


Construction and Evaluation of a Prediction Model for Neonatal Hyperbilirubinemia

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Objective: To investigate the factors that contribute to neonatal hyperbilirubinemia (NHB), develop a prediction model and predictive factors, which provide reference base for the early detection of NHB.

Methods: A retrospective study was done to collect clinical data of 683 neonates and their mothers which delivered in the hospital's obstetrics department between January 2019 and January 2023, of these neonates 216 were hyperbilirubinemic and 467 were not. Clinical data and laboratory results of newborns and their mothers were collected and analysed. Multifactorial logistic regression analysis was utilised to develop an early prediction model and identify determinants of newborn hyperbilirubinemia.

Results: The logistic regression model revealed that Delayed meconium (OR=4.024, P=0.002), maternal age (OR=1.106, P<0.01), maternal-infant blood group incompatibility (OR=4.457, P=0.001), Gestational Diabetes Mellitus (GDM) (OR=5.356, P=0.03), Pre-pregnancy co-morbidity (OR=2.810, <0.01), and Weight Growth Rate (WGR) during pregnancy (OR=28.367, P=0.048) were independent risk factors for NHB; 25-(OH)D3 (OR=0.880, P=0.002). The Conjoint predictor ROC curve is below 0.851 (P<0.01, 95% CI:0.821–0.882). The highest Youden's index was 0.55, with a sensitivity of 0.81 and a specificity of 0.76, indicating that the predictor had a decent predictive effect.

Conclusion: This study identified the risk factors and protective factors associated with NHB. Additionally, a joint prediction model was developed to more accurately predict the risk of hyperbilirubinemia which can serve as a foundation for the clinical identification of pertinent susceptibility factors and the development of intervention measures.

Keywords: neonatal hyperbilirubinemia, GDM, weight growth rate, 25-(OH) D3, prediction model

Introduction

Neonatal Hyperbilirubinemia (NHB) is a prevalent condition in infants, ranking as the most common problem among neonatal inpatient illnesses, with a prevalence ranging from 30% to 50%.¹ According to the 2016 Global Burden of Disease (GBD) study, neonatal jaundice causes 1008 deaths per 100,000 babies, making it the seventh leading cause of mortality in the early neonatal period (0–6 days).² National studies suggest that approximately 30% of neonates are hospitalized due to jaundice.³ Although hyperbilirubinemia is typically self-limiting and resolves without treatment within two weeks after birth, elevated bilirubin levels can lead to acute bilirubin encephalopathy or kernicterus—a rare but severe neurological condition associated with cerebral palsy, hearing loss, and visual impairments.⁴ Kernicterus resulting from severe hyperbilirubinemia carries substantial risks of mortality and long-term disability.⁵ Thus, hyperbilirubinemia remains a critical neonatal health issue that warrants careful monitoring, risk assessment, and timely management.

Exclusive breastfeeding has been widely recognized as a significant factor associated with an increased risk of neonatal jaundice, particularly within the first week of life, due to factors such as caloric deprivation and dehydration.⁶ Nonetheless, the benefits of breastfeeding outweigh the risks, and current guidelines encourage supportive lactation practices alongside bilirubin monitoring.⁷

Although glucose-6-phosphate dehydrogenase (G6PD) deficiency is a well-established risk factor for severe hyperbilirubinemia, especially in populations with high prevalence such as in Africa and Asia,⁸ we excluded neonates with

G6PD deficiency from this study. This exclusion was implemented because G6PD deficiency can lead to hemolytic jaundice through a distinct pathological mechanism, which may confound the identification of other predictive factors related to non-hemolytic NHB.⁹

This study aims to identify maternal and neonatal factors associated with NHB and to develop a predictive model that can facilitate early intervention and minimize complications.

Patients and Methods

This study was retrospectively on a total of 683 women and their newborn babies (from the beginning of January 2019 to the end of December 2023). There were 216 neonates with NHB and 467 neonates was not. The diagnosis of NHB was in accordance with the diagnostic criteria in the Expert Consensus on Diagnosis and Treatment of NHB: hyperbilirubinemia was diagnosed when the bilirubin level was above the 95th percentile.⁹ Exclusion criteria: include congenital defects such as bile duct obstruction, hereditary metabolic illnesses such as hepatitis, chromosomal abnormalities, and congenital organic diseases. Additionally, neonates with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, as identified by testing, are also excluded. As noted, G6PD-deficient individuals were excluded to isolate non-hemolytic etiologies and avoid confounding due to known hemolytic pathways.

