Research Article

Establishment and Evaluation of Influencing Factors and Risk Prediction Model of Severe Neonatal Hyperbilirubinemia Complicated with Acute Bilirubin Encephalopathy

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Objective. To explore the influencing factors of severe hyperbilirubinemia in neonates complicated with acute bilirubin encephalopathy (ABE) and then build relevant prediction models and evaluate the prediction performance of the models.

Methods. The data of 120 neonates with severe hyperbilirubinemia were collected by retrospective analysis. Univariate and multivariate analysis methods were used to analyze the data of 120 children. R software was used to visualize the results of multivariate analysis, and a nomogram model was obtained. The receiver operating characteristic curve (ROC), calibration curve, and decision-making curve (DC) were used to evaluate the discrimination, accuracy, and clinical net profit rate of the model.

Results. Multivariate analysis showed that non-full breastfeeding, high-risk symptoms, and pregnancy complications were independent risk factors for ABE in neonates with severe hyperbilirubinemia. At the same time, the risk of ABE in neonates with severe hyperbilirubinemia increased with the increase of B/A and Hb levels. The ROC curve showed that the area under the curve for the model was 0.908 (95% CI: 0.839–0.960). The calibration curve shows that the actual prediction curve of the model is in good agreement with the corrected prediction curve. Using the cutoff value of the ROC curve as the diagnostic criterion, the threshold probability of the model was calculated to be 38%. The decision curve shows that when 38% is used as the basis for judging whether to take measures to intervene, the profit rate is 61%.

Conclusion. The occurrence of ABE in neonates with severe hyperbilirubinemia is affected by many factors, and there is a certain degree of interaction between these factors. Combining multiple factors to construct a risk nomogram model can provide a reference for early clinical detection of high-risk neonates.

1. Introduction

Neonatal hyperbilirubinemia is the most common disease in neonatal wards. After birth, the level of bilirubin in the body is in a process of dynamic change, and factors such as hemolysis, infection, and breast milk can cause increased blood bilirubin production or decreased bilirubin excretion (it may also be caused by two or more reasons for hyperbilirubinemia in neonates). The main symptoms of the neonate are yellowing of the skin and sclera (the white part around the eyeball), as well as hepatosplenomegaly. At present, physical phototherapy and drug therapy are mainly used in clinical practice. Most neonates have a good prognosis, but early severe hyperbilirubinemia can progress to acute bilirubin encephalopathy (ABE) and kernicterus [1, 2]. ABE can easily lead to neonatal neurological sequelae and may directly threaten the lives of neonates. With the development of phototherapy, neonatal exchange transfusion, and other technologies, the incidence of ABE in neonates with hyperbilirubinemia in developed countries has decreased significantly. However, ABE is still uncommon in developing countries, especially in areas with underdeveloped economic and medical conditions [3, 4]. Exploring the influencing factors of severe neonatal hyperbilirubinemia complicated by ABE in neonates can provide a basis for taking targeted measures to intervene, which is conducive to improving the prognosis of neonates with hyperbilirubinemia.

The level of free bilirubin in the blood is closely related to the occurrence of ABE, but the degree to which the level of
total bilirubin crosses the blood-brain barrier and causes neurotoxicity is still uncertain. It is generally believed that the peak serum total bilirubin (TSB) in term infants with ABE is above 427.5 μmol/L. However, it is often found clinically that some neonates have a high tolerance to serum total bilirubin, and no brain damage occurs even if the TSB is much greater than 427.5 μmol/L [5, 6]. At the same time, some neonates have low tolerance and are particularly sensitive to bilirubin toxicity. It can be seen that the effects of bilirubin on neonates are not exactly the same.

