Model to Predict Hyperbilirubinemia in Healthy Term and Near-Term Newborns with Exclusive Breast Feeding


Department of Pediatrics, Taipei City Hospital, Heping FuYou Branch, Taipei, Taiwan
Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
Molecular and Genomic Epidemiology Center, China Medical University Hospital, Taichung, Taiwan
Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
Department of Pediatrics, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
Department of Pediatrics, Cardinal Tien Hospital, Yung Ho Branch, Taiwan

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Background: The aim of this study was to identify high-risk newborns who will subsequently develop significant hyperbilirubinemia Days 4 to 10 of life by using the clinical data from the first three days of life.

Methods: We retrospectively collected exclusively breastfeeding healthy term and near-term newborns born in our nursery between May 1, 2002, to June 30, 2005. Clinical data, including serum bilirubin were collected and the significant predictors were identified. Bilirubin level ≥15mg/dL during Days 4 to 10 of life was defined as significant hyperbilirubinemia. A prediction model to predict subsequent hyperbilirubinemia was established. This model was externally validated in another group of newborns who were enrolled by the same criteria to test its discrimination capability.

Results: Totally, 1979 neonates were collected and 1208 cases were excluded by our exclusion criteria. Finally, 771 newborns were enrolled and 182 (23.6%) cases developed significant hyperbilirubinemia during Days 4 to 10 of life. In the logistic regression analysis, gestational age, maximal body weight loss percentage, and peak bilirubin level during the first 72 hours of life were significantly associated with subsequent hyperbilirubinemia. A prediction model was derived with the area under receiver operating characteristic (AUROC) curve of 0.788.
1. Introduction

Neonatal hyperbilirubinemia is the leading cause of readmission of newborns in their first week of life. After implementation of the breastfeeding promotion in maternal facilities program to promote exclusive breastfeeding in Taiwan, the incidence of neonatal hyperbilirubinemia increased significantly. Severe neonatal hyperbilirubinemia can occur without apparent reason in healthy breastfeeding term infants and some develop kernicterus. The American Academy of Pediatrics (AAP) clinical practice guideline recommends that all newborn healthy breastfed term infants and some develop ker-
nicterus. The American Academy of Pediatrics (AAP) clinical practice guideline recommends that all newborn infants should be assessed before discharge for the risk of developing significant neonatal hyperbilirubinemia. The peak serum bilirubin level usually occurs during Days 4 to 6 of life. Dalal et al found that single transcutaneous bilirubin measurements at 30–48 hours can be used to predict subsequent hyperbilirubinemia at 5 days old; however, the case number is relatively small. The aim of this study was to establish a predicting model by using clinical data from the first 3 days of life for prediction of subsequent significant hyperbilirubinemia in exclusively breastfed term and late preterm neonates.

2. Methods

2.1. Study group

We retrospectively collected exclusively breastfeeding healthy term and late preterm newborns born in our nursery between May 1, 2002, and June 30, 2005. Infants who weighed above 2500 g at birth with a gestational age of at least 35 weeks were eligible for the study. Those neonates who had evidence of hemolysis, Glucose-6-phosphate dehydrogenase deficiency, cephalohematoma, congenital infection, perinatal asphyxia, or any major organ anomalies were excluded. Neonates who developed early hyperbilirubinemia within 72 hours of age were also excluded. Serum bilirubin was checked routinely at 3 days old or if icteric skin appearance was identified. All neonates with serum bilirubin above 11 mg/dl were scheduled for routine outpatient follow-up 2 days later.

Clinical data, including gestational age, sex, birth mode, Apgar scores, feeding (formula or breast milk), birth body weight, daily body weight, maximal body weight loss, daily stool passage times, daily urine output times, and total serum bilirubin (TSB) were collected from review of the medical records. Hyperbilirubinemia during Days 4 to 10 of life was defined as serum bilirubin level ≥15mg/dL.

2.2. Statistical analysis

Exhaustive review of clinical risk factors and univariate logistic regression analysis with stepwise variable selection were performed to identify significant predictors among the collected clinical data. Then multivariate logistic regression was performed to establish predicting model for subsequent hyperbilirubinemia. The area under receiver operating characteristic (AUROC) curve was calculated for the measurement of diagnostic discrimination.

2.3. Model validation

This risk prediction model was externally validated in another study of newborns who were born in our nursery between January 1, 2009, and April 30, 2009. They were enrolled by the same inclusion and exclusion criteria. Model validation was performed in this study to test the discrimination capability of our prediction model.

