Literature Review: Risk Factors Associated with the Occurrence of Hyperbilirubinemia in Neonates

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Article Info

Article History
Submitted, 2026-04-12
Accepted, 2026-05-19
Published, 2026-06-30

Keywords: ABO incompatibility, birth weight, nutritional intake, hyperbilirubinemia

Abstract

Neonatal hyperbilirubinemia, a condition characterized by increased serum bilirubin levels in newborns, remains a global health problem due to its potential to cause serious neurological complications such as kernicterus. Various risk factors are known to be associated with hyperbilirubinemia, but ABO incompatibility, low birth weight, and nutritional intake are the most frequently identified. This literature review aims to analyze the relationship between ABO incompatibility, birth weight, and nutritional intake and the incidence of hyperbilirubinemia in neonates based on research findings from 2021–2025. The method used is a literature review with articles sourced from Google Scholar, PubMed, and ProQuest. The reviewed articles consist of national and international studies discussing risk factors for neonatal hyperbilirubinemia. The review results indicate that ABO incompatibility is the most dominant factor influencing hyperbilirubinemia because it causes erythrocyte hemolysis, resulting in a significant increase in indirect bilirubin production. Low birth weight is also associated with hyperbilirubinemia due to immaturity of liver function and low bilirubin conjugation capacity in neonates. Furthermore, inadequate nutritional intake, particularly suboptimal breastfeeding, increases the enterohepatic circulation of bilirubin due to delayed meconium excretion. Most studies have shown a significant association between these three factors and the incidence of neonatal hyperbilirubinemia. The conclusion of this literature review is that ABO incompatibility, low birth weight, and nutritional intake play a significant role in the incidence of neonatal hyperbilirubinemia, with ABO incompatibility being the most influential factor. Therefore, early detection, regular bilirubin monitoring, and optimization of breastfeeding are necessary to prevent complications of hyperbilirubinemia in neonates.

Introduction

Neonatal hyperbilirubinemia is one of the most common health problems in newborns and a leading cause of hospitalization during the neonatal period. This condition is characterized by elevated serum bilirubin levels, which cause jaundice in the baby's skin and sclera. Physiologically, neonates have immature bilirubin metabolism due to the short lifespan of erythrocytes and low activity of bilirubin-conjugating enzymes in the liver. If bilirubin levels increase excessively, this condition can progress to bilirubin encephalopathy and even kernicterus, which causes permanent neurological damage (Prema et al., 2023).

Globally, neonatal hyperbilirubinemia remains a significant health problem, particularly in developing countries. A systematic review and meta-analysis reported that the prevalence of severe neonatal jaundice in hospitalized neonates reached 14.26% of all cases of neonatal jaundice. The prevalence of severe hyperbilirubinemia in hospitalized neonates ranged from 0.73% to 3.34% across various WHO regions, with the highest rates found in Africa and Southeast Asia. This high prevalence indicates that hyperbilirubinemia remains a significant cause of neonatal morbidity and mortality worldwide (Diala et al., 2023).

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Neonatal hyperbilirubinemia is influenced by various physiological and pathological risk factors. These factors include prematurity, ABO blood type incompatibility, low birth weight, hemolytic disorders, G6PD deficiency, and inadequate nutritional intake in newborns. Identifying risk factors is crucial because delayed diagnosis and treatment can increase the risk of permanent neurological complications (Lin et al., 2022).

ABO incompatibility is one of the main pathological causes of hyperbilirubinemia in neonates. This condition occurs when maternal antibodies attack the baby's red blood cells due to differences in blood type between the mother and baby, triggering hemolysis. Hemolysis causes a rapid and excessive increase in indirect bilirubin production, while the neonate's liver's ability to conjugate bilirubin is still limited. Research shows that infants with ABO incompatibility have a higher risk of developing severe hyperbilirubinemia than infants without blood type incompatibility (Hutapea et al., 2023).

In addition to ABO incompatibility, low birth weight is also a significant factor associated with neonatal hyperbilirubinemia. Low birth weight babies generally have immature liver function, resulting in slower bilirubin conjugation. Furthermore, erythrocytes in lowbirth weight babies have a shorter lifespan, resulting in increased red blood cell breakdown and higher bilirubin production. These conditions make low birth weight babies more susceptible to hyperbilirubinemia than babies of normal birth weight (Gerungan et al., 2022).

