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# Transcutaneous Bilirubin Nomogram for Prediction of Significant Neonatal Hyperbilirubinemia



**WHAT'S KNOWN ON THIS SUBJECT:** TcB measurements are being used throughout the world to estimate the risk of significant hyperbilirubinemia. Despite such use, available data on their predictive performance are limited, and a predictive TcB-based tool has not yet been developed.



**WHAT THIS STUDY ADDS:** We provide a TcB-based predictive nomogram that could allow for a noninvasive, risk-based approach to neonatal hyperbilirubinemia and may guide clinicians in targeting evaluations of and planning appropriate follow-up strategies for jaundiced neonates.

## abstract

**OBJECTIVE:** The goal was to develop a predictive nomogram, based on transcutaneous bilirubin (TcB) measurements, for assessment of the risk of significant hyperbilirubinemia in healthy term and near-term neonates.

**METHODS:** A total of 10 382 TcB measurements were performed with 2039 healthy neonates (gestational age of  $\geq 35$  weeks and birth weight of  $\geq 2000$  g), with a BiliCheck bilirubinometer (SpectRx, Norcross, GA), at designated time points between 12 and 120 hours of life. According to their severity, these TcB measurements were selectively cross-checked with a direct spectrophotometric device, and significant hyperbilirubinemia was defined on the basis of the hour-specific threshold values for phototherapy proposed by the American Academy of Pediatrics. With the use of likelihood ratios (LRs), the high- and low-risk demarcators for each designated time were calculated and presented on an hour-specific nomogram.

**RESULTS:** Significant hyperbilirubinemia was documented for 122 neonates (6%). At 24 hours of life, the high-risk zone of the nomogram had 73.9% sensitivity and a positive LR of 12.1 in predicting significant hyperbilirubinemia, whereas the low-risk zone had 97.7% sensitivity and a negative LR of 0.04. At 48 hours, the high-risk zone had 90% sensitivity and a positive LR of 12.1, whereas the low-risk zone had 98.8% sensitivity and a negative LR of 0.02. In our study population, the probability of significant hyperbilirubinemia would be  $>35\%$  for values in the high-risk zone and  $<0.5\%$  for values in the low-risk zone of the nomogram.

**CONCLUSIONS:** We provide a predictive TcB tool that could allow for a noninvasive, risk-based approach to neonatal hyperbilirubinemia. *Pediatrics* 2009;124:1052–1059

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### KEY WORDS

hyperbilirubinemia, jaundice, neonates, predictive nomogram, transcutaneous bilirubin

### ABBREVIATIONS

TSB—total serum bilirubin

TcB—transcutaneous bilirubin

AAP—American Academy of Pediatrics

LR—likelihood ratio

ROC—receiver operating characteristic

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Hyperbilirubinemia has been recognized as the most common cause of readmission after early hospital discharge for healthy newborns.<sup>1-4</sup> Therefore, identification of infants at risk for developing significant hyperbilirubinemia has become particularly challenging. Prediction of significant hyperbilirubinemia is based on predischARGE total serum bilirubin (TSB) measurements, with the use of the nomogram developed by Bhutani et al.<sup>5-9</sup> However, determination of TSB levels remains an invasive, stressful, time-consuming procedure. In contrast, current transcutaneous bilirubin (TcB)-measuring devices have been shown to be accurate and time-effective for estimating bilirubin concentrations in neonates.<sup>10-17</sup> Although there are limited data on their predictive performance, TcB measurements are being used with increasing frequency in the screening of newborn infants for significant hyperbilirubinemia.<sup>2,6,8,9,17-21</sup>

The purpose of the present study was to assess the value of TcB measurements at designated time points, from 12 to 72 hours of life, for predicting significant hyperbilirubinemia in healthy term and near-term newborns. Moreover, these hour-specific TcB values were used, according to their positive and negative likelihood ratios (LRs), for the development of a predictive nomogram. We present a TcB measurement-based predictive tool that may guide clinicians in targeting evaluations of and planning appropriate follow-up strategies for neonates with jaundice.

