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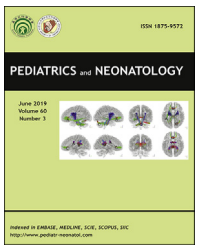

Original Article

Transcutaneous bilirubin nomogram for Taiwanese newborns — A single center study

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Key Words
hyperbilirubinemia;
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Background: Hour-specific bilirubin nomogram has been recommended to predict post-discharge hyperbilirubinemia in newborns. However, it may not be applicable in Taiwan due to ethnic differences. The aim of this study was to construct a 12-h specific transcutaneous bilirubin (TCB) nomogram in newborns for clinical reference.
Methods: We prospectively enrolled full term or late preterm neonates born in a tertiary care hospital between October 2013 and July 2014. The exclusion criteria included chromosome anomaly, glucose-6-phosphate dehydrogenase deficiency, and receiving phototherapy within 60 h after birth. TCB measurements were performed by a single technician using the Bilichek device, and measured every 12 h until neonates were discharged. Patient data including sex, delivery mode, gestational age, body weight with daily change, and feeding pattern were collected for analysis. A TCB nomogram was constructed with 40th, 75th, and 95th percentile lines.
Results: A total of 498 newborns were enrolled, and the characteristics between the hyperbilirubinemia and nonhyperbilirubinemia groups were not different. The mean TCB curve revealed that the peak TCB level was 14.2 ± 2.9 mg/dL at 100.6 ± 3.6 h of age. The peak 95th percentile TCB level was 19.4 mg/dL at 121.9 ± 5 h of age. Mean TCB levels increased at a rate of 0.01–0.21 mg/dL/h initially, followed by a decrease after 96–108 h of age. Twenty newborns (4%) were diagnosed with hyperbilirubinemia. Regarding TCB distribution, 11 of 60 (18%) had peak TCB levels above the 95th percentile, 5 of 151 (3%) had TCB levels between the 75th and 95th percentile, 4 of 200 (2%) had levels between the 40th and 75th percentiles, and none had a level below the 40th percentile.
Conclusion: A 12-h specific TCB nomogram could be a useful reference for workup for hyperbilirubinemia, particularly when it is above the 95th percentile line.

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1. Introduction

Neonatal jaundice is a common issue, and some newborns may develop severe hyperbilirubinemia, which can result in bilirubin-induced neurologic dysfunction.[1,2] Risk factors of hyperbilirubinemia include prematurity, bruising, being breastfed, cephalohematoma, and a family history of jaundice or anemia.[3] The American Academy of Pediatrics (AAP) has recommended a predischarge measurement of serum bilirubin levels for predicting neonatal hyperbilirubinemia.[4,5] Bhutani et al. recommended an hour-specific nomogram of total serum bilirubin (TSB) for predicting postdischarge hyperbilirubinemia, but their study was derived from a population with few Asian newborns (4%).[6,7] Because of differences in the incidence of hyperbilirubinemia among ethnic groups, whether the application of the Bhutani nomogram is appropriate in Taiwan is unknown.[8]

A TSB assessment is an invasive, stressful, and time-consuming process that requires obtaining blood samples from newborns. It is difficult to estimate bilirubin levels visually, particularly in infants with different skin colors.[9,10] Compared with TSB, transcutaneous bilirubin (TCB) measurement offers a rapid check for jaundice, with noninvasive stress, shorter time, lower cost, and an accurate estimation of bilirubin level.[11–15] The use of TCB has become popular among health professionals in nurseries.[14,16–18] Numerous guidelines have recommended predischarge TCB measurements for early detection of hyperbilirubinemia.[2,19]

Because of the high correlation between TCB and TSB, a TCB nomogram has been used to predict neonatal hyperbilirubinemia.[18,20–22] A study on TCB revealed that being exclusively breastfed and experiencing a loss of body weight were risk factors for late neonatal hyperbilirubinemia, but no data regarding trends or peak TCB levels were obtained.[23] Numerous studies have used only single predischarge measurements of bilirubin levels for predicting hyperbilirubinemia. Measurements have been performed before patients are 3 days old, when the bilirubin level has not reached its peak.[24,25] Whether serial measurements of TCB could predict hyperbilirubinemia within the first 4–6 days after birth remains unknown. This aim of this study was to construct a 12-h serial TCB nomogram with 40th, 75th, and 95th percentile risk zones in full term and near-term newborns during their first 3–6 days in nursery to provide a clinical reference.

