Original Article

Development and validation of a prediction model for rebound hyperbilirubinemia: a Chinese neonatal cohort study

Huiyi Li[1#], Xihua Huang[1#], Zhenyu Liang[1], Haijian Liang[1], Si He[1], Li Tang[1,2]

[1]Department of Neonatology, the Affiliated Guangdong Second Provincial General Hospital of Jinan University, Guangzhou, China; [2]Department of Nursing, the Affiliated Guangdong Second Provincial General Hospital of Jinan University, Guangzhou, China

Contributions: (I) Conception and design: L Tang, H Li, X Huang; (II) Administrative support: L Tang; (III) Provision of study materials or patients: H Li, X Huang; (IV) Collection and assembly of data: H Li, X Huang, H Liang, S He; (V) Data analysis and interpretation: H Li, X Huang, Z Liang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Li Tang, MM. Department of Neonatology, the Affiliated Guangdong Second Provincial General Hospital of Jinan University, No. 466 Xingang Middle Road, Guangzhou 510317, China; Department of Nursing, the Affiliated Guangdong Second Provincial General Hospital of Jinan University, No. 466 Xingang Middle Road, Guangzhou 510317, China. Email: ltang_gzsehos@hotmail.com.

Background: Rebound hyperbilirubinemia (HBB) is still present in as high as 10% of newborn babies. However, the applicability of established prediction models for rebound HBB to Chinese newborns is unclear. This study aimed to establish a model to predict HBB rebound after phototherapy among Chinese neonates.

Methods: A retrospective cohort study was conducted on 1,035 HBB infants receiving phototherapy. Rebound HBB was defined as total serum bilirubin (TSB) returning to or above the American Academy of Pediatrics (AAP) phototherapy threshold within 72 hours after the end of phototherapy. The predictive effects of previously published two- and three-variable scores were verified. Neonates were randomly assigned in a 6:4 ratio to the training (n=621) group and the testing (n=414) group. All variables in the training set were used to select predictors by least absolute shrinkage and selection operator (LASSO) regression analysis. The internal validation of the prediction model was performed using the testing set. The model's predictive performance was evaluated by area under the curve (AUC), accuracy, sensitivity, and specificity, each with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) and calibration curves were constructed to evaluate the discrimination ability and fitting effect of the prediction model, respectively.

Results: Rebound HBB was observed in 210 patients (20.3%). The AUC for the two- and three-variable scores were 0.498 (95% CI: 0.455–0.540) and 0.498 (95% CI: 0.457–0.540), respectively. Predictive factors for the risk of rebound HBB included formula feeding (>3 times/day), standard phototherapy irradiation time, TSB levels and age at termination of phototherapy, neonatal weight, and differences between TSB levels at the phototherapy termination and phototherapy threshold. The prediction model's AUC was 0.935 (95% CI: 0.911–0.958), the sensitivity was 0.880 (95% CI: 0.809–0.950), the specificity was 0.831 (95% CI: 0.790–0.871), and the accuracy was 0.841 (95% CI: 0.805–0.876).

Conclusions: The established model performed well in predicting rebound risk among Chinese infants with HBB, which may be beneficial in treating and managing HBB in infants.

Keywords: Hyperbilirubinemia (HBB); rebound; prediction model; Chinese neonates

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Introduction

Neonatal hyperbilirubinemia (HBB) is a prevalent disease, with jaundice occurring in around 50% of full-term and 80% of preterm babies within the first week of life (1). In most cases, HBB is a benign self-limiting disease. However, severe cases of HBB occasionally occurs, which may be related to irreversible brain damage, particularly in premature babies (2,3). Elevated levels of bilirubin can result in specifically encephalopathy, kernicterus, neurotoxicity, and even permanent neurodevelopmental disorders (4-6). HBB is the primary cause of re-hospitalization and the seventh leading cause of death among newborns globally within the first week of life (7,8).

