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Validation And Comparison Of 3-Variable Model And 2-Variable Model Scores In Predicting Rebound Hyperbilirubinemia Among Late Preterm And Term Neonates Following Phototherapy

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ABSTRACT

Aim: Obtaining repeat bilirubin level after discontinuation of phototherapy is practiced in many neonatal units which is unnecessary. We compared the efficacy of two prediction rules in detecting rebound hyperbilirubinemia.

Methods: Subjects for this prospective cohort study were low risk neonates born ≥ 35 weeks gestation that received phototherapy and subjected for rebound bilirubin estimation. Infants with sepsis and hemolysis were excluded. We defined rebound hyperbilirubinemia as the return of total serum bilirubin (TSB) to phototherapy threshold within 72 hours of termination. The prediction scores by 2 variable model and 3 variable model were compared with the rebound bilirubin.

Results: Of the 467 neonates treated with phototherapy, 5.6% had rebound hyperbilirubinemia. Both models performed well with an area under the receiver operating characteristic curve of 0.974 (95% CI, 0.95–0.98) and 0.993 (95% CI, 0.98–0.99) for 2 variable and 3 variable models respectively. The sensitivity and specificity were 100% and 90.7% for 2 variable model and 100% and 98.2% for 3 variable model. Due to imbalanced data, precision-recall curve was put revealed 0.579 and 0.848 area under curve for 2 variable and 3 variable models respectively. Approximately 70% of infants had scores <20, which correspond to a <4% probability of rebound hyperbilirubinemia.

Conclusion: The risk of rebound hyperbilirubinemia can be quantified with 3 variable model. Clinical implementation of this score can avoid rebound bilirubin estimation.

1. INTRODUCTION

Phototherapy in neonatal hyperbilirubinemia decreases total serum bilirubin (TSB) below the threshold for treatment.[1]Underlying alteration in bilirubin production and excretion may persist and causes bilirubin rebound after stopping phototherapy. The main risk of discontinuing phototherapy is the potential for rebound hyperbilirubinemia, necessitating re-initiation of phototherapy and possible prolonged stay in hospital. The need of measurement of bilirubin rebound after stopping phototherapy has been addressed previously by many observational studies.[2-6] These studies have included neonates born at term or preterm gestation, those with or without positive direct Coombs test, and have concluded that significant bilirubin rebound is rare and therefore, measurement of bilirubin rebound is not needed. The 2004 American Academy of Pediatrics (AAP) guideline on the evaluation and management of hyperbilirubinemia in the newborn infant states that

"discharge from the hospital need not be delayed to observe the infant for rebound" bilirubin levels.[7] In addition, routine measurement of bilirubin rebound may increase workload, add to expenses and prolong the hospital stay. Despite these recommendations, common practice of measuring 8 – 12 hours total serum bilirubin (TSB) rebound levels after discontinuation of phototherapy exists.[8] Chang et al in 2017 devised a 3-variable clinical prediction rule that quantifies the rebound risk after the first inpatient phototherapy according to an infant's gestational age (GA), age at phototherapy initiation, and TSB level relative to the AAP phototherapy threshold at treatment termination.[9] The same principal investigator determined a parsimonious 2-variable model, with GA and the TSB relative to the threshold at phototherapy initiation, which achieved similar accuracy as their previous 3-variable model.[10] These two models were applied in western population and currently there is lack of published data among Indian population. The present study aimed to assess the clinical utility of 3-variable and 2-variable model scores in predicting rebound hyperbilirubinemia among late preterm and term neonates after first phototherapy.

