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Identifying term breast-fed infants at risk of significant hyperbilirubinemia

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BACKGROUND: The aim of this study was to establish a model to identify term breast-fed infants who are at risk of developing significant neonatal hyperbilirubinemia.

METHODS: A prospective study was designed to investigate the effects of birth weight, mode of delivery, cephalohematoma, glucose-6-phosphate dehydrogenase (G6PD) deficiency, predischarge total serum bilirubin, variant uridine 5'diphospho-glucuronosyltransferase 1A1 (*UGT1A1*) gene, and hepatic solute carrier organic anion transporter 1B1 (*SLCO1B1*) gene on significant hyperbilirubinemia in term breast-fed neonates. Significant hyperbilirubinemia was defined as a bilirubin level exceeding the hour-specific phototherapy treatment threshold recommended by the American Academy of Pediatrics in 2004.

RESULTS: Of 240 exclusively breast-fed term neonates, 26 (10.8%) had significant hyperbilirubinemia. The predischarge total serum bilirubin on the third day (odds ratio (OR) = 2.63; 95% confidence interval (CI): 1.87–3.70; $P < 0.001$) and the variant *UGT1A1* gene at nucleotide 211 (OR = 5.00; 95% CI: 1.08–23.03; $P < 0.05$) were significant risk factors. The area under the receiver operating characteristic (ROC) curve of the predictive probability was 0.964 (95% CI: 0.932–0.984; $P < 0.0001$).

CONCLUSION: Combining the total serum bilirubin on the third day and the variant *UGT1A1* gene at nucleotide 211 can predict hyperbilirubinemia well in term breast-fed infants.

Infants who are breast-fed have higher serum bilirubin levels than infants who are formula-fed (1). In recent years, the policy of exclusive breastfeeding and a short hospitalization has been associated with hyperbilirubinemia and kernicterus in term neonates (2). The incidences of severe hyperbilirubinemia and kernicterus are high in Asian infants (3). These data suggest that demographic, environmental, and genetic factors are involved in the development of hyperbilirubinemia in breast-fed neonates. In breast-fed neonates, variants in uridine 5'diphospho-glucuronosyltransferase 1A1 (*UGT1A1*) at nucleotide position 211, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and hepatic solute carrier organic anion transporter 1B1 (*SLCO1B1*) are all known risk factors for hyperbilirubinemia (4–7). Infants who are healthy at discharge may not be exempt from subsequent severe hyperbilirubinemia. Recognition of breast-fed neonates with high risk for significant hyperbilirubinemia is important to avoid bilirubin toxicity. We need to establish a predictive model for significant hyperbilirubinemia when the newborns are discharged from the hospital. We hypothesized that bilirubin levels on the third day, birth weight, sex, mode of delivery, G6PD deficiency, variant *UGT1A1* gene, and *SLCO1B1* gene are risk factors and aimed to set up a diagnostic model to predict significant hyperbilirubinemia in Taiwanese breast-fed neonates.

RESULTS

A total of 240 breast-fed term neonates (123 males and 117 females) were enrolled in this study. Among these 240 neonates, 26 (10.8%, 18 males and 8 females) infants had significant hyperbilirubinemia. The remaining 214 breast-fed neonates (105 males and 109 females) without hyperbilirubinemia served as control infants (**Figure 1**). Birth weight, the percentage of weight loss, gestational age, maternal age, Apgar score, sex, and cephalohematoma were not significantly different between the hyperbilirubinemia and control groups. G6PD deficiency was significantly different between the study and the control groups (**Table 1**). The G6PD-deficient subjects were 1 male and 3 female infants. In the phototherapy group, there were 1 male and 2 female G6PD-deficient babies.

The *UGT1A1* gene (wild-type; variation in promoter; variations at nucleotides 211, 686, 1091, and 1456; and compound heterozygous variation) and the variations at nucleotide 388 and 521 of *SLCO1B1* gene were identified in the hyperbilirubinemia and control groups (**Table 2**). Thirteen of 26 (50%) breast-fed infants with significant hyperbilirubinemia had at least one mutation of the *UGT1A1* gene. The percentage of the neonates having the variant nucleotide 211 was significantly different between the hyperbilirubinemia and control groups (**Table 2**). Eleven of 26 (42.3%) breast-fed infants with hyperbilirubinemia had mutation of nucleotide 211. Variation at nucleotide 211 of *UGT1A1* gene is the most common mutation associated with hyperbilirubinemia.