The guidelines of the American Academy of Pediatrics (AAP) and Canadian Pediatric Society (CPS) recommend screening all newborns for total serum bilirubin (TSB) or transcutaneous bilirubin within 72 hours of birth or sooner if they exhibit clinical symptoms of jaundice (9,10). Patients with moderate or severe elevated levels of bilirubin should receive immediate treatment in order to reduce circulating bilirubin concentration and prevent from long-term nervous system complications. Phototherapy is a method with safety and efficacy for the treatment of neonatal unconjugated HBB (11). Treatment is initiated based on the infant's age, gestational age (GA), and serum bilirubin levels. Although intensive phototherapy therapy can promote clearance, rebound HBB is still present in as high as 10% of newborn babies (9). Chang *et al.* (12,13) reported bi-variate and tri-variate risk prediction models for rebound HBB in newborns, with the area under the curve (AUC) of 0.881 and 0.876, respectively. The GA <38 weeks, age at phototherapy initiation, and the difference between the treatment threshold and the TSB levels at the end of phototherapy were associated with the risk of rebound HBB (13). However, these models have not been externally validated. To the best of our knowledge, it is uncertain whether these models can be applied to Chinese newborns. It is necessary to evaluate the risk of rebound after phototherapy for neonatal HBB in domestic clinical practice and to identify predictive factors to fill in the gaps in related fields in China.

Herein, a model was developed to predict the risk of rebounding HBB after phototherapy in Chinese neonates, which helps clinicians identify neonates in need of active treatment and frequent early follow-up, improve the therapeutic effect of the first phototherapy, and reduce the hospitalization duration of neonates. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-21/rc).

Highlight box

Key findings

- The established model performed well in predicting rebound risk among Chinese infants with hyperbilirubinemia (HBB).

What is known and what is new?

- The applicability of established prediction models for rebound HBB to Chinese newborns is unclear.
- A model was developed to predict the risk of rebounding HBB after phototherapy in Chinese neonates.

What is the implication, and what should change now?

- The prediction model may help clinicians identify neonates in need of active treatment and frequent early follow-up, improve the therapeutic effect of the first phototherapy, and reduce the hospitalization duration of neonates.

Methods

Study design and population

This study was conducted in the Department of Neonatology of the Affiliated Guangdong Second Provincial General Hospital of Jinan University. All infants with HBB who underwent phototherapy were eligible for enrolment. Groups were divided according to whether rebound occurred within 72 hours after phototherapy termination, and infants were classified into rebound and non-rebound groups. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This current study was supported by the Institutional Review Board (IRB) of the Affiliated Guangdong Second Provincial General Hospital of Jinan University (No. 2022-KY-KZ-139-02), and informed consent for this retrospective analysis was waived by the Affiliated Guangdong Second Provincial General Hospital of Jinan University.

Inclusion and exclusion criteria

Inclusion criteria: (I) GAs ≥35 weeks; (II) newborns with HBB [levels of serum TSB exceeding 95th percentile, measured in hours (14)]; (III) newborns who met the phototherapy indications and received the first phototherapy within 14 days after birth; (IV) newborns who reached the

termination indication at the end of phototherapy; and (V) newborns with complete clinical data.

Exclusion criteria: (I) infants who had ≥2 mg/dL TSB levels before or during phototherapy; (II) newborns with congenital malformation or chromosomal abnormality; and (III) neonates with organic diseases such as congenital biliary tract disease, hepatitis B surface antigen positivity, or other liver diseases caused by HBB.

Study variables

Potential predictors

Clinical information and laboratory examination data of infants were collected before treatment, including sex (male and female), GA (weeks), birth length (cm), blood type (A, B, O, AB), birth weight (cm), direct antiglobulin test (DAT, positive and negative), glucose 6-phosphate dehydrogenase (G6PD), and hemolysis (homologous immune hemolysis, G6PD deficiency, none, and homologous immune hemolysis with G6PD deficiency). The delivery modes (vaginal delivery and cesarean section) and single/multiple births of the mothers were also recorded.

At the beginning of phototherapy, levels of TSB at the end of phototherapy, differences between levels of TSB when phototherapy started and phototherapy threshold, differences between levels of TSB at the termination of phototherapy and threshold of phototherapy, feeding patterns during phototherapy, age at phototherapy termination, phototherapy strength, irradiation time (standard and intense phototherapy), and feeding patterns during phototherapy (exclusive breastfeeding, 1–3 times/day, and >3 times/day formula feeding) were noted. The Vitros BuBc Neonatal Bilirubin method (Ortho Clinical Diagnostics, Raritan, NJ, USA) was used to determine the levels of TSB.

