Global Pediatric Health
Volume 9: 1–5

DOI: 10.1177/2333794X221086568
journals.sagepub.com/home/gph
SAGE

Prediction of Significant Hyperbilirubinemia in Peruvian Term Newborns

Manuel André Virú-Loza, MD[1]* and Mónica Jehnny Pajuelo, PhD[2]

Introduction

Neonatal hyperbilirubinemia is common.[1] However, severe cases require hospitalization.[2] Moreover, significant hyperbilirubinemia (SH) can cause neurological sequelae.[3]

Excessive weight loss is associated with newborn jaundice.[4] Newborns generally lose weight during the first 3 days of life before their weight begins to rebound.[5] On this third day total bilirubin (TB) peaks,[1] allowing for the possibility that weight variation (WV) during these 3 days could be prognostic of SH. Two studies have evaluated WV measured at both fixed ages[6] and variable ages[7] for the identification of SH. In clinical practice WV is usually only available at variable ages. However, Chang et al[7] do not show measures of discriminant performance. Clinical prediction of SH could be useful in low-resource settings where transcutaneous bilirubinometer is not available. In order to have data to guide us in carrying out subsequent prospective studies, we first performed a retrospective study.

The main objective of this study was to determine if WV measured at variable ages in the first 72 hours of life is able to predict SH in jaundiced term newborns. Moreover, we evaluated whether other variables related to WV were better predictors of SH and explored predictive models.

Methods

We conducted a retrospective cohort study using medical records of jaundiced newborns from the Daniel Alcides Carrión National Hospital (HNDAC) in Lima, Peru. Infants were included if they were born at term; had at least 1 weight measurement made when the baby was bed-sharing with the mother; and had at least 1 total bilirubin measurement (TBM) made in the emergency service or when the baby was bed-sharing with the mother. Subjects were excluded if they had conjugated hyperbilirubinemia; had TBMs completed only after 120 hours of age or recorded incorrectly; had weight measurements taken only at ≤24 or >72 hours of age or were illegible; or were hospitalized due to infection or risk of sepsis.

Period 1 (P1) was defined as being >24to 48 hours of age and Period 2 (P2) being >48to 72 hours. Our outcome was SH, defined as a TB for age >95th percentile.[8] Using this outcome is an approach used elsewhere[9,10] as it is almost identical to the phototherapy threshold for "medium risk" infants from the American Academy of Pediatrics guideline.[9,11] WV was defined as the percentage of weight loss relative to birth weight. Standardized WV (SWV) was defined as WV divided by the age in hours at which that weight was measured. Difference of WV (DWV) was defined as WV in P2 minus WV of P1.

Bilirubin was measured using colorimetric technique in Wienner lab cb400i and cb350i processors. Weight was measured at 7 am every day. Other variables were birth weight, sex, gestational age, cesarean delivery, blood group incompatibility (as determined based on charted blood types), maternal age, and parity.

R software 3.5.0 (R Foundation of Computational Statistics, Vienna, Austria) was used for sample size calculation of ROC analyses, while the rest of the analyses were completed on Stata IC 15.1 software (StataCorp, College Station, TX). At all points, $\alpha = 0.05$ was used. Two hundred six subjects were necessary to calculate AUCs (β: 20%; estimated AUC for P1 and P2 were 0.63 and 0.70, respectively[6]) and 400 were necessary to build and cross-validate predictive models.[12] In order to

[1]Hospital Nacional Daniel Alcides Carrión, Peru
[2]Universidad Peruana Cayetano Heredia, Lima, Peru

*This author is now affiliated to "Dos de Mayo" National Hospital, Lima, Peru.

Corresponding Author:
Manuel André Virú-Loza, "Dos de Mayo" National Hospital, Parque "Historia de la Medicina Peruana", S/N, Miguel Grau Avenue 13, Cercado de Lima, Lima, Peru.
Email: m.andre.viru@gmail.com

Table 1. AUCs of Potential Predictors, Models, and Scores to Predict SH up to 120 hours of Age in Jaundiced Term Neonates Born in the HNDAC Between 2016 and 2017. Cross-Validated AUCs of Models Are Also Shown.