In 683 neonates, detailed records were maintained regarding foetal sex, body mass at birth, conditions at birth (gestational age, delayed meconium, scalp haematoma, neonatal hypoxic, neonatal infections), total bilirubin, and indirect bilirubin. Basic conditions of all mothers during pregnancy, such as the maternal age, the presence of anaemia, prematurity, hypertension, gestational diabetes mellitus (GDM), pre-pregnancyco-morbidity, adverse maternal history, the place of residence, the rate of maternal weight growth during pregnancy, and the incompatibility of the mother and baby's blood groups. The mother's laboratory tests were recorded, which included serum maternal folic acid and 25-(OH) D3 levels. All laboratory values were averaged across measurements taken during the first, second, and third trimesters to represent overall pregnancy exposure. Calculation of maternal growth rate: (maternal weight gain during pregnancy - newborn's birth weight)/weeks of gestation of the pregnant woman. Maternal weight gain = weight before delivery - Pregnant women's first prenatal weight. Clinical staff were responsible for collecting the mother and neonatal's medical records through interviews and reviewing hospital charts. It is important to note that data on feeding patterns (eg, exclusive breastfeeding, formula feeding, or mixed feeding) were not consistently documented in the retrospective medical records and were therefore not included in the present analysis.

Statistical Analysis

All these variables were entered into the Statistical Package of Social Science software program, version 23 (SPSS), and analysed. The data were summarised using the mean and standard deviation for quantitative variables, and the median and interquartile range for qualitative variables. Frequencies and percentages were used for qualitative variables. Comparisons between groups were performed using the Mann-Whitney test for quantitative variables and the Chi-square test for qualitative variables.

Using univariate analysis, mothers with and without NHB newborns were compared for the occurrence of specific clinical and laboratory parameters. The parameters with significant association with NHB were regarded as possible predictors of NHB. These factors were then entered into multivariate logistic regression model to determine their independent contributions to the development of ABE. Statistical significance was established when the P-value was <0.05. The predictive model is constructed by incorporating all relevant variables, which assessed by the goodness of fit by using the Hosmer-Lemeshow test and discrimination by using area under the curve (AUC).

Results

Univariate Analysis Results

Tables 1 and 2 shows the univariate predictors. In univariate analysis, nine related factors were identified: seven from the mothers and two from the infants. The difference between NHB and the non-NHB in terms of gestational age, delayed

Table 1 Univariate Analysis of Influencing Maternal Factors for NHB

Variables		NHB (n=216) (n, %)	Non-NHB (n=467) (n, %)	χ^2/Z	P
Residence	Urban	162 (75.00)	364 (77.94)	0.723	0.395
	Rural	54 (25.00)	103 (22.06)		
Maternal-infant blood group incompatibility	Yes	110 (50.93)	107 (22.91)	18.502	<0.001
	No	106 (49.07)	360 (77.09)		
Parity	Singleton	108 (50.00)	221 (47.32)	0.495	0.781
	Second pregnancy	82 (37.96)	190 (40.69)		
	≥ multiple pregnancy	26 (12.04)	56 (11.99)		
Adverse maternal history	Yes	39 (18.06)	91 (19.49)	0.196	0.658
	No	177 (81.94)	376 (80.52)		
Mode of delivery	Natural labour	81 (37.50)	188 (40.26)	0.470	0.493
	Caesarean section	135 (62.50)	279 (59.74)		
Placenta previa	Yes	10 (4.63)	23 (4.93)	0.028	0.867
	No	206 (95.37)	444 (95.07)		
Premature rupture	Yes	55 (25.46)	82 (17.56)	5.754	0.016
	No	161 (74.54)	385 (82.44)		
Abnormal amniotic fluid	Yes	23 (10.65)	50 (10.71)	0.001	0.982
	No	193 (89.35)	417 (89.29)		
GDM	Yes	125 (57.87)	105 (22.48)	22.943	<0.001
	No	91 (42.13)	362 (77.52)		
Pre-pregnancy co-morbidity	Yes	43 (19.91)	43 (9.21)	15.362	0.001
	No	173 (80.09)	424 (90.79)		
Preconception anemia	Yes	59 (32.96)	120 (67.04)	0.200	0.655
	No	157 (31.15)	347 (68.85)		
Maternal growth rate (%)		0.32 (0.28~0.35)	0.33 (0.30~0.37)	-4.014	<0.01
Maternal age (year)		30 (27~34)	28 (25~30)	-5.718	0.001
Folic acid (ng/mL)		12.30 (8.20~15.40)	12.60 (9.53~15.70)	-1.762	0.078
25-(OH)D3 (ng/mL)		17.80 (15.80~20.76)	20.40 (16.90~24.30)	-4.123	0.002