Outcome variables

The follow-up included whether and when HBB rebound occurred and the levels of TSB. The endpoint of follow-up was 72 hours after the termination of phototherapy. Rebound HBB was the primary outcome, which was defined as TSB returning to or above the AAP phototherapy threshold within 72 hours after the end of phototherapy. A time frame of 72 hours was selected because it can reasonably be attributed to the same HBB episode.

Prediction model development and validation

All HBB infants were randomly assigned into training group and testing group according to 6:4. All variables in the training set were used to select predictors using least absolute shrinkage and selection operator (LASSO) regression analysis. Six screened predictors were utilized to conduct the prediction model for the rebound HBB risk. Variable importance was analyzed using a random forest analysis. The prediction model underwent internal validation using the testing group. The model's predictive performance was evaluated using the AUC, sensitivity, accuracy, and specificity, along with 95% confidence intervals (CIs). The discrimination ability and fitting effect of the prediction model were evaluated by drawing receiver operating characteristic (ROC) curves and calibration curves, respectively.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of the measured data. The measurement data for the normal distribution were measured using an independent samples *t*-test and are presented as mean ± standard deviation. The measurement data that did not follow a normal distribution were analyzed by the Mann-Whitney *U* rank-sum test. The results were described as median and quartile [mean (Q1, Q3)]. The data of enumeration type were analyzed using either the chi-squared test or Fisher's test and described by case number and constituent ratio [n (%)]. The two-sided $P<0.05$ was considered as statistical differences. Multiple interpolations were performed for missing values using R mice, and data before and after interpolation were compared between groups using sensitivity analysis (Table S1). ROC and calibration curves were generated using Python 3.8 software from the Python Software Foundation, Delaware, USA. The remaining analyses were performed using SAS software version 9.4 from SAS Institute Inc., in Cary, NC, USA.

Results

External validation

Our data were used to verify the predictive effect of previously published scores (10,11), and the results are shown in *Table 1*. The AUC of model I (two-variable score) was 0.498 (95% CI: 0.455–0.540), the sensitivity was 0.343 (95% CI: 0.279–0.407), and the specificity was 0.629 (95% CI: 0.596–0.662). The AUC of model II (three-variable score) was 0.498 (95% CI: 0.457–0.540), the sensitivity was 0.176 (95% CI: 0.125–0.228), and the specificity was

0.739 (95% CI: 0.709–0.769). The above findings indicated published prediction models are not suitable for predicting HBB rebound in Chinese newborns.

Evaluation of the balance between training set and test set

Totally 1,035 infants with HBB were assigned randomly into training set (n=621) and testing set (n=414). There was no statistical difference in the characteristics of infants between the training and test groups in any variable (all P>0.05, Table S2).

Characteristics of HBB infants in training set

Infants in the training set were split into rebound (n=127) and non-rebound (n=494) groups according to whether rebound occurred within 72 hours after phototherapy termination. The characteristics of infants with HBB in the training set can be seen in *Table 2*. No statistical differences were found in birth length (49.55 *vs.* 50.17 cm), birth weight (2,999.13 *vs.* 3,116.73 g), DAT positive (9.72% *vs.* 25.98%), G6PD (1.91 *vs.* 1.99), hemolysis, age at phototherapy termination time (9.00 *vs.* 7.00 days), standard phototherapy irradiation time (5.00 *vs.* 3.00 hours), and feeding patterns during phototherapy between non-rebound group and rebound group.

Prediction model development and validation

Figure 1 shows all of the variables in training set selected for LASSO regression analysis. Formula feeding (>3 times/day), standard phototherapy irradiation time, TSB levels at phototherapy termination, age at phototherapy termination, neonatal weight, and differences between the levels of TSB at the end of phototherapy and the threshold of phototherapy were predictive factors for the risk of rebound HBB. The variable importance of these predictors is shown in *Figure 2*. *Table 3* shows the established model's predictive performance. The AUC was 0.942 (95% CI: 0.924–0.960), the sensitivity was 0.898 (95% CI: 0.845–

Table 1 Validation of the previous models

Previous models	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Accuracy (95% CI)
Model I	0.343 (0.279–0.407)	0.629 (0.596–0.662)	0.498 (0.455–0.540)	0.571 (0.540–0.601)
Model II	0.176 (0.125–0.228)	0.739 (0.709–0.769)	0.498 (0.457–0.540)	0.625 (0.595–0.655)

Model I: two-variable score; model II: three-variable score. CI, confidence internal; AUC, area under the curve.