2. METHODS

This prospective cohort consisted of late preterm and term newborns born in a tertiary care teaching institute in South India between October 2020 and July 2022. Consecutively treated, otherwise healthy late preterm and term who has post-phototherapy total serum bilirubin (TSB) determinations performed at 12 hours (between 10 and 14 hours) after discontinuation of phototherapy were included. Neonates with conjugated bilirubin level of >2 mg/dL before or during their first phototherapy admission, sick neonates and who received other forms of therapy for neonatal hyperbilirubinemia along with phototherapy were excluded. Neonates were routinely evaluated for the following etiological entities for their hyperbilirubinemia using clinical data or employing standard laboratory tests. As per institution protocol, the decision to start phototherapy was made on the basis of the age of the baby in hours and total serum bilirubin (TSB) levels, as per American Academy of Pediatrics (AAP) guidelines.[7] Phototherapy was provided with babies lying supine in open bassinets using blue compact fluorescent tubes (Philips 20WTL20/52) placed about 25 cm above the baby. Irradiance of the phototherapy unit at level of skin of abdomen of the neonate was monitored on day using a standard luxmeter (LUTRON LUXMETER) sensitive to wavelengths of 455-465 nm. Light intensity, measured at the level of the skin of the baby's abdomen, was set to yield a mean output of 60 mW/cm2/nm. The tubes were replaced during the study period as and when they are visibly discolored or were producing less light or when the irradiance fall to less than 15 µW/cm2/nm. Breast feeding was encouraged in all infants. During phototherapy TSB levels were determined at least once daily, and more frequently if deemed necessary by clinical assessment. Treatment was discontinued when TSB values become lower than levels set by AAP guidelines. As per unit policy, rebound bilirubin was measured 12 $\pm$ 2 hours after stopping phototherapy. Rebound hyperbilirubinemia (RH) in the present study was defined as post-phototherapy bilirubin level needing reinstitution of phototherapy. TSB was measured by using Autoanalyzer Hitachi902 (Roche's Company, US). The prediction scores were calculated and the probability of rebound hyperbilirubinemia was determined by applying the calculated score to the probability curve. The formulas for calculation of the two scores models are: 3-variablemodel score = 15 (if gestational age < 38 weeks) − 7 × (age in days at phototherapy initiation) − 4 × (AAP phototherapy threshold − TSB at phototherapy termination) + 50[9]; 2-variablemodel score = 15.5 (if GA < 38 weeks) – 4.3 * (AAP phototherapy threshold – TSB at phototherapy termination). [10]

Data entry and analysis were done using Microsoft Excel sheet. Continuous data with normal distribution were analyzed by student t-test and nonnormally distributed data by Mann-Whitney U test. A p value of < 0.05 was considered significant. Correlation coefficient analysis was performed simultaneously to evaluate 3 variable model score and 2 variable model score with rebound bilirubin value. A significance level of 10% was used for all the statistical tests.

3. RESULTS

There were 3146 live births during the study period. Of which 467 eligible neonates had significant hyperbilirubinemia needing phototherapy. There were 245 male and 222 female babies. The median gestational age at enrollment was 37 weeks with IQR between 34 and 38 weeks. The mean birth weight of the study population was 2897 ± 592 grams. The demographic details are depicted in table 1. All 457 neonates treated with phototherapy underwent rebound bilirubin estimation and 26 babies (5.6%) had rebound hyperbilirubinemia (RH). Among babies with RH, bilirubin increased by 2.8 mg/dL (95% CI 1.7-3.2) at 12 hours after stopping phototherapy. Risk factors for RH included birth at early term gestation (15.6% *vs* 4.2%, RR 4.3, 95% CI 1.5-12.0) and jaundice onset before 60 h of age (14.1% *vs* 4.8%, RR 3.3, 95% CI 1.2-9.0). There was no statistical significance between occurrence of RH and previous sibling with history for neonatal hyperbilirubinemia.

Table 1: Demographic details of the study population

Parameter		Rebound hyperbilirubinemia	
		No (n = 441)	**Yes (n = 26)**
Gestational age category	Late preterm	14	0
	Early term	209	24
	Term	218	02
Sex	Male	236	09
	Female	205	17
Birth weight category (in grams)	1500 – 2500	107	07
	2501 – 4000	332	18
	>4001	02	0
Duration of phototherapy	24 – 48 hrs	388	06
	48 – 72 hrs	70	03

Comparison of the Variable Model scores

Receiver operating characteristic curve was obtained in which both 2 variable and 3 variable models performed well. The area under the curve of 0.974 (95% CI, 0.95–0.98) and 0.993 (95% CI, 0.98–0.99) was obtained for 2 variable and 3 variable models respectively (Figure 1 & 2). The sensitivity and specificity were 100% and 90.7% for 2 variable model and 100% and 98.2% for 3 variable model.