2. Subjects and methods

2.1. Population

The study was conducted in a tertiary care hospital. Newborns with gestational ages greater than or equal to 36 weeks, who were cared for in a nursery between October 2013 and July 2014, were prospectively enrolled. The exclusion criteria included glucose-6-phosphate dehydrogenase (G6PD) deficiency, chromosome anomaly (e.g. Down syndrome), significant hyperbilirubinemia within 60 h, and errors in medical records. Newborns with a suspicion of infection, congenital heart disease, polycythemia, hemolytic disorder, or other illnesses requiring treatment were admitted for workup in the sick baby ward or intensive care unit and were excluded from our study. Patients with subsequent hyperbilirubinemia were also recorded. The TCB profiles were measured using a Bilichek Bilirubinometer (SpectRx Bilicheck, Philips, USA). According to specifications published on the firm's website, the application of TCB measurement ranges from 0 to 20 mg/dL. The definition of hyperbilirubinemia in this study was based on the AAP guideline: TSB levels elevated to over 5 mg/dL in 1 day, above 0.5 mg/dL/hour, over 15 mg/dL, or TSB levels exceeding the 95th percentile (high-risk zone) of the Bhutani nomogram.[6]

The study was approved by the institutional review board of the university hospital (project number was B-ER-102-178). The parents of the newborns had provided informed consent. The study process was noninvasive and no economic benefit was gained. TCB measurement was performed on the forehead of newborns by a single technician, and the total examining time was approximately 30 s.[26] We also recorded sex; delivery mode; gestational age; body weight with daily change; and feeding exclusively with breast milk, exclusively with formula, or with a mix of both.[20,27] TCB was measured twice per day, and the time interval was approximately 12 h until discharge, transfer to the neonatal intensive care unit, or significant hyperbilirubinemia that required treatment. If TCB was above the 95th percentile curve, denoting the high risk zone, TSB was measured using a total bilirubin meter (APEL BR-501, Japan).

2.2. Statistics

Data were pooled and entered into a custom-designed spreadsheet (Microsoft Excel 2010). SPSS version 20 was used for comparison, and TCB level after every 12-h interval was plotted for changes by age, according to the 40th, 75th, and 95th percentiles. A nomogram was employed to designate neonates in terms of a high risk zone (above the 95th percentile line), a high intermediate risk zone (between the 75th and 95th percentile lines), a low intermediate risk zone (between the 40th and 75th percentile lines), and a low risk zone (below the 40th percentile line). Graphpad Prism 5 was used to illustrate the graphs with the data. TCB percentile curves were created and plotted, and demographic and perinatal factors for significant hyperbilirubinemia were assessed with a chi-squared test. The differences between the groups were presented as 95% confidence intervals. A p value of less than 0.05 was considered statistically significant.[28]

3. Results

A total of 519 newborns were enrolled, and 21 were removed according to the exclusion criteria: 13 had G6PD deficiency, 1 was diagnosed with Down syndrome, 2 received phototherapy before 60 h of age, and 5 had errors in their medical records. In total, 498 newborns and 3226 TCB records were available for analysis. We checked TSB when TCB levels were higher than 15 mg/dL and collected 143 paired samples. The correlation between TCB and TSB values revealed TSB = 0.7673 * TCB +0.9306 (mg/dL), $r = 0.696$, $r^2 = 0.484$.

All the fathers of the newborns in this study were Taiwanese. Maternal ethnicities were 489 Taiwanese, 6 Chinese, 1 Japanese, 1 Turkish, and 1 Vietnamese; no mother was classified as having Caucasian origin. No newborns born to non-Taiwanese mothers had hyperbilirubinemia. There were 250 newborns delivered through vaginal delivery and 248 through cesarean section; the male-to-female ratio was approximately 1:1. The mean gestational age was 38.2 ± 1.2 weeks, and 120 newborns had a gestational age of less than 38 weeks, accounting for 24.1% of the study group. Mean body weight was 3052.1 ± 384.5 g. Seventy-one newborns (14%) had a body weight loss greater than or equal to 10% and the maximal body weight loss was 14.6%. Regarding feeding pattern, 199 were exclusively breastfed, 16 were exclusively formula-fed, and 283 received mixed feeding. Total body weight loss of over 10% showed a correlation to hyperbilirubinemia or maximal TCB level ($n = 498$, $r = 0.330$, $r^2 = 0.109$, $p < 0.0001$). Most of the newborns were discharged when they were between 3 and 7 days of age. The numbers of newborns available for TCB measurement were 498 on day 1, 497 on day 2, 494 on day 3, 426 on day 4, 243 on day 5, 183 on day 6, and 13 on day 7. Newborns born vaginally were discharged on day 3, and those born via cesarean section were discharged on day 5 unless they had clinical problems.

