ORIGINAL ARTICLE

Risk Factors for Non-Hemolytic Jaundice in Neonates: A Retrospective Cohort Study at Naresuan University Hospital

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Background: Neonatal hyperbilirubinemia is a common neonatal condition requiring immediate diagnosis and treatment to prevent severe hyperbilirubinemia that can cause brain damage known as kernicterus. Identifying risk factors and monitoring at-risk infants can help reduce the incidence of severe hyperbilirubinemia.

Materials and Methods: The present study was a retrospective cohort study analyzed medical records of infants with gestational age (GA) of more than 35 weeks born at Naresuan University Hospital between January 2019 and December 2020. One thousand fifteen infants were enrolled and divided into two groups: the hyperbilirubinemia group comprising 287 infants (28.3%), and the non-hyperbilirubinemia group consisting of 728 infants (71.7%).

Results: The incidence of neonatal hyperbilirubinemia in infants with GA of more than 35 weeks was 30.7% (345 out of 1,122). Compared to vaginal delivery, cesarean section reduced the risk of neonatal hyperbilirubinemia by 32% (adjusted odds ratio 0.68). Sepsis increased the risk of neonatal hyperbilirubinemia by 73% (adjusted odds ratio 1.73). Infants in the hyperbilirubinemia group had a longer hospital stay, averaging approximately 28 hours.

Conclusion: Vaginal delivery and neonatal sepsis were identified as significant risk factors for neonatal hyperbilirubinemia. Close monitoring of infants identified as at-risk may aid in the prevention of severe hyperbilirubinemia.

Keywords: Risk factor; Neonatal hyperbilirubinemia; Neonatal jaundice; Route of delivery

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Neonatal jaundice, a common postnatal condition, requires close monitoring to prevent permanent brain damage from severe hyperbilirubinemia[1]. Most cases of neonatal jaundice manifest as indirect hyperbilirubinemia, which can be either physiologic or pathologic jaundice. Physiologic jaundice is usually not severe and can spontaneously resolve within 10 to 14 days, while pathologic jaundice requires treatment with phototherapy or, in severe cases, exchange transfusion[2].

Indirect hyperbilirubinemia has diverse etiologies, classified into hemolytic and non-hemolytic jaundice. Hemolytic jaundice is associated with risk factors such as blood group incompatibility, inherited red blood cell membrane abnormalities, and glucose-6-phosphate dehydrogenase (G6PD) deficiency, which are unavoidable and require close monitoring. Conversely, non-hemolytic jaundice, including breastfeeding-related jaundice and unspecified jaundice, lacks well-defined predictors, potentially making it amenable to prevention strategies.

The authors' hospital adheres to the 2004 American Academy of Pediatrics Clinical Practice Guideline for the screening, treatment, and follow-up of neonates with a gestational age of 35 weeks or more[3]. This guideline advocates blood microbilirubin testing within 48 hours of birth or upon clinical suspicion based on skin examination. The authors promoted exclusive breastfeeding unless contraindicated, with infant formula supplementation as needed. Additionally, the authors assessed tongue-tie severity, closely monitor feeding progress, and intervene promptly with feeding position adjustments

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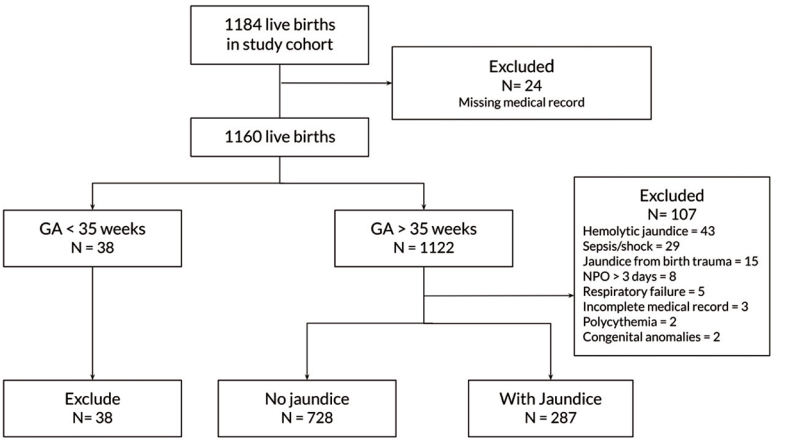

Figure 1. Summary of neonates in the study cohort.

or bedside tongue-tie correction by a neonatologist within 3 to 4 days for persistent feeding difficulties.