3. Results

During the study period, a total of 1979 neonates were born, of whom 310 neonates were excluded because they met our exclusion criteria. In addition, a further 795 infants were excluded from this study because they were not exclusively breastfed. The remaining 874 infants were further analyzed. Among them, 67 neonates who developed significant hyperbilirubinemia within 72 hours of life and 36 infants lacked TSB data within 72 hours of life. Finally, 771 exclusively breastfeeding neonates were enrolled and 182 newborns (23.6%) developed subsequent significant hyperbilirubinemia during Days 4 to 10 of life (Figure 1).

In the univariate logistic regression analysis, gestational age, maximal body weight loss percentage and bilirubin level during first 72 hours of life were significantly associated with subsequent hyperbilirubinemia (Table 1). In the multivariate logistic regression analysis, the multivariate-adjusted odds ratio (95% confidence interval) of gestational age, maximal body weight loss percentage, and peak bilirubin level during the first 72 hours of life were 0.78 (0.66–0.91), 1.22 (1.11–1.35), and 1.58 (1.44–1.74), respectively (Table 2). Therefore, the estimated probability of developing subsequent significant hyperbilirubinemia (i.e., the predicted
value, denoted as \( \hat{P} \), could be calculated using the following equation:

\[
\hat{P} = \frac{e^{2.1016 - 0.2510 \times GA + 0.1993 \times \text{maxloss} + 0.4584 \times \text{peakbil}}}{1 + e^{2.1016 - 0.2510 \times GA + 0.1993 \times \text{maxloss} + 0.4584 \times \text{peakbil}}},
\]

where GA is gestational age in weeks, maxloss\% is the maximal body weight loss within 72 hours of life in percentage, and peakbil is the peak TSB level within 72 hours of life. The AUROC curve showed that this prediction model incorporating gestational, maximal body weight loss percentage, and peak bilirubin level during the first 72 hours of life has better diagnostic discrimination (AUROC = 0.788) as compared with using bilirubin level before discharge only (AUROC = 0.766; Figure 2A). By using the predicted probability of 0.177 as the cut-off point, the sensitivity was 90% and specificity was 66.0%.

**Table 1** Gestational age, maximal body weight loss percentage, and serum bilirubin level were strongly associated with subsequent significant hyperbilirubinemia in univariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Crude OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex of baby</td>
<td>1.16 (0.84–1.60)</td>
</tr>
<tr>
<td>GA</td>
<td>0.74 (0.64–0.85)</td>
</tr>
<tr>
<td>BBW, per 100gm</td>
<td>1.01 (0.97–1.06)</td>
</tr>
<tr>
<td>Max BW loss (%)</td>
<td>1.16 (1.07–1.26)</td>
</tr>
<tr>
<td>Bil24h</td>
<td>1.48 (1.26–1.73)</td>
</tr>
<tr>
<td>Bil48h</td>
<td>1.74 (1.51–2.00)</td>
</tr>
<tr>
<td>Bil72h</td>
<td>1.85 (1.61–2.11)</td>
</tr>
<tr>
<td>Peak bilirubin before 72 hrs</td>
<td>1.57 (1.44–1.72)</td>
</tr>
</tbody>
</table>

Bil24h = serum bilirubin level at 24 hours of age; BBW = birth body weight; CI = confidence interval; GA = gestational age; Max BW loss = maximal body weight loss; OR = odds ratio.

**Table 2** In multivariate logistic regression, 3 significant predictors were used to establish the prediction model. The estimated probability (\( \hat{P} \)) can be calculated by the functional equation.

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.1016</td>
<td>0.5182</td>
</tr>
<tr>
<td>GA</td>
<td>-0.2510</td>
<td>0.78 (0.66–0.91)</td>
</tr>
<tr>
<td>Max BW loss (%)</td>
<td>0.1993</td>
<td>1.22 (1.11–1.35)</td>
</tr>
<tr>
<td>Peak Bil before 72 h</td>
<td>0.4584</td>
<td>1.58 (1.44–1.74)</td>
</tr>
</tbody>
</table>

Prediction equation:

\[
\hat{P} = \frac{e^{2.1016 - 0.2510 \times GA + 0.1993 \times \text{maxloss} + 0.4584 \times \text{peakbil}}}{1 + e^{2.1016 - 0.2510 \times GA + 0.1993 \times \text{maxloss} + 0.4584 \times \text{peakbil}}},
\]

CI = confidence interval; GA = gestational age; Max BW loss = maximal body weight loss; OR = odds ratio.
From January 1, 2009, to April 30, 2009, we retrospectively collected 760 exclusively breastfeeding healthy term and near-term newborns who were born in our nursery by the same criteria. A total of 144 neonates were excluded by our exclusion criteria and 333 further infants were excluded because they were not exclusively breast fed, leaving a total of 283 infants. Among them, 73 neonates who developed significant hyperbilirubinemia within 72 hours of life received phototherapy or blood exchange therapy before discharge. One baby lacked TSB data within 72 hours of life. Finally, 209 exclusive breastfeeding newborns were enrolled and 50 newborns (23.9%) developed subsequent significant hyperbilirubinemia during Days 4 to 10 of life (Figure 1). Applying the derived model to this separate population ($N = 209$) showed similar good discrimination capability (AUROC $= 0.8340$; Figure 2B).

