubin assessment and management program is to avoid bilirubin neurotoxicity, particularly the kernicterus spectrum disorders.[6,7,17-19] As much as possible, each element of the bilirubin management program should support that aim, using evidence-based approaches derived from robust, reproduced, and validated data. Although much work remains to construct the best possible bilirubin program, our present project fills gaps in knowledge needed to make key improvements.

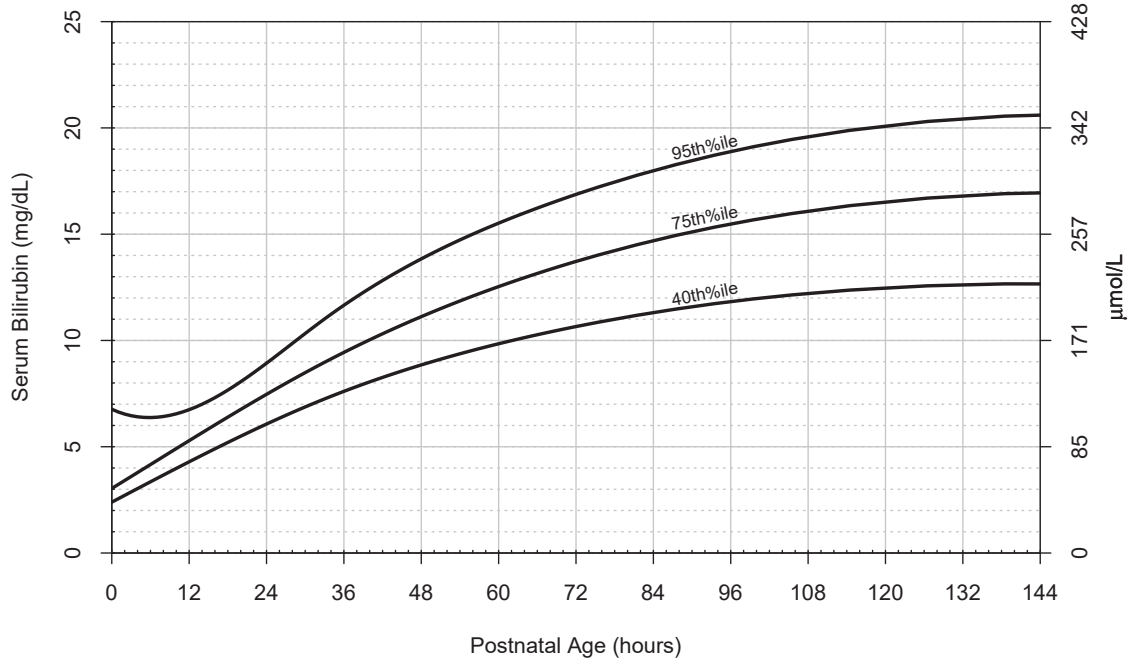

Figure 2. The new neonatal bilirubin nomogram.

