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A clinical prediction rule for acute bilirubin encephalopathy in neonates with extreme hyperbilirubinemia

A retrospective cohort study

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Abstract

To establish a clinical prediction rule for acute bilirubin encephalopathy (ABE) in term/near-term neonates with extreme hyperbilirubinemia.

A retrospective cohort study was conducted between January 2015 and December 2018. Six hundred seventy-three out of 26,369 consecutive neonates with extreme hyperbilirubinemia were enrolled in this study. Data included demographic characteristics, total serum bilirubin (TSB), albumin, bilirubin/albumin ratio (B/A), direct antiglobulin test, glucose-6-phosphate deficiency, asphyxia, sepsis, acidosis. ABE was defined as a bilirubin induced neurological dysfunction score of 4 to 9. We used stepwise logistic regression to select predictors of ABE and devised a prediction score.

Of the 673 eligible infants, 10.8% suffered from ABE. Our prediction score consisted of 3 variables: TSB (as a continuous variable; odds ratio [OR] 1.16; 95% confidence interval [CI], 1.02–1.31; logistic coefficient 0.15), B/A (as a continuous variable; OR 1.88; 95% CI, 1.19–2.97; logistic coefficient 0.67), and sepsis (OR 3.78; 95% CI, 1.40–10.21; logistic coefficient 1.19). Multiplying the logistic coefficients by 10 and subtracting 75, resulted in the following equation for the score: Score = 12 × (if sepsis) + 1.5 × (TSB) + 7 × (B/A) − 75. The model performed well with an area under the curve of 0.871.

The risk of ABE can be quantified according to TSB, B/A, and sepsis in term/near-term neonates with extreme hyperbilirubinemia.

Abbreviations: AAP = American Academy of Pediatrics, ABE = acute bilirubin encephalopathy, AUC = area under the curve, B/A = bilirubin/albumin ratio, BIND = bilirubin induced neurological dysfunction, CI = confidence interval, DAT = direct antiglobulin test, G6PD = glucose-6-phosphate dehydrogenase, OR = odds ratio, TSB = total serum bilirubin, ZUCH = Zhejiang University Children's Hospital.

Keywords: acute bilirubin encephalopathy, hyperbilirubinemia, neonate, predictor

1. Introduction

Acute bilirubin encephalopathy (ABE) is a severe complication of extreme hyperbilirubinemia. Infants who had intermediate or advanced phases of ABE are at high risk of developing death or chronic bilirubin encephalopathy (kernicterus). The American Academy of Pediatrics (AAP) guidelines for jaundiced term/near-term infants to prevent kernicterus are based on total serum bilirubin (TSB) levels.[1] However, TSB is poor predictor of bilirubin neurotoxicity.[2–5] Moreover, recent research reporting that kernicterus occurred only very rarely, and only at very high (>35 mg/dL) TSB levels,[6,7] suggests that previously recommended phototherapy and exchange transfusion treatment thresholds may be unnecessarily aggressive. Therefore, it is necessary to investigate clinical predictors of ABE for preciser intervention. To establish a clinical prediction rule for ABE, we conducted a retrospective cohort study in term/near-term neonates with extreme hyperbilirubinemia.

2. Methods

2.1. Design and subjects

We selected subjects for this retrospective cohort study from the population of 26,369 neonates admitted to 1 hospital in

Editor: Jing Liu.

This work was supported by the National Natural Science Foundation of China (81571263, 81871012, and 81300975), the Zhejiang Provincial Technology Plan (2015C37105), the Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education, and the Key Laboratory for Diagnosis and Therapy of Neonatal Diseases of Zhejiang Province. These organizations had no part in the study design, data collection and analysis, publication decisions, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

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How to cite this article: Zhang F, Chen L, Shang S, Jiang K. A clinical prediction rule for acute bilirubin encephalopathy in neonates with extreme hyperbilirubinemia: A retrospective cohort study. Medicine 2020;99:9(e19364).

Received: 25 October 2019 / Received in final form: 28 January 2020 / Accepted: 30 January 2020

http://dx.doi.org/10.1097/MD.0000000000019364

southeast area of China between January 1, 2015 and December 31, 2018. We enrolled subjects who had TSB ≥25 mg/dL (428 μmol/L), gestational age ≥35 weeks, and admission age ≤14 days (n = 676). We excluded infants (n = 3) who had a conjugated bilirubin level ≥20% TSB and infants with chromosomal disorder and infants with encephalitis. After these exclusions, the study cohort had 673 infants. Infants were treated by exchange transfusion and/or phototherapy according to the guidelines of AAP subcommittee on hyperbilirubinemia.[1]

The institutional review board of the Zhejiang University Children's Hospital (ZUCH) approved the study and waived the requirement for obtaining informed consent due to the retrospective nature of this study (2019-IRB-014).