Analyses of sex, gestational age, body weight loss, delivery mode, and feeding pattern revealed no difference between the hyperbilirubinemia and nonhyperbilirubinemia groups (Table 1). In addition, by plotting the mean TCB levels by age, the effects of feeding pattern showed no significant difference. Total mean TCB values at a 12-h interval are listed and analyzed with the TCB increment rate calculated by age (Table 2). The mean peak of TCB level was 14.2 ± 2.9 mg/dL, detected at 100.6 ± 3.6 h of age. On the 95th percentile TCB curve, the peak TCB level is 19.4 mg/dL at 121.9 ± 5.0 h of age (Fig. 1). The mean TCB level increased by 0.01–0.21 mg/dL/h initially and declined between 96 and 108 h of age, followed by a decrement.

Of the newborns, 60, 211, 411, and 87 had peak TCB levels above the 95th percentile, above the 75th percentile, above the 40th percentile, and below the 40th percentile before 72 h of age, respectively. Eleven of the 60 (18%) neonates with peak TCB levels above the 95th percentile, 5 of the 151 (3%) between 75th and 95th percentile, 4 of the 200 (2%) between the 40th and 75th percentiles, and none of those below the 40th percentile developed hyperbilirubinemia. In total, 20 newborns (4%) were diagnosed with hyperbilirubinemia according to the AAP guidelines: 2 were diagnosed between 72 and 96 h, 8 between 96 and 120 h, 3 between 120 and 144 h, 3 between 144 and 168 h, and 4 between 192 and 216 h after birth. Approximately half of the newborns who developed hyperbilirubinemia had TCB levels above the 95th percentile in the first 72 h of life.

4. Discussion

TCB measurements could be performed on the forehead or mid-sternum with a favorable linear correlation,[26] and have been used as a noninvasive screening test

Table 1 Differences of characteristics between the hyperbilirubinemia and non-hyperbilirubinemia groups.

	Hyperbilirubinemia (n = 20)	Non-hyperbilirubinemia (n = 479)	p value
Gender			
male	10	240	1
female	10	238	
Delivery mode			
CS	9	239	0.82*
NSD	11	239	
Gestational age			
≧38 weeks	14	364	0.593*
<38 weeks	6	114	
Body weight loss			
≧10%	4	67	0.200†
<10%	16	411	
Feeding pattern			
Breast feeding	11	188	0.307*
Formula feeding	0	16	
Mixed breast and formula feeding	9	274	

*P-value was calculated by Chi-square test.
†P-value was calculated by Yate's correction of contingency.
P value: probability value; NSD: normal spontaneous delivery; CS: cesarean section.

Table 2 Transcutaneous bilirubin pattern according to postnatal age and mean transcutaneous bilirubin increment rates.

		Ages (hour)											
	mean	4.9	11.7	20.7	28.4	44.4	51.7	68.1	76.3	92.1	100.6	115.9	121.9	139.7	148.7
	SD	2.3	2.4	5.4	5.7	5.5	5.6	5.5	4.6	4.8	3.6	4.6	5	3.1	1.9
TCB(mg/dl)															
	mean	2.7	4.7	6.2	7.8	10.1	11.3	12.6	13.4	13.5	14.2	13.6	12.9	11.5	10.5
	SD	1.3	1.3	1.7	2	2.3	2.5	2.7	2.9	2.7	2.9	3.2	3.9	4.5	4.3
	Percentile														
	40th	2.2	4.2	5.7	7.2	9.4	10.6	11.8	12.6	12.9	13.6	12.9	12.9	12	12.2
	75th	3.4	5.6	7.2	9	11.5	12.9	14.2	15.7	15.2	16	16.1	15.7	15	13.2
	95th	4.9	7.2	9.3	11.4	14.3	15.8	17.6	17.7	18.3	18.7	18.8	19.4	16.9	14.4
Time interval (hour)			12–24	24–36	36–48	48–60	60–72	72–84	84–96	96–108	108–120	120–132	132–144	144–156	
Mean increment rate (mg/dl/h)			0.16	0.21	0.15	0.16	0.08	0.1	0.01	0.08	−0.04	−0.11	−0.08	−0.11	

TCB: transcutaneous bilirubin; SD: standard deviation.

with considerable accuracy in clinical practice.[12] TCB–TSB discrepancies were approximately 0.84 ± 1.78 mg/dL in a related study.[29] Many studies have demonstrated positive correlations between TCB and TSB in different ethnic groups.[15,29–31] In this study, we only measured TSB when TCB was above 15 mg/dL; for this approach, the correlation between TCB and TSB was acceptable.

