Journal of Biosciences and Medicines, 2025, 13(8), 335-347
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Advances in Biomarkers of Neonatal Hyperbilirubinemia

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How to cite this paper: Sun, Q.S., Ye, Z.X., Wu, T.T. and Fan, Q.H. (2025) Advances in Biomarkers of Neonatal Hyperbilirubinemia. *Journal of Biosciences and Medicines*, **13**, 335-347.
https://doi.org/10.4236/jbm.2025.138026

Received: July 12, 2025
Accepted: August 16, 2025
Published: August 19, 2025

Abstract

Neonatal hyperbilirubinemia (NHB) is a common neonatal disease in clinical practice, and bilirubin encephalopathy caused by excessive free bilirubin across the blood-brain barrier causes irreversible neurological damage to the central nervous system, which is the most serious complication. Therefore, early prediction of NHB, early diagnosis, and intervention are significant to prevent the emergence of serious complications of NHB. In recent years, with the development of science and technology, molecular biology and genomics, a variety of novel biomarkers have been discovered and applied to the clinic. This article focuses on NHB-related biomarkers and also discusses the value of these biomarkers in disease prediction, diagnosis, prognosis assessment, and treatment monitoring, which will provide a reference for clinical practice and future research.

Keywords

Neonatal Hyperbilirubinemia, Bilirubin Encephalopathy, Biomarker

1. Current Status of Monitoring Hyperbilirubinemia

Neonatal hyperbilirubinemia is a common and widespread disease in the neonatal period [1], in the neonatal period, erythrocyte destruction will be converted to unconjugated bilirubin under the action of enzymes, and free bilirubin will be bound to albumin in the liver, and the abnormally increased amount of free bilirubin will pass the blood-brain barrier to damage the neuronal cells, which will cause irreversible damage to the nervous system, resulting in acute bilirubin encephalopathy (ABI). Bilirubin encephalopathy (ABE) and kernicterus may put newborns at risk for bilirubin-induced death or long-term neurodevelopmental

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disorders [2]. Bilirubin damage to neuronal cells in the early stages can be restored; however, neurological damage is irreversible when bilirubin encephalopathy develops. Therefore, early recognition of the onset of NHB and early monitoring and detection of bilirubin-induced neurological deficits are particularly critical [3] [4].

Visual assessment, transcutaneous bilirubinometry (TcB), and total serum bilirubin (TSB) are the main universal screening and detection tools in the management and follow-up of newborns and hyperbilirubinemic children in China and abroad, but due to the differences in ethnicity, the visual assessment will be the same as the actual bilirubin level. actual bilirubin levels. Also, TCB can be affected by skin color. The method has the advantage of being non-invasive and rapid, but there is some error with TSB levels, so visual assessment and TcB are used for the initial screening of children in need of TSB testing. However, a single test may not accurately reflect the severity of the condition. Therefore, in recent years, researchers have worked to find more sensitive and specific biomarkers that can detect the emergence of neonatal hyperbilirubinemia earlier and predict the development of bilirubin encephalopathy more sensitively, to minimize the incidence of neurological damage and the rate of morbidity and mortality.

2. Serologic Markers

2.1. Serum Total Bilirubin (TSB)

At present, domestic and international standards for the detection of neonatal jaundice and phototherapy are often based on the serum total bilirubin level as the gold standard to predict the risk of bilirubin encephalopathy by the rate of rise of bilirubin [5] [6]. Phototherapy threshold curves were plotted according to different gestational ages, days of age, and the presence or absence of risk factors for bilirubin neurotoxicity to guide the treatment of NHB.TSB reflects bilirubin overload in neonates and may reflect the severity of NHB to some extent; however, in a related study, neonates with a TSB level greater than 13.5 mg/dl (230.9 umol/L) were compared with neonates with a TSB less than 13.5 mg/dl were compared [7], with no significant difference in the incidence of cerebral palsy, deafness, developmental delays, or visual abnormalities over a two-year follow-up. It has also been shown that when total bilirubin (TBIL) is less than 205 μmol/L, it may cause neurological damage, whereas TBIL greater than 600 μmol/L may not occur [5]-[9]. Therefore, the level of bilirubin and the degree of its elevation are not completely consistent with the risk of neurological damage, and it is not specific for the prediction of damage to organ function, the degree of neurotoxicity, or the incidence of ABE or neurological damage.