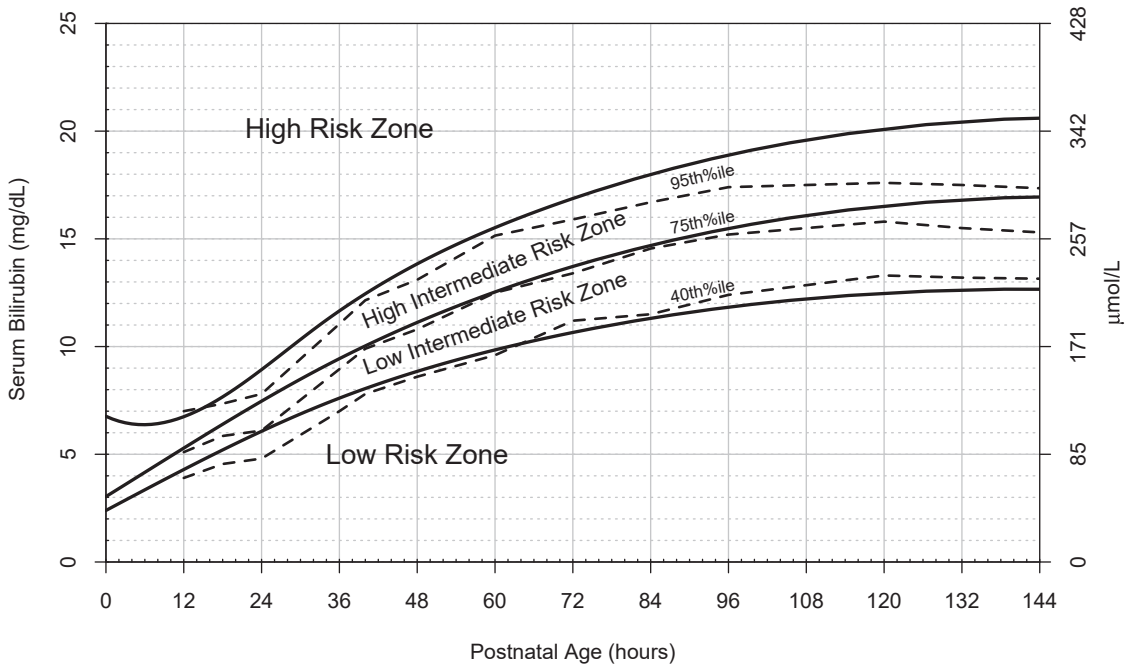

Figure 3. The new neonatal bilirubin nomogram (*solid lines*) with the1999 Bhutani nomogram superimposed in the dashed lines.

One gap that our nomogram fills is the absence, in the 1999 version, of bilirubin values between birth and 12 hours. In the new version, we have robust hour-specific TSB information in that first 12-hour period. Another gap the new nomogram fills is a basic validation of the Bhutani nomogram that has been used for the past 20 years. By making use of a different population of neonates, from a different geographic location, and with 140 times the amount of data, we created a nomogram with remarkable overall similarity to the 1999 version. Other gaps the new nomogram fill include (1) clarifying that there is no difference in TSB values between male and female neonates, (2) clarifying that there are higher TSB values among late-preterm vs term neonates, and (3) clarifying that neonates of Black race have lower initial TSB values[20-23] and those of Asian race have higher initial TSB values.[24,25]

There have been criticisms that the 40th percentile in the 1999 nomogram was higher than on other nomograms that were available around that time.[8,9] Our current nomogram estimates a 40th percentile similar to the 1999 nomogram. Unlike the 1999 Bhutani nomogram, inclusion of newborns for the current nomogram did not depend on follow-up. In addition, the current nomogram included 100-200 times the number of values used in any of the previously published nomograms. These points suggest that the 1999 nomogram's estimates may have been valid. Another possibility is that both estimates of the 40th percentile (from our current nomogram and the 1999 nomogram) are spuriously elevated. The recent publication by Kaplan and Maisels supports this possibility. It presents an hour-specific bilirubin nomogram based on global transcutaneous measurements and shows a 50th percentile lower than the 40th percentile in this current report and the 1999 nomogram.[26]

The racial make-up of the 1999 Bhutani curve included 60% Black neonates, whereas the current nomogram includes <1%. However, because of the much larger number of neonates in our present dataset, the absolute number of neonates of Black race in the new nomogram exceeds those in the 1999 version by almost 2-fold. The lower percentage of Black neonates in our data set might explain why after 60 hours the 75th and 95th percentile values in the 1999 nomogram are 1 to 2 mg/dL lower than in the new version. A possible weakness of the present nomogram and the 1999 nomogram is that neither was created from a cohort with proportions of races and ethnicities equal to global averages. Though the differences in hour-specific bilirubin percentiles between maternally identified Black, Asian, and Caucasian newborns were statistically significant, we did not conclude that these differences were large enough to warrant the use of race-specific nomograms.

A critical question for clinicians caring for newborn infants is, how do we use the bilirubin nomogram, either the 1999 version or the new version, to know when to start phototherapy.[27] This important issue is beyond the scope of the present study. TSB levels associated with neurologic dysfunction are variable and a "normal range" is difficult to define. For this reason, we utilized the principle of the reference interval (including the use of the 95th percentile as the upper limit) because it is the most widely used tool for interpretation of individual patient laboratory test results.[28,29] In recent years, risks of phototherapy have been reported,[30,31] fostering debate regarding whether too many neonates are receiving