The results of the multivariate logistic regression model revealed that the total serum bilirubin (TSB) on the third day (odds ratio (OR) = 2.63; 95% confidence interval (CI): 1.87–3.70; $P < 0.001$) and the variant *UGT1A1* gene at nucleotide

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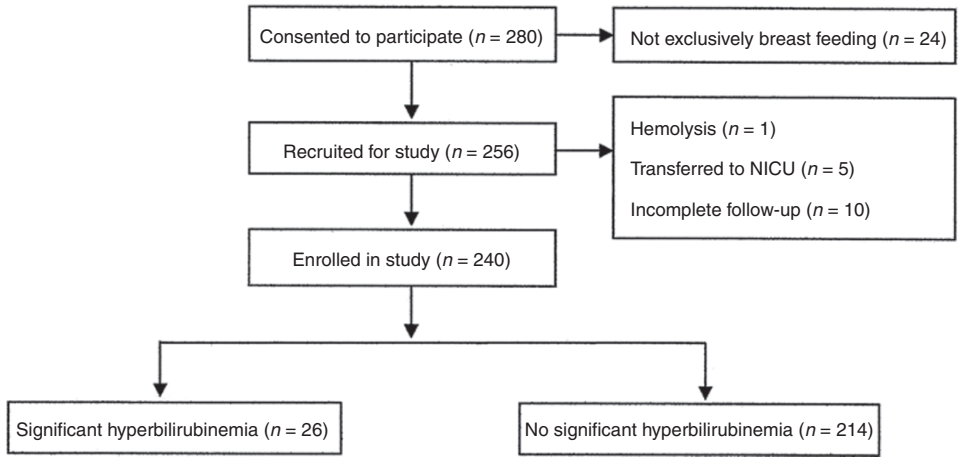

Figure 1. Assembly of study sample. NICU, neonatal intensive care unit.

Table 1. The demographic characteristics of the hyperbilirubinemia and control groups

	Hyperbilirubinemia ($n = 26$)	Control ($n = 214$)
Gestational age (wk)	38.6 ± 1.1	38.9 ± 1.1
Birth weight (g)	3,294.8 ± 314.7	3,224.1 ± 460.2
Weight loss (%)	3.1 ± 4.6	3.5 ± 6.5
Maternal age (y)	30.8 ± 4.9	30.4 ± 4.4
Apgar score (at 5 min)	9.1 ± 0.3	9.1 ± 0.8
Sex (male/female)	18/8	105/109
Cephalohematoma	0	2
Delivery mode (vaginal/cesarean)	20/6	137/77
G6PD deficiency	3*	1*

G6PD, glucose-6-phosphate dehydrogenase.

*$P < 0.05$ for comparison with hyperbilirubinemia and control groups.

Table 2. Variations in *UGT1A1* gene and *SLCO1B1* gene among breast-fed newborn infants with hyperbilirubinemia and controls

	Hyperbilirubinemia ($n = 26$)	Control ($n = 214$)
Variant *UGT1A1* gene		
Wild type	13 (50%)	127 (59.3%)
Promoter	1 (3.8%)	20 (9.3%)
Nucleotide 211 G to A	11 (42.3%)*	51 (23.8%)*
211 G to A/normal	10	45
211 G to A/211 G to A	1	6
Nucleotide 686 C to A	0 (0%)	6 (2.8%)
Nucleotide 1091C to T	0 (0%)	4 (1.9%)
Nucleotide 1456 T to G	0 (0%)	1 (0.5%)
Compound variations	1 (3.8%)	5 (2.3%)
6/7, 1091 C to T/normal	1	0
211 G to A/normal, 686 C to A/normal	0	2
211 G to A/normal, 1091 C to T/normal	0	1
1091C to T, 1456 T to G	0	2
Variant *SLCO1B1* gene		
Nucleotide 388 A to G	11 (42.3%)	80 (37.4%)
Nucleotide 521 T to C	2 (7.7%)	24 (11.2%)
Compound variations	1 (3.8%)	10 (4.7%)
Coexpression of *UGT1A1* and *SLCO1B1*	7 (26.9%)	44 (20.6%)
G6PD deficiency with coexpression of *UGT1A1* and *SLCO1B1*	1 (3.8%)	0 (0%)

*$P < 0.05$ for comparison with hyperbilirubinemia and control groups.

211 (OR = 5.00; 95% CI: 1.08–23.03; $P < 0.05$) were independent factors for significant hyperbilirubinemia in breast-fed neonates (Table 3). The area under the receiver operating characteristic (ROC) curve (AUC) of the predictive probability was 0.964 (95% CI: 0.932–0.984; $P < 0.0001$).