## METHODS

### Subjects

This is a prospective study that was performed in the well-infant nursery of the University Hospital of Patras (Patras, Greece) between September 2005 and December 2007. Included were healthy term or near-term new-

borns with gestational ages of  $\geq 35$  weeks (determined on the basis of the date of the last menstrual period or first-trimester ultrasound findings) and birth weights of  $\geq 2000$  g. Exclusion criteria were admission to the ICU, positive direct Coombs test results, jaundice requiring intervention during the first 24 hours, and glucose-6-phosphate dehydrogenase deficiency.

All newborns whose mothers were Rh factor-negative or had positive indirect Coombs test results were evaluated for blood group and direct Coombs test results.<sup>6</sup> Neonates who required phototherapy also were evaluated for blood group, direct Coombs test results, and glucose-6-phosphate dehydrogenase deficiency.

## Protocol

### TcB Measurements

TcB determinations were made with a BiliCheck (SpectRx, Norcross, GA), a hand-held bilirubinometer that measures TcB levels by using multiwavelength spectral reflectance analysis. All measurements were performed with the same device by properly trained physicians, according to the manufacturer's instructions and the standard described technique,<sup>11,12,17</sup> in ambient daylight or in the fluorescent white light of the nursery.

### TSB Measurements

Blood samples (50  $\mu$ L) for TSB measurements were collected by using the heel stick technique, and measurements were performed by using a Unistat bilirubinometer (Richert, Depew, NY), a direct spectrophotometric device with accuracy (bias) of  $\pm 5\%$ . All measurements were made by skilled physicians, according to the manufacturer's instructions regarding calibration and quality controls. Special care was taken to avoid exposure of the collected samples to light.

In addition, for infants who required phototherapy, TSB levels were determined in the laboratory (1-mL venous sample) with a diazo method, in an Olympus AU640 analyzer (Olympus, Center Valley, PA), as part of the routine evaluation of significant hyperbilirubinemia. These TSB levels were used to estimate the accuracy of TSB measurements made with the spectrophotometric method.

### Inpatient Follow-up Monitoring

The study adhered strictly to our institution's protocol for the management of neonatal jaundice. TcB determinations were obtained at  $12 \pm 2$ ,  $18 \pm 2$ , and  $24 \pm 2$  hours during the first postnatal day and at 12-hour intervals ( $36 \pm 2$ ,  $48 \pm 2$ ,  $60 \pm 2$ , and  $72 \pm 2$  hours) thereafter. A final TcB measurement was made between 96 and 120 hours. At least 5 measurements were obtained for each infant. TcB levels were evaluated by using the hour-specific bilirubin nomograms proposed by the American Academy of Pediatrics (AAP).<sup>6</sup>

TcB measurements were followed immediately by TSB determinations if the TcB level was  $> 15$  mg/dL or if the TcB level was  $\leq 15$  mg/dL but exceeded or was within 2 mg/dL of the phototherapy threshold level. In addition, all infants underwent TcB and TSB measurements before discharge, when blood was sampled for the required universal metabolic screening. TcB and TSB levels were recorded on a flow sheet attached to the medical file of each infant.

### Significant Hyperbilirubinemia

Significant hyperbilirubinemia was defined as any TSB level that exceeded the hour-specific threshold value for phototherapy, according to the guidelines presented by the AAP.<sup>6</sup>

### Outpatient Follow-up Evaluations

Our institution has adopted a discharge policy of  $\geq 72$  hours for new-

borns delivered vaginally and  $\geq 96$  hours for newborns delivered through cesarean section. A follow-up evaluation within 24 to 48 hours after discharge is offered to all neonates. Therefore, the parents of vaginally delivered infants were advised to return to the nursery for a follow-up evaluation at postnatal age between 96 and 120 hours. After 120 hours, additional follow-up evaluations for all infants involved either a visual inspection or repeat TcB (and, if needed, TSB) measurements at the physician's discretion. This latter monitoring was performed in the hospital outpatient department. Resolution of hyperbilirubinemia was confirmed at the age of 12 to 14 days, in cooperation with the primary care pediatrician.

