Original Article

Predictive Factors for Term Infants with Neonatal Hyperbilirubinemia Requiring Readmission for Phototherapy

Sariya Prachukthum[1], Chamnan Tanprasertkul[2], Sukkrawan Intarakhao[1]

Abstract

Background: Neonatal jaundice is one of the most common problems which often develops after term infants are discharged at the age of 48 hours. Identifying risk factors may prevent severe hyperbilirubinemia which can cause an irreversible neuronal damage.

Objectives: To predict which term infants would need phototherapy after 48 hours of age.

Methods: A prospective cohort study of 2,841 healthy newborns with gestational age of 37 weeks or more, born at Thammasat University Hospital between June 1st, 2017 and April 19th, 2018 was conducted. Risk factors and serum bilirubin level at 48 hours of life were obtained from individual chart review. We used multivariate logistic regression to identify risk factors, and receiver operator characteristic curve (ROC curve) to compare predictive accuracy.

Results: There were 115 (3.8%) term infants with neonatal hyperbilirubinemia requiring readmission for phototherapy after 48 hours of age. Significant risk factors were predischarge bilirubin in high intermediate risk zone (adjusted odds ratio [aOR] 80.36, 95% confidence interval [CI] 37.47 - 172.36, $P < 0.01$), predischarge bilirubin in low intermediate risk zone (aOR 9.71, 95% CI 4.91 - 19.21, $P < 0.01$), gestational infants at 37-38 weeks (aOR 4.26, 95% CI 2.7 - 6.71, $P < 0.01$), cesarean section (aOR 2.44, 95% CI 1.6 - 3.73, $P < 0.01$), and weight loss more than 5% two days after birth (aOR 1.76, 95% CI 1.09 - 2.86, $P = 0.02$). The predictive performance of these risk factors in combination (AUC = 0.859, 95% CI = 0.82 - 0.89) was significantly different from the predictive accuracy of the predischarge bilirubin risk zone (AUC = 0.793, 95% CI = 0.76 - 0.83).

Conclusions: Predicting neonatal hyperbilirubinemia requiring readmission for phototherapy is important. The predischarge bilirubin risk level, combined with the clinical risk factors (gestational age, delivery mode, and bodyweight percentage lost at 2 days of age), was more prediction accuracy than using predischarge bilirubin risk level or either clinical risk factors.

Keywords: Jaundice, Neonatal hyperbilirubinemia, Predict, Readmission, Term infant

Received:16 September 2019 **Revised: 4 December 2020** **Accepted: 7 December 2020**

[1] Department of Pediatrics, Faculty of Medicine, Thammasat University

[2] Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat University

Corresponding author: Sariya Prachukthum, MD, Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani 12120, Thailand Tel: 02-9269514; Fax: 02-9269513 Email: sariyarpd238@yahoo.com

Introduction

Neonatal jaundice is one of the most common problems in newborns, affecting up to 60% of term infants.[1, 2] High serum bilirubin levels can cause kernicterus secondary to bilirubin-induced neuronal necrosis. These infants have clinical manifestations such as athetoid cerebral palsy, hearing loss, dental dysplasia, and paralysis of upward gaze.[3] Although kernicterus is rare and irreversible, it is preventable through awareness, close monitoring and proper management with phototherapy. Most infants develop severe hyperbilirubinemia after 48 hours of age, so the American Academy of Pediatrics (AAP) clinical practice guideline recommends all newborn infants should have bilirubin levels measured along with a risk assessment of developing significant hyperbilirubinemia before discharge.[4]

The purpose of our study was to identify early postnatal factors within 48-hour age associated with requirement of readmission for phototherapy

Methods

This prospective cohort study was conducted at Thammasat University Hospital. Infants who were born at gestational age 37 weeks or more, between June 1st, 2017 and April 19th, 2018 were enrolled. Infants were admitted to neonatal intensive care unit or sick newborn unit for more than 24 hours, or having severe congenital anomalies or chromosomal abnormalities such as trisomy 13, 18, or 21, incomplete medical information, neonatal hyperbilirubinemia needing phototherapy within 48 hours of age, or with parents who could not understand Thai or English or being non-contactable 14 days after birth were excluded.