At the same time, factors other than bilirubin, such as gestational age, hemolytic disease, infection, mode of delivery, feeding method, etc., may also have an impact on children with severe hyperbilirubinemia complicated by ABE [7, 8]. In addition, multiple studies have shown that there is often an interaction between multiple factors that lead to the occurrence and development of the disease [9–11]. Indicators with statistical significance in univariate analysis may not still be statistically significant after multivariate analysis. Therefore, a comprehensive analysis of multiple influencing factors may be more helpful in identifying high-risk neonates. By reviewing the literature, it is found that there are few relevant studies on the prediction model of severe hyperbilirubin neonates complicated with ABE, and the relevant factors are not comprehensive enough. Therefore, based on the clinical data of neonates, this study constructed a nomogram prediction model of severe hyperbilirubin in neonates complicated with ABE, aiming to provide a reference for improving the quality of life of neonates with severe hyperbilirubin. The report is as follows.

2. Materials and Methods

2.1. Research Objects. A retrospective analysis was used to collect and analyze the data of neonates with severe hyperbilirubinemia admitted to our hospital from August 2010 to December 2021. The children included in the study must meet the following criteria: (1) meet the diagnostic criteria for hyperbilirubinemia, neonatal age within 24 hours: transcutaneous bilirubin (TCB) ≥100 μmol/L; within 48 hours: TCB ≥150 μmol/L; within 72 hours: TCB ≥200 μmol/L; and >72 hours: TCB ≥250 μmol/L [12]; (2) peak of total bilirubin in serum >342 μmol/L [12]; (3) singleton pregnancy; and (4) the gestational age is between 35 and 42 weeks. Neonates with one of the following conditions were excluded: (1) gastrointestinal malformations and biliary digestive system diseases; (2) congenital heart disease; (3) severe asphyxia; (4) severe hereditary metabolic disease; (5) hepatitis syndrome; and (6) incomplete clinical data required for this study.

2.2. Data Collection Methods. Two full-time investigators in this research group screened eligible cases through our hospital’s electronic medical record query system and filled in the data of the children in the data collection form. Consistency analysis was performed on the two data sets to ensure that the data were correct before conducting the study. A total of 120 case data sets were finally included in the study.

The data collected in this study include the following: (1) basic characteristics of children: whether ABE occurs, gender, gestational age, birth weight, feeding method, acidosis, and high-risk symptoms. High-risk symptoms include hemolysis, infection, and glucose-6-phosphate dehydrogenase (G-6-PD). The diagnostic criteria for ABE should meet any one of the following: abnormal neurological manifestations after hyperbilirubinemia, such as screaming, breast rejection, changes in consciousness, staring, muscle tone changes, and convulsions. At the same time, it can exclude neonatal hypoxic-ischemic encephalopathy, genetic metabolic disease, intracranial hemorrhage, internal environment disorder, intracranial infection. (2) Abnormal brainstem auditory evoked potentials, which cannot be explained by other reasons. (3) Brain MRI showed that T1M1 showed symmetrical globus pallidus hyperintensity or hyperintensity in the subthalamic nucleus at the same time. Laboratory examination data: peak serum total serum bilirubin (TSB), TSB-to-albumin ratio (B/A), hemoglobin (Hb), hematocrit (Hct), alkaline phosphatase (ALP), and creatine kinase-MB (CK-MB). (3) Information on the mother of the neonates: maternal age, mode of delivery, parity, pregnancy complications (high fever, anemia, diabetes, hypertension, and acute appendicitis), childbirth complications (premature rupture of membranes, contamination of amniotic fluid, abnormal umbilical cord, and intrauterine distress).

2.3. Model Construction and Verification. R Studio software was used to conduct a multivariate analysis on the data of 120 neonates. The multivariate analysis results were visualized to obtain a nomogram model, and the receiver operating characteristic curve (ROC), calibration curve, and decision-making curve (DC) were used to evaluate the discriminative degree, accuracy, and clinical net profit rate of the model.

2.4. Statistical Analysis. The SPSS 25.0 statistical software was used to analyze the research data. Qualitative data were expressed by frequency and percentage, and χ² test was performed. Quantitative data conforming to a normal distribution were presented in the form of (X ± s), and a t-test was performed. The comparison of all the data indicated that the difference was significant at P < 0.05.