	AUC	95% CI
Measurements in period 1		
Weight variation (%) (num.)	0.48	0.41-0.54
Weight variation (%) (cat.)	0.54	0.49-0.58
Standardized weight variation (% in 12 hours) (num.)	0.47	0.41-0.54
Standardized weight variation (% in 12 hours) (cat.)	0.55	0.51-0.59
Model 1	0.69	0.63-0.75
Model 1 (cross-fold validation)	0.65	0.59-0.71
Score 1	0.66	0.60-0.72
Measurements in period 2		
Weight variation (%) (num.)	0.59	0.50-0.68
Weight variation (%) (cat.)	0.58	0.50-0.66
Standardized weight variation (% in 12 hours) (num.)	0.63	0.54-0.72
Standardized weight variation (% in 12 hours) (cat.)	0.64	0.56-0.72
Model 2	0.78	0.71-0.86
Model 2 (cross-fold validation)	0.75	0.67-0.83
Score 2	0.78	0.71-0.86
Measurements in periods 1 and 2		
Difference of weight variations (%) (num.)	0.67	0.58-0.76
Difference of weight variations (%) (cat.)	0.66	0.58-0.73
Model 3	0.82	0.75-0.89
Model 3 (cross-fold validation)	0.77	0.69-0.85
Score 3	0.82	0.75-0.89

Period 1: >24 to 48 hours of age.
Period 2: >48 to 72 hours of age.
Abbreviations: Num., numerical; Cat., categorical.

estimate proportions of reasons for exclusion, a sample of 350 excluded subjects were analyzed (β: 20%; estimated proportion: 50%; margin of error: 5.2%).

Quantitative variables were analyzed in their true and categorized forms. Stepwise forward logistic regression was used to build predictive models for P1, P2, and both periods (Models 1, 2, and 3, respectively). A P value $<.2$ was the entry criterion and there were ≤ 10 events per variable. The Hosmer-Lemeshow test was performed using deciles. Cross-validation was done using 5 folds. Scores were generated by multiplying coefficients by 10 and rounding to the nearest integer. AUCs were calculated for variables of interest and for each model.

The project was approved by the HNDAC Institutional Research Ethics Committee (Official Letter No. 906-2018/HN.DAC-C-DG/OADI) and by the Ethics Committee of the Universidad Peruana Cayetano Heredia (SIDISI Code 102782).

Results

Out of 2079 jaundiced term newborns, 342 met the selection criteria. The proportion of subjects with a weight measurement in P1, P2, and both periods was 95.9%, 44.4%, and 40.4%, respectively. Complete information for the rest of the variables was available. TB was similar in P1 (15.5 ± 4.0 mg/dl) and P2 (15.7 ± 3.4 mg/dl). Of all subjects, 60.2% had SH, 51.5% were female, 31.3% had blood group incompatibility risk and 29.2% were born by cesarean delivery. In P1 and P2, WV (%) was 5.6 ± 2.3 and 7.1 ± 2.3, respectively. DWV (%) was 7.1 ± 2.3.

Among excluded subjects, 55.1% lacked a TBM, 15.1% had TBMs taken only in an in-patient setting, 21.1% had weight measurements illegible or taken only at ≤ 24 or >72 hours of age, 12.9% were hospitalized due to infection or risk of sepsis and 12.4% had TBMs completed only after 120 hours of age or recorded incorrectly. No cases of conjugated hyperbilirubinemia were found.

Among WV, SWV, and DWV, DWV in its quantitative form exhibited the highest AUC (0.67) (Table 1).

Three predictive models were developed (Table 2). All models had a P value $\geq .05$ on the Hosmer-Lemeshow test. Cross-validated AUCs did not differ significantly from original AUCs, with both values falling within each other's confidence interval (Table 1). Model 3 offered the highest AUC (0.82) and best score (AUC: 0.82) (Table 1).

Table 2. Stepwise Forward Logistic Regression Models to Predict SH until 120 h of Age in Jaundiced Term Neonates Born in the HNDAC Between 2016 and 2017.