4. Discussion

Bilirubin level obtained before discharge can be plotted on an hour-specific bilirubin nomogram to calculate an infant’s bilirubin percentile with respect to age in hours. Although the predischarge bilirubin “risk zone” has been shown to be a good predictor of subsequent risk of hyperbilirubinemia, clinical risk factors are known to modify the course of neonatal hyperbilirubinemia. Some studies have identified that some clinical risk factors significantly improve prediction of subsequent hyperbilirubinemia compared with serum bilirubin levels alone. Some studies used clinical risk factors associated with bilirubin screen as risk indexes for predicting hyperbilirubinemia in infants. However, risk indexes of most studies were not validated in a group of infants separated from the group in which it derived, which may cause overestimation of its discrimination. Here, we provide a prediction model: a prediction equation in which the estimation of the risk of subsequent neonatal hyperbilirubinemia in each individual infant could be possible and we showed its good discrimination capability.

Gestational age was identified as a strong predictor of significant hyperbilirubinemia. Other clinical factors did not increase the predictive accuracy, which was compatible with a previous study. Some reported risk factors, such as blood type, positive direct Coombs test, or sibling history of phototherapy were not taken into analysis because they were not routinely checked in general practice. It was our aim to establish a friendly practical prediction model, so only common clinical parameters were used. Maximal body weight loss percentage was identified as a good new predictor in our study as well as previous reports. Inadequate calorie intake and dehydration were known to be strongly associated with neonatal hyperbilirubinemia. Maximal body weight loss percentage could reflect the effect of inadequate feeding and dehydration.

In the univariate logistic regression, we found that TSB at Days 1 (24 hours), 2 (48 hours), and 3 (72 hours) of life or peak value were all significantly associated with subsequent significant hyperbilirubinemia (all with $p$ value $< 0.0001$). All TSB levels, checked at any time within the first 3 days of life, were strongly associated with hyperbilirubinemia. This result further confirmed previous studies to the effect that TSB levels were the strongest predictor for subsequent hyperbilirubinemia. Because first- and second day bilirubin levels were only checked when icteric appearance was noted by clinical judgments, the predicting model was derived according to Day 3 TSB value or peak TSB value. In multivariate logistic regression and the calculated AUROC, model with peak TBS level showed the best predictive accuracy. Although the peak TSB usually occurred on the third day, the earlier elevated TSB has some interference on subsequent significant hyperbilirubinemia. Since this is a retrospective study, one limitation is that the peak bilirubin level may have been influenced by the timing of blood sampling. If we measure the bilirubin levels at a specific time point, then we can obtain the real peak bilirubin level for each case, which may improve the accuracy of our prediction model. However, for clinical practice, measuring the bilirubin level at a specific time point for individual cases is not practicable in most hospitals. Therefore, to use the peak bilirubin levels before 72 hours may be an appropriate alternative to predict subsequent hyperbilirubinemia that has been validated in two different data sets.
In the era of universal bilirubin screen, the incidence of severe hyperbilirubinemia has decreased but there was an increase in the use of phototherapy.\textsuperscript{18,19} This is, at least in part, due to an early discharge strategy. By risk calculation and stratification, individualized follow-up programs and management plans are possible. In our predicting model, by using the predicted probability of 0.177 as the cut-off point, the sensitivity was 90\% and specificity was 66.0\%. By using this prediction model, we expect that we can identify the high-risk infants in order to arrange more frequent outpatient department (OPD) follow-up and family education to prevent subsequent hyperbilirubinemia. However, further study is required to prove this.

5. Conclusion

Gestational age, maximal body weight loss percentage, and peak TSB level during the first 3 days of life have the highest predictive value of subsequent significant hyperbilirubinemia. We provide a prediction model to calculate the risk of each newborn, and the external validation proves the discrimination capability of this tool. Therefore, we hope that the individualized follow-up plan and management can be achieved by using this prediction model so as to decrease the incidence of subsequent hyperbilirubinemia that requires phototherapy.

References