Using our previous unpublished data, our readmission rate for phototherapy was 7%. After comparing potential risk factors, gestational age (GA) at birth was determined to be most relevant and rendered greatest amount of participants. For example, readmitted term infants were 38.05 ± 0.74 weeks GA at birth; in contrast, infants without readmission were GA at 38.24 ± 0.5 weeks. We enrolled 3,000 term infants.

All infants received standard of care such as routine weigh-ins at 6 am every morning and a serum bilirubin measurement at 48 hours of life. After a discharge examination with serum bilirubin assessment, primary care physicians decide whether to initiate phototherapy or discharge the infant with follow up at the general pediatric clinic within 2 weeks, or discharge with the routine well-child follow up at 1- 2 months of age.

Infants who were readmitted after 48 hours of age for phototherapy when total serum bilirubin level exceeded or was within 1 mg/dL of the hour-specific range indicating phototherapy by AAP guidelines[4] were used to identify risk factors as compared to infants who did not returned to our hospital for treatment.

Medical charts from admission and follow-ups were reviewed for maternal, infant, and delivery information. A research assistant phoned parents to ask if their infants developed neonatal hyperbilirubinemia requiring phototherapy within 14 days after discharge home.

The study protocol was approved by the Human Research Ethics Committee No.1, Faculty of Medicine, Thammasat University, Thailand.

Statistical analysis

Baseline information was reported as percentages and mean ± standard deviation (SD). Chi-square and t-test were used to compare between groups: $P < 0.05$ was considered significant. We determined risk factors by using multivariate logistic regression, and then stepwise variable selection was performed to identify significant predictors among the collected data. We also examined the test parameters, including sensitivity, specificity, the area under receiver operating characteristic (AUROC) curve, positive likelihood ratio (LR+), and negative likelihood ratio (LR–) to compare predictive accuracy. Our prediction model was performed to assess internal validity.

Results

There were 3520 term newborns born in the study period. Then, 520 term infants were excluded due to: neonatal hyperbilirubinemia requiring phototherapy within 48 hours of age (n = 116), admission to neonatal intensive care unit or sick newborn unit more than 24 hours (n = 387), no documented serum bilirubin at 48 hours of age (n = 2), parents did not understand Thai or English (n = 10), chromosomal abnormalities (n = 3), and

major organ anomalies (n = 2); 3000 were finally enrolled. Unfortunately, parents of 159 (5.3%) infants did not respond to follow-up calls; these infants were also excluded. Therefore 2841 infants were analyzed.

There were 115 (3.8%) infants readmitted for neonatal hyperbilirubinemia requiring phototherapy (jaundice group), did not need total exchange transfusion. The causes of neonatal hyperbilirubinemia were inconclusive jaundice (42.6%), breastfeeding jaundice (40.9%) and breast milk jaundice (9.6%). These infants had GA 38.4 ± 1 weeks at birth, and 65.2 % of them were born by cesarean section which was significantly different from those infants (control group) not having hyperbilirubinemia (GA 38.8 ± 0.9 weeks, cesarean section rate of 49.7 %) (Table 1).

Table 1 Baseline characteristics

Characteristics	Jaundice (n = 115)	Control (n = 2726)	*P*
Maternal age (y), mean ± SD	30.4 ± 5.4	29.6 ± 6	0.17
Maternal hypertension, n (%)	4 (3.5)	44 (1.6)	0.13
Maternal diabetes, n (%)	15 (13)	237 (8.7)	0.1
Gestational age (weeks), mean ± SD	38.4 ± 1	38.8 ± 0.9	< 0.01*
Parity, median (range)	1 (1 - 4)	2 (1 - 8)	0.7
Cesarean section, n (%)	75 (65.2)	1355 (49.7)	< 0.01*
Apgar at 1 min, median (range)	9 (6 - 9)	9 (3 - 9)	0.04*
Apgar at 5 min, median (range)	10 (7 - 10)	10 (8 - 10)	0.6
Male, n (%)	65 (56.5)	1346 (49.4)	0.13
Birthweight (g), mean ± SD	3127.4 ± 385	3118.2 ± 380.2	0.8

* $P < 0.05$ was considered statistically significant

For the clinical data potentially associated with hyperbilirubinemia requiring phototherapy, infants in the jaundice group are characterized by: having a family history of other previous infants with jaundice (16.5%), GA ≤ 38 weeks at birth (40.9%), being firstborn (58.3%), having predischarge bilirubin levels in low intermediate (53.9%) and high intermediate risk zones (37.4%), having bodyweight loss (BWL) > 5% on second day of life (73.1%); all of these were statistically significant versus the control group (Table 2).