2.2. Laboratory analysis

TSB and albumin levels, glucose-6-phosphate dehydrogenase (G6PD) quantification and direct antiglobulin test (DAT) were determined in the clinical laboratory at ZUCH. TSB was measured by the spectrophotometric method using the ABL800 FLEX analyzer (Radiometer Medical Aps, Denmark, Bronshoj). Albumin was measured by the bromocresol purple method using Chemistry Analyzer AU5800 (Beckman Coulter, Brea, CA). Quantitative G6PD assay was performed by fluorometric method using a G6PDH kit (PerkinElmer, Finland, Turku). The DAT (also known as direct Coombs test) was performed using the LISS/Coombs method (DiaMed GmbH, Switzerland, Pra Rond).

2.3. Definitions

ABE is defined as a bilirubin induced neurological dysfunction (BIND) score of 4 to 9.[8] The BIND score was based on clinical changes in mental state, muscle tone, and cry; a score of 0 to 3 was assigned to each category, yielding a total score ranging from 0 to 9. The BIND score describes the progression of ABE. Scores of 4 to 6 represent moderate ABE, and scores of 7 to 9 indicate severe ABE that is highly associated with kernicterus or death. Infants with BIND scores of 1 to 3 are referred to as having mild neurotoxicity that is likely to be reversible without sequelae.

G6PD deficiency was defined as G6PD activity <2.6 U/g hemoglobin.[9] Sepsis was defined as clinical deterioration in the presence of leukocytosis, leucopenia, a positive C-reactive protein (>8 mg/L) or positive blood culture.[10] As per AAP and American College of Obstetrics and Gynecology, all the following must be present for designation of asphyxia such as, profound metabolic or mixed academia (pH <7) in cord, persistence of Apgar scores 0 to 3 for longer than 5 minutes, neonatal neurological sequel and multiple organ involvement.[11]

2.4. Statistical analyses

All these variables were compared between the non-ABE and ABE group. *t* test was used to compare continuous variables consistent with normal distribution. Skew distribution data was tested by Kruskal–Wallis test. Categorical data was text by Chi-squared test and Fisher exact test was conducted if any theoretical frequency was expected less than 10.

We obtained multivariate odds ratios (ORs) by logistic regression. To generate a parsimonious rule, we included variables if they were significant ($P < .05$) by using entering logistic regression. To formulate the score, we summed the 3 highest ranked predictor variables, each multiplied by 10 times its logistic regression coefficient (to avoid decimals), and subtracted 75 to the total (to avoid negative scores). Because the logistic coefficients are equal to the logarithms of the ORs, summing them is equivalent to multiplying their ORs. We assessed goodness of fit by using the Hosmer–Lemeshow test and discrimination by using area under the curve (AUC). We performed analyses by using SPSS (version 20) program (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

3. Results

3.1. Cohort characteristics

Characteristics of the study cohort are shown in Table 1. The median gestational age was 38^{+6} ($38–39^{+4}$) weeks. 409 (60.7%) infants were male. The mean birth weight was 3286 ± 432 grams. 162 (24.1%) infants were born by cesarean section. 55 (8.2%) infants' weight were lost over 12%. 431 (64.0%) infants got breast milk feeding. The mean TSB was 29.0 ± 4.1 mg/dL. The mean age at admission was 6 (4–8) days. The mean serum albumin was 3.85 ± 0.46 g/dL. The mean bilirubin/albumin ratio (B/A) was 7.51 ± 1.23 mg/g. 149 (22.1%) infants had positive DAT. 60 (8.9%) infants had G6PD deficiency. No infants had asphyxia. Of the infants with sepsis, 15 had positive blood culture and 21 were proven sepsis compared to clinical sepsis with negative cultures. One infant had acidosis. 195 (29.0%) infants were given exchange transfusion.

3.2. Predictors of ABE

Of the 673 eligible infants, 73 (10.8%) met our definition of ABE (Table 1). Thirty-one infants (4.6%) were scored 4 to 6 and 42 infants (6.2%) were scored 7 to 9 according to the BIND score.

Table 1

Cohort characteristics (N = 673).