### Statistical Analyses and Design of Predictive Nomogram

Demographic data were analyzed by using SPSS 15.0 for Windows (SPSS, Chicago, IL). Receiver operating characteristic (ROC) curve analysis, performed with MedCalc 8.1 (MedCalc, Mariakerke, Belgium), was used to assess the predictive ability and to obtain the positive and negative LRs for the TcB values. The precision of the spectrophotometric method was evaluated with the Bland-Altman method (MedCalc 8.1), by using a percent difference plot and adopting acceptance limits of 3% for SEs and 10% for total errors.<sup>22</sup> The critical TcB values for each designated time point were calculated on the basis of positive and negative LRs. Measurements made after the initiation of phototherapy were not used in the analysis. Because a positive LR of  $>10$  or a negative LR of  $<0.1$  denotes a conclusive increase or decrease, respectively, in the likelihood of the disease,<sup>23,24</sup> the lower TcB values with positive LRs of  $>10$  and the higher TcB values with negative LRs of  $<0.1$  were considered high- and

**TABLE 1** Demographic Characteristics of the Study Population With Respect to Significant and Nonsignificant Hyperbilirubinemia

Parameter	n (%)		<i>P</i> <sup>a</sup>
	Nonsignificant Hyperbilirubinemia	Significant Hyperbilirubinemia	
Study sample	1917	122	
Male	936 (48.8)	63 (51.6)	.61
Gestational age			
35–37 $\frac{1}{2}$ wk	402 (20.9)	35 (28.7)	.07
38–39 $\frac{1}{2}$ wk	1093 (57)	68 (55.7)	
$\geq 40$ wk	422 (22.1)	19 (15.6)	
Mode of delivery			
Cesarean section	721 (37.6)	53 (43.4)	.23
Vaginal delivery	1196 (62.4)	69 (56.6)	
Feeding			
Breast	824 (43)	48 (39.3)	.73
Formula	863 (45)	58 (47.6)	
Both	230 (12)	16 (13.1)	

<sup>a</sup> Determined with the  $\chi^2$  test.

low-risk demarcators, respectively, for the development of significant hyperbilirubinemia. We also calculated the higher TcB values with negative LRs of 0, which were considered minimal-risk demarcators. These TcB values were used to design an hour-specific nomogram with Microsoft Excel (Microsoft, Redmond, WA). Intervals above, between, and below the tracks of risk demarcators were defined as zones, that is, high-risk (above the high-risk demarcator track), low-risk (below the low-risk demarcator track), and intermediate-risk zones.

To calculate the posttest probability of significant hyperbilirubinemia, we applied Bayes' theorem by using a specific nomogram.<sup>25</sup> Furthermore, the predictive characteristics of the developed nomogram were compared with the predictive performance of the TSB nomogram developed by Bhutani et al,<sup>5</sup> as applied to our study population.

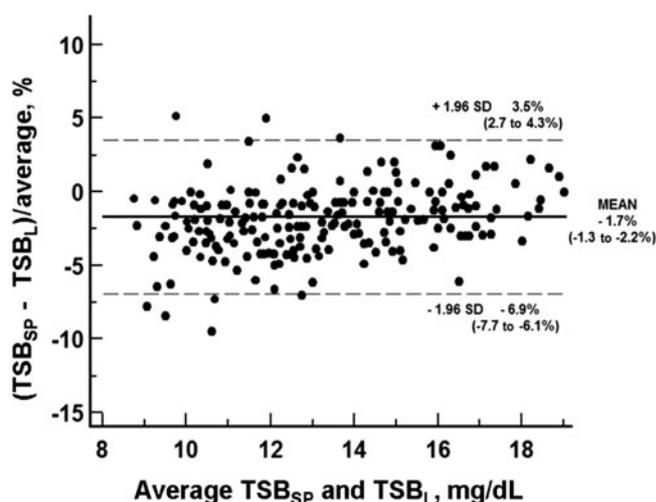
### Ethics Considerations

The study was approved and monitored by the ethics committee of the University Hospital of Patras. The assignment of any medical intervention (TcB measurements, blood sampling for TSB determination, or phototherapy) was conformable to our institu-

tion's protocol for the management of neonatal jaundice and was not at the discretion of the investigators. No personal data were recorded, and informed consent was obtained from one of the parents.