2.2. Bilirubin/Albumin Ratio (B/A)

Bilirubin bound to albumin does not easily cross the blood-brain barrier and has no significant neurotoxicity, whereas the bilirubin/albumin ratio reflects bilirubin overload and albumin-bilirubin binding capacity. The bilirubin/albumin ratio is

considered to be valuable in the monitoring of NHB progression, prediction of bilirubin neurological damage, and prognostic assessment of ABE in related studies. Handan ŞAHAN, Selvi GÜLAŞI [10] and May Ahmed Khairy, Walaa Alsharany Abuelhamd and other scholars [11] studied cord blood bilirubin/albumin levels on the first day of life of newborns as an indicator for screening newborn hyperbilirubinemia thereafter, and by determining the levels of cord blood bilirubin, albumin levels on the first day of life, and by measuring bilirubin on the days of postnatal follow up, it was concluded that the cord blood B/A was significantly increased and $P < 0.001$ was statistically significant, and in ROC curve analysis, the cord B/A ratio had a good predictive value for the development of hyperbilirubinemia in newborns when it reached a critical value. However, the B/A ratio may also be affected by drugs or other components of plasma that bind free bilirubin, In cases of low bilirubin kernicterus, an elevated B/A ratio may help predict the risk of neurological damage. However, bilirubin-induced neurological damage occurs at total bilirubin levels, and low albumin levels are considered harmless.

In a study by Wenqing Kang, Xiao Yuan *et al.* [3]. Serum bilirubin and albumin values were measured in neonates with confirmed ABE, and B/A was analyzed by logistic regression analysis in a certain number of groups presenting with ABE adverse outcomes, with the conclusion suggesting that B/A was correlated with the adverse outcomes, suggesting that it could predict the occurrence of adverse outcomes. Some scholars have also selected predictors of ABE by logistic regression analysis by measuring bilirubin, albumin, B/A levels, and direct anti-human globulin test in children with established ABE [12], which identified B/A as an independent risk factor. However, related studies have concluded that the B/A ratio is not more valuable in predicting bilirubin encephalopathy than the determination of TSB levels alone [13].

2.3. End-Tidal Carbon Monoxide (ETCO), Carboxyhemoglobin (COHb)

Bilirubin maintains a certain balance between production and metabolism. In ABO hemolysis, red blood cells are destroyed in large quantities and thus produce too much bilirubin to upset this balance, leading to early onset of jaundice and even higher levels of hyperbilirubinemia [14], so early prediction and identification of ABO hemolysis in the newborn, as well as prevention of acute or chronic neurological impairment, are also particularly important.

In the latest edition of the NHB Clinical Guidelines [15], it is also recommended that ETCO or COHb be recommended as a predictor for screening and evaluation of hemolytic disease in newborns. Since hemoglobin is metabolized to produce equimolar amounts of carbon monoxide and bilirubin due to enzyme catalysis, CO production can be considered as an alternative to being able to measure bilirubin production, and CO is exchanged for oxygen in respiration, thus allowing for the use of ETCO or COHb in the blood as a means of assessing hemolysis [16]. However, COHb is mostly used for laboratory tests.

ETCO, on the other hand, as a noninvasive test, is considered to be clinically

useful for identifying the occurrence of hemolysis in newborns and predicting the risk of NHB [17]. Initially, at birth, there is a transient decrease in ETCO due to physiologic destruction of red blood cells, but when a newborn develops jaundice, there is a persistent or increased level of ETCO, suggesting increased hemoglobin metabolism. This assay was statistically validated in several studies, and it was concluded in various experiments that $P < 0.05$ was statistically significant [14] [17]-[19], and it was concluded that early identification of at-risk infants could be improved with this method.