Table 2 Characteristics of HBB infants in the training set

Variables	Total (n=621)	Non-rebound (n=494)	Rebound (n=127)	Statistics	P
Gender				χ^2=1.398	0.24
Male	337 (54.27)	274 (55.47)	63 (49.61)		
Female	284 (45.73)	220 (44.53)	64 (50.39)		
GA (weeks)	37.92±1.43	37.95±1.43	37.77±1.40	*t*=1.28	0.20
Birth length (cm)	49.67±2.48	49.55±2.59	50.17±1.92	*t*=−3.04	0.003
Birth weight (g)	3,023.18±521.09	2,999.13±525.86	3,116.73±493.00	*t*=−2.28	0.02
Blood type				χ^2=4.379	0.22
A	194 (31.24)	154 (31.17)	40 (31.50)		
AB	38 (6.12)	28 (5.67)	10 (7.87)		
B	170 (27.38)	129 (26.11)	41 (32.28)		
O	219 (35.27)	183 (37.04)	36 (28.35)		

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Total (n=621)	Non-rebound (n=494)	Rebound (n=127)	Statistics	P
DAT				χ^2=23.572	<0.001
Negative	540 (86.96)	446 (90.28)	94 (74.02)		
Positive	81 (13.04)	48 (9.72)	33 (25.98)		
G6PD ratio	1.93 (1.66, 2.06)	1.91 (1.69, 2.02)	1.99 (1.45, 2.23)	*Z*=2.284	0.02
Hemolysis				χ^2=29.752	<0.001
Homologous immune hemolysis	58 (9.34)	35 (7.10)	23 (18.11)		
G6PD deficiency	46 (7.41)	32 (6.48)	14 (11.02)		
None	504 (81.16)	422 (85.43)	82 (64.57)		
Homologous immune hemolysis with G6PD deficiency	13 (2.09)	5 (1.01)	8 (6.30)		
Age at the onset of icterus (days)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	*Z*=−1.682	0.09
Age at the beginning of phototherapy (days)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	*Z*=0.959	0.34
TSB levels when phototherapy started (mg/dL)	309.74±75.01	307.80±79.90	317.29±51.35	*t*=−1.64	0.10
ΔTSB[†]	−3.72 (−6.62, −1.35)	−3.95 (−6.83, −1.12)	−3.43 (−5.73, −1.39)	*Z*=0.936	0.35
Age at phototherapy termination (days)	8.00 (7.00, 11.00)	9.00 (7.00, 11.00)	7.00 (5.00, 10.00)	*Z*=−5.075	<0.001
TSB levels at phototherapy termination (mg/dL)	145.60 (118.30, 169.30)	143.70 (114.90, 171.40)	152.00 (132.20, 165.20)	*Z*=1.679	0.09
ΔTSB[‡]	8.51 (6.67, 10.44)	8.70 (6.67, 10.64)	8.34 (6.60, 9.69)	*Z*=−1.551	0.12
Phototherapy strength				χ^2=0.914	0.63
Standard phototherapy	557 (89.69)	445 (90.08)	112 (88.19)		
Intense phototherapy	9 (1.45)	6 (1.21)	3 (2.36)		
Intense phototherapy followed by standard phototherapy	55 (8.86)	43 (8.70)	12 (9.45)		
Irradiation time (hours)					
Standard phototherapy	5.00 (3.00, 6.00)	5.00 (4.00, 7.00)	3.00 (2.00, 5.00)	*Z*=−6.877	<0.001
Intense phototherapy	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	*Z*=0.880	0.38
Feeding patterns during phototherapy				χ^2=168.601	<0.001
Exclusive breastfeeding	306 (49.28)	291 (58.91)	15 (11.81)		
1–3 times/day formula feedings	81 (13.04)	80 (16.19)	1 (0.79)		
>3 times/day formula feedings	234 (37.68)	123 (24.90)	111 (87.40)		

Data are presented as n (%), mean ± SD, or M (Q1, Q3). [†], differences between TSB level when phototherapy started and phototherapy threshold; [‡], differences between TSB levels at phototherapy termination and phototherapy threshold. HBB, hyperbilirubinemia; GA, gestational age; DAT, direct antiglobulin test; G6PD, glucose 6-phosphate dehydrogenase; TSB, total serum bilirubin; SD, standard deviation; M, median; Q1, 1st quantile; Q3, 3rd quantile.