The formula for the predictive probability (P) is as follows:

$$\text{Ln}(P/1 - P) = -16.098 + 0.967 \times \text{TBIL(mg/dl)} + 1.609 \times \text{NT 211}$$
(0 point for no variation, and 1 point for variation)

where Ln is the natural logarithm, TBIL is TSB on the third day, and NT 211 is the variation at nucleotide 211 of *UGT1A1* gene. On the basis of the different TSB values on the third day and the status of variant nucleotide 211 in *UGT1A1* gene, the probability of subsequent hyperbilirubinemia could be given as shown in Table 4. If the goal of screening is to identify all true significant hyperbilirubinemia, then a relatively low probability needs to be used as the positivity criterion. For example, using a probability of 0.35 as the positivity criterion could identify 73% of infants who would develop significant hyperbilirubinemia (i.e., sensitivity = 0.73). More stringent positivity criteria (i.e., higher probability thresholds) may give an improved specificity and a decline in sensitivity (Table 4). The AUC for predicting jaundice in healthy term breast-fed infants was 0.964 (95% CI: 0.932–0.984; $P < 0.0001$). The AUC of predictive probability from the 10-fold cross-validation method was 0.950 (95% CI: 0.915–0.914; $P < 0.0001$). The predictive performance (AUC) from the final model was the same

Table 3. Logistic regression models for variables associated with significant hyperbilirubinemia of breast-fed infants

	UV		MV	
Variables	OR	95% CI	OR	95% CI
Predischarge TSB	2.46**	1.81–3.35	2.63**	1.87–3.70
G6PD deficiency	27.78*	2.79–279.44		
Vaginal delivery	1.87	0.72–4.86		
Variant *UGT1A1* gene				
Wild type	0.69	0.30–1.55		
Promoter	0.39	0.50–3.02		
Nucleotide 211	2.34*	1.01–5.43	5.00*	1.08–23.03
Compound heterozygous	1.67	0.19–14.89		
Variant *SLCO1B1* gene				
Nucleotide 388	1.23	0.54–2.81		
Nucleotide 521	0.66	0.15–2.97		
Compound variations	0.82	0.10–6.65		

CI, confidence interval; G6PD, glucose-6-phosphate dehydrogenase; MV, multivariate analysis; OR, odds ratio; TSB, total serum bilirubin; UV, univariate analysis. * $P < 0.05$; ** $P < 0.001$.

Table 4. Predictive probability of subsequent significant hyperbilirubinemia in breast-fed infants

TBIL (mg/dl)	Variant NT 211	Predictive probability	Sn (%)	Sp (%)	PPV (%)	NPV (%)
16	0	0.35	73.1	96.2	67.9	96.7
	1	0.73	50.0	99.1	86.7	94.2
16.5	0	0.46	65.4	97.7	77.2	95.9
	1	0.81	50.0	100	100	94.3
17	0	0.58	61.5	99.1	88.9	95.5
	1	0.88	38.5	100	100	93.0
17.5	0	0.70	50.0	99.1	86.7	94.2
	1	0.92	30.8	100	100	92.2
18	0	0.79	50.0	100	100	94.3
	1	0.95	26.9	100	100	91.8
18.5	0	0.86	42.3	100	100	93.5
	1	0.97	23.1	100	100	91.5
19	0	0.91	30.8	100	100	92.2
	1	0.98	23.1	100	100	91.5

NPV, negative predictive value; NT 211, nucleotide 211 in *UGT1A1*: 0 points for no variation and 1 point for variation; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; TBIL, total serum bilirubin level at the third day.

as that of 10-fold cross-validation (Z statistic= 2.085; probability of difference between the two AUCs = 0.037) (**Figure 2**).