Nutritional intake, especially breastfeeding, is also closely related to the incidence of hyperbilirubinemia in neonates. Infants who experience insufficient breast milk intake tend to experience delayed meconium passage, resulting in intestinal bilirubin being reabsorbed into the bloodstream through the enterohepatic process. This condition leads to increased serum bilirubin levels in neonates. Conversely, adequate breastfeeding can help accelerate bilirubin elimination through feces and reduce the risk of hyperbilirubinemia (Erliana et al., 2025).

Based on the above description, neonatal hyperbilirubinemia remains a health problem that requires serious attention due to its high prevalence and the risk of complications it causes. ABO incompatibility, low birth weight, and nutritional intake are the most frequently reported risk factors associated with hyperbilirubinemia. Therefore, this literature review was conducted to analyze the risk factors associated with neonatal hyperbilirubinemia based on the results of recent research. This can serve as a basis for improving the quality of neonatal health services and reducing the number of complications caused by hyperbilirubinemia.

Methods

This study used a systematic literature review to identify, evaluate, and analyze research findings on risk factors associated with neonatal hyperbilirubinemia. Articles were searched through electronic databases Google Scholar, PubMed, ScienceDirect, and ProQuest, covering publication years 2021–2025. Keywords used in the article search included "ABO incompatibility", "birth weight", "nutritional intake", "hyperbilirubinemia". The article search and selection process used the PICO (Population, Intervention, Comparison, Outcome) approach to facilitate the identification of articles relevant to the research topic. Inclusion criteria for this study included: (1) original research articles, (2) using a quantitative research design, (3) available in full text, (4) published between 2021–2025, (5) in Indonesian or English, and (6) discussing risk factors associated with hyperbilirubinemia, especially ABO incompatibility, birth weight, and nutritional intake. Meanwhile, the exclusion criteria include: (1) articles in the form of theses or dissertations, (2) literature review articles, and (3) articles that cannot be accessed in full.

Results and Discussion

A literature review was conducted on 8 selected articles. The publications ranged from 2021 to 2025. The results of the journal analysis are presented in Table 1 as follows:

Table 1. Results of Journal Analysis

No	Research	Method	Results
1.	Faktor-Faktor Yang Berhubungan Dengan Kejadian Ikterus Pada Bayi Baru Lahir Di RSU UMMI. *Sehat Rakyat* (Rahmadani & Sutrisna, 2022)	The method used is an analytical research design with a crosssectional approach. The sample in this study are 55 mothers who have newborn babies and chosen by using accidental sampling technique. This study uses SPSS with a chi-square bivariate statistical test.	There was a relationship between low birth weight, breastfeeding frequency, ABO incompatibility with the incidence of jaundice in newborns (p 0.000)
2.	Hubungan Pemberian ASI Dengan Kejadian Hiperbilirubinemia Pada Neonatus Di	This research is a quantitative research using correlational method with cross sectional approach. Sampling used a non-probability sampling technique,	There is a relationship between breastfeeding and the incidence of hyperbilirubinemia in neonates in the Perinatology