Variables	n	%
Gestational age, wk, median ($P_{25–75}$)	38^{+6}($38–39^{+4}$)	–
Male sex	409	60.7
Birth wt, g, mean (SD)	3286 (432)	–
Cesarean section	162	24.1
Weight loss >12%	55	8.2
Breast milk feeding	431	64.0
TSB at admission, mg/dL, mean (SD)	29.0 (4.1)	–
Age at admission, d, median (*P*25–75)	6 (4–8)	–
Serum albumin, g/dL, mean (SD)	3.85 (0.46)	–
Bilirubin/Albumin, mg/g, mean (SD)	7.51 (1.23)	–
Positive DAT	149	22.1
G6PD deficiency	60	8.9
Asphyxia	0	0.0
Sepsis	36	5.3
Acidosis	1	0.1
BIND score		
0	532	79.0
1–3	68	10.1
4–6	31	4.6
7–9	42	6.2
Exchange transfusion	195	29.0

BIND = bilirubin induced neurological dysfunction, DAT = direct antiglobulin test, SD = standard deviation, – = not applicable.

Table 2

Univariate predictors of ABE.

Variables	Non-ABE n = 600	ABE n = 73	P
Gestational age, wk, median (P25–75)	39 (38–39^{+4})	38^{+3}(37–39^{+1})	.014
Male sex, n (%)	362 (60.3)	47 (64.4)	.503
Birth wt, g, mean (SD)	3301 (428)	3165 (449)	.899
Cesarean section, n (%)	136 (22.7)	26 (35.6)	.015
Weight loss >12%, n (%)	51 (8.5)	4 (5.5)	.374
Breast milk feeding, n (%)	379 (63.2)	52 (71.2)	.175
TSB at admission, mg/dL, mean (SD)	28.2 (3.1)	35.3 (5.9)	<.001
Age at admission, d, median (P25–75)	6 (4–8)	7 (4–8)	.702
Serum albumin, g/dL, mean (SD)	3.86 (0.45)	3.73 (0.57)	.257
Bilirubin/Albumin, mg/g, mean (SD)	7.29 (0.97)	9.34 (1.59)	<.001
Positive DAT, n (%)	125 (20.8)	24 (32.9)	.019
G6PD deficiency, n (%)	41 (6.8)	19 (26.0)	<.001
Asphyxia, n (%)	0 (0.0)	0 (0.0)	–
Sepsis, n (%)	23 (3.8)	13 (17.8)	<.001
Acidosis, n (%)	1 (0.2)	0 (0.0)	–

ABE = acute bilirubin encephalopathy, DAT = direct antiglobulin test, SD = standard deviation, – = not applicable.

Table 2 shows the univariate predictors and Table 3 shows the multivariate predictors of ABE. In univariate analysis, 7 predictors were captured. Compared to the non-ABE group, the ABE group had lower gestational age (38^{+3}[37–39^{+1}] vs 39 [38–39^{+4}] wk, $P = .014$), more cesarean section (26[35.6%] vs 136[22.7%], $P = .015$), higher TSB (35.3 ± 5.9 vs 28.2 ± 3.1 mg/dL, $P < .001$), higher B/A (9.34 ± 1.59 vs 7.29 ± 0.97 mg/g, $P < .001$), more positive DAT (24[32.9%] vs 125[20.8%], $P = .019$), more G6PD deficiency (19[26.0%] vs 41[6.8%], $P < .0001$) and more sepsis (23[3.8%] vs 13[17.8%], $P < .0001$) (Table 2). In adjusted analysis, three independent risk factors for ABE were indentified, which were TSB, B/A, and sepsis (Table 3). TSB was associated with higher odds of ABE, especially infants whose TSB ≥35 mg/dL, for whom the OR was 9.52 compared with infants whose TSB ≤30 mg/dL. Furthermore, infants whose B/A >8.5 mg/g had higher odds of ABE, as did those whose B/A <7.5 mg/g (OR 5.66; 95% confidence interval [CI], 1.83–17.48)

Table 3

Multivariate predictors of ABE.

Variables	OR	95% CI	P
Gestational age	0.81	0.64–1.02	.078
Cesarean section	0.62	0.32–1.22	.167
TSB at admission, mg/dL	1.16	1.02–1.31	.027
25–30	Reference	–	–
30–35	1.83	0.73–4.62	.200
≥35	9.52	3.12–29.06	<.001
Bilirubin/Albumin, mg/g	1.88	1.19–2.97	.007
<7.5	Reference	–	–
7.5–8.5	2.51	1.02–6.22	.046
>8.5	5.66	1.83–17.48	.003
Positive DAT	1.93	0.97–3.88	.063
G6PD deficiency	1.63	0.69–3.87	.270
Sepsis	3.78	1.40–10.21	.009
No	Reference	–	–
Yes	3.73	1.46–9.55	.006

ABE = acute bilirubin encephalopathy, CI = confidence interval, DAT = direct antiglobulin test, OR = odds ratio, TSB = total serum bilirubin, – = not applicable.