3. Results

3.1. Univariate Analysis. Among the 120 newborns in this study, 21.67% (26/120) were complicated with ABE. The neonates with ABE were counted as the ABE group, and the rest of the neonates were counted as the non-ABE group. Univariate analysis was performed on the data of the two groups of neonates, and the results showed that there were significant differences in indicators such as feeding methods, neonatal high-risk symptoms, TSB, B/A, Hb, Hct levels, and pregnancy complications between the two groups (P < 0.05) (Table 1).
3.2. Multivariate Analysis.

LX_ The indicators with significant differences between the ABE group and the non-ABE group in the univariate analysis of the experimental cohort were used as independent variables, and the occurrence of ABE in neonates was used as the dependent variable, and multivariate logistic regression analysis was performed (see Table 2 for variable assignments). Multivariate analysis showed that nonfull breastfeeding (OR = 8.194, \( P = 0.025 \)), high-risk symptoms (OR = 10.325, \( P = 0.020 \)), and maternal pregnancy complications (OR = 6.261, \( P = 0.019 \)) were independent risk factors for ABE in children with severe hyperbilirubinemia. At the same time, the risk of ABE in children with severe hyperbilirubinemia increased with the increase of B/A (OR = 3.416, \( P = 0.009 \)) and Hb (OR = 1.086, \( P = 0.001 \)) levels, as shown in Table 3.

3.3. Construction of the Model.

LX_ From the multivariate analysis results, it was concluded that the occurrence of ABE in neonates with severe bilirubinemia was affected by multiple factors, and the nomogram prediction model shown in Figure 1 was constructed by combining these factors. The model consists of each factor and its corresponding line segment of a certain length. The user can directly obtain the

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### Table 1: Univariate analysis of ABE in neonates with severe hyperbilirubinemia.

| Factor                      | ABE group (n = 26) | Non-ABE group (n = 94) | \( \chi^2/t \) | \( P \) |
|-----------------------------|-------------------|------------------------|----------------|--------|
| Gender                      |                   |                        |                |        |
| Male                        | 17 (23.29)        | 56 (76.71)             | 0.289          | 0.591  |
| Female                      | 9 (19.15)         | 38 (80.85)             |                |        |
| Gestational age (weeks)     | 38.96 ± 0.92      | 39.09 ± 0.69           | 0.788          | 0.432  |
| Birth weight (kg)           | 3.15 ± 0.52       | 3.22 ± 0.46            | 0.667          | 0.506  |
| Feeding method              |                   |                        |                |        |
| Nonfull breastfeeding       | 14 (33.33)        | 28 (66.67)             | 5.182          | 0.023  |
| Full breastfeeding          | 12 (15.38)        | 66 (84.62)             |                |        |
| Acidity                     |                   |                        |                |        |
| Yes                         | 6 (31.58)         | 13 (68.42)             | 1.307          | 0.253  |
| No                          | 20 (19.80)        | 81 (80.20)             |                |        |
| High-risk symptoms          |                   |                        |                |        |
| Yes                         | 11 (35.48)        | 20 (64.52)             | 4.702          | 0.030  |
| No                          | 15 (16.85)        | 74 (83.15)             |                |        |
| TSB (\( \mu \)mol/L)       | 476.20 ± 38.25    | 449.07 ± 36.31         | 3.333          | 0.001  |
| B/A (mg/g)                  | 8.05 ± 0.81       | 7.21 ± 0.79            | 4.716          | <0.001 |
| Hb (g/L)                    | 168.51 ± 16.08    | 152.76 ± 14.92         | 4.685          | <0.001 |
| Hct (%)                     | 47.09 ± 5.17      | 43.15 ± 4.97           | 3.547          | 0.001  |
| ALP (g/L)                   | 35.64 ± 3.85      | 34.71 ± 3.61           | 1.146          | 0.254  |
| CK-MB (U/L)                 | 31.25 ± 2.97      | 30.11 ± 2.74           | 1.844          | 0.068  |
| Maternal age (years)        |                   |                        |                |        |
| > 35                        | 9 (27.27)         | 24 (72.73)             | 0.843          | 0.359  |
| ≤ 35                        | 17 (19.54)        | 70 (80.46)             |                |        |
| Delivery mode               |                   |                        |                |        |
| Cesarean delivery           | 13 (26.00)        | 37 (74.00)             | 0.948          | 0.330  |
| Vaginal delivery            | 13 (18.57)        | 57 (81.43)             |                |        |
| Parity                      |                   |                        |                |        |
| Firstborn                   | 18 (26.47)        | 50 (73.53)             | 2.134          | 0.144  |
| N-firstborn                 | 8 (15.38)         | 44 (84.62)             |                |        |
| Pregnancy complications     |                   |                        |                |        |
| Yes                         | 10 (37.04)        | 17 (62.96)             | 4.849          | 0.028  |
| No                          | 16 (17.20)        | 77 (82.80)             |                |        |
| Childbirth complications    |                   |                        |                |        |
| Yes                         | 5 (31.25)         | 11 (68.75)             | 0.999          | 0.318  |
| No                          | 21 (20.19)        | 83 (79.81)             |                |        |