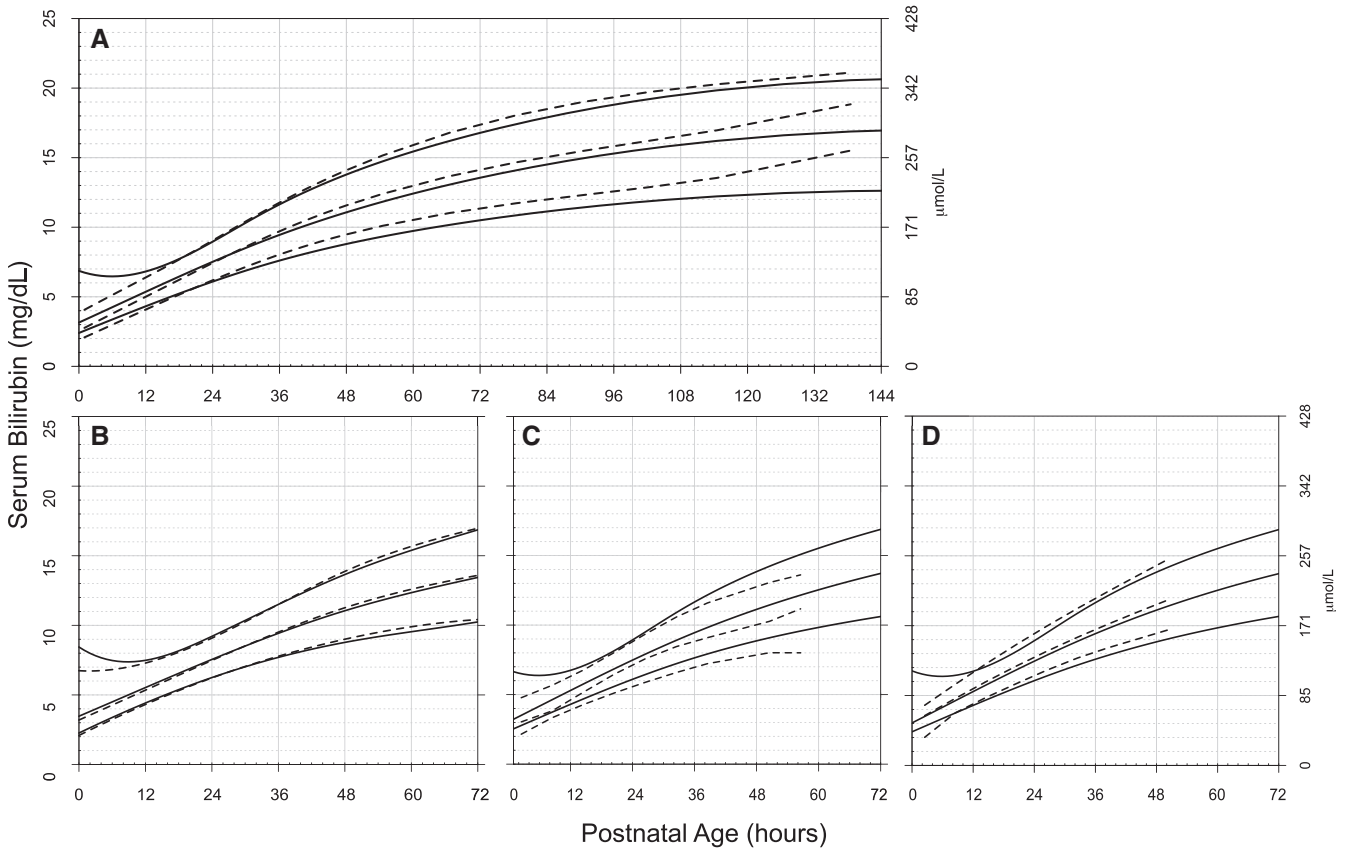

Figure 4. The 40th, 75th, and 95th percentile curves for TSB by hour for population subgroups. **A,** Percentile curves for 24 958 neonates born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation (*dashed lines*) are superimposed on curves for those born ≥37 weeks (*solid lines*; n = 372 437). **B,** Percentile curves for 204 017 male neonates (*dashed lines*) and 193 378 female neonates (*solid lines*) born at ≥35 weeks of gestation. **C,** Percentile curves for 2868 Black neonates (*dashed lines*) born at ≥35 weeks of gestation are superimposed on the analogous curves (solid lines) for the non-Black neonates born at ≥35 weeks of gestation (n = 394 527). **D,** Percentile curves for 5866 Asian neonates (*dashed lines*) born at ≥35 weeks of gestation are superimposed on the analogous curves (*solid lines*) for the non-Asian neonates born at ≥35 weeks of gestation (n = 391 529).

phototherapy and being exposed to unbalanced risks. Certainly, epidemiologic data by Newman et al suggest that phototherapy could be associated with later development of cancer, seizures, diabetes, and asthma.[32-35] These and related issues persuade us to renew our efforts to base phototherapy initiation on evidence of benefit and risk, which might involve reigning back the proportion of well babies who are receiving phototherapy.