		Model 1 (198/328)**			Model 2 (83/152)**			Model 3 (75/138)**		
Variables		β	95% CI	Score	β	95% CI	Score	β	95% CI	Score
BW (g)	<2855 or >3825	Ref.			Ref.			Ref.		
	≥2855 and ≤3825	.857	0.342-1.371	9	.776	0.004-1.548	8	.795	−0.043 to 1.633	8
CD	No	Ref.			Ref.			Ref.		
	Yes	−.708	−1.239 to −0.176	−7	−1.063	−1.839 to −0.286	−11	−1.203	−2.054 to −0.352	−12
MP	No	Ref.			Ref.			Ref.		
	Yes	.443	−0.132 to 1.019	4	1.470	0.369-2.570	15	1.327	0.151-2.503	13
GA (weeks)	=37	Ref.			Ref.			Ref.		
	>37	.524	−0.184 to 1.233	5	1.349	0.110-2.587	13	1.670	0.337-3.003	17
Int.		−2.675	−4.322 to −1.027	−27	−2.880	−4.55 to −1.21	−29	−3.897	−5.769 to −2.026	−39
MA (num.) (years)		.052	0.010-0.095	A*						
MA (cat.) (years)	<25				Ref.			Ref.		
	≥25				1.474	0.415-2.534	15	1.975	0.813-3.138	20
SWV1 (% in 12 hours)	≥2.29 and <2.58	Ref.								
	<2.29 or ≥2.58	.840	0.148-1.531	8						
SWV2 (% in 12 hours)	<1.45				Ref.					
	≥1.45				1.083	0.325-1.840	11			
DWV (%)	<0.61							Ref.		
	≥0.61							1.717	0.785-2.649	17

Variables that failed to enter all models: sex, BW (num.), GA (num.), maternal parity (num.), and blood group incompatibility risk.
Other variables that failed to enter model 1: AWM1 (num. and cat.), MA (cat.), WV1 (num. and cat.), and SWV1 (num.).
Other variables that failed to enter model 2: AWM2 (num. and cat.), MA (num.), WV2 (num. and cat.), and SWV2 (num.).
Other variables that failed to enter model 3: AWM2 (num. and cat.), MA (num.), DWV (num.), WV2 (num. and cat.), and SWV2 (num. and cat.).
Abbreviations: num., numerical; cat., categorical; BW, birth weight; CD, cesarean delivery; MP, mother's primiparity; GA, gestational age; Int., intercept; MA, maternal age; WV1, WV in P1; WV2, WV in P2; AWM1, age at the time of weight measurement in P1 (hours), AWM2, age at the time of weight measurement in P2 (hours).
*A: The mother's numerical age in years was the score assigned (ie, if a mother was 25 years old, the score assigned would be 25).
**Number of subjects with SH/total number of subjects.

Discussion

In this retrospective cohort study, we found that WV, SWV, and DWV were not great predictors of SH on their own (Table 1). However, when other variables were incorporated into our models, the AUCs of Model 2 (AUC: 0.78, 95% CI: 0.71-0.86) and Model 3 (AUC: 0.82, 95% CI: 0.75-0.89) were remarkable (Table 1).

A previous study has shown that WVs from within the first 24 hours of life are less indicative of TB levels than WVs of P1 or P2.[6] This is likely because TB levels peak closer to the 72 hours mark, thus weight measurements taken later on are more representative of the state of the newborn at that moment. For this reason, we excluded from our analyses WVs taken within the first 24 hours of life. Similarly, we excluded subjects with TB values taken only after 120 hours of age as those values would not be representative of the TB peak.

We excluded subjects who had TBMs taken only in an in-patient setting for 2 reasons. First, in-depth medical records of what occurred throughout the course of hospitalization were not always available, and, in many instances, TBMs were taken long after admission, thus making it difficult to identify the factors that would have needed to be incorporated into our models. More importantly, however, is the fact that by not including laboratory values as inputs into our models, they are more suited for use in those settings lacking access to rapid laboratory testing.

Hospitalized infants at risk of sepsis or with an infectious diagnosis were also excluded. The majority of newborns with sepsis begin to exhibit signs within the first 6 hours of life[13] and will inevitably undergo a series of laboratory tests, so it is likely that hyperbilirubinemia would be quickly identified, resulting in an SH prediction model being of little use.