In the management of NHB, ETCO is also recognized as a predictor for assessing the need for extended phototherapy. In a study by Bahr TM *et al.*, the relationship between ETCO levels and duration of phototherapy in children with NHB was investigated and it was concluded that elevated ETCO levels were associated with earlier initiation or longer duration of phototherapy and it was statistically concluded that when ETCO was elevated by 1 ppm earlier initiation and longer duration of phototherapy was required and this conclusion was placed at the 95% credible interval [20] however the cases included in this study were more likely to have a high risk of NHB than those included in the study. The cases included in this study were mostly normal newborns and a few children with lower TSB levels. The same conclusion that children with higher levels of ETCO need longer phototherapy was made in the study by Yuan-Li Zhan *et al.* [17], but the cases included in this study were characterized by significant hyperbilirubinemia and TSB levels. All of the above studies clarified the relationship between ETCO and duration of phototherapy, but did not show the rationale for this conclusion, and did not include a certain number of children with mild NHB in the study. Therefore, the reason why the initial ETCO level was used to predict the duration of treatment is not clear, and the conclusion that the level of this index is related to the prediction of the duration of treatment can necessarily be used in children with mild NHB has not been confirmed by studies, and needs to be confirmed by further studies by more scholars.

2.4. Nucleated Red Blood Cells (nRBC)

Bilirubin is converted from hemoglobin, which originates from the destruction of red blood cells. Bilirubin acts as an antioxidant, and its antioxidant capacity is enhanced at elevated levels. Therefore, its relationship with NHB has been explored. In a study by Orhon [21] *et al.*, a statistical analysis of neonatal umbilical cord blood nRBC counts showed that nRBC counts were elevated in neonatal hyperbilirubinemia and were statistically different at $P < 0.05$ by intergroup comparison, which led to the conclusion that elevated Nucleated Red Blood Cell (NRC) counts could be used to predict the occurrence of NHB. This procedure is non-invasive and simple, and is considered to be a novel biomarker for the follow-up of newborns. However, in this study, nRBC counts at a certain cut-off value in children with NHB were not investigated to indicate the need for phototherapeutic interventions, and there was insufficient evidence that this marker could iden-

tify neonates in need of phototherapy. In a further study by Sadgunraju Chakrahari and other scholars, it was found that when the nRBC count was above the cutoff value, it had a high sensitivity and percentage of negative predictive value in prediction, however, it had a low percentage of positive predictive value, and when it was less than the cutoff value, some neonates had NHB as well [22]. Therefore, nRBC may also help clinicians to identify newborns who do not require further evaluation and avoid further invasive procedures such as refinement of serum bilirubin.

2.5. Reticulocyte Count (RC), Erythropoietin (EPO)

Excessive destruction of red blood cells causes high bilirubin, Erythropoietin stimulates the hematopoietic system and regulates the process of erythrocyte elevation, Reticulocytes are the earliest anucleate red blood cells observed in peripheral blood cells, EPO may precede the elevation of RC, which also responds to the increase in the level of EPO [23]. In a study by Sadgunraju Chakrahar and other scholars, the relationship between reticulocytes and NHB was investigated, and this biomarker predicted the occurrence of NHB with specificity and sensitivity. And it was concluded that RC has a high negative predictive value, which can exclude, to some extent, that neonates are at risk of NHB, but it cannot be considered inevitable that neonates will develop NHB [22]. Elfarargy M S *et al.* concluded that EPO can predict the occurrence of NHB and that this biomarker has significant specificity and sensitivity by comparing the cord blood EPO levels of children who developed pathologic jaundice and did not develop pathologic jaundice that did not need to be treated with a statistically significant difference in the levels of EPO after the two groups, $P = 0.001$, and concluded that EPO can predict the occurrence of NHB, and that this biomarker has significant specificity and sensitivity [23].

2.6. Peripheral Blood Biomarkers (PBBIs)

Peripheral blood biomarkers are thought to be useful in differentiating the severity of disease in newborns with hyperbilirubinemia [24] [25]. These include: red blood cell (RBC), white blood cell (WBC) counts and their classification: absolute lymphocyte count (ALC), absolute neutrophil count (ANC), monocyte count, Alteration in platelet (PLT), mean cell volume (MCV), neutrophil to lymphocyte (NLR), platelet to lymphocyte ratio (PLR), and other blood cells. This may be related to the fact that bilirubin is not only an antioxidant and immunomodulator, but also an anti-inflammatory factor, which may promote or inhibit hematopoiesis, differentiation [24] [26]. Therefore, the relationship between the above markers and hyperbilirubinemia can be explored.