The ethnic background of the newborns revealed that all fathers and 98% of the mothers were Taiwanese, and no mother was of Caucasian origin. Furthermore, noneonates born to non-Taiwanese mothers had hyperbilirubinemia.

For newborns who are exclusively breastfed, dehydration may occur due to the relative scarcity of milk during the first week after birth.[32] Physiological body weight loss is common in early life and a high body weight loss may be a predisposing factor for neonatal hyperbilirubinemia.[9] However, we observed no difference in TCB level between newborns with body weight loss (BWL) less than 10% and those with a BWL of greater than or equal to 10% (significant BWL). In this study, only 71 newborns had significant BWL; this number is relatively low compared with that of a previous report.[27] In addition, we supplemented newborns with formula if the BWL was more than 7% unless the family refused, and this practice may explain the low number of neonates with significant BWL.

We analyzed the effects of exclusive breast-feeding, exclusive formula-feeding, and mixed feeding on TCB levels, and observed no difference in the incidence of hyperbilirubinemia among these groups. The result was similar to those of previous studies in Taiwan.[23,27] TSB or TCB levels normally reached a peak on day 4–6 after birth despite feeding patterns in this study, which was also consistent with a related study.[15,23,25,33]

In this study, 20 (4%) newborns had hyperbilirubinemia, most of which occurred between 96 and 120 h after birth, and approximately half of these 20 newborns who developed hyperbilirubinemia had TCB levels above the 95th percentile in the first 72 h of life, indicating those with TCB higher than the 95th percentile were high risk for hyperbilirubinemia. The risk was lower if TCB levels were in the intermediate or lower risk zones. This result supports the necessity of close following up the TCB or TSB levels of high-risk newborns after discharge. Because no raw data were available in Bhutani's study, we could not compare our data with their curves. Currently, there is no TCB nomogram in Taiwan, and the proposed TCB nomogram that measures TCB levels above the 95th percentile after every 12-h interval could be employed as a clinical reference for workups. However, more data are required to confirm whether the nomogram can be applied to Taiwanese newborns.

Our study had several limitations. First, the project was conducted within a single hospital. Compared with studies predicting hyperbilirubinemia according to predischarge bilirubin levels, we could not accurately predict hyperbilirubinemia[22] due to the hospital discharge of a considerable number of newborns after 4 days of age due to the reimbursement policy of Taiwan's National Health Insurance.

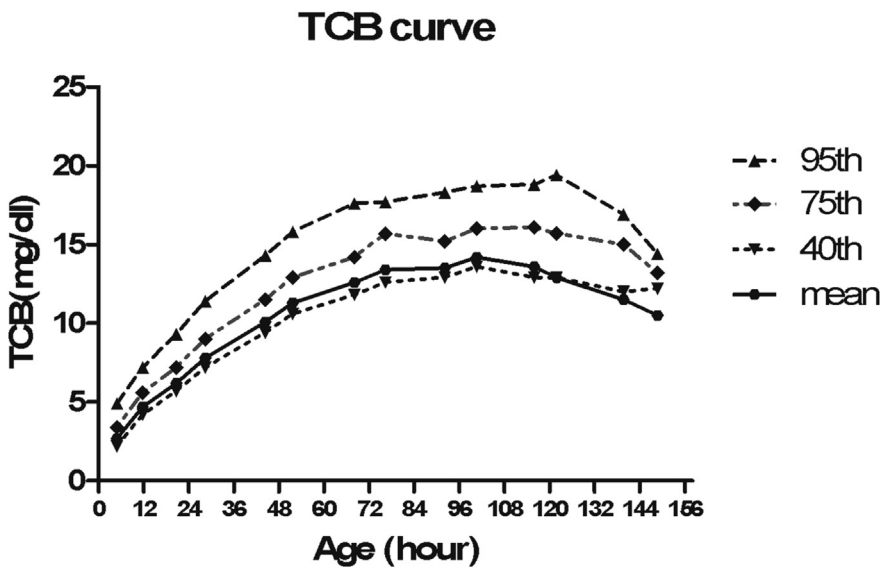

Fig. 1 Transcutaneous bilirubin levels for different risk zones. Values above the 95th percentile are in the high-risk zone. The 75th percentile represents the intermediate risk zone. The low-risk zone is below the 40th percentile.

5. Conclusion

A 12-h TCB nomogram could be a useful reference for workup for hyperbilirubinemia, particularly in newborns with TCB levels above the 95th percentile.

Conflicts of interests

The authors have no conflicts of interest relevant to this article.

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