Table 2 Variables potentially associated with neonatal hyperbilirubinemia

Characteristics	Jaundice (n = 115)	Control (n = 2726)	*P*
Previous infant with jaundice, n (%)	19 (16.5)	282 (10.3)	0.03*
Previous infant having phototherapy, n (%)	16 (13.9)	245 (9)	0.07
Gestational age ≤ 38 weeks, n (%)	47 (40.9)	603 (22.1)	< 0.01*
Firstborn, n (%)	67 (58.3)	1310 (48.1)	0.03*
Polycythemia, n (%)	1 (0.87)	16 (0.59)	0.83
Predischarge bilirubin (mg/dL), mean ± SD	10.4 ± 1.3	8.3 ± 1.6	< 0.01*
Predischarge bilirubin percentile, n (%)			< 0.01*
0 - 40th (low risk)	10 (8.7)	1505 (55.2)	
41 - 75th (low intermediate risk)	62 (53.9)	1082 (39.7)	
76 - 95th (high intermediate risk)	43 (37.4)	139 (5.1)	
> 95th (high risk)	0	0	

Table 2 Variables potentially associated with neonatal hyperbilirubinemia (Cont.)

Characteristics	Jaundice (n = 115)	Control (n = 2726)	*P*
Day 1 bodyweight loss %, mean ± SD	2.7 ± 2.1	3 ± 1.6	0.07
Day 2 bodyweight loss %, mean ± SD	6 ± 2	5.4 ± 2	< 0.01*
Weight loss > 5% on Day 2, n (%)	91 (73.1)	1656 (60.8)	< 0.01*
Weight loss > 7% at Day 2, n (%)	32 (27.8)	532 (19.5)	0.03*
Feeding, n (%)			0.36
Breast milk	78 (67.8)	1826 (67)	
Breast milk + formula	35 (30.4)	752 (27.6)	
Formula	2 (1.7)	148 (5.4)	

* $P < 0.05$ was considered statistically significant

Table 3 Risk factors associated with phototherapy readmission

Risk factors	Adjusted odds Ratio	95% CI	*P*
Gestational age ≤ 38 weeks	4.26	2.70 - 6.71	< 0.01*
Cesarean section	2.44	1.60 - 3.73	< 0.01*
Previous infant having jaundice	1.74	0.93 - 3.25	0.08
Predischarge bilirubin percentile			
41 - 75th (low intermediate risk)	9.71	4.91 - 19.21	< 0.01*
76 - 95th (high intermediate risk)	80.36	37.47 - 172.36	< 0.01*
Firstborn	1.58	1.00 - 2.51	0.05
Weight loss > 5% on Day 2	1.76	1.09 - 2.86	0.02*

* $P < 0.05$ was considered statistically significant

The AUROC curve showing a combination of GA ≤ 38 weeks, predischarge bilirubin zone, birth by cesarean section and BWL > 5% on second day of life produced a better prediction model (AUROC = 0.859, 95% CI = 0.82 - 0.89) (Table 4). Predictive scores generated four (4) risk factors given equal weight; final predictive scores were calculated by summing individual item values within a range of 0-25 (Table 5) and the cut point of prediction was shown in Table 6.