	Ruang Perinatologi Rs Tk.II Udayana (Sukmandari et al., 2023)	namely accidental sampling as many as 26 people. The research data were analyzed using chi square.	Room of Rs Tk.II Udayana (p=0,001)
3.	Factors Associated With The Incidence Of Hyperbilirubinemia In Neonates (Nurafni et al., 2023)	This is study descriptive approach quantitative, design cross sectional research. Population study Whole Treated neonates with hyperbilirubinemia in space neonates of RSUP Dr. Rivai Abdullah Palembang in 2022 totaling 102 respondents. Sample in study This done with technique *non-random sampling* in a manner *total sampling*. Test statistics used is test *Chi Square*	there is relationship breastfeeding with incident hyperbilirubinemia (p value = 0.009 <0.05), OR = 0.038)
4.	Faktor - Faktor Yang Mempengaruhi Terjadinya Hiperbilirubinemia Pada Neonatus Di RS Budi Kemuliaan Periode Januari–Juli 2023 (Hermansyah et al., 2025)	The research method used case control design with consecutive sampling technique on secondary data from medical records. The subjects of this study were neonates born at Budi Kemuliaan Hospital who experienced hyperbilirubinemia in the period January-July 2023, in the case group as many as 78 and the control group as many as 78 with a total of 156 neonates. Test statistics used is test Chi Square	The results of this study showed that there was a significant association between nutritional intake and hyperbilirubinemia (P=0.000, OR=8.4)
5.	Factors Associated with Hyperbilirubinemia in Newborns at Tanjungpura University Hospital, Pontianak (Panjaitan et al., 2025)	This research used an analytical observational design with a cross-sectional approach. The sample consisted of 67 respondents selected through total sampling. Test statistics used is test Chi Square	The results of the Chi-Square Continuity Correction test showed p=0.038 for gestational age, p=0.018 for ABO incompatibility, p=0.001 for birth weight. In conclusion, there is a significant relationship between gestational age, ABO incompatibility, and birth weight with the occurrence of hyperbilirubinemia.
6	Kejadian Hiperbilirubin Pada Bayi Di Ruang Vinolia RS Pertamina Balikpapan (Novitasari & Sofiyanti, 2025)	This type of research uses quantitative research with a descriptive research design. The research population was all newborn babies with hyperbilirubinemia in the Vinolia Room at Pertamina Hospital Balikpapan, and the sampling technique used was a total sampling of 76 people. Data collection uses data collection format sheet. Data analysisis a univariate analysis using a percentage frequency distribution test.	The description of the incidence of hyperbilirubi in babies based on characteristics mostly occurs in male gender as manyas 40 people (52.6%) and gestational age < 37 weeks as many as 53 people (69.7%). The description of ABO incompatibility in babies was mostly found in the yes category, namely 51 people (67.1%). The description of low birth weight in babies was mostly found in the yes category, namely 50 people (65.8%).
7	Predictive factors for readmission due to neonatal hyperbilirubinemia: A retrospective case-control study (Cai et al., 2025)	This retrospective case-control study included 421 neonates born at ≥35 weeks of gestation with hyperbilirubinemia between January and December 2021. The neonates were divided into a readmission group and a control group, and logistic regression was used to identify predictive factors associated with readmission.	Logistic regression analysis identified preterm birth (<37 weeks), ABO hemolysis, Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, and Total Serum Bilirubin (TSB) level at discharge as significant predictive factors for readmission due to hyperbilirubinemia in newborns (p=0,013)
8	Factors Associated With Neonatal Jaundice Among	This hospital-based, unmatched retrospective case-control study was conducted between February	Factors significantly associated with increased odds of neonatal jaundice were history of

	Neonates Admitted To Three Hospitals In Burao, Somaliland: A Facility-Based Unmatched Case-Control Study (Yosef et al., 2025)	and April 2025. Cases were neonates diagnosed with jaundice, whereas controls were neonates admitted without jaundice A total of 320 neonates (64 cases and 256 controls). Bivariate and multivariate logistic regression analyses were performed to identify factors associated with neonatal jaundice.	jaundice in previous siblings (AOR = 5.26, 95% CI: 2.16–12.84, p < 0.001), low birth weight < 2500 g (AOR = 2.40, 95% CI: 0.85–6.82, p < 0.05), and neonatal polycythemia (AOR = 6.27, 95% CI: 1.54–25.62, p = 0.011). Premature rupture of membranes showed a protective effect (AOR = 0.15, 95% CI: 0.03 0.83, p = 0.030). ABO incompatibility was more common in the cases (32.81%) than in the controls (18.36%, p = 0.011).

Based on an analysis of eight articles conducted by researchers, the factors associated with the occurrence of hyperbilirubinemia in neonates are:

ABO Incompatibility

ABO incompatibility is one of the main factors associated with an increased risk of hyperbilirubinemia in neonates. This condition occurs when the mother's blood type is incompatible with the baby's, causing maternal antibodies to attack the baby's red blood cells, causing hemolysis. This hemolysis process increases red blood cell breakdown, resulting in excessive indirect bilirubin production, exceeding the capacity of the neonate's liver to conjugate bilirubin. As a result, bilirubin accumulates in the blood, causing hyperbilirubinemia (Cai et al., 2025).

Research conducted by Cai et al. (2025) showed that ABO hemolysis is a significant predictor of neonatal readmission due to hyperbilirubinemia. Logistic regression analysis showed that ABO incompatibility increases the risk of severe hyperbilirubinemia in neonates, especially in premature infants with immature liver function. The underlying mechanism for this condition is the massive destruction of red blood cells, which produces high levels of indirect bilirubin, making it impossible for the neonate's bilirubin metabolism system to compensate (Cai et al., 2025).