In the study of Li Zhang *et al.*, it was concluded that bilirubin was negatively correlated with leukocyte count, and TSB could regulate the elevated or decreased leukocyte count. However, elevated leukocyte counts can reflect enhanced cellular oxidative stress, and the antioxidant function of bilirubin may play a role and thus

be depleted, whereupon bilirubin concentrations are reduced [26]. In that study, only the correlation was explored without a clear causal relationship.

In the study of Çay, Özlem Özcanlı and other scholars, it was concluded that there was a statistically significant difference in WBC, ALC, monocyte count, ANC, and lymphocyte/monocyte before and after phototherapy at $P < 0.05$, and it was concluded that phototherapy is related to the inflammatory process, and that the above mentioned hematological markers may reflect the prognosis to some extent [27].

In a further study by Dereje Mengesha Berta *et al.* [24]. Newborns with hyperbilirubinemia were categorized into three groups of low, medium, and high risk, and venous blood of the children was taken for complete blood count and analyzed statistically. It was concluded that there was a significant decrease in RBC and MCV in the high-risk group, and bilirubin toxicity may also induce hemolysis, causing premature dispersion of erythrocytes, resulting in changes in number and volume. There was a decrease in ALC in the high-risk group, and this may be related to the fact that bilirubin induces the production of inflammatory factors and inhibits the production of ALC. There was a significant increase in ANCs, NLRs, and PLRs with the rise in bilirubin concentration, and it was suggested that the possible mechanisms were bilirubin-induced inflammatory cell production and inhibition of bone marrow hematopoiesis by bilirubin toxicity. Elevated bilirubin affects platelet aggregation, apoptosis, and thus platelet count.

3. Gene-Related Markers

Bilirubin is metabolized by heme, which is metabolized by various enzymes, such as heme oxygenase (HO-1) and biliverdin reductase A (BLVRA). Excessive elevation of bilirubin is the cause of neonatal hyperbilirubinemia, and elevated bilirubin levels are also affected by a variety of causes, among which are impaired hepatic uptake and binding, and increased enterohepatic circulation, where bilirubin needs to be bound to organic anion transporter polypeptide 2 (OATP2), a member of the organic anion transporter family, before entering the intestinal-hepatic cycle. OATP2) to enter the liver and subsequently bind to uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) for excretion into the intestine [28].

Mutations in the genes of the above enzymes can lead to alterations in the structure or function of the enzyme, which can affect the metabolism and elimination of bilirubin, leading to the development of NHB, and may also be associated with a dangerous degree of jaundice or even increase the need for phototherapy. Genes are polymorphic, and mutations may occur at different sites in the coding region, and mutations at different sites may also yield different results, which may be related to the effects of different ethnic and geographic differences. Mutations at different loci or multilocus mutations may also have inhibitory or protective effects on the development of NHB.

In a study by Nguyen TT *et al.* [29], it was suggested that mutations in the UGT1A1 gene were associated with the development of hyperbilirubinemia in Vi-

etnamese newborns, and that the pure polymorphisms were positively correlated with the severity of bilirubin levels. Similarly, in Atasilp *et al.* [30] also suggested that UGT1A1 polymorphisms (e.g., UGT1A1*28 and *6) are risk factors for severe hyperbilirubinemia in Thai newborns. However, in a study by XiuJu Liu *et al.* [31], it was concluded that polymorphisms in the UGT1A1 gene in neonatal hyperbilirubinemia patients in southern China affect bilirubin concentration, with statistically significant differences in bilirubin levels between mutations at different loci, where the CC genotype and the C allele in rs1188849 reduce the risk of NHB, whereas the opposite is true for the G allele. Bilirubin levels were low in rs4148325 carrying the CT genotype. However, in previous studies by different scholars, it was concluded that rs11888492 was not associated with TSB levels and rs4148325 may be associated with high levels of bilirubin, which may be influenced by different populations. Meanwhile, in this study, BLVRA variants rs699512 and rs7738 had no statistically significant increase in gene frequency in children with hyperbilirubinemia, and were not considered to have a significant effect on high bilirubin levels. Domestic scholars Yang *et al.* [32] found statistically significant differences in TSB levels between Han and Uyghur newborns with mutations in the UGT1A1 gene, and concluded that genetic polymorphisms in this gene are genetic regulators of the risk of NHB among different ethnic groups.