The availability of information in the clinical records was a limitation. In spite of this, the AUCs of Models 2 and 3 are comparable to other models available in the literature.[9,10,14] The model developed by Han et al[14] (AUC: 0.85) is the most robust in size and was validated. However, some variables in that model—such as the feeding method[14]—were not registered in HNDAC's clinical records.

The number of subjects in our study precluded an external validation of our models. Still, cross validation is a well-established alternative.[12,15]

As HNDAC caters newborns with and without risk factors, it is reasonable to infer that this study population reflects birth cohort of the surrounding region.

Of those excluded from the study, 55.1% lacked a TBM. Probably, these subjects were considered to be "mild" cases by visual assessment and that no testing was merited. This limits the applicability of our models to "moderate" and "severe" cases by visual assessment. Therefore, in future prospective studies in Peru, TBMs in all term newborns must be performed.

In conclusion, in this initial retrospective study—the first on SH in Peru—it can be observed that SWV (in P2) and DWV have the potential to be considered in the generation of future models for predicting SH. Besides, subsequent prospective Peruvian models need to be built not only in jaundiced term newborns, but rather in all term newborns.

Acknowledgments

We thank Zach Silverstein (George Washington University) for useful comments and suggestions on the manuscript.

Author Contributions

Conceptualization and design: MAV and MJP. Data collection and analysis: MAV. Writting and reviewing the manuscript: MAV and MJP.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Manuel André Virú-Loza https://orcid.org/0000-0001-6637-6463

Mónica Jehnny Pajuelo https://orcid.org/0000-0003-3662-2250

References

1. Lauer BJ, Spector ND. Hyperbilirubinemia in the newborn. *Pediatr Rev*. 2011;32(8):341-349. doi:10.1542/pir.32-8-341
2. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. *Lancet Child Adolesc Health*. 2018;2(8):610-620. doi:10.1016/S2352-4642(18)30139-1
3. Rose J, Vassar R. Movement disorders due to bilirubin toxicity. *Semin Fetal Neonatal Med*. 2015;20(1):20-25. doi:10.1016/j.siny.2014.11.002
4. Boskabadi H, Maamouri G, Bagheri S. Significant neonatal weight loss related to idiopathic neonatal hyper bilirubinemia. *Int J Pediatr*. 2014;2(10):225-231. doi:10.22038/ijp.2014.3168
5. Flaherman VJ, Schaefer EW, Kuzniewicz MW, Li SX, Walsh EM, Paul IM. Early weight loss nomograms for exclusively breastfed newborns. *Pediatrics*. 2015;135(1):e16-e23. doi:10.1542/peds.2014-1532

6. Yang WC, Zhao LL, Li YC, et al. Bodyweight loss in predicting neonatal hyperbilirubinemia 72 hours after birth in term newborn infants. *BMC Pediatr*. 2013;13(145):145. doi:10.1186/1471-2431-13-145
7. Chang RJ, Chou HC, Chang YH, et al. Weight loss percentage prediction of subsequent neonatal hyperbilirubinemia in exclusively breastfed neonates. *Pediatr Neonatol*. 2012;53(1):41-44. doi:10.1016/j.pedneo.2011.11.008
8. 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(1):6-14. doi:10.1542/peds.103.1.6
9. 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(4):415-421. doi:10.1136/adc.2004.060079
10. 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(9):612-617. doi:10.1038/jp.2009.43
11. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. *Pediatrics*. 2009;124(4):1193-1198. doi:10.1542/peds.2009-0329
12. Hastie T, Tibshirani R, Friedman J. Model assessment and selection. In: Hastie T, Tibshirani R, Friedman J, eds. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. 2nd ed. Springer; 2009:219-259.
13. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. *Clin Microbiol Rev*. 2014;27(1):21-47. doi:10.1128/CMR.00031-13
14. Han S, Yu Z, Liu L, et al. A model for predicting significant hyperbilirubinemia in neonates from China. *Pediatrics*. 2015;136(4):e896-e905. doi:10.1542/peds.2014-4058
15. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925-1931. doi:10.1093/eurheartj/ehu207