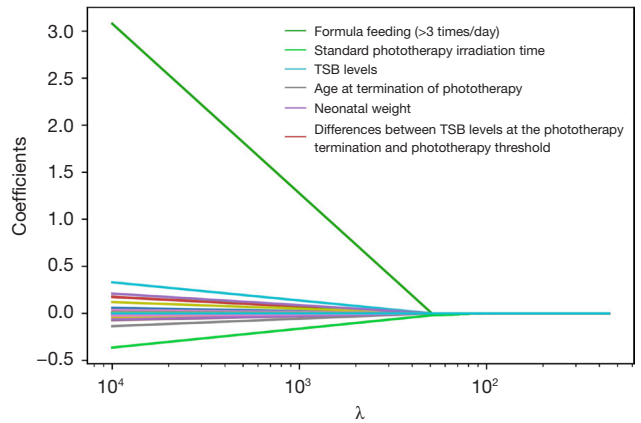

Figure 1 The process of the predictive factor screening. TSB, total serum bilirubin.

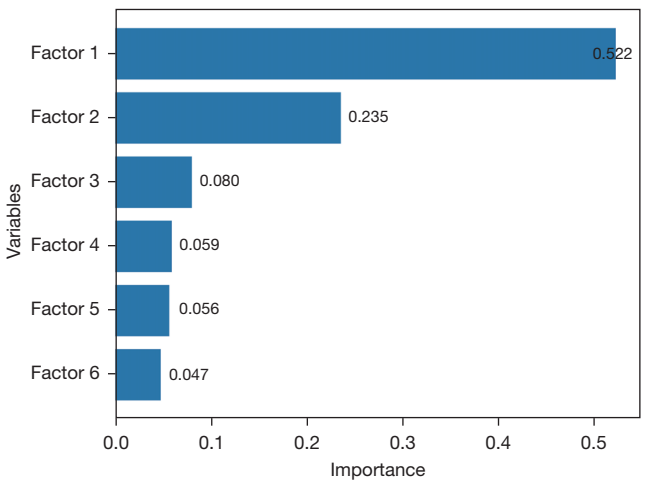

Figure 2 The variable importance of the predictors. Factor 1: formula feedings (>3 times/day); factor 2: standard phototherapy irradiation time; factor 3: TSB levels at phototherapy termination; factor 4: age at phototherapy termination; factor 5: neonatal weight; factor 6: differences between TSB levels at phototherapy termination and phototherapy threshold. TSB, total serum bilirubin.

0.950), the specificity was 0.848 (95% CI: 0.817–0.880), and the accuracy was 0.858 (95% CI: 0.831–0.886) in the training set.

The testing set was used to perform internal validation of the developed model, and the AUC was 0.935 (95% CI: 0.911–0.958), the sensitivity was 0.880 (95% CI: 0.809–0.950), the specificity was 0.831 (95% CI: 0.790–0.871), and the accuracy was 0.841 (95% CI: 0.805–0.876). *Figure 3* shows the ROC curves and fitting effect of the model.

Predictive performance of the model in premature and full-term neonates

Our model was evaluated for performance in premature and full-term infants (*Table 4*). Our model among premature infants predicted the risk of rebound HBB with an AUC of 0.917 (95% CI: 0.841–0.992), a sensitivity of 0.750 (95% CI: 0.505–0.995), a specificity of 0.765 (95% CI: 0.664–0.866), and an accuracy of 0.762 (95% CI: 0.669–0.856). The AUC value in full-term delivery infants was 0.936 (95% CI: 0.911–0.961), the sensitivity was 0.901 (95% CI: 0.832–0.971), the specificity was 0.848 (95% CI: 0.805–0.891), and the accuracy was 0.859 (95% CI: 0.822–0.897).

Discussion

The current study assessed the clinical application of bi-variate and tri-variate predictive scores in Chang *et al.* (12,13) for rebound HBB in Chinese newborns receiving phototherapy while in hospital. However, the results showed that the AUCs of the bi-variate and tri-variate prediction scores (PSs) in our cohort were 0.498 and 0.498, respectively, indicating that the external applicability of these PS needs further exploration and cautious interpretation. Therefore, there is a need to establish a model for predicting suitable for the rebound risk of newborn HBB in China.