### RESULTS

During the study period, a total of 2745 live births took place at the University Hospital of Patras. Three hundred eleven neonates did not meet the enrollment criteria, and another 395 failed to complete the follow-up process. The remaining 2039 neonates constituted our study population, from which a total of 10 382 TcB measurements were obtained. The mean birth weight was  $3202 \pm 439$  g, and the mean gestational age was  $271 \pm 10$  days ( $38\frac{5}{7} \pm 1\frac{3}{7}$  weeks). Demographic data are listed in Table 1. The number of TcB measurements for each designated time point was as follows: 1130 at 12 hours, 1215 at 18 hours, 1410 at 24 hours, 1112 at 36 hours, 1319 at 48 hours, 1265 at 60 hours, and 1307 at 72 hours of postnatal age. A number of 1624 neonates (79.6% of the population studied) had final TcB measurements between 96 and 120 postnatal hours. This sample included the 774 neonates who were delivered through



**FIGURE 1**

Error distribution of paired spectrophotometric TSB ( $TSB_{sp}$ ) and laboratory TSB ( $TSB_L$ ) values ( $n = 223$ ). The mean errors and 95% confidence intervals (upper and lower limits of agreement) are shown.

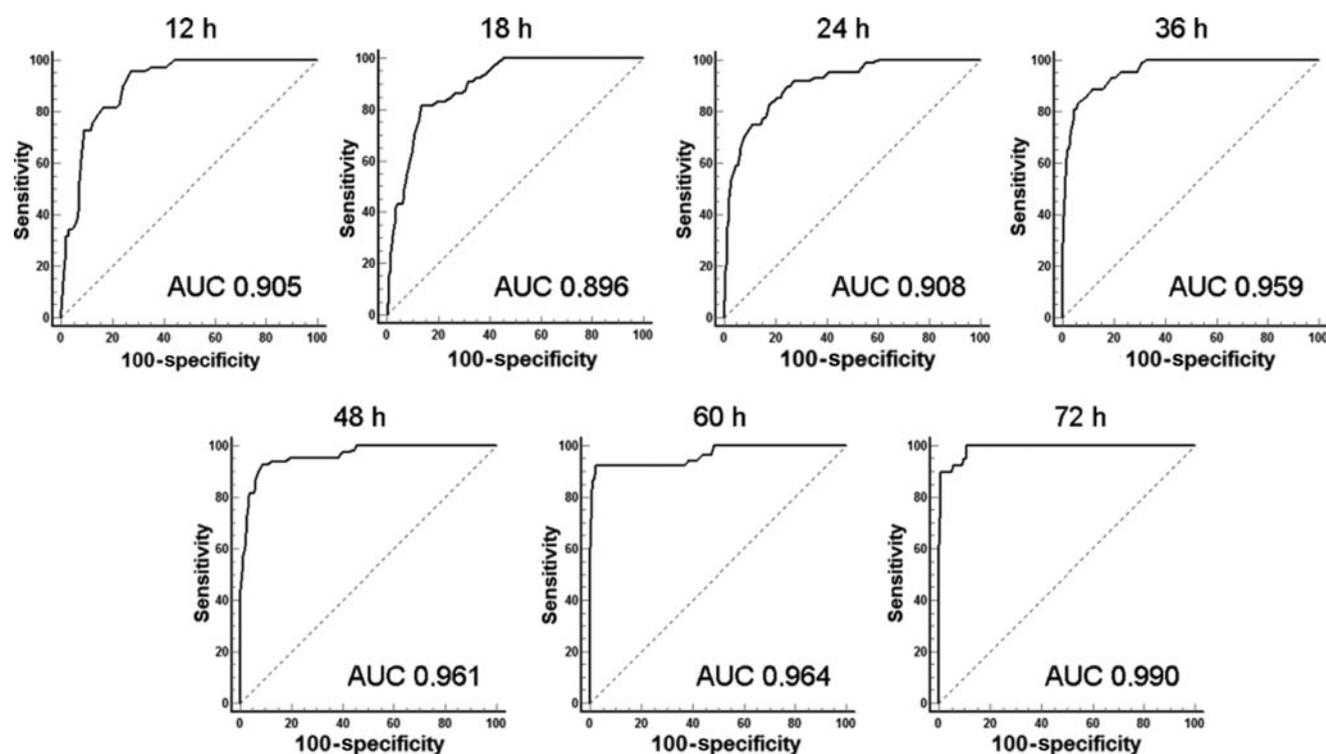
cesarean section (discharged after 96 hours) and 850 newborns who were delivered vaginally and returned for follow-up evaluations. Additional follow-up assessments (visual inspection and/or repeat bilirubin deter-

minations) were performed for 534 neonates until the resolution of hyperbilirubinemia. A total of 3249 TSB measurements were obtained, and significant hyperbilirubinemia was documented for 122 neonates (6%).