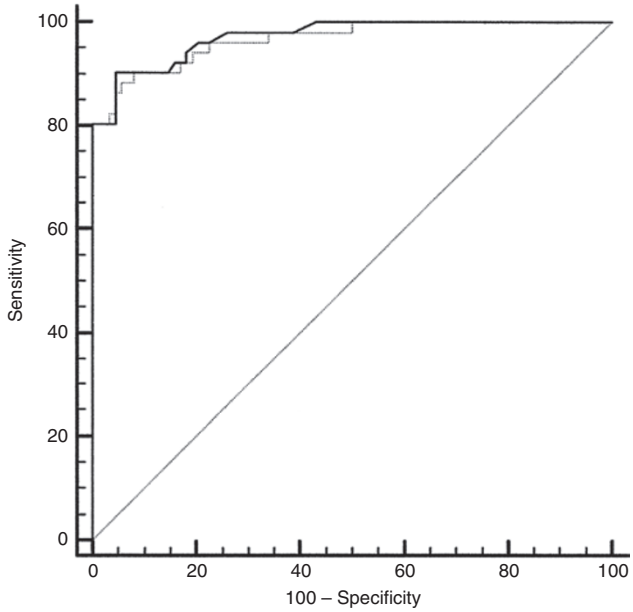

Figure 2. The comparison result of AUC from final model (solid line) was the same as that of 10-fold cross-validation (dashed line). AUC, area under the receiver operating characteristic curve.

DISCUSSION

Numerous studies have reported an association between breastfeeding and an increased incidence and severity of hyperbilirubinemia, both within the first few days of life (8–11). Breast-fed infants in Taiwan presumably have significantly higher bilirubin levels than do breast-fed infants in the United States or in Europe, so that when we use US criteria for initiating phototherapy, ~11% of our breast-fed infants require phototherapy, which is about double the number who receive phototherapy in the United States.

In our study, we found that the combination of TSB values on the third day and variation at nucleotide 211 of the *UGT1A1* gene could predict the risk of significant hyperbilirubinemia. Of note, some risk factors listed in previous reports, including G6PD deficiency, were not found to be significant predictors of hyperbilirubinemia in this study (7). It is not surprising that G6PD deficiency did not enter the model because there were very few babies with this condition. If the infant had a higher predischarge bilirubin level and the 211 G-to-A variation in the *UGT1A1* gene, a clinician could expect that infant to be at risk of developing significant hyperbilirubinemia. Previous studies suggested that the predischarge bilirubin level is a good predictive factor for significant neonatal hyperbilirubinemia (12–18). The effect of gestational age on the risk of subsequent hyperbilirubinemia is well documented and quite profound. The measurement of the predischarge bilirubin is a powerful predictor of subsequent hyperbilirubinemia and, when combined with gestational age, is even more powerful (13–15). However, our subjects were "full-term" healthy babies (gestational age ≥ 37 weeks), and there are only 26 cases in our study, so it is not surprising that we cannot find the relationship between gestational age and the risk of subsequent hyperbilirubinemia. It might be a type II error. In this study, we prospectively built a multivariable logistic regression model to predict development of significant hyperbilirubinemia in healthy term breast-fed infants using clinical risk factors and predischarge bilirubin values. Our model can estimate the risk of subsequent clinically significant hyperbilirubinemia as high

(probability > 0.75), intermediate (0.5 ≤ probability ≤ 0.75), or low (probability < 0.5). We recommend that high-risk neonates return within 48 h of discharge, and that intermediate-risk neonates be scheduled to return between 48 and 72 h of discharge, whereas those with low risk can return to visit after longer intervals. We recommend this risk-based guideline for evaluation, intervention, and follow-up.

The results of our study revealed that variation at nucleotide 211 of the *UGT1A1* gene is the most common mutation associated with hyperbilirubinemia in breast-fed infants. On the other hand, the percentage of $A(TA)_7TAA$ in breast-fed neonates with hyperbilirubinemia was not different from that of healthy control infants, which is different from the previous findings in Caucasians (7,19–21). These ethnic differences were also observed in the Chinese and Japanese populations (22,23). This suggests that breastfeeding may act as an external factor for certain variant genotypes predisposing to the development of hyperbilirubinemia. The breast-fed neonates who carry variant 211 in the *UGT1A1* gene had increased risk of the development of hyperbilirubinemia (7). Our results suggest that if DNA-based test results could be made available before discharge, they may be helpful in predicting the risk of hyperbilirubinemia requiring phototherapy. In our institution, the cost of detection of one "hot spot" mutation site of the *UGT1A1* gene (such as nucleotide 211) is 300 New Taiwan dollars (equal to 10 US dollars). The UGT screening could be a staged testing based on bilirubin level. For example, a term breast-fed infant with a bilirubin level of 16.5 mg/dl on the third day and no variant 211 in the *UGT1A1* gene would have a predictive probability of 0.46, placing this baby in the low-risk group of developing significant hyperbilirubinemia. If an infant who carried variant 211 in the *UGT1A1* gene had a bilirubin level of 16.5 mg/dl on the third day, a clinician could predict that the infant is in the high-risk group, with a significantly higher probability (0.81) of developing significant hyperbilirubinemia after discharge (**Table 4**). Application of this model would predict significant hyperbilirubinemia in Asian breast-fed infants to prevent bilirubin toxicity.