A prediction model for rebound HBB was developed

Table 3 The performance of the prediction model in the training and testing sets

Our model	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Accuracy (95% CI)
Training set	0.898 (0.845–0.950)	0.848 (0.817–0.880)	0.942 (0.924–0.960)	0.858 (0.831–0.886)
Testing set	0.880 (0.809–0.950)	0.831 (0.790–0.871)	0.935 (0.911–0.958)	0.841 (0.805–0.876)

CI, confidence interval; AUC, area under the curve.

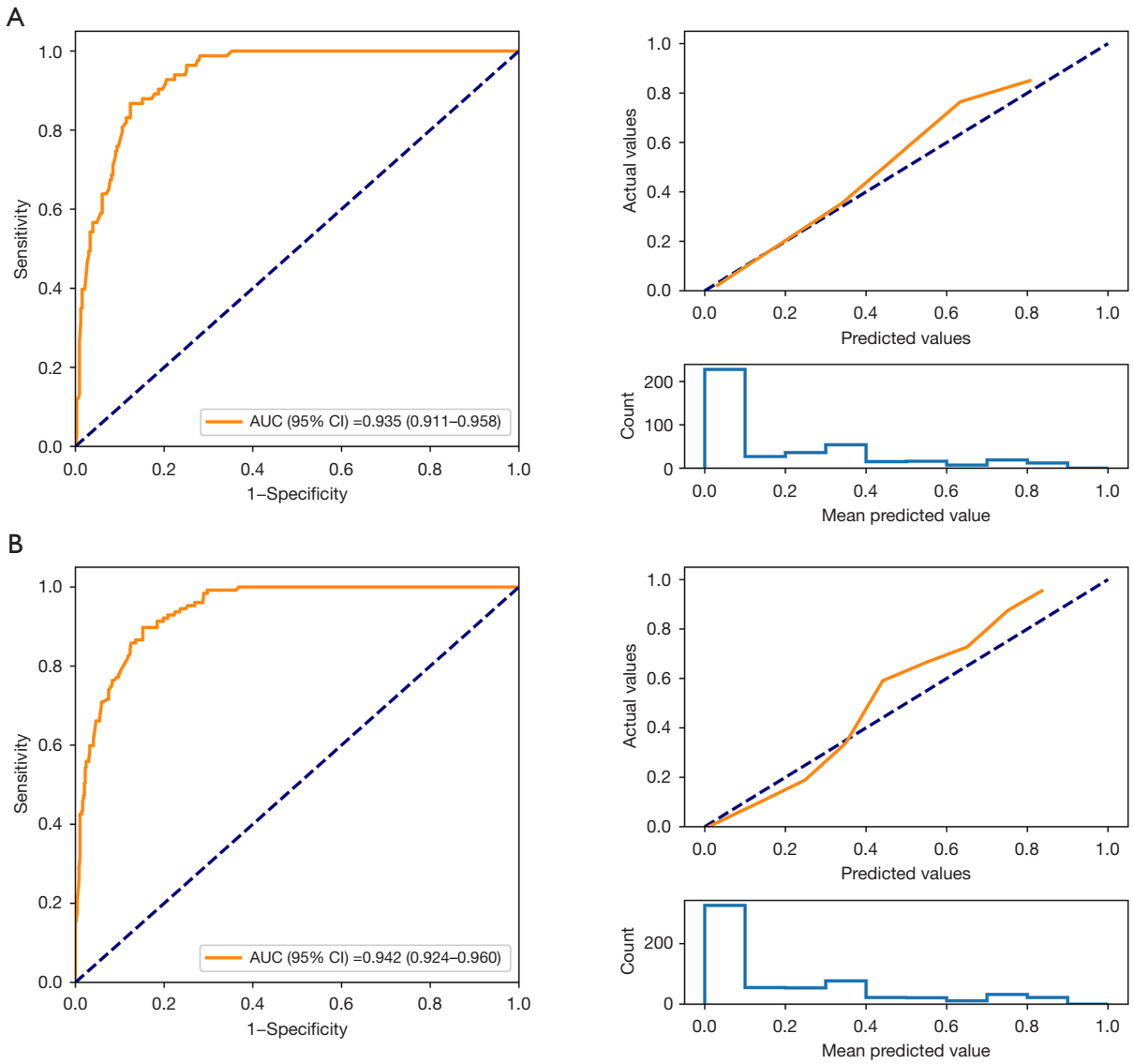

Figure 3 The ROC and calibration curves of the prediction model. (A) Training set; (B) testing set. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Table 4 The performance of the prediction model in premature and term delivery infants