None of the neonates developed significant hyperbilirubinemia after termination of the follow-up process.

The precision of the spectrophotometric method was evaluated by comparing 223 paired spectrophotometric TSB and laboratory TSB measurements. As illustrated in Fig 1, the Bland-Altman method using a percent difference plot demonstrated good agreement between the 2 methods; the mean difference between paired spectrophotometric and laboratory TSB measurements was  $-1.7\%$  (95% confidence interval:  $-6.9\%$  to  $3.5\%$ ).

In Fig 2 are presented the ROC curves for the designated time points, indicating the ability of TcB measurements to predict significant hyperbilirubinemia. High- and low-risk demarcating TcB levels were calculated on the basis of positive and negative LR<sub>s</sub> (Table 2), and these values were subsequently used for the



**FIGURE 2**

ROC curves for the performance of TcB measurements for designated study times in predicting subsequent significant hyperbilirubinemia. AUC indicates area under the curve.

**TABLE 2** Critical TcB Values for Designated Times

Time, h	TcB Level (mg/dL)		
	High-Risk Demarcator (Positive LR of >10)	Low-Risk Demarcator (Negative LR of <0.1)	Minimal-Risk Demarcator (Negative LR of 0)
12	6.5	4.5	4.2
18	7.7	5.0	4.8
24	8.0	5.8	5.3
36	9.3	8.0	7.8
48	11.0	9.5	8.8
60	12.5	11.0	10.0
72	13.5	13.0	12.5

development of the predictive nomogram illustrated in Fig 3.

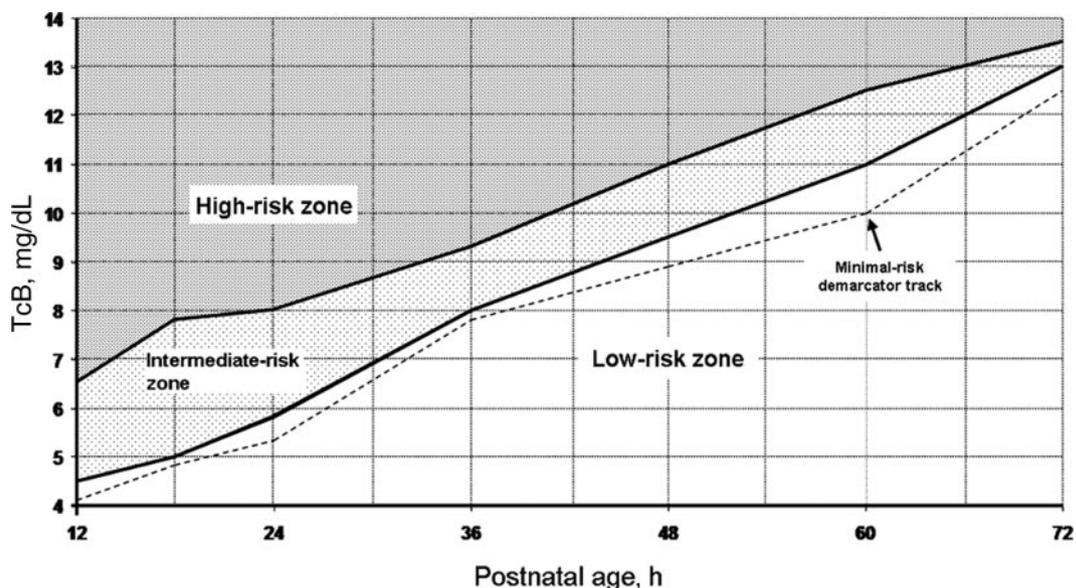
The predictive characteristics of the TcB nomogram at 24 and 48 hours of life were calculated and compared with the predictive performance of the TSB nomogram<sup>5</sup> when applied to our study population (Table 3). The application of Bayes' theorem in our study population (pretest probability of significant hyperbilirubinemia: 6%) by using the specific nomogram yielded posttest probabilities of >35% for values in the high-risk zone (positive LR of >10) and <0.5% for values below the low-risk demarcator track (negative LR of <0.1) (Fig 4).