Conclusion

Although bilirubin screening before discharge is very important, it is not sufficient and must be combined with the assessment of clinical risk factors. Combination of the predischarge bilirubin values on the third day and variation at nucleotide 211 of the *UGT1A1* gene can predict the development of significant hyperbilirubinemia accurately.

METHODS

From 1 April 2008 to 31 October 2011, term (≥37 wk gestation) Taiwanese neonates who were exclusively fed breast milk were recruited in Far Eastern Memorial Hospital, New Taipei City. The breastfeeding rate at our hospital is >90%. This study was approved by the institutional research board of the Far Eastern Memorial Hospital, New Taipei, Taiwan. All the parents, either of study group infants or of control group infants, gave informed consent to let their babies participate this study for surveillance of the *UGT1A1* gene and the *SLCO1B1* gene. A prospective cohort study was conducted to investigate the effects of birth weight, sex, mode of delivery, G6PD deficiency, variant *UGT1A1* gene, and *SLCO1B1* gene on hyperbilirubinemia in Taiwanese breast-fed neonates. All term breast-fed babies routinely underwent blood sampling to do newborn screening for inborn errors of metabolism by tandem mass spectrometry. In the meantime, the analyses of TSB levels were obtained on the third day (between 64 and 72 h postnatal life) before they were discharged from the hospital. A return visit was recommended for all neonates. The follow-up total serum bilirubin levels were obtained within 24–48 h after discharge and later if indicated. All neonates received outpatient follow-up until bilirubin levels declined. In our study, blood types (ABO and Rh) and a quantitative spectrophotometric analysis of G6PD were routinely checked to exclude ABO or Rh incompatibility and G6PD deficiency. The pediatricians check babies every day. If the clinician identified any babies who possibly had pathologic jaundice, these babies would receive blood tests before 64 h of life to exclude hemolytic anemia, hypoalbuminemia, G6PD deficiency, sepsis, liver diseases, and hypothyroidism.

Universal G6PD screening has been implemented nationwide in Taiwan since 1987. A quantitative spectrophotometric analysis with the PerkinElmer Neonatal G6PD Kit (ND-1000; PerkinElmer, Boston, MA) was used to diagnose G6PD deficiency. The diagnostic threshold was ≤2.9 U/gHb (24). For the *UGT1A1* and *SLCO1B1* genes, total genomic DNA was isolated from cord blood cells using a blood DNA isolation kit (Maxim Biotech, San Francisco, CA). The PCR restriction fragment length polymorphism method was used to detect the known variant sites $(A(TA)_7TAA$ promoter variant and nucleotides 211, 686, 1091, and 1456) in the *UGT1A1* gene and the two known variants (nucleotides 388 and 521) of the *SLCO1B1* gene in Taiwanese (4,25). The PCR amplification was performed in a DNA thermal cycler (PerkinElmer Cetus, Norwalk, CT) as described previously (4,25,26). If the bilirubin level exceeded the hour-specific phototherapy treatment threshold recommended by the American Academy of Pediatrics in 2004 (27), the clinician made the decision to start phototherapy. These neonates were assessed until bilirubin levels declined.

We analyzed the data with IBM SPSS statistics software, version 19.0 (SPSS, Chicago, IL) and MedCalc software, version 12.3.0.0 (MedCalc, Mariakerke, Belgium). The clinical risk factors were examined using *t*-tests for continuous predictors and Pearson χ^2 and Fisher exact tests for categorical predictors. A forward stepwise logistic regression analysis was performed to identify risk factors for hyperbilirubinemia in healthy term breast-fed infants. ORs and 95% CIs for various risk factors were estimated with multiple logistic regression models. A P value <0.05 or a 95% CI for OR >1.0 was defined as statistically significant. Variables were entered into the model and removed at a cutoff P value of 0.05. We plotted a ROC curve and estimated the AUC to assess the predictive accuracy of this final model. The performance of this final model was evaluated using a 10-fold cross-validation method. All 240 breast-fed neonates were randomly divided into 10 subsets of almost equal size. Nine subsets were used for training, and the remaining subset was used for testing. We ran this procedure 10 times; each time we picked a different subset for testing and the nine remaining subsets for training. Therefore, we acquired a predictive probability for every observation after testing. Finally, the ROC curve was obtained by the probability. The AUC from the final model and 10-fold cross-validation method were compared.

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