Despite these measures, the authors' institution's neonatal hyperbilirubinemia incidence was approximately 33%, significantly exceeded the Thai national average of 7.7% to 23.9%[2,4]. Hyperbilirubinemia in infants contributes to extended hospital stays, resulting in increased expenses, maternal anxiety, and family concerns.

While extensive research has explored risk factors for neonatal jaundice, no definitive consensus has been reached regarding the relationship between the route of delivery: cesarean section or vaginal delivery, and hyperbilirubinemia. Studies suggest that cesarean section reduces the risk of hyperbilirubinemia[1,5,6], while others regard it as a risk factor[7,8]. This lack of consensus highlights the need for further research to identify preventable risk factors for neonatal jaundice, particularly among neonates delivered via cesarean section. The primary objective of the present study was to address this gap by identifying preventable risk factors associated with non-hemolytic jaundice in neonates with a gestational age greater than 35 weeks.

Materials and Methods

Participants

This retrospective cohort study was approved by the Naresuan University Institutional Review Board (P3-0006/2565) and complied with the ethical principles of the Declaration of Helsinki. The authors retrospectively analyzed medical records of all live-born neonates with a gestational age greater than 35 weeks, born at Naresuan University Hospital between January 2019 and December 2020. The exclusion criteria were neonates with one or more of the following conditions, hemolytic jaundice, direct hyperbilirubinemia, hyperbilirubinemia secondary to birth trauma such as cephalhematoma, subgaleal hematoma, or bruising, jaundice persisting beyond two weeks of life, polycythemia, disseminated intravascular coagulation (DIC), septic shock, respiratory distress requiring endotracheal intubation, congenital anomalies such as cyanotic heart disease, gastrointestinal anomalies, or chromosomal anomalies, NPO status exceeding three days, and incomplete medical records. Of 1,184 infants born during the study period, 1,015 met the inclusion criteria. These participants were divided into two groups, the hyperbilirubinemia group comprising 287 infants (28.3%), and the non-hyperbilirubinemia group consisting of 728 infants (71.7%), as shown in Figure 1. The hyperbilirubinemia group included infants who received phototherapy or exchange transfusion.

Statistical analysis

Statistical analyses were performed using Stata/MP, version 17 (StataCorp LLC, College Station, TX, USA). Descriptive data were expressed as frequency, percentage, mean, and standard deviation (SD). Normally distributed data are presented as median and non-nominal data as interquartile ranges. Differences between the two groups were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared using the independent t-test. Factors associated with neonatal jaundice were analyzed using univariable analysis presented as crude odd ratio and multivariable analysis presented as adjusted odd ratio. Statistical significance was defined as p-value of less than 0.05.

Table 1. General characteristics of the studied neonates

	Hyperbilirubinemia		p-value
	Yes (n=287)	No (n=728)	
Maternal history			
Age (years); mean±SD	30.63±6.30	30.25±6.20	0.377
Presence of underlying disease; n (%)	90 (31.4)	240 (33.0)	0.656
Infant characteristics			
Birth body weight (g); mean±SD	3,022.89±393.06	3,080.66±411.41	
BW <2500 g; n (%)	27 (9.4)	56 (7.7)	0.375
Body proportion; n (%)			0.165
• Appropriate for gestational age (AGA)	270 (94.1)	661 (90.8)	
• Small for gestational age (SGA)	4 (1.4)	10 (1.4)	
• Large for gestational age (LGA)	13 (4.5)	57 (7.8)	
Male; n (%)	145 (50.5)	372 (51.1)	0.889
Apgar score at 1 minute; mean±SD	8.87±0.83	9.03±0.71	0.003
Apgar score at 5 minutes; mean±SD	9.91±0.33	9.91±0.47	0.911