Research by Panjaitan et al. (2025) also showed a significant association between ABO incompatibility and the incidence of hyperbilirubinemia in newborns, with a p-value of 0.018. This study confirmed that infants with ABO incompatibility are more susceptible to elevated serum bilirubin than infants without incompatibility. Physiologically, hemolysis due to antigen-antibody reactions leads to increased bilirubin produced by hemoglobin degradation. Furthermore, neonates' bilirubin conjugation capacity is still low because the activity of the enzyme uridine diphosphate glucuronosyltransferase (UGT1A1) is not optimal, allowing indirect bilirubin to accumulate more easily in the bloodstream (Panjaitan et al., 2025).

Research by Rahmadani & Sutrisna (2022) also found a relationship between ABO incompatibility and the occurrence of jaundice in newborns, with a p-value of 0.000. This study indicates that ABO incompatibility is a significant risk factor in the development of neonatal hyperbilirubinemia. Continuous hemolysis causes elevated indirect bilirubin levels, increasing the risk of pathological jaundice, especially when accompanied by other factors such as prematurity and low birth weight (Rahmadani & Sutrisna, 2022).

Similar findings were also reported by Novitasari & Sofiyanti (2025), who showed that the majority of infants with hyperbilirubinemia had a history of ABO incompatibility (67.1%). These data demonstrate that ABO incompatibility is a common factor in cases of hyperbilirubinemia. Hemolysis triggered by blood type incompatibility rapidly increases bilirubin production, causing serum bilirubin levels to easily reach pathological levels in neonates (Novitasari & Sofiyanti, 2025).

Research by Yosef et al. (2025) also reported that ABO incompatibility was more common in the case group than in the control group, with a p-value of 0.011. These results indicate that blood type incompatibility between mother and infant contributes to the increased risk of neonatal jaundice. Mechanistically, maternal IgG antibodies can cross the placenta and destroy fetal erythrocytes, resulting in increased indirect bilirubin due to intravascular and extravascular hemolysis (Yosef et al., 2025).

Birth Weight

Low birth weight is a significant risk factor for hyperbilirubinemia in neonates. Low birth weight babies generally have immature livers, thus limiting their ability to metabolize bilirubin. Furthermore, low birth weight babies tend to be premature, resulting in underdeveloped bilirubin conjugation enzymes. This condition causes indirect bilirubin to accumulate more

easily in the blood, triggering hyperbilirubinemia (Rahmadani & Sutrisna, 2022; Cai et al., 2025; Novitasari & Sofiyanti, 2025; Panjaitan et al., 2025; Yosef et al., 2025).

Research by Panjaitan et al. (2025) showed a significant association between birth weight and hyperbilirubinemia with a p-value of 0.001. Low birth weight babies have a higher risk of developing hyperbilirubinemia than babies with normal birth weight. Physiologically, low birth weight neonates experience increased erythrocyte breakdown and immaturity of hepatic function, disrupting the conjugation and excretion of bilirubin (Panjaitan et al., 2025).

Rahmadani and Sutrisna also reported a relationship between low birth weight and neonatal jaundice with a p-value of 0.000. Low birth weight infants have lower albumin reserves, reducing the ability to bind indirect bilirubin in the blood. As a result, free bilirubin increases more easily, leading to hyperbilirubinemia. Furthermore, low birth weight infants often experience delayed nutritional intake, which worsens the enterohepatic circulation of bilirubin (Rahmadani & Sutrisna, 2022).

Research by Yosef et al. (2025) showed that infants weighing less than 2500 grams have a higher risk of developing neonatal jaundice, with an AOR of 2.40. This risk is related to the immaturity of organs, particularly the liver, which leads to a decreased ability to conjugate bilirubin. Furthermore, erythrocytes in low birth weight infants have a shorter lifespan, resulting in more rapid hemolysis and increased bilirubin production (Yosef et al., 2025).

Research by Novitasari & Sofiyanti (2025) showed that the majority of infants with hyperbilirubinemia had low birth weight (65.8%). This finding reinforces the notion that low birth weight is a common characteristic of neonatal hyperbilirubinemia. Low birth weight infants have immature physiological systems, making them more susceptible to bilirubin metabolism disorders and elevated serum bilirubin levels (Novitasari & Sofiyanti, 2025).