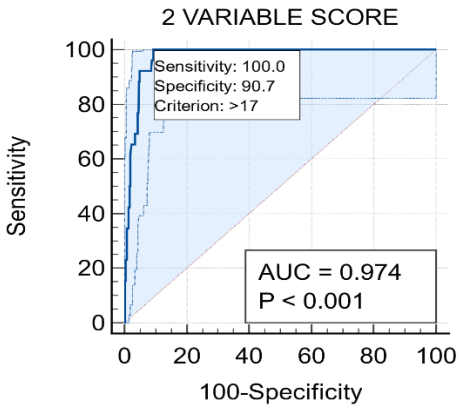


Figure 1: ROC curve for 2 variable score

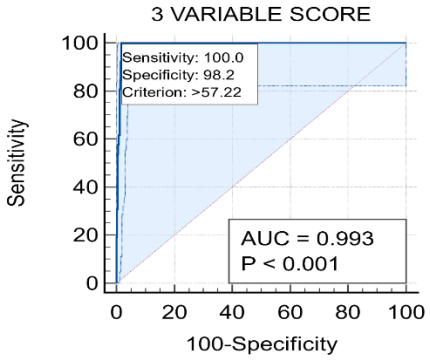


Figure 2: ROC curve for 3 variable score

Upon statistical analysis, it was evident that the data was imbalanced, i.e., 431 Vs 26 in no RH and RH group. Hence precision-recall curve was derived which revealed 0.579 and 0.848 area under curve for 2 variable and 3 variable models respectively (Figure 3 & 4). Approximately 70% of infants had scores <20, which correspond to a <4% probability of rebound hyperbilirubinemia.

Figure 3: Precision curve for 2 variable score

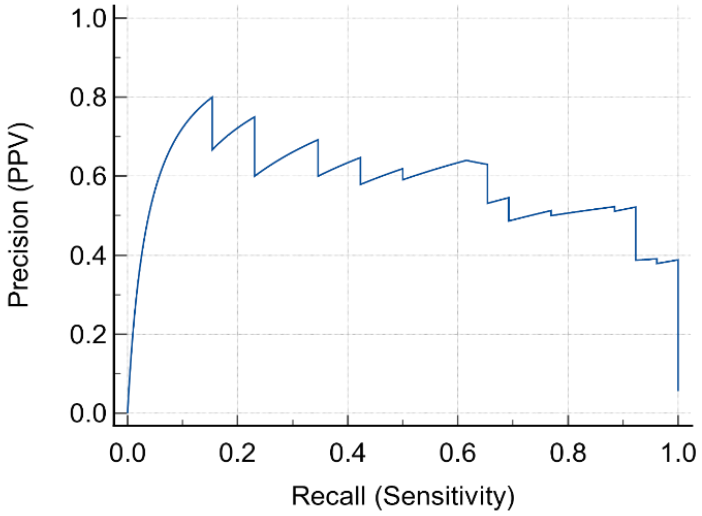
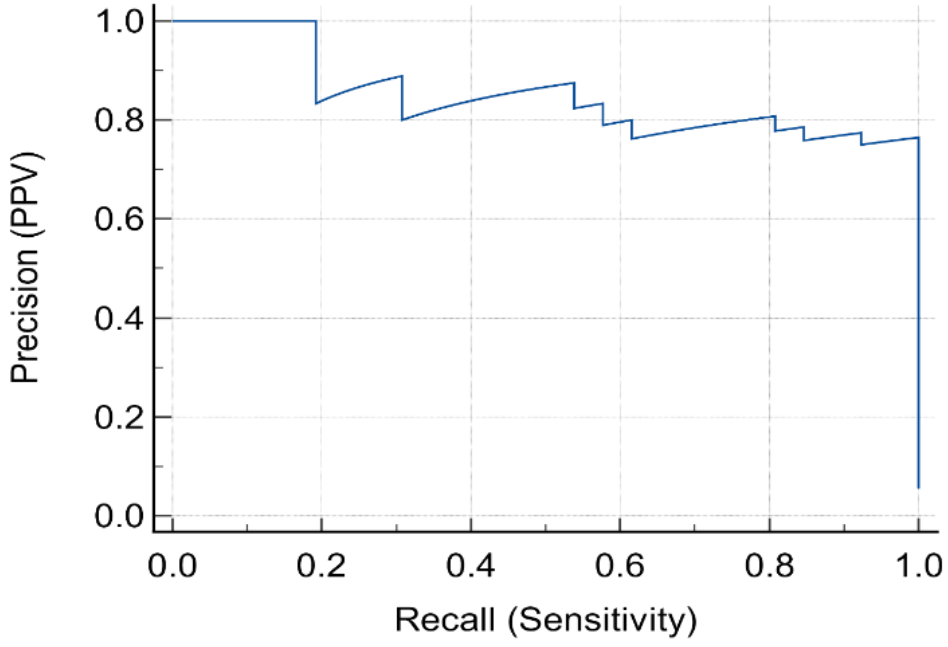