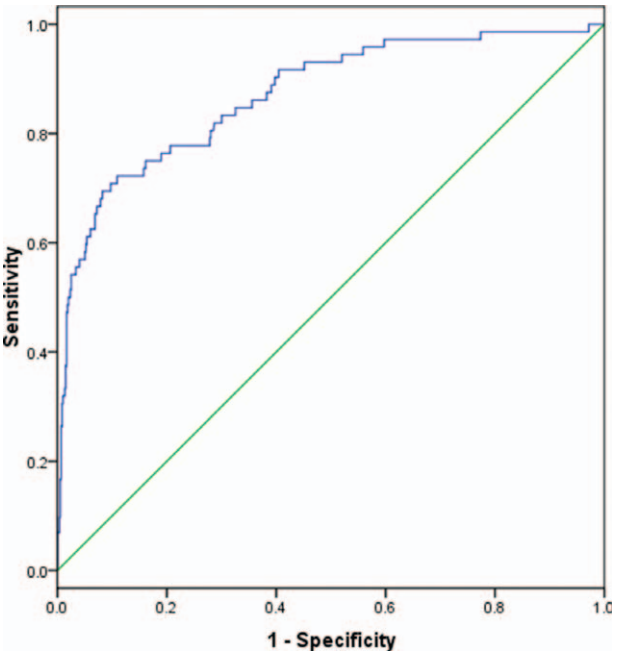

Figure 1. Receiver operating characteristic curve of the prediction score. Area under receiver operating characteristic curve = 0.871.

In addition, the odds of ABE were higher for infants with sepsis (OR 3.73; 95% CI, 1.46–9.55).

3.3. Prediction rule and score

After stepwise selection, the prediction rule consisted of 3 predictors: TSB (as a continuous variable; OR 1.16; 95% CI, 1.02–1.31; logistic coefficient 0.15), B/A (as a continuous variable; OR 1.88; 95% CI, 1.19–2.97; logistic coefficient 0.67), and sepsis (OR 3.78; 95% CI, 1.40–10.21; logistic coefficient 1.19). Multiplying the logistic coefficients by 10 and subtracting 75, as previously described, resulted in the following equation for the score:

$$\text{Score} = 12 \times (\text{if sepsis}) + 1.5 \times (\text{TSB}) + 7 \times (\text{B/A}) - 75.$$

For example, an infant with sepsis whose TSB was 35 mg/dL and B/A was 8.5 mg/g would have a score of 12 + (1.5 × 35) + (7 × 8.5) − 75 = 44, whereas a score for the same baby without sepsis would be 12 fewer, or 32.

The discrimination and fit of the predictive model using the generated score were excellent. The Hosmer–Lemeshow x^2 (8 degrees of freedom) was 4.7 ($P = .79$) and the AUC was 0.871 (95% CI, 0.824–0.919) (Fig. 1).

The probability of ABE was <12% with a prediction score of <30 and <5% with a prediction score of <20 (Table 4 and Fig. 2).

4. Discussion

Our study showed that TSB, B/A, and sepsis have strong association with ABE in term/near-term neonates with extreme hyperbilirubinemia. Based on these 3 predictors, we devised a prediction score to quantify the probability of ABE. Clinical implementation of this prediction rule via a Web-based calculator

Table 4

Risk of ABE by score.

Prediction score	Infants with ABE	
	N	%
≤9	1/114	0.9
10–19	10/282	3.5
20–29	9/132	6.8
30–39	10/68	14.7
40–49	8/27	29.6
≥50	34/45	75.6

ABE = acute bilirubin encephalopathy.

or integration into electronic medical records could help guide management of neonatal hyperbilirubinemia.