Note: Table 1 is a preliminary analysis of neonatal-related data.

### Table 2: Assignment of each factor.

| Variable | Assignment |
|----------|------------|
| Dependent variable | ABE = “ABE,” 0 = “N-ABE” |
| Independent variable | Feeding method 1 = “N-full breastfeeding,” 0 = “full breastfeeding” |
|                      | High-risk symptoms 1 = “Yes,” 0 = “No” |
|                      | TSB Enter the actual value |
|                      | B/A Enter the actual value |
|                      | Hb Enter the actual value |
|                      | Hct Enter the actual value |
| Pregnancy complications | 1 = “Yes,” 0 = “No” |
corresponding single score according to the situation of each factor, and the single score of all factors is added to obtain the total score. Mark the position of the total score on the total score axis and draw a vertical line downward to obtain the risk value corresponding to the total score.

3.4. Verification of the Nomogram Model. In order to ensure the generality of the model, the model is verified. From the ROC curve in Figure 2, the area under the curve of the model is 0.908 (95% CI: 0.839–0.960). The calibration curve shows that the actual prediction curve of the model is in good agreement with the corrected prediction curve, Brier = 0.093 (see Figure 3). Using the cutoff value of the ROC curve as the diagnostic criterion, the threshold probability of the model was calculated to be 38%. The decision curve shows that the threshold probability of the model ranges from 5% to 99% (see Figure 4). When 38% was used as the basis for deciding whether to take measures to intervene, 61 neonates out of every 100 children could benefit without harming the interest of others.

4. Discussion

Hyperbilirubinemia is one of the common neonatal diseases, which can be divided into mild, moderate, and severe according to the bilirubin level. Most neonates can return to normal within a short period of time after symptomatic care [13]. However, our country’s large population, unbalanced distribution of medical and health resources, and lack of family members’ awareness of ABE have led to the development of ABE in some neonates with severe hyperbilirubinemia. ABE can lead to dysfunction of intelligence, hearing, and movement in neonates with hyperbilirubinemia, which brings a heavy burden to neonates, their families, and society [14, 15]. In recent years, scholars have been devoted to finding indicators that can easily, sensitively, and specifically assess the risk of ABE in neonates with severe hyperbilirubinemia, so as to take targeted measures for intervention.

This study found that neonates who were not exclusively breastfed had a higher risk of ABE than those who were exclusively breastfed. Adequate breast milk has a positive
effect on the intestinal motility of neonates. Compared with infants fed with formula milk or mixed feeding, it is more conducive to the excretion of meconium and can reduce the enterohepatic circulation and production of bilirubin [16].

At the same time, breast milk contains a variety of nutrients and anti-infective substances, which can promote neonatal brain development and reduce the infection rate [17]. Therefore, the author suggests that qualified mothers should breastfeed as much as possible to help newborns build intestinal beneficial bacteria, store them in intestinal peristalsis, and enhance their anti-infection ability.

In the research on the occurrence factors of ABE, hemolysis, infection, and G-6-PD deficiency are currently recognized as the main factors that increase the risk of ABE in neonates [18–20]. The results of this study also showed that children with these high-risk symptoms had a significantly higher risk of ABE than those without these symptoms. For neonates with severe hyperbilirubinemia, infection and hemolysis share common features, that is, both can directly lead to red blood cell destruction and increase blood indirect bilirubin [18, 19].