In addition to low birth weight, prematurity also contributes to the incidence of hyperbilirubinemia. Cai et al. (2025) reported that premature infants with gestational age less than 37 weeks were a significant predictor of hyperbilirubinemia. Prematurity is associated with low activity of the glucuronyl transferase enzyme which functions to conjugate indirect bilirubin into direct bilirubin so that bilirubin is more difficult to excrete through bile and feces (Cai et al., 2025).

Nutritional Intake

Inadequate nutritional intake, particularly suboptimal breastfeeding, is closely associated with the incidence of hyperbilirubinemia in neonates. Infants who do not receive sufficient breast milk intake will experience decreased bowel movements, which hinders the excretion of bilirubin through feces. This condition increases the enterohepatic circulation of bilirubin because bilirubin in the intestine is reabsorbed into the bloodstream. As a result, serum bilirubin levels increase and trigger hyperbilirubinemia (Rahmadani & Sutrisna, 2022; Nurafni et al., 2023; Sukmandari et al., 2023; Hermansyah et al., 2025).

Research by Sukmandari et al. (2023) showed a significant association between breastfeeding and the incidence of hyperbilirubinemia in neonates with a p-value of 0.001. Infants who receive inadequate breast milk are at greater risk of developing hyperbilirubinemia than infants who receive optimal breastfeeding. Physiologically, insufficient breast milk intake delays meconium excretion, resulting in bilirubin in the digestive tract being reabsorbed into the bloodstream through the enterohepatic process (Sukmandari et al., 2023).

Research by Nurafni et al. (2023) also found a relationship between breastfeeding and the incidence of hyperbilirubinemia with a p-value of 0.009. This study suggests that adequate breastfeeding can be a protective factor against hyperbilirubinemia. This protective mechanism occurs because breast milk helps increase intestinal motility and accelerates meconium excretion, allowing bilirubin to be eliminated more effectively through feces (Nurafni et al., 2023).

Hermansyah et al. (2025) reported a significant relationship between nutritional intake and the incidence of hyperbilirubinemia with a p-value of 0.000 and an OR of 8.4. Infants with inadequate nutritional intake have a significantly higher risk of developing hyperbilirubinemia. Insufficient nutritional intake leads to decreased hydration and the frequency of bilirubin elimination through the gastrointestinal tract, resulting in more indirect bilirubin being reabsorbed back into the bloodstream (Hermansyah et al., 2025).

Rahmadani & Sutrisna (2022) also found that breastfeeding frequency was associated with the incidence of neonatal jaundice with a p-value of 0.000. Infants who breastfeed infrequently tend to experience elevated serum bilirubin due to delayed meconium excretion and increased enterohepatic circulation of bilirubin. Furthermore, insufficient breast milk intake can cause mild dehydration in neonates, which exacerbates elevated blood bilirubin levels (Rahmadani & Sutrisna, 2022).

In general, providing adequate nutrition to neonates is crucial to prevent hyperbilirubinemia. Early and frequent breastfeeding can help accelerate bilirubin elimination by increasing intestinal motility and meconium excretion. On the other hand, nutritional deficiencies or delayed breastfeeding can increase the enterohepatic circulation of bilirubin,

thus increasing the risk of hyperbilirubinemia (Sukmandari et al., 2023; Hermansyah et al., 2025).

Conclusion

Based on the results of various studies, the most influential factor in the occurrence of hyperbilirubinemia in neonates is ABO incompatibility because this factor directly causes erythrocyte hemolysis which increases the production of indirect bilirubin rapidly and excessively so that it exceeds the ability of the neonate's liver to conjugate bilirubin. In addition, several studies have shown a consistent and significant relationship between ABO incompatibility and hyperbilirubinemia compared to other factors such as low birth weight and nutritional intake. Low birth weight and prematurity still play an important role because immaturity of liver function causes bilirubin metabolism disorders, while inadequate nutritional intake increases the enterohepatic circulation of bilirubin due to delayed meconium excretion. Therefore, it is recommended that health workers carry out early detection of ABO incompatibility from the antenatal period and after delivery, accompanied by regular bilirubin monitoring, optimization of breastfeeding, and close supervision of lowbirth weight infants to prevent complications of severe hyperbilirubinemia.

Acknowledgments

We would like to express our gratitude to the Rector of Ngudi Waluyo University, the Dean of the Faculty of Health, the Head of the Undergraduate Midwifery Study Program, the lecturers, and all those who have assisted.

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