Abbreviations: NHB, neonatal hyperbilirubinemia; P, p-value.

Table 2 Univariate Analysis of Influencing Factors for Neonates with Hyperbilirubinemia

Variables		NHB (n=216) (n, %)	Non-NHB (n=467) (n, %)	χ^2	P
Fetal gender	Male	115 (53.24)	249 (53.32)	0.001	0.985
	Female	101 (46.76)	218 (46.68)		
Birth weight	≥2.5 (kg)	65 (30.09)	123 (26.34)	1.043	0.307
	≤2.5 (kg)	151 (69.91)	344 (73.66)		
Delayed meconium	Yes	95 (43.98)	79 (16.92)	16.982	0.001
	No	121 (56.02)	388 (83.08)		
Gestational age	<37week	70 (32.41)	91 (19.49)	13.687	0.001
	≥37week	146 (67.59)	376 (80.51)		
Scalp hematomas	Yes	59 (27.31)	104 (22.27)	2.069	0.15
	No	157 (72.69)	363 (77.73)		
Neonatal infection	Yes	47 (21.76)	75 (16.06)	3.270	0.071
	No	169 (78.24)	392 (83.94)		
Neonatal hypoxic	Yes	39 (9.38)	67 (14.35)	1.549	0.213
	No	177 (81.62)	400 (85.65)		

Abbreviations: NHB, neonatal hyperbilirubinemia; P, p-value.

fetal stool, GDM, premature rupture, Maternal-infant blood group incompatibility, pre-pregnancy co-morbidity, as well as maternal age, maternal growth rate, 25-(OH)D3 (ng/mL).

Multivariate Logistic Regression Analysis Results

The occurrence of NHB was used as the dependent variable, with those that did not occur being assigned value of 0 and those that did occur being assigned value of 1. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis, and the categorical variables were assigned in the following ways: Gestational age (≥ 37 weeks = 1, < 37 weeks = 0), Delayed meconium (yes = 1, no = 0), GDM (yes = 1, no = 0), Premature rupture (yes = 1, no = 0), Maternal-infant blood group incompatibility (yes = 1, no = 0), Pre-pregnancy co-morbidity (yes=1, no=0), and the continuous variables Maternal weight growth rate, Maternal age, and 25-(OH)D3 were carried at their original values.

The results of the multivariate logistic regression analysis (Table 3) showed that maternal–infant blood group incompatibility (OR = 4.457, 95% CI: 2.885–6.885, $P = 0.001$), delayed meconium passage (OR = 4.024, 95% CI: 2.579–6.278, $P = 0.002$), weight growth rate during pregnancy (OR = 28.367, 95% CI: 1.029–781.702, $P = 0.048$), maternal age (OR = 1.106, 95% CI: 1.055–1.159, $P < 0.01$), pre-pregnancy comorbidities (OR = 2.810, 95% CI: 1.575–5.012, $P < 0.01$), and gestational diabetes mellitus (GDM) (OR = 5.356, 95% CI: 3.474–8.257, $P = 0.03$) were independent risk factors for NHB. In contrast, 25-(OH)D3 level (OR = 0.880, 95% CI: 0.838–0.924, $P = 0.002$) was identified as a protective factor. Gestational age and premature rupture of membranes were not significantly associated with NHB ($P > 0.05$).