High levels of indirect bilirubin increase the permeability of the blood-brain barrier, leading to a large amount of blood bilirubin entering the brain tissue and increasing the risk of ABE. G-6-PD has the effect of protecting cells from oxidative stress damage. Neonates with G-6-PD deficiency are more prone to acute injury due to diseases such as infection, intracranial hemorrhage, or hemolysis due to the lack of the protective effect of G-6-PD [20]. When the above factors coexist in the same neonate, the serum bilirubin level of the neonate can rise rapidly (exceeding the albumin binding capacity), deposit in the brain tissue through the molecular transmembrane diffusion across the blood-brain barrier, and then induce ABE.

The bilirubin of neonates with severe hyperbilirubinemia exceeds the buffer capacity of the blood tissue, and a large amount of unconjugated bilirubin (free bilirubin) enters the
brain through the blood-brain barrier, causing brain tissue damage [21]. Free bilirubin is the most direct and sensitive indicator of bilirubin toxicity, but there is no effective method for detecting free bilirubin. B/A is a surrogate parameter for free bilirubin; therefore, it can be considered that the risk of neonatal ABE increases with the increase of the B/A level. In Campbell’s study, neonatal polycythemia was a risk factor for severe hyperbilirubinemia [22]. The results of this study suggest that elevated Hb levels increase the risk of ABE in neonates with severe hyperbilirubinemia. In addition, pregnancy comorbidities also increase the risk of neonatal ABE. Scholars such as Thielenmans also indicated in their studies that maternal complications such as preeclampsia during pregnancy increase the risk of neonatal ABE [23].

It is worth noting that, in the univariate analysis, the peak TSB and Hct levels were significantly different from ABE in neonates with severe neonatal bilirubin encephalopathy, but after multivariate analysis, no significant association between these two factors and ABE was found. This result suggests that there is a certain degree of interaction between the above factors, and the influence of peak TSB and Hct level on ABE is weakened or even ignored in the interaction with other factors. This further illustrates the importance of combining multiple factors in predicting severe neonatal hyperbilirubinemia complicated by ABE.

From the above analysis, it can be seen that the occurrence of ABE is the result of a variety of risk factors, and family members and medical staff should pay attention to newborns with the above characteristics. First of all, relevant departments should improve the awareness and recognition ability of primary medical staff and parents about neonatal hyperbilirubinemia and increase the importance of neonatal hyperbilirubinemia. Secondly, when the primary medical institutions lack the necessary equipment to detect bilirubin, the standard for starting phototherapy can be appropriately relaxed. Finally, the vast majority of neonates with hyperbilirubinemia only need to be screened, evaluated, and tested for bilirubin so that they can be treated promptly. Neonatal hyperbilirubinemia should neither be overtreated nor delayed. In short, do a good job in perinatal health care and prenatal screening for hemolytic diseases and improve the follow-up mechanism after discharge. At the same time, for newborns with high serum bilirubin, enough attention should be paid to early intervention to reduce the occurrence of hyperbilirubinemia and ABE.

5. Strengths and Limitations

The advantage of this study is that it can analyze the clinical data of children with severe hyperbilirubinemia, obtain the influencing factors of ABE in such children, and construct a nomogram model that can predict the risk of ABE. These findings are helpful for early detection of high-risk children in clinical practice and relevant measures for intervention, thereby reducing the risk of ABE. However, this study also has certain limitations. For example, this study is retrospective, and the accumulation of research data was not controlled by the research group. Therefore, there may be some information bias that affects the reliability of the results. In addition, this study belongs to a single-center study with a small sample size, and the results of the study have not yet been applied in clinical practice, which means a large number of multicenter studies are still needed to be verified.

6. Conclusions

The occurrence of ABE in neonates with severe hyperbilirubinemia is affected by many factors, and there is a certain degree of interaction between these factors. This study combined multiple factors to construct a risk nomogram model. The validated model has high predictive performance for ABE in children with severe neonatal hyperbilirubinemia and can provide a reference for early clinical detection of high-risk neonates.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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