## DISCUSSION

Early postnatal discharge of healthy newborn infants has become a worldwide trend. Because bilirubin levels peak between the third and fifth days of life, however, this practice has been associated with increased risk of undetected severe hyperbilirubinemia.<sup>1-4</sup> Attempts to identify neonates at risk currently are based on pre-discharge risk assessments using hour-specific TSB measurements together with the predictive nomogram developed by Bhutani et al.<sup>5</sup> This approach is included in the latest hyperbilirubinemia guidelines of the AAP<sup>6</sup> and has been

validated and widely accepted.<sup>6-9</sup> However, determination of TSB levels remains a time-consuming, invasive procedure that involves pain, neonatal stress, and risk of infection. Under these circumstances, noninvasive determination of bilirubin concentrations seems advantageous, because it minimizes blood sampling and allows for universal neonatal screening. Because the new-generation, noninvasive, TcB-measuring devices have been shown to be reliable for estimating bilirubin concentrations,<sup>10-17</sup> TcB measurements are being used throughout the world for estimations of the risk of significant hyperbilirubinemia.<sup>2,6,8,9,17-21</sup> Despite such use, available data on their predictive performance are limited<sup>17-21</sup> and a predictive TcB tool, similar to the TSB nomogram developed by Bhutani et al,<sup>5</sup> has not yet been developed.

In this study, we provide data on the predictive ability of TcB measurements obtained with the BiliCheck device between 12 and 72 hours of life, in a white Greek population of term and near-

**FIGURE 3**

TcB nomogram for assessing the risk of subsequent significant hyperbilirubinemia in healthy term and near-term newborns. The high-risk zone is defined by the track of TcB values with positive LR of >10 and the low-risk zone by the track of TcB values with negative LR of <0.1. The minimal-risk demarcator track (negative LR of 0) is also presented (dotted line). The nomogram was developed by using a total of 10 382 TcB measurements from 2039 neonates with gestational ages of  $\geq 35$  weeks and birth weights of  $\geq 2000$  g.

**TABLE 3** Comparison of Predictive Characteristics for the TcB Nomogram of the Study and the TSB Nomogram Developed by Bhutani et al,<sup>5</sup> at 24 and 48 Hours of Life

Time and Demarcator Track	N	SSHB, n	Predictive Characteristics					
			Sensitivity, %	Specificity, %	PPV, %	NPV, %	Positive LR	Negative LR
24 h								
TcB nomogram								
Above high risk	146	65	73.9	93.9	44.5	98.2	12.1	0.28
Above low risk	691	86	97.7	54.2	12.4	99.7	2.1	0.04
Above minimal risk	724	88	100	51.9	12.2	100	2.1	0
TSB nomogram								
Above 95th percentile	146	65	73.9	93.9	44.5	98.2	12.1	0.28
Above 75th percentile	455	79	89.8	71.6	17.4	99.1	3.2	0.14
Above 40th percentile	802	88	100	46	11	100	1.9	0.0
48 h								
TcB nomogram								
Above high risk	164	72	90	92.6	43.9	99.3	12.1	0.11
Above low risk	411	79	98.8	73.2	19.2	99.9	3.7	0.02
Above minimal risk	527	80	100	63.9	15.2	100	2.8	0.0
TSB nomogram								
Above 95th percentile	70	53	66.3	98.6	75.7	97.8	48.3	0.34
Above 75th percentile	164	72	90	92.6	43.9	99.3	12.1	0.11
Above 40th percentile	631	80	100	55.5	12.7	100	2.2	0.0

SSHB indicates subsequent significant hyperbilirubinemia; PPV, positive predictive value; NPV, negative predictive value.

<sup>a</sup> Of a total of 1410 neonates evaluated at 24 hours, 88 developed subsequent significant hyperbilirubinemia.