ROC Curve Analysis Results

Figure 1 shows the ROC curve of the combined predictors. The combined predictor included maternal–infant blood group incompatibility, delayed meconium passage, weight growth rate during pregnancy, maternal age, pre-pregnancy comorbidities, gestational diabetes mellitus (GDM), and 25-(OH)D3. The area under the ROC curve (AUC) for the combined predictor was 0.851 (95% CI: 0.821–0.882, $P < 0.01$), indicating good discriminative ability. The maximum Youden index was 0.55, with a sensitivity of 0.81 and a specificity of 0.76, demonstrating that the combined predictor had strong predictive performance.

Discussion

NHB is one of the common diseases in the neonatal period. In the current study, we investigated the relevant indicators of NHB in mothers during pregnancy and the presentation of neonates after birth, and constructed predictive factors for early identification of the condition, so as to provide reference for early clinical intervention and reduce its incidence.

The World Health Organization (WHO) found that the mortality rates for jaundice-related diseases in the Eastern Mediterranean, Africa, Southeast Asia, and Europe were 13.02%, 7.52%, 2.01%, and 0.07%, respectively.¹⁰ A survey of the reasons of hospitalised neonates in the United States revealed that NHB placed second in the screening of causes of

Table 3 Multivariate Logistic Regression Analysis of Influencing Factors of NHB

	B	SE	WaldX ²	P	OR	95% CI of OR
Maternal-infant blood group incompatibility	1.494	0.222	45.360	0.001	4.457	2.885–6.885
Delayed meconium	1.392	0.227	37.626	0.002	4.024	2.579–6.278
Gestational age	−0.187	0.233	0.641	0.424	0.830	0.526–1.310
Weight growth rate	3.345	1.692	3.909	0.048	28.367	1.029–781.702
Maternal age	0.101	0.024	17.739	<0.01	1.106	1.055–1.159
25 (OH)D3	−0.127	0.025	26.137	0.002	0.880	0.838–0.924
Premature rupture	0.357	0.248	2.076	0.150	1.430	0.879–2.325
Pre-pregnancy co-morbidity	1.033	0.295	12.245	<0.01	2.810	1.575–5.012
GDM	1.678	0.221	57.757	0.03	5.356	3.474–8.257
Constant	−3.997	1.048	14.538	0.000	0.018	

Abbreviations: NHB, neonatal hyperbilirubinemia; P, p-value.

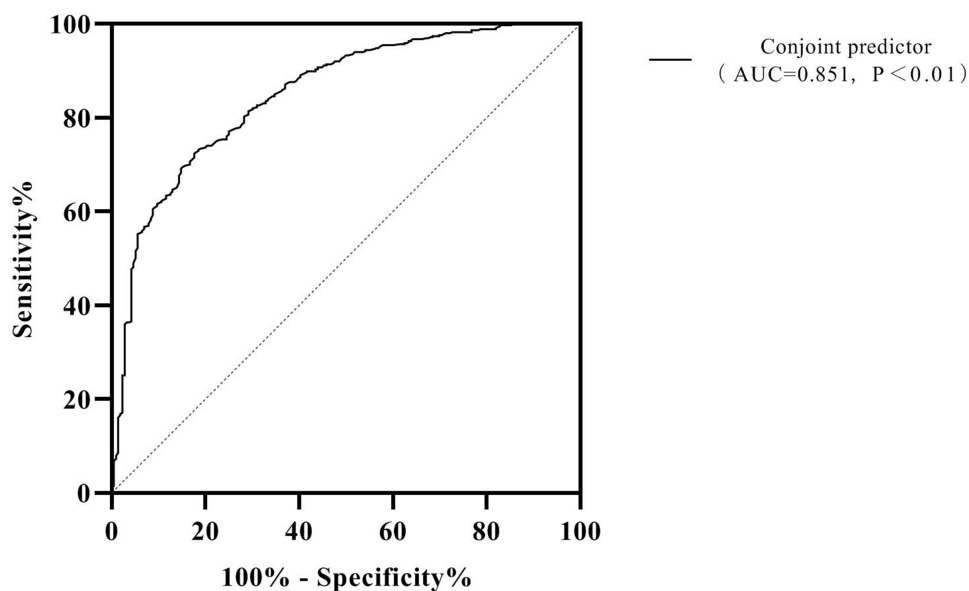


Figure 1 ROC curve for the Combined predictor of NHB.