TSB is a well-established risk factor for bilirubin neurotoxicity.[12–14] In Nigeria, a multicenter study also identified TSB as a predictor for ABE, which was consistent with our study.[15] In northern California, 4 children had ABE all had TSB >38 mg/dL[7]. TSB represents 3 forms of bilirubin in circulation: unconjugated bilirubin bound to albumin; conjugated bilirubin, comprising mainly monoglucuronides and diglucuronides; conjugated bilirubin bound to albumin. However, the neurotoxicity of bilirubin is thought to be primarily determined by the unconjugated bilirubin not bound to albumin (known as free or unbound bilirubin),[16] which is not included in TSB. The limitation of sole reliance on TSB as a predictor of neurotoxicity has been highlighted in several reports.[17] The combination of TSB with other clinical predictors for predicting ABE has not been investigated in previous studies.

The use of B/A as a surrogate for plasma free bilirubin has been suggested because it contains 2 of the 3 components for deriving free bilirubin.[18] Amin et al found that free bilirubin was a more sensitive and specific predictor of auditory neuropathy spectrum disorder than TSB.[19] Morioka et al reported that free bilirubin may be helpful for identifying extremely low birth weight infants at risk for developing kernicterus.[20] 1 g albumin can bind to 8.5 mg bilirubin, which varies with body environment. Our study found that when B/A >8.5 mg/g, the risk of ABE was significantly increased. This was in line with previous theory. Iskander et al found that B/A was a strong predictor of neurotoxicity, but B/A did not improve prediction over TSB alone.[8] Our study indicated that B/A was a better predictor of ABE than TSB. In Iskander's study, they encountered uncertainties in assigning risk factors for ABE and therefore they did not adjust the risk factors. This might be 1 reason of the contrary result.

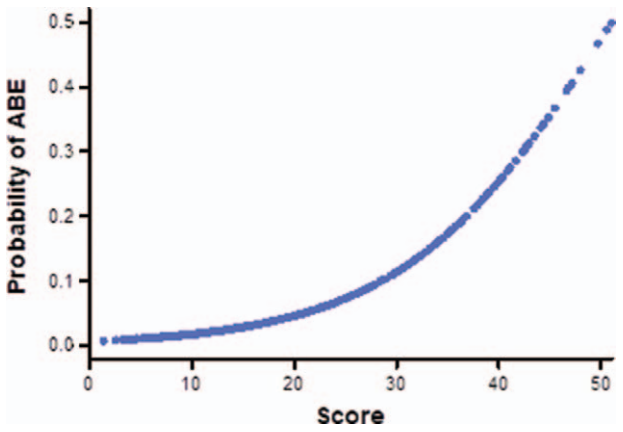

Figure 2. Probability of acute bilirubin encephalopathy (ABE) by score. Score = 12 × (if sepsis) + 1.5 × (TSB) + 7 × (B/A) − 75. TSB = total serum bilirubin.

Sepsis is thought to be one of the risk factors for bilirubin neurotoxicity,[21] but data ranked the risk factors are limited. Our study identified sepsis as an independent predictor of ABE. The strength of the association between other risk factors (eg, hemolytic disease, G6PD deficiency) and ABE was attenuated after controlling other variables. Consistent with our study, Gamaleldin et al reported that ABO compatibility and G6PD deficiency created minimal if any additional risk compared with idiopathic jaundice.[22] One possible explanation to the attenuation is that hemolytic disease or G6PD deficiency may produce brain damage by influencing the bilirubin level. Increase in pro-inflammatory cytokines such as TNF-α, interleukin-1β, and interleukin-6 are frequently observed in infants suffering from neonatal sepsis.[23] These events might damage the endothelial integrity and increase blood brain barrier permeability,[24,25] which could facilitate the entry of free bilirubin to the brain. This may be 1 possible explanation of the association between sepsis and ABE.

Our prediction score quantifies the probability of ABE to help physicians and parents evaluate need for phototherapy or exchange transfusion. For example, consider an infant who has sepsis. The infant whose TSB is 25 mg/dL and B/A is 6.5 mg/g gives a score of 20 and an estimated 4.6% probability of ABE. In comparison, the probability of ABE would increase to 17.3% if the infant's TSB is 35 mg/dL and 16.0% if the infant's B/A is 8.5 mg/g.

Our study has some limitations. First, this is a single-center retrospective study. Additionally, we did not evaluate auditory pathway toxicity. Alterations in brainstem auditory evoked potentials are common and may be the only manifestation of bilirubin-induced brain injury. Finally, the sample size did not allow us to validate our prediction rule.

More prospective observational studies from multiple centers are needed in the future to provide more clinical data about ABE in neonates with extreme hyperbilirubinemia. A more precise prediction rule with better generalization capacity would be developed.