<sup>b</sup> Of a total of 1319 neonates evaluated at 48 hours, 80 developed subsequent significant hyperbilirubinemia.

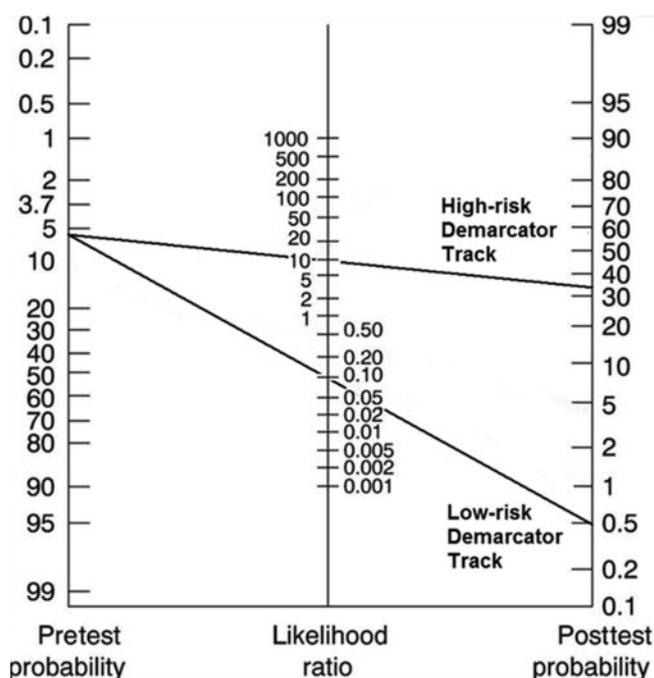
term newborns. As demonstrated with ROC curve analysis, the predictive performance of TcB measurements was

acceptable during the first 24 hours of life and improved thereafter (Fig 1). In addition, risk-demarcating TcB values

for the development of significant hyperbilirubinemia were calculated and used for the development of an hour-specific predictive nomogram.

There are important differences between our study and similar published reports. Bhutani et al<sup>5</sup> developed a nomogram based on hour-specific TSB values, defining values of  $\geq 95$ th percentile as indicating significant hyperbilirubinemia. In a subsequent study, the authors attempted to evaluate the predictive ability of TcB measurements by using the TSB predictive nomogram, and they suggested that neonates with TcB values above the 75th percentile of the nomogram should be considered at high risk for developing excessive hyperbilirubinemia.<sup>17</sup> Maisels and Kring<sup>20</sup> also presented a nomogram, based on TcB measurements obtained with the JM-103 bilirubinometer (Draeger Medical, Telford, PA). That nomogram, which also was percentile-based, in fact represents the natural history of TcB measurements in their study population.

In the present study, we evaluated the predictive performance of TcB measurements obtained with the BiliCheck device and, depending on severity, we selectively cross-checked these measurements with a direct spectrophotometric method. We defined significant hyperbilirubinemia on the basis of TSB values, according to the AAP guidelines.<sup>6</sup> Although this approach may be open to discussion,<sup>26</sup> it is safe and closer to daily clinical practice. Furthermore, the proposed risk demarcators were calculated by using positive and negative LRs instead of TcB percentiles. LRs are not affected by the prevalence of disease, and they provide more-reliable estimations of disease probability, even among heterogeneous populations.<sup>23,24</sup> In addition, LRs have the advantage of immediate quantitative clinical utility through direct application of Bayes' theorem.<sup>25</sup>

**FIGURE 4**

Nomogram for converting pretest probabilities into posttest probabilities by using LRs. Extension of a straight line, connecting the pretest probability (left vertical axis) with the LR for a diagnostic test (central vertical axis), determines the posttest probability (right vertical axis) of the disease. The posttest probabilities for high- and low-risk demarcator tracks (TcB nomogram) are presented for our study population (pretest probability of significant hyperbilirubinemia: 6%).

As shown in our study population, the probability of significant hyperbilirubinemia would be >35% for values within the high-risk zone and <0.5% for values within the low-risk zone (Fig 4).