hospitalization.¹¹ NHB has been on the rise in recent years in China, according to studies of Ding Guihua et al.¹² In 2018, 13 hospitals in Jiangsu Province of China reported severe hyperbilirubinemia cases, which accounted for 2.70% of all cases admitted to newborn units.¹³ In this study, hyperbilirubinemia children accounted for 31.63% of newborns, which is consistent with the findings that reported the incidence of neonatal jaundice was 29.08%.¹⁴ The prevalence of the NHB differs across countries and regions, potentially attributed to factors such as ethnicity, genetics, location, socio-economic situations, and healthcare quality. The incidence of NHB is higher in low-and middle-income countries than that in developed countries. This is primarily due to the absence of effective data collection and interventions, delayed diagnosis, and underreporting.

In the present study, we identified seven indicators that are associated with NHB by analyzing clinical data. These indicators are Delayed meconium, GDM, Maternal-infant blood group incompatibility, Pre-pregnancy co-morbidity, Maternal weight growth rate, Maternal age, and 25-(OH)D3. Based on these related factors, we constructed ConConjoint predictor. The area under the curve (AUC) of the Conjoint predictor was 0.851, with a predictive sensitivity of 81% and specificity of 76%, indicating that the combined predictive factor has good predictive value.

In this study, Gestational diabetes mellitus (GDM) is a risk factor for NHB. GDM is a metabolic disorder that occurs during pregnancy due to insufficient secretion or defective action of insulin.¹⁵ During pregnancy, the placenta secretes a variety of hormones that can hinder insulin function in cells, leading to elevated glucose levels and impacting outcomes for the newborns.^{16–18} Furthermore, the vasoconstriction and calcification of blood vessels in the placenta of pregnant women with GDM, combined with inadequate perfusion in the chorionic villous space, lead to fetal distress and substantial hemolysis in neonates postpartum. This condition can readily lead to hyperbilirubinemia.¹⁹ The most prevalent complication observed in neonates born to mothers with gestational diabetes mellitus, both domestically and internationally, is hyperbilirubinemia,^{20,21} which is consistent with the findings of our investigation.

In addition, our investigation revealed a correlation between maternal age and NHB, consistent with findings from prior research studies.²² The development of society and economy, the improvement of personal standards of living, and the application of national fertility programs could help to explain this phenomena. As a result, there has been a gradual increase in the number of advanced age women with fertility needs, leading to a rise in pregnancies among this demographic.

Maternal-infant blood group incompatibility as a risk factor for hyperbilirubinemia is consistent with the findings of Lin et al.²³ The maternal blood group antibodies bind to the corresponding antigens on the surface of the fetus' red blood

cells, leading to their sensitization. In neonates, macrophages and natural killer cells eliminate sensitized erythrocytes, potentially resulting in hemolysis, jaundice, and exacerbation of NHB.

Delayed meconium reduces bilirubin excretion and increases absorption into the bloodstream through enterohepatic circulation. This will impact the metabolism of hepatic and enterohepatic circulations, leading to worsening jaundice, similar to the previous findings.^{24,25}

This study employed the rate of weight gain during pregnancy as a measure to investigate the association between maternal weight gain and hyperbilirubinemia. In comparison to weight growth and BMI, the rate of weight gain provides a more accurate reflection of maternal weight gain during pregnancy. Weight gain during pregnancy is essential for fetal health. However, excessive weight gain has been associated with adverse fetal outcomes and pregnancy complications.²⁶ The association between the rate of mother weight and the raised risk of newborn hyperbilirubinemia may be ascribed to the excessive mother substrate-induced fetal hyperinsulinemia, which raises the fetal oxygen absorption during glycolysis, so producing increased erythropoiesis.²⁷ This leads to the development of hyperbilirubinemia as it exceeds the neonatal liver's capacity to metabolize bilirubin.