SD=standard deviation; BW=birth weight

Table 2. Suspected risk factors associated with neonatal jaundice

Risk Factors	Hyperbilirubinemia		p-value
	Yes (n=287)	No (n=728)	
Maternal history; n (%)			
• Primigravida (G1)	139 (48.4)	304 (41.8)	0.058
• Other gravida (G2-G7)	148 (51.6)	424 (58.2)	
• Multifetal pregnancy (twins)	5 (1.7)	16 (2.2)	0.808
Labor history; n (%)			
• Received perinatal medication	117 (40.8)	249 (34.2)	0.059
• Received oxytocin	81 (28.2)	150 (20.6)	0.010
Route of delivery; n (%)			
Cesarean section	145 (50.5)	427 (58.7)	0.020
Vaginal delivery	142 (49.5)	301 (41.3)	
Infant risk factors			
Presence of infant co-morbidities			
• Respiratory complication; n (%)	32 (11.1)	54 (7.4)	0.061
• Hypoglycemia; n (%)	18 (6.3)	34 (4.7)	0.342
• Sepsis, n (%)	45 (15.7)	68 (9.3)	0.005
• Age of feeding initiation (hours); mean±SD	3.55±4.15	3.45±4.06	0.728
• Feeding problem (tongue-tie); n (%)	26 (9.1)	46 (6.3)	0.136
• Percent weight loss at discharge; mean±SD	3.30±3.63	3.06±22.50	0.859
• Length of hospital stay (hours); mean±SD	129.38±51.08	101.01±50.77	<0.001

SD=standard deviation

Results

Of the 1,122 live-born infants with a gestational age greater than 35 weeks, 30.7% (345 out of 1,122) had hyperbilirubinemia, with 25.6% (287 out of 1,122) classified as non-hemolytic jaundice. In the hyperbilirubinemia group, 50.5% (145 out of 287) were males and 49.5% (142 out of 287) were females. No significant differences were observed in maternal age or underlying diseases between the two groups. Table 1 summarizes the general characteristics of the enrolled infants. Infants in the hyperbilirubinemia group demonstrated significantly lower 1-minute APGAR scores (p=0.003).

Risk factor analysis for hyperbilirubinemia revealed no significant differences between the two groups in terms of gravida, twin birth status,

Table 3. Multivariable analysis of factors associated with neonatal jaundice

Risk factors	Crude odds ratio (95%CI)	p-value	Adjusted odds ratio (95%CI)	p-value
1-minute APGAR score	0.77 (0.64 to 0.92)	0.004	0.71 (0.58 to 0.85)	<0.001
Oxytocin	1.52 (1.11 to 2.07)	0.009	1.32 (0.93 to 1.89)	0.122
Cesarean section	0.72 (0.55 to 0.95)	0.019	0.68 (0.50 to 0.94)	0.021
Sepsis	1.80 (1.20 to 2.70)	0.004	1.73 (1.14 to 2.61)	0.009

CI=confidence interval

perinatal medication, respiratory complications, hypoglycemia, time to start feeding, tongue-tie, and percentage of weight loss before discharge. However, statistically significant differences were found in perinatal oxytocin exposure (p=0.010), route of delivery (p=0.020), sepsis (p=0.005), and length of hospital stay (p<0.001) (Table 2).

The authors categorized the route of delivery into two groups as vaginal delivery with 443 infants and cesarean section with 572 infants. Neonates delivered by cesarean section had a significantly lower incidence of hyperbilirubinemia at 25.3% (145 out of 572) compared to those delivered vaginally at 32.1% (142 out of 443), with p=0.020.