Table 4 Risk factor combination to predict readmission for phototherapy

Combined risk factors	AUROC**	95% CI	*P*
Predischarge bilirubin zone	0.7930	0.76 - 0.83	< 0.01***
Weight loss > 5% on Day 2	0.5919	0.55 - 0.63	
GA* ≤ 38 weeks + Predischarge bilirubin zone	0.8372	0.8 - 0.87	
GA* ≤ 38 weeks + cesarean section + Weight loss > 5% on Day 2	0.6659	0.61 - 0.72	
GA* ≤ 38 weeks + Weight loss > 5% on Day 2 + Predischarge bilirubin zone	0.8455	0.81 - 0.88	
GA* ≤ 38 weeks + Cesarean section + Weight loss > 5% on Day 2 + Predischarge bilirubin zone	0.8590	0.82 - 0.89	

* GA = gestational age
**AUROC = area under receiver operating characteristic curve
*** $P < 0.05$ was considered statistically significant

Table 5 Predictive scores

Risk factors	Coefficient	Predictive score
Gestational age ≤ 38 weeks	1.42	5
Cesarean section	0.9	3
Predischarge bilirubin percentile (zone)		
41-75th (low intermediate risk zone)	2.31	8
76-95th (high intermediate zone)	4.46	15
Weight loss > 5% on Day 2	0.57	2

Table 6 The cut point of prediction

Predictive score cut point	sensitivity	specificity	LR+	LR-
≥ 11	82.61%	73.18%	3.08	0.24
≥ 16	53.04%	92.41%	6.99	0.51
≥ 21	23.48%	98.61%	16.84	0.78

Predictive scores of 11-15 (OR = 6.47, 95% CI: 3.69 - 11.33), 16 - 20 (OR = 26.67, 95% CI: 15.65 - 45.44) and 21-25 (OR = 139.65, 95% CI: 40.85 - 477.42) (Table 7) had the highest risk of hyperbilirubinemia requiring readmission for phototherapy. Readmission rates, calculated by internal validation, for the three aforementioned risk groups were 6.1%, 21.1%, and 58.3%, respectively.

Table 7 Predictive scores associated with phototherapy readmission

Predict score	Odds Ratio	95% CI	*P*
11 - 15	6.47	3.69 - 11.33	
16 - 20	26.67	15.65 - 45.44	< 0.01*
21 - 25	139.65	40.85 - 477.42	

*$P < 0.05$ was considered statistically significant

Discussion

Most healthy term infants are discharged at the age of 48 hours. In our study, almost 4% were readmitted for phototherapy-requiring neonatal hyperbilirubinemia, higher than in Bhutani VK, et al[5] (0.65%) and Maisels MJ, et al[2] (0.4%). Three reasons may be responsible for this disparity. First, in the previous studies, patients sometimes received home phototherapy which is not available in Thailand. Second, these earlier studies were also incorporated a wider variety of ethnic groups, including African-American infants who generally have lower hyperbilirubinemia risk.[6] Our study included only Thai and Myanmar infants, and it is recognized that Asian infants have a far higher risk of hyperbilirubinemia. Third, the difference in the serum bilirubin levels used as a treatment threshold for phototherapy.

Follow-ups are important to prevent severe neonatal hyperbilirubinemia or kernicterus. Several factors have been associated with risk such as a history of a sibling with jaundice with or without phototherapy; the presence of extravasation such as cephalohematoma; predischarge bilirubin risk zone[7, 8, 9]; GA < 38 weeks[7, 8, 10, 11]; breastfeeding[7, 8, 9, 10, 12]; a history of and breastfeeding with significant weight loss.[13, 14, 15] Studies have agreed on which GA and which level of predischarge bilirubin present the most significant risk, but there is disagreement on the other relevant factors in the creation of a definitive follow-up guideline.

Keren R, et al[6] predicted jaundice risk from birth to 14 days with the addition of three factors; using GA, weight loss % per day, and predischarge bilirubin risk zone was better than using only predischarge bilirubin risk zone or clinical risk factors. Maisels MJ, et al[16] suggested phototherapy readmission predictions for infants who had total serum bilirubin (TSB) ≥ 17 mg/dL needed to combine three variables: GA, exclusive breast-feeding, and predischarge transcutaneous bilirubin (TcB). Using only predischarge TcB or the rising rate of TcB did not improve predictions. Newman TB, et al[17] predicted a risk of TSB level of 20 mg/dL or higher at age 48 hours or older by combining a partial index including race, sex maternal age, gestational age, breast feeding, cephalhematoma with prediacharge TSB percentile category was better than using only predischarge TSB zone.