Author contributions

Dr. Zhang conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Chen and Dr. Shang carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Jiang designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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References

[1] 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.
[2] Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114:e130–53.
[3] Scheidt PC, Graubard BI, Nelson KB, et al. Intelligence at six years in relation to neonatal bilirubin levels: follow-up of the National Institute of Child Health and Human Development Clinical Trial of Phototherapy. Pediatrics 1991;87:797–805.

[4] Seidman DS, Paz I, Stevenson DK, et al. Neonatal hyperbilirubinemia and physical and cognitive performance at 17 years of age. Pediatrics 1991;88:828–33.
[5] Ozmert E, Erdem G, Topcu M, et al. Long-term follow-up of indirect hyperbilirubinemia in full-term Turkish infants. Acta paediatrica 1996;85:1440–4.
[6] Ebbesen F, Bjerre JV, Vandborg PK. Relation between serum bilirubin levels >/=450 mumol/L and bilirubin encephalopathy; a Danish population-based study. Acta Paediatr 2012;101:384–9.
[7] Kuzniewicz MW, Wickremasinghe AC, Wu YW, et al. Incidence, etiology, and outcomes of hazardous hyperbilirubinemia in newborns. Pediatrics 2014;134:504–9.
[8] Iskander I, Gamaleldin R, El Houchi S, et al. Serum bilirubin and bilirubin/albumin ratio as predictors of bilirubin encephalopathy. Pediatrics 2014;134:e1330–9.
[9] Fu C, Luo S, Li Q, et al. Newborn screening of glucose-6-phosphate dehydrogenase deficiency in Guangxi, China: determination of optimal cutoff value to identify heterozygous female neonates. Sci Rep 2018;8:833.
[10] Makkar M, Gupta C, Pathak R, et al. Performance evaluation of hematologic scoring system in early diagnosis of neonatal sepsis. J Clin Neonatol 2013;2:25–9.
[11] American Academy of Pediatrics Subcommittee on Fetus and Newborn, American College of Obstetricians and Gynecologists Subcommittee on Obstetric PracticeUse and abuse of the Apgar score. Pediatrics 1996; 98:141–2.
[12] Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003;112:773–9.
[13] Arun Babu T, Bhat BV, Joseph NM. Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyperbilirubinemia. Indian J Pediatr 2012;79:202–6.
[14] Helal NF, Ghany E, Abuelhamd WA, et al. Characteristics and outcome of newborn admitted with acute bilirubin encephalopathy to a tertiary neonatal intensive care unit. World J Pediatr 2019;15:42–8.
[15] Diala UM, Wennberg RP, Abdulkadir I, et al. Patterns of acute bilirubin encephalopathy in Nigeria: a multicenter pre-intervention study. J Perinatol 2018;38:873–80.
[16] Cayabyab R, Ramanathan R. High unbound bilirubin for age: a neurotoxin with major effects on the developing brain. Pediatr Res 2019;85:183–90.
[17] Wennberg RP, Ahlfors CE, Bhutani VK, et al. Toward understanding kernicterus: a challenge to improve the management of jaundiced newborns. Pediatrics 2006;117:474–85.
[18] Sato Y, Morioka I, Miwa A, et al. Is bilirubin/albumin ratio correlated with unbound bilirubin concentration? Pediatr Int 2012;54:81–5.
[19] Amin SB, Wang H, Laroia N, et al. Unbound bilirubin and auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice. J Pediatr 2016;173:84–9.
[20] Morioka I, Nakamura H, Koda T, et al. Serum unbound bilirubin as a predictor for clinical kernicterus in extremely low birth weight infants at a late age in the neonatal intensive care unit. Brain Dev 2015;37:753–7.
[21] Maisels MJ, Bhutani VK, Bogen D, et al. Hyperbilirubinemia in the newborn infant > or=35 weeks' gestation: an update with clarifications. Pediatrics 2009;124:1193–8.
[22] Gamaleldin R, Iskander I, Seoud I, et al. Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia. Pediatrics 2011;128: e925–31.
[23] Khaertynov KS, Boichuk SV. Comparative assessment of cytokine pattern in early and late onset of neonatal sepsis. J Immunol Res 2017; 2017:8601063.
[24] Ardid-Ruiz A, Harazin A, Barna L, et al. The effects of Vitis vinifera L. phenolic compounds on a blood-brain barrier culture model: expression of leptin receptors and protection against cytokine-induced damage. J Ethnopharmacol 2019;112253.
[25] Geng J, Wang L, Zhang L, et al. Blood-brain barrier disruption induced cognitive impairment is associated with increase of inflammatory cytokine. Front Aging Neurosci 2018;10:129.