Subgroups	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Accuracy (95% CI)
Premature infants				
Our model	0.750 (0.505–0.995)	0.765 (0.664–0.866)	0.917 (0.841–0.992)	0.762 (0.669–0.856)
Full-term delivery infants				
Our model	0.901 (0.832–0.971)	0.848 (0.805–0.891)	0.936 (0.911–0.961)	0.859 (0.822–0.897)

CI, confidence interval; AUC, area under the curve.

for Chinese neonates. We found that formula feeding (>3 times/day), standard phototherapy irradiation time, TSB levels at phototherapy termination, age at phototherapy termination, neonatal weight, and differences between the levels of TSB at the end of phototherapy and the threshold of phototherapy were predictors of the risk of rebound HBB. The AUCs of our prediction model for the training set and testing set were 0.942 and 0.935, which presented great predictive ability for rebound HBB risk in neonates, similar to premature and full-term delivery babies.

Previous studies have reported clinical PS for rebound HBB after inpatient phototherapy (12,13,15). A large cohort of 7,048 HBB infants at birth age ≥35 weeks was used to investigate the risk of rebound HBB (12). Predictors were identified using stepwise logistic regression analysis, including GA <38 weeks [adjusted odds ratio (OR) =4.7], age at phototherapy initiation (adjusted OR =0.51), and the difference between the treatment threshold and the TSB levels at the end of phototherapy (adjusted OR =1.5). A three-variable PS was then calculated, with an AUC of 0.881. In 2019, their group proposed a simpler two-variable PS [GA and ΔTSB (the difference between the levels of TSB at the end of the phototherapy session and the treatment threshold at the start of phototherapy session)] for rebound HBB in the same cohort, with an AUC of 0.876 (13). The two scores maintained a similar discrimination to assess the risk of rebound in newborns with HBB. In addition, So *et al.* (15) explored the discrimination and calibration of these PS in Canadian neonates receiving phototherapy while in hospital. The low performance of these published scores were found, which was consistent with our findings. The differences may be due to the fact that the incidence of rebound HBB varied widely from 4.6% in the study by Chang *et al.* to 20.3% in our cohort. Chang *et al.*'s study analyzed neonates receiving phototherapy while in hospital and after discharge. The establishment of a prediction model for the risk of rebound HBB is helpful for Chinese clinicians in identifying high-risk HBB newborns and effectively managing their rebound.

Formula feeding (>3 times/day) was associated with HBB rebound. We discovered that the frequency of formula feeding (>3 times/day) was lower in the rebound group than in the non-rebound group (47.43% *vs.* 52.56%). Breastfeeding has many health benefits for both baby and mother, and the AAP recommends that baby should be exclusively breastfed for 6 months and continued to be breastfed no less than 1 year (9,16). The use of formula may reduce breastfeeding (17-19). Supplementing small amounts of formula for a limited period of time after breastfeeding may not adversely affect breastfeeding (20). Formula supplementation may reduce TSB levels (21,22). Elhawary *et al.* (23) reported that low birth weight is a hazard factor for neonatal rebound HBB after phototherapy. Similarly, in our study, neonatal weight was associated with rebound HBB, which may be due to an increase of plasma bilirubin associated with the weight and immaturity of the liver and liver enzymes responsible for bilirubin binding and coupling (24). We also found that the differences in TSB levels at the termination of phototherapy and the threshold of phototherapy were related to rebound HBB, consistent with Chang *et al.*'s study (12,13).

This study developed a model to predict the rebound risk of HBB using a newborn Chinese cohort. Our findings showed that the model performed well for the rebound of infants with HBB. However, several limitations must be considered when interpreting these results. This cohort study was retrospective and single-center. Although this prediction model performed well for predicting the rebound HBB risk, future studies need to further validate the clinical application for Chinese newborns with HBB. In addition, formula use times were recorded, and information about the type and amount of formula was missing during hospitalization.

Conclusions

A prediction model for rebound HBB performed well in Chinese neonates, which helps clinicians identify neonates in need of active treatment and frequent early follow-up, improve the therapeutic effect of the first phototherapy, and reduce the hospitalization duration of neonates.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-21/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-21/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-21/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This current study was supported by the Institutional Review Board (IRB) of the Affiliated Guangdong Second Provincial General Hospital of Jinan University (No. 2022-KY-KZ-139-02), and informed consent for this retrospective analysis was waived by the Affiliated Guangdong Second Provincial General Hospital of Jinan University.