Pre-pregnancy co-morbidity increase the likelihood of newborn hyperbilirubinemia. The prevalent comorbidities include hypertension, diabetes mellitus, HBV infection, thyroid problems, thrombocytopenia, and various other conditions. In general, about 1–5% of women of reproductive age have chronic hypertension. According to a study conducted by Mohamed Rezka et al, there was a significant association between NHB and the use of antihypertensive medications during pregnancy.²⁸ Thyroid disorders, including hyperthyroidism and hypothyroidism, during pregnancy are associated with an increased risk of fetal growth restriction, placental abruption, neurological dysplasia, teratogenicity, preterm delivery, neonatal respiratory distress syndrome and other adverse outcomes.²⁹ Specifically, maternal thyroid dysfunction can be linked to NHB through several mechanisms. Maternal thyroid hormones are crucial for the maturation of the fetal liver and its enzymatic systems, including UDP-glucuronosyltransferase (UGT1A1), the key enzyme responsible for bilirubin conjugation.

Hypothyroidism may lead to delayed maturation of this system, impairing the neonate's ability to process bilirubin.³⁰ Furthermore, some studies suggest that thyroid autoantibodies may cross the placenta and contribute to transient neonatal thyroid dysfunction, which can indirectly affect bilirubin metabolism.³¹ When pregnancy is combined with pre-existing medical disorders, the physiological strain on the body is further exacerbated, which increases the dangers for both the pregnant mother and the fetus. Hence, it is crucial to regularly monitor pregnant women with pre-existing medical conditions in order to optimize the outcomes of their pregnancies.

Our study revealed that elevated levels of 25-(OH)D3 served as a protective factor against NHB, indicating its potential role in reducing the incidence of this condition. This is likely attributable to the susceptibility of neonatal erythrocytes to oxidative damage, which can lead to elevated bilirubin levels, and vitamin D possesses antioxidant properties which can reduce this damage.³²

Limitations and Future Directions

This study has several limitations that should be acknowledged. First, due to the retrospective nature of this study, detailed data on infant feeding practices (exclusive breastfeeding, formula supplementation, etc) were not available for analysis. This is a significant limitation, as established literature consistently identifies inadequate intake associated with exclusive breastfeeding as a key contributor to early-onset hyperbilirubinemia. The absence of this variable might have influenced the predictive accuracy of our model and potentially led to an overestimation of the effect sizes of the maternal factors we identified. Future prospective studies should prioritize the systematic collection of feeding data, including frequency, duration, and supplementation, to build more comprehensive and accurate prediction models for NHB. Despite this limitation, our model focused on identifying readily available antenatal and early postnatal maternal-neonatal factors, which remain valuable for initial risk stratification before feeding patterns are fully established.

In conclusion, our study analyzed the occurrence of hyperbilirubinemia in neonates, which is associated with various factors. Analyzed using a logistic regression model, the predictive impact of several risk variables for hyperbilirubinemia was assessed by the calculation of Conjoint predictors and the construction of a ROC curve. Age, delayed meconium, maternal-infant blood group incompatibility, gestational diabetes mellitus, concomitant underlying disorders, and weight

growth rate during pregnancy were identified as independent risk factors for NHB. Additionally, 25-(OH)D3 was found to be an independent protective factor against NHB. It is important for us to recognize and prevent the specific risk factors that pregnant women may face. We should also focus on the variables that can protect them. By conducting early screenings and providing prompt intervention, we can effectively limit the occurrence of newborn hyperbilirubinemia. It is important for us to recognize and prevent the specific risk factors that pregnant women may face. We should also focus on the variables that can protect them. By conducting early screenings and providing prompt intervention, we can effectively limit the occurrence of newborn hyperbilirubinemia.

The subsequent phase of this study will involve validating the associated prediction model and predictors. Simultaneously, a multi-center study will be conducted to encompass a larger number of hospitals, research subjects, and influencing factors. The aim is to identify additional factors that are correlated with NHB, thereby establishing a foundation for early prevention of NHB.

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Disclosure

The authors report no conflicts of interest in this work.

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