Multivariable analysis of statistically significant risk factors revealed that a lower 1-minute APGAR score (adjusted odds ratio 0.71, 95% CI 0.58 to 0.85, p<0.001), cesarean section (adjusted odds ratio 0.68, 95% CI 0.50 to 0.94, p=0.021), and sepsis (adjusted odds ratio 1.73, 95% CI 1.14 to 2.61, p=0.009) were associated with neonatal jaundice (Table 3).

Discussion

The incidence of hyperbilirubinemia in neonates with gestational age of more than 35 weeks born at Naresuan University Hospital between 2019 and 2020 was 30.7% (345 out of 1,122). This prevalence is significantly higher than the national average in Thailand of 7.7% to 23.9% and other countries at 4.8% to 15.5%[1,2,4,9]. Within the hyperbilirubinemia group, the male-to-female ratio was nearly equal, with 145 infants (50.5%) being male and 142 (49.5%) being female. This finding deviates from a prior study conducted in Northern Thailand, which reported a higher incidence of hyperbilirubinemia in female infants[4]. However, this observed lack of gender difference in the present study may be due to the exclusion of infants with hemolytic jaundice, particularly those with G6PD deficiency, which is a condition that predominantly affects male infants.

Analysis of the general characteristics in the present study revealed a statistically significant lower 1-minute APGAR score (p=0.003) in the hyperbilirubinemia group, although the outcome was not clinically significant. The 1-minute APGAR score in the hyperbilirubinemia group was 8 and in the non-hyperbilirubinemia group was 9, indicating no significant prognostic implications. Other characteristics, including maternal age, maternal underlying diseases, infant size, infant gender, and 5-minute APGAR score, exhibited no significant differences between the two groups.

The authors investigation identified risk factors for hyperbilirubinemia in infants, although none were statistically significant. These factors included primigravida status, perinatal medication administration, respiratory complications, hypoglycemia, and tongue-tie, all of which were more prevalent in the hyperbilirubinemia group. Previous studies suggested that primigravida mothers may encounter breastfeeding challenges, potentially leading to insufficient milk production in the first few days and consequently increasing the risk of hyperbilirubinemia[10]. Nonetheless, the present study did not establish a definitive association between the number of pregnancies and the risk of hyperbilirubinemia.

The time to initiate feeding was slightly delayed in the hyperbilirubinemia group. It was 3.55 hours while in the non-hyperbilirubinemia group it was 3.45 hours, but this difference was not statistically significant. Tongue-tie was more frequent in the hyperbilirubinemia group, potentially hindering the sucking process and leading to inadequate milk intake[11,12]. By recognizing frenulectomy as an effective way to improve tongue-tie and increase maternal breastfeeding self-efficacy[13]. The authors addressed this issue by assessing tongue-tie severity and closely monitoring feeding progress in all infants. If necessary, bedside frenotomy was performed within 3 to 4 days, effectively eliminating any statistical differences.

Percentage weight loss at discharge did not differ significantly between the two groups, as the authors' hospital offers a comprehensive support system,

including a lactation clinic, tongue-tie corrections performed by neonatologists, and infant formula supplementation for mothers with insufficient breast milk. These interventions minimized infant weight fluctuations at discharge.

Significant differences were exhibited between the two groups for perinatal oxytocin administration (p=0.010), route of delivery (p=0.020), sepsis (p=0.005), and length of stay (p<0.001). Previous research has suggested a link between oxytocin use during labor for augmentation and elevated neonatal total bilirubin levels. This could be attributed to oxytocin's ability to stimulate uterine contractions, leading to a redistribution of blood between the placenta and the fetus, thereby increasing red cell mass and bilirubin production from red blood cell degradation[14], resulting in neonatal hyperbilirubinemia.