References

1. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Lancet Child Adolesc Health 2018;2:610-20.
2. Horn D, Ehret D, Gautham KS, et al. Sunlight for the prevention and treatment of hyperbilirubinemia in term and late preterm neonates. Cochrane Database Syst Rev 2021;7:CD013277.
3. Slaughter JL, Kemper AR, Newman TB. Technical Report: Diagnosis and Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2022;150:e2022058865.
4. Qattea I, Farghaly MAA, Elgendy M, et al. Neonatal hyperbilirubinemia and bilirubin neurotoxicity in hospitalized neonates: analysis of the US Database. Pediatr Res 2022;91:1662-8.
5. Can E, Verim A, Başer E, et al. Auditory neuropathy in late preterm infants treated with phototherapy for hyperbilirubinemia. Int J Audiol 2015;54:89-95.
6. Lin Q, Zhu D, Chen C, et al. Risk factors for neonatal hyperbilirubinemia: a systematic review and meta-analysis. Transl Pediatr 2022;11:1001-9.
7. Hanin EA, Rayan H, Hani T, et al. Breastfeeding and Readmission for Hyperbilirubinemia in Late Preterm and Term Infants in Beirut, Lebanon. Indian Pediatr 2022;59:218-21.
8. Bravo G, Miller MR, Zizzo AN. Factors associated to hospital re-admission of infants previously treated for hyperbilirubinemia. Pediatr Med 2022;5:4.
9. Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2022;150:e2022058859.
10. Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation) - Summary. Paediatr Child Health 2007;12:401-18.
11. Hansen TWR, Maisels MJ, Ebbesen F, et al. Sixty years of phototherapy for neonatal jaundice - from serendipitous observation to standardized treatment and rescue for millions. J Perinatol 2020;40:180-93.
12. Chang PW, Kuzniewicz MW, McCulloch CE, et al. A Clinical Prediction Rule for Rebound Hyperbilirubinemia Following Inpatient Phototherapy. Pediatrics 2017;139:e20162896.
13. Chang PW, Newman TB. A Simpler Prediction Rule for Rebound Hyperbilirubinemia. Pediatrics 2019;144:e20183712.
14. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14.
15. So V, Coo H, Khurshid F. Validation of published rebound hyperbilirubinemia risk prediction scores during birth hospitalization after initial phototherapy: a retrospective chart review. Pediatr Res 2022;91:888-95.
16. Kuzniewicz MW, Escobar GJ, Newman TB. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. Pediatrics 2009;124:1031-9.

17. Chantry CJ, Dewey KG, Peerson JM, et al. In-hospital formula use increases early breastfeeding cessation among first-time mothers intending to exclusively breastfeed. J Pediatr 2014;164:1339-45.e5.
18. Flaherman VJ, Cabana MD, McCulloch CE, et al. Effect of Early Limited Formula on Breastfeeding Duration in the First Year of Life: A Randomized Clinical Trial. JAMA Pediatr 2019;173:729-35.
19. Parry JE, Ip DK, Chau PY, et al. Predictors and consequences of in-hospital formula supplementation for healthy breastfeeding newborns. J Hum Lact 2013;29:527-36.
20. Flaherman VJ, Aby J, Burgos AE, et al. Effect of early limited formula on duration and exclusivity of breastfeeding in at-risk infants: an RCT. Pediatrics 2013;131:1059-65.
21. Zhao LL, Lee EP, Kuo RN, et al. Effect of Early Supplemental Formula Intervention on Body Weight and Hyperbilirubinemia in Neonates During 72 h After Birth. Front Pediatr 2021;9:625536.
22. Gulcan H, Tiker F, Kilicdag H. Effect of feeding type on the efficacy of phototherapy. Indian Pediatr 2007;44:32-6.
23. Elhawary IM, Abdel Ghany EAG, Aboelhamed WA, et al. Incidence and risk factors of post-phototherapy neonatal rebound hyperbilirubinemia. World J Pediatr 2018;14:350-6.
24. Watchko JF, Maisels MJ. Jaundice in low birthweight infants: pathobiology and outcome. Arch Dis Child Fetal Neonatal Ed 2003;88:F455-8.

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