For us, incorporating the four risk factors of GA ≤ 38 weeks at birth, cesarean section, weight loss > 5% at 48 hours of life, and predischarge bilirubin risk zone were better readmission predictors versus just using predischarge bilirubin risk zone, weight loss alone, or other risk factor combinations. Our limitations included variations in hyperbilirubinemia outcome collection from medical records: some participants were not booked for follow-up appointments, and others received a follow-up phone call instead.

For our hospital, it would be ideal to create a guideline. Based on the data here, we recommend the use of a predictive score for booking follow-ups. With a score ≤ 10, the health care team should advise parents to bring the baby back to the hospital if the infant looks progressively yellow from head to torso or still has jaundice at the age of 7 days. Infants with scores in the 11 - 20 and 21 - 25 ranges require follow-up appointments within 3 - 4 days and 2 days after discharge, respectively.

In conclusion, term infants who have characteristics such as GA ≤ 38 weeks at birth, predischarge bilirubin in low intermediate to high intermediate risk zones, cesarean section, and weight loss > 5% on the second day of life, should have follow-up appointments to prevent severe neonatal hyperbilirubinemia, especially if they have more than one risk factor.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank Mrs. Kim Liwiski for editing the manuscript.

References

1. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2009;94:317-322.
2. Maisels MJ, Kring E. Length of stay, jaundice and hospital readmission. *Pediatrics.* 1998; 101:995-998.
3. Maisels MJ. Jaundice. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology: Pathophysiology and Management of the Newborn.* Philadelphia, PA: JB Lippincott, Co; 1999:765-819.
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114:297-316.
5. Bhutani VK, Johnson LH, Schwoebel A, Gennaro S. A systems approach for neonatal hyperbilirubinemia in term and near-term newborns. *J Obstet Gynecol Neonatal Nurs.* 2006; 35:444-455.
6. Keren R, Luan X, Friedman S, Saddlemire S, Cnaan A, Bhutani VK. A Comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and near-term infants. *Pediatrics.* 2008;121:170-179.
7. Keren R, Bhutani VK, Luan X, Nihtianova S, Cnaan A, Schwartz JS. Identifying newborns at risk of significant hyperbilirubinaemia: a comparison of two recommended approaches. *Arch Dis Child.* 2005;90:415-421.
8. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. *Arch Pediatr Adolesc Med.* 2005;159:113-119.
9. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. *Pediatrics.* 2001;108:31-39.
10. Chou SC, Palmer RH, Ezhuthachan S, et al. Management of hyperbilirubinemia in newborns: measuring performance by using a benchmarking model. *Pediatrics.* 2003;112:1264-1273.
11. Sarici SU, Serdar MA, Korkmaz A, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. *Pediatrics.* 2004;113:775-780.
12. Seidman DS, Ergaz Z, Paz I, et al. Predicting the risk of jaundice in full-term healthy newborns: a prospective population-based study. *J Perinatol.* 1999;19:564-567.
13. Tarcan A, Tiker F, Vatandas NS, Haberal A, Gurakan B: Weight loss and hypernatremia in breast-fed babies: frequency in neonates with non-hemolytic jaundice. *J Paediatr Child Health.* 2005;41:484-487.
14. Salas AA, Salazar J, Burgoa VC, De-Villegas AC. Significant weight loss in breastfed term infants readmitted for hyperbilirubinemia. *BMC Pediatrics.* 2009;9:82.
15. Yang WC, Zhao LL, Li YC, et al. Bodyweight loss in predicting neonatal hyperbilirubinemia 72 hours after birth in term newborn infants. *BMC Pediatrics.* 2013;13:145.
16. Maisels MJ, Deridder JM, Kring EA, Balasubramaniam M. Routine transcutaneous bilirubin measurements combined with clinical risk factors improve the prediction of subsequent hyperbilirubinemia. *J Perinatol.* 2009;29:612-617.
17. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. *Arch Pediatr Adolesc Med.* 2005;159:113-119.