The relationship between the route of delivery and hyperbilirubinemia remains inconclusive. Studies suggest that cesarean section reduces the risk of hyperbilirubinemia, citing factors such as increased conjugate enzyme levels and routine formula supplementation in the first 48 hours postpartum to mitigate insufficient milk intake[1,5,6]. Conversely, other studies indicate cesarean section as a risk factor for developing hyperbilirubinemia due to potential lactogenesis delays and inadequate milk intake[7,8]. In contrast, another study highlighted the risk associated with vaginal delivery, as mothers are often discharged from the hospital 24 hours postpartum despite having insufficient milk production, which can lead to hyperbilirubinemia in the infant[15].

The results of the present study's multivariable analysis established the following significant factors for non-hemolytic neonatal hyperbilirubinemia, APGAR score at 1 minute (p<0.001), cesarean delivery (p=0.021), and sepsis (p=0.009). First, an increase in APGAR score at 1 minute was associated with a 29% decrease in the risk of neonatal jaundice, though not clinically significant (adjusted odds ratio 0.71). The 1-minute APGAR score indicates intrauterine condition and toleration of the infant during the birth process but does not indicate the long-term outcome of the infants as the 5-minute APGAR score does[16]. Second, cesarean section was linked to a 32% reduction in the risk of hyperbilirubinemia compared to vaginal delivery (adjusted odds ratio 0.68). This finding suggests that cesarean section serves as a protective factor against hyperbilirubinemia, which is consistent with the results of previous studies[1,5,6]. Additionally, the cesarean section group exhibited a higher average milk intake on the third day of life of 41±28 mL/kg, compared to the vaginal delivery group at 36±26 mL/kg (p=0.001). This increased milk intake potentially reduced the risk of hyperbilirubinemia through an enhanced hepatic circulation process, corroborating the findings of Osborn et al.'s study[5]. Third, sepsis was associated with a 73% increase in the risk of hyperbilirubinemia (adjusted odds ratio 1.73). Infants with sepsis may present with various clinical manifestations, including bloating, vomiting, and feeding intolerance, predisposing them to inadequate milk intake and subsequent hyperbilirubinemia. While sepsis complicated by DIC can also cause hyperbilirubinemia, severe sepsis cases were excluded from the present study.

The average length of stay in the hyperbilirubinemia group was approximately 28 hours longer than in the non-hyperbilirubinemia group. This difference can be linked to the approximate 24-hours duration of phototherapy treatment in hyperbilirubinemia cases.

A significant strength of the present study is the inclusion of a substantial number of subjects, making it represent the overall population of infants born at Naresuan University Hospital. This extensive dataset enabled the authors to comprehensively assess risk factors and the incidence of jaundice within the population. In addition, the present study's detailed medical records, including information on daily milk intake, feeding methods, and the timing of initial feeding, offer valuable information for future research. However, the retrospective nature of the present study introduces limitations. The authors suggest future research employs a prospective cohort study design for a more in-depth exploration of these factors. The authors also recommend that future studies align with the updated 2022 Guidelines from the American Academy of Pediatrics[17] to ensure the use of the most current and relevant information.

Conclusion

The present study reveals a significant incidence of hyperbilirubinemia among infants with a gestational age exceeding 35 weeks at 30.7%, surpassing both national and international averages. Key risk factors associated with hyperbilirubinemia included vaginal delivery and sepsis. All infants diagnosed with hyperbilirubinemia received standard phototherapy treatment, following the 2004 American Academy of Pediatrics Clinical Practice Guideline. Furthermore, the present study analysis indicates a 28-hour increase in the average length of stay for

the hyperbilirubinemia group. Close monitoring of infants identified as at-risk may aid in the prevention of severe hyperbilirubinemia.

What is already known on this topic?

Route of delivery affects the risk of developing hyperbilirubinemia but remains inconclusive. There is still argument about whether cesarean section reduces or increases the risk for developing hyperbilirubinemia.

What does this study add?

Cesarean section reduces the risk of hyperbilirubinemia compared to vaginal delivery.

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Conflicts of interest

The authors declare no conflict of interest.

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