Figure 4: Precision curve for 3 variable score



4. DISCUSSION

The principle behind the management of neonatal hyperbilirubinemia is avoiding potentially 'neurotoxic' levels of bilirubin.[11] Such bilirubin level varies with gestational age at birth, age at onset of jaundice, rate of rise of serum bilirubin, serum albumin concentration, time of initiation and type of treatment and associated hemolysis and comorbidities.[11] One of the standard practice for lowering serum bilirubin levels is by starting phototherapy. Natural history of bilirubin levels after stopping phototherapy is still unclear. The grey areas which need more investigations are the effects of bilirubin in late neonatal period, and whether untreated rebound bilirubin may reach neurotoxic levels. There is a limited amount of research

addressing the potential clinical utility of early (<12 hours) rebound bilirubin levels.[12-14] In 1999, Del Vecchio et al analyzed 48 infants with rebound levels ranging from 6 to 8 hours and found a decrease in average rebound bilirubin level compared with level at cessation of phototherapy.[12] A 2002 retrospective analysis by Al-Saedi evaluated 301 infants with rebound bilirubin level times averaging 8.3 ± 5.3 hours and found no significant increase in early rebound bilirubin levels.[13] Bansal et al recommended that a rebound bilirubin level must be obtained in high-risk neonates (born at less than 35 weeks gestation or birthweight <2000 gm or onset of phototherapy within 60 h of age) 18-24 h after stopping phototherapy. Also, discharge may be delayed for this purpose if follow-up is not ensured.[15] Hence it was customary in many neonatal units to obtain rebound bilirubin levels after stopping phototherapy.

In the present study, we have reported 5.6% is the incidence of rebound hyperbilirubinemia (RH) after stopping phototherapy. Literature review on international data indicate that RH is rare and therefore it is unnecessary measure rebound bilirubin or prolong the hospital stay after phototherapy has been discontinued to check for rebound bilirubin values.[16-18] Factors reported to influence incidence of RH include proportion of premature neonates and hemolytic jaundice, severity and onset of hyperbilirubinemia, mode of feeding and presence of other risk factors like G6PD deficiency.[19,20] Bansal et al observed the risk factors of RH to be gestation at birth<35 weeks, birth weight<2000 gm and onset of jaundice at <60 h of postnatal age.[15] Our observed risk factors were early term gestation and jaundice onset before 60 hours of life.

To the best of our knowledge this is the first report from India about applying the variable model scores for its clinical utility in detecting the probability for rebound hyperbilirubinemia.

5. CONCLUSION

The risk of rebound hyperbilirubinemia can be quantified well with 3 variable model. Clinical implementation of this score either by calculating the score and interpretation with curves or by web-based calculator can help avoiding rebound bilirubin estimation.

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