We maintain that improving the bilirubin nomogram, as we did in this study, is 1 step toward evidence-based phototherapy decision-making. We are currently using this nomogram routinely in our hospitals in Utah for phototherapy initiation (when a neonate has a TSB exceeding the 95th percentile) and for discharge risk stratification.[36] This reduces phototherapy usage in that hospital to about 5% of well babies, whereas we had previously been administering phototherapy to 8%-10% of well babies.[36] Newborns with predischarge TSB >75th percentile, and, thus, at higher risk for subsequently exceeding the 95th percentile, receive a recommendation for follow-up within 24 hours. Therefore, in contrast to the 1999 and 2004 AAP guidelines, we utilize 1 nomogram for bilirubin management instead of 3. Determining whether the nomogram is appropriate for widespread use outside our state and health care systems will require further evaluation both inside and outside our current setting. Follow-up information on rehospitalization for jaundice treatment, highest subsequent TSB, and neurodevelopment, will provide information important to evaluating this new approach. We also anticipate the publication of updated guidelines from the AAP on managing hyperbilirubinemia in the newborn infant, which will provide expert opinion on possible improvements to the management of newborn hyperbilirubinemia.

We recognize limitations of our new nomogram. First, the time at which the first bilirubin was obtained was not random and may have been biased by confounding factors. For example, a newborn with severe visible jaundice may have been more likely to have a TSB obtained early in the birth hospitalization. On the other hand, newborns who had a prolonged hospitalization for maternal reasons and did not

appear jaundiced in the first days of life were more likely to have their first total serum bilirubin obtained at >72 hours of life. A second limitation is the absence of data regarding breastfeeding vs bottle feeding, a known factor that affects bilirubin levels.[37,38] Finally, a third limitation of our nomogram is the small number of babies for which we obtained follow-up data. This was a secondary objective of the study and was limited by the necessity of manual chart review to ensure accurate data.

We anticipate that with concerted efforts by multiple investigative teams, neonatal bilirubin assessment and management programs will become more evidence-based, more effective, less expensive, more focused on neonates likely to benefit from phototherapy, and better able to prevent bilirubin-induced toxicities.[36] We believe that our new version of the Bhutani bilirubin nomogram is 1 step toward achieving those goals. ■

Submitted for publication Dec 1, 2020; last revision received May 13, 2021; accepted May 14, 2021.

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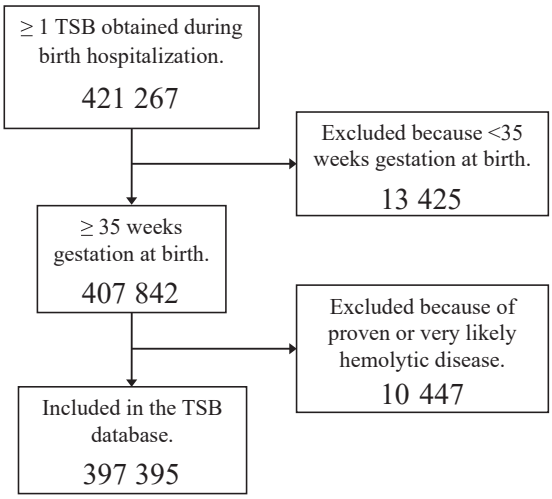

Figure 1. Consort diagram to illustrate the process of arriving at the new bilirubin nomogram data set. Of the 10 447 neonates excluded because of proven or likely hemolytic disease, n=7 had hereditary spherocytosis and a positive DAT.

Table II. A summary of the number of TSB values within epochs, and epoch width (in hours), according to hours after birth, used to construct the new bilirubin nomogram

Epochs	Number of epochs	Epoch width (h per epoch)	Minimum and maximum number of TSB values/epoch
1 h epochs from 0 h to 7 h	8	1	68-378
1 h epochs from 8 h to 22 h	15	1	502-7 094
1 h epochs from 23 to 44 h	22	1	9 173-28 247
1 h epochs from 45 to 72 h	28	1	233-8 398
6 h epochs from 73 to 108 h	6	6	88-764
12 h epochs from 109 to 144 h	3	12	44-124