4. Metabolomic Markers

4.1. Insulin-Like Growth Factor-1 (IGF-1)

IGF-1 is a key factor in the regulation of cell metabolism, growth, and decay, and it activates downstream pathways that inhibit apoptosis of neural stem cells and attenuate neuronal cell damage [33] [34]. In several studies, researchers measured IGF-1 levels in the serum of hyperbilirubinemic and non-hyperbilirubinemic children and concluded that IGF-1 levels were statistically lower than those of the control group in hyperbilirubinemic children at $P < 0.05$, and that the difference in IGF-1 levels between children with different degrees of hyperbilirubinemia was also statistically significant [35] [36]. Thus, it can be concluded that IGF-1 levels are negatively correlated with high bilirubin levels and that this indicator has value in the prediction of children with NHB. In addition, IGF-1 can also be used to predict the efficacy of phototherapy in a study by Qianfei Wang, Ping Li, *et al.* By comparing the IGF-1 levels of phototherapy-sensitive and non-phototherapy-sensitive children, the difference was found to be statistically significant at $P < 0.05$, with a certain degree of specificity and sensitivity [37].

4.2. 25-Hydroxyvitamin D [25-Hydroxyvitamin D, (25-(OH)-D)]

Relevant studies have suggested that 25-hydroxyvitamin D levels have an impact on neonatal outcomes, among them Fernando M, WANG, WU *et al.* 25-(OH)-D is associated with neonatal jaundice [38]-[40]. In the meta-analysis of Huang *et al.* [41], the vitamin D level of hyperbilirubinemic neonates was lower than that of healthy neonates, with a statistically significant $P < 0.05$, which suggests that

the vitamin D level is associated with the development of NHB. In this meta-analysis, children with high bilirubin levels had lower vitamin D levels than healthy children, and it is considered that low vitamin D levels are associated with higher levels of bilirubin. However, in a study by Zhou *et al.* [42], 25-(OH)-D levels were lower in children in the NHB group than in the control group, but the difference was not statistically significant, and it was concluded that 25-(OH)-D levels do not have an absolute value in predicting the risk of developing NHB. The mechanism of the association between 25-hydroxyvitamin D and hyperbilirubinemia in newborns has not yet been well investigated either, and the possible mechanism may be related to the fact that vitamin D can reduce EPO levels and erythrocyte lysis, in addition to the antioxidant effect of vitamin D can reduce oxidative damage to erythrocytes, thus reducing bilirubin production; and both bilirubin and vitamin D metabolism are also produced in the liver [41] [42]. The relationship between the two is also controversial, so more research is needed to confirm this.

5. Proteomic Markers

5.1. Maternal Anti-A/B IgG Titer (Maternal Anti-A/Anti-B IgG Titer)

ABO antibody exists naturally, it is IgM class, not easy to pass through the placenta, while erythrocyte antigen enters the mother to stimulate the mother to produce the corresponding maternal antibody is IgG class, this antibody can pass through the placenta into the fetal circulation, when the fetus and the mother there is ABO blood group incompatibility, easy to hemolysis, Grethe R. Krog, *et al.* through the measurement of prenatal and perinatal maternal anti-A/B IgG titer, to explore its role in NHB, and to determine the role of maternal anti-A/B IgG titer, and to determine its role in NHB. , to explore its value and predictive significance in NHB, and the results showed that the antibody titer in the group with ABO hemolysis requiring phototherapy was significantly higher than that in the group with ABO hemolysis but not meeting the criteria for phototherapy, and the $P < 0.001$ was statistically significant [43]. In early pregnancy, due to the transit of IgG antibodies through the placenta, antibody titers may be at a low level, and in late pregnancy, due to the increase in maternal blood volume, antibody titers may be diluted and show a decreasing trend, however, in the group of ABO hemolyzed and subjected to phototherapy, there was a steady state in the anti-A/B IgG titers as detected in the group of ABO hemolyzed and subjected to phototherapy [43]. This led to the conclusion that maternal anti-A/B IgG titer has a predictive value for neonatal hyperbilirubinemia, and that there is an association between increased titer and hemolytic neonatal hyperbilirubinemia. By testing the sensitivity or specificity of different predictors in hemolytic jaundice, Cheng Xiaoqin and other scholars in their study concluded that anti-A/B IgG titer does not have high sensitivity and specificity in predicting hemolytic jaundice [44].