At 24 hours of life, the high-risk demarcator of our TcB nomogram coincided with the 95th percentile of the TSB nomogram developed by Bhutani et al<sup>15</sup>; at 48 hours, however, it approached the 75th percentile of the TSB nomogram (Table 3). This discrepancy could be partially attributed to the differences in methods between the 2 studies. As noted previously,<sup>7,20</sup> the TSB nomogram was developed by using postdischarge TSB measurements that were obtained from a rather small number of infants; therefore, these values are likely to represent a biased sample, leading to false high-sensitivity estimates. When the TSB nomogram was applied to our population, disproportionately large numbers of measurements were classified within the intermediate- and high-risk zones (Table 3). At 24 hours of life, 691 measurements (49%) were classified into the high- and intermediate-risk zones of the TcB nomogram, compared with 802 (56.9%) classified as high/intermediate risk with the TSB nomogram. Similarly, at 48 hours of life, 411 TcB measurements (31.1%) were classified as high/intermediate risk with the TcB nomogram, compared with 631 (47.9%) with the nomogram developed by Bhutani et al.<sup>5</sup> Another noticeable observation is that the 95th percentile of the TcB nomogram developed by Maisels and Kring<sup>20</sup> is placed between the high-risk and low-risk demarcator tracks of our nomogram after 18 hours of life. However, those authors acknowledged that the 95th percentile of their nomogram

was unexplainably lower than that reported in other studies.<sup>20</sup>

Although minimal-risk demarcators were calculated, we defined the low-risk zone of the nomogram on the basis of the low-risk demarcators. A neonate with a TcB value below the low-risk demarcator track (negative LR of <0.1) must be considered as having a very small probability of developing significant hyperbilirubinemia. With knowledge of the prevalence of significant hyperbilirubinemia in the population, this probability can be calculated with the nomogram illustrated in Fig 4, and a rational follow-up strategy can be planned. In contrast, a TcB value below the minimal-risk demarcator track (negative LR of 0) would indicate that the expected risk would be 0 regardless of the prevalence of hyperbilirubinemia. We think that this would not be a safe approach for such a frequent and potentially dangerous condition as neonatal jaundice.

Our study has some potential limitations. We report data obtained from a Greek population of white newborn infants from a single center. However, the new versions of transcutaneous bilirubinometers such as the BiliCheck have been shown not to be affected by skin pigmentation.<sup>11,12,14,15</sup> Furthermore, because the developed nomogram is based on LRs, it should be applicable even among heterogeneous populations. However, a multicenter study is needed for confirmation of that assumption and for assessment of the clinical applicability of our nomogram in different racial groups. Also, it should be mentioned that a large proportion (38%) of the neonates studied were delivered through cesarean section and as many as 45.2% of the infants were exclusively formula fed. However, as shown in Ta-

ble 1, these factors did not have an effect on the prevalence of significant hyperbilirubinemia.

The intermediate-risk zone should not be considered a disadvantage of the presented nomogram. The idea of a cutoff vector that could reliably classify a TcB measurement as high-risk or low-risk seems unattainable. The 75th percentile of the TSB nomogram, which has been proposed as such a demarcator,<sup>17</sup> had poor overall predictive performance for our population at 24 hours (positive LR: 3.2; negative LR: 0.14) and could not rule out significant hyperbilirubinemia at 48 hours of life (negative LR: 0.11). It is also worth noting that the intermediate-risk zone of our nomogram is quite wide before the first 24 hours, but it narrows gradually thereafter (Fig 3). This pattern most likely reflects the gradual improvement of the predictive ability of TcB values in the second and third days of life (Fig 2).

## CONCLUSIONS

Universal predischarge neonatal screening with TcB measurements has become a common practice throughout the world. In the present study, we demonstrate the ability of TcB measurements obtained between 12 and 72 hours of life to predict significant hyperbilirubinemia. We also provide a TcB-based, predictive nomogram for assessment of the risk of significant hyperbilirubinemia in healthy term and near-term neonates. Application of this predictive tool could allow for a noninvasive, risk-based approach for neonatal hyperbilirubinemia and could guide clinicians in targeting evaluations and planning appropriate follow-up strategies for neonates with jaundice.

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## Transcutaneous Bilirubin Nomogram for Prediction of Significant Neonatal Hyperbilirubinemia

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