5.2. S100B

S100 protein is used clinically to assess neuropathy, brain diseases and some tu-

mors, but not much research has been done on the relationship between S100 protein and bilirubin encephalopathy. S100B protein is derived from glial cells in the brain tissue, and when its concentration is increased, it can exacerbate inflammatory responses and neuronal cell death [45]. In the study of Zhang Menglan *et al*, S100B was considered to be a risk factor for jaundice, and its level was higher in jaundiced children than in non-jaundiced children, and there was a statistically significant positive correlation between the levels of S100B and TSB with $P < 0.05$ [46]. CUI *et al*. continued to compare the levels of S100B between jaundiced children with brain injury and non-brain-injured children, and found that the group of brain-injured children had higher levels of S100B, $P < 0.05$ [45].Levels were higher with a statistically significant $P < 0.05$, and the authors concluded that this indicator has diagnostic value for brain injury. In the subsequent follow-up, S100B was found to be highly sensitive in the prediction of prognosis [45]. Although the relationship between S100B and jaundice was investigated in the above study, there are not many similar studies, and there are some limitations in this study, for example, S100B was considered to have diagnostic value in brain damage, but there were no related neurological symptoms in the children included in the study, so the value of this index in the prediction of neurological damage needs to be further explored.

6. Conclusions

In clinical practice, the conventional serum marker TSB is frequently utilized to evaluate the presence of jaundice in newborns and determine the necessity for intervention. While these levels can serve as an indication of the presence of NHB, they do not serve as a definitive confirmation of the occurrence of bilirubin-induced neurological damage. Conversely, low levels of bilirubin may still result in neurological damage, while elevated bilirubin levels do not necessarily lead to neurological dysfunction. However, the onset of acute bilirubin encephalopathy, or kernicterus, can result in adverse outcomes, including death, in newborns. Consequently, identifying additional biological markers to predict the occurrence of NHB and neurological damage, to guide early detection and intervention in clinical practice, and to prevent adverse outcomes is of great importance. However, reliance on a solitary marker is inadequate in itself.

The advent of scientific and technological progress, coupled with the proliferation of disparate academic disciplines, has prompted numerous scholars to delve into the intricate interplay between disparate biomarkers in human serum, genes, metabolism, and proteins, and the manifestation of NHB or neurological impairment. In the human serum profile, TSB, B/A, ETCO, COHb, and RC have been identified as potential predictors of NHB occurrence. Specifically, B/A has been shown to have a certain predictive role for neurological damage, while ETCO, nRBC, and peripheral blood cells can serve as guides for the determination of the necessity of phototherapy. Genetic mutations and alterations at different loci have been associated with the occurrence, severity, and need for phototherapy in NHB.

In the field of proteomics, maternal anti-A/B IgG titers have been observed to increase in cases of hemolytic jaundice, and S100B levels have been shown to be positively correlated with TSB levels. In the domain of metabolomics, IGF-1 and 25-(OH)-D have been identified as potential predictors of neurological damage.

Limitation

The reliability and specificity of a single biomarker must be confirmed by a large number of clinical trials. In the future, there is a need to identify more specific biomarkers and explore the value of combined testing of related biomarkers. In addition, simpler, non-invasive, and more reliable methods for earlier identification of NHB and neurological damage are needed to avoid adverse outcomes.

Conflicts of Interest

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

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