Factors associated with the incidence of neonatal hyperbilirubinemia in Perinatology Ward of Wangaya General Hospital, Denpasar

Fitriana Melinda\textsuperscript{a}, I Wayan Bikin Suryawan, Anak Agung Made Sucipta

ABSTRACT

Background: Hyperbilirubinemia is a condition defined by an increased total serum bilirubin level exceeding 5 mg/dL and clinically characterized by the presence of jaundice. Jaundice can be observed on the skin and sclera if the bilirubin level increases more than 5 mg/dL. Several risk factors, including birth weight, asphyxia, gestational age, mode of delivery, and breastfeeding practices, have been studied regarding their relationship to the incidence of hyperbilirubinemia, with varying results. Therefore, the purpose of this study was to determine the relationship between these risk factors and the incidence of hyperbilirubinemia.

Methods: An analytical observational cross-sectional study was conducted by collecting secondary data from the Perinatology Ward registry and the medical records department. The subjects were neonates treated in the Perinatology Ward of Wangaya Hospital, Denpasar. The data that met the inclusion and exclusion criteria were then analyzed with the SPSS 25.

Results: There were 59 neonates with hyperbilirubinemia and 135 neonates without hyperbilirubinemia among the 194 research subjects. The results of the chi-square test were the following: p-value for birth weight = 0.002, p-value for asphyxia = 0.002, p-value for breastfeeding practice = 0.003, p-value for gestational age = 0.000, and p-value for delivery mode = 0.110.

Conclusion: There was a significant relationship between birth weight, asphyxia, gestational age, breastfeeding practices, and the incidence of neonatal hyperbilirubinemia in the Perinatology Ward, Wangaya Hospital, Denpasar City. Meanwhile, no relationship was observed between the mode of delivery and newborn hyperbilirubinemia.

Keywords: Hyperbilirubinemia, low birth weight, asphyxia, breastfeeding, gestational age.

INTRODUCTION

Hyperbilirubinemia is a prevalent condition affecting newborns. This is due to a combination of increased heme catabolism and physiologic immaturity of the liver in bilirubin conjugation and excretion.\textsuperscript{1,2} Hyperbilirubinemia is a condition defined by an increased total serum bilirubin level exceeding 5 mg/dL and clinically characterized by the presence of jaundice. Jaundice can be observed on the skin and sclera if the bilirubin level increases more than 5 mg/dL.\textsuperscript{3-5} Biologically, the bilirubin level will increase after birth, then stabilize and decrease after seven, 3–5% of neonates with hyperbilirubinemia have a pathological condition predisposing them to a higher risk of kernicterus.\textsuperscript{2} Kernicterus is a preventable brain injury caused by bilirubin toxicity.\textsuperscript{6}

More than 85% of full-term neonates were readmitted in the first week of life due to this condition.\textsuperscript{7} Maisels et al. reported that hyperbilirubinemia developed in 60% of full-term neonates > 35 weeks and 80% of preterm neonates < 35 weeks.\textsuperscript{7} The incidence of jaundice in full-term neonates in Indonesia ranges from 13.7 to 85% in several teaching hospitals, including RSCM, Dr. Sardjito Hospital, Dr. Soetomo Hospital, and Dr. Kariadi Hospital. Per the findings of a study in Wahidin Sudiro Husodo General Hospital, Mojokerto, of 958 neonates with hyperbilirubinemia, 142 died (14.8%). Based on neonatology registration data from December 2014 to November 2015 at Sanglah Central General Hospital Denpasar Bali, 165 (15.09%) of 1093 neonates had neonatal jaundice.\textsuperscript{8,9} Studies to determine the relationship between these risk factors and the incidence of hyperbilirubinemia are needed to enhance our understanding of the hyperbilirubinemia causes. Furthermore, the data collection and analysis result may be a reference for future study.

METHODS

The design of this study was an analytic observational cross-sectional study. This study used secondary data obtained from registers and medical records. Collected data will be analyzed further. The study was conducted in the Perinatology Ward and Medical Record Department of Wangaya Hospital, Denpasar, in August 2021.
The minimum sample size required in this study is 194 samples. The subjects were all neonates treated in the Perinatology Ward of Wangaya Hospital from May 2020 to May 2021 and met the inclusion and exclusion criteria. Inclusion criteria were neonates treated in the Perinatology Ward of Wangaya Hospital in May 2020 - May 2021. Exclusion criteria were the following: neonates born in other hospitals and hyperbilirubinemia with specific causes such as HBO and rhesus incompatibility, G6PD deficiency, polycythemia, patients with congenital abnormalities, and incomplete medical records data. This study used a simple random sampling technique. Data collection included sex/gender, history of maternal disease, mode of delivery, gestational age, the incidence of asphyxia, birth weight, breastfeeding practices, and incidence of hyperbilirubinemia. Data met the inclusion and exclusion criteria were included as the research subjects. Data will be analyzed using descriptive and analytical approach with Statistical Package for Social Science (SPSS) software.

RESULTS

The characteristics of all 194 participants are presented in Table 1. The majority of the research participants were males (55.7%), had an instrumental mode of delivery (57.7%), had no history of the maternal disease (62.9%), were full-term gestational age (74.7%), with normal birth weight (66.5%), no asphyxia (75.3%), partially breastfed (80.4%), and no hyperbilirubinemia (69.6%).

The results of the analysis by the Chi-Square test were the following: p-value for birth weight = 0.002 (Table 3), p-value for the incidence of asphyxia = 0.002 (Table 4), p-value for the breastfeeding practice = 0.003 (Table 5), p-value for gestational age = 0.000 (Table 6), and p-value for mode of delivery p = 0.110 (Table 7). Multivariate analysis for each risk factor for hyperbilirubinemia as seen in Table 8. The value of p<0.005 indicated a significant relationship of each variable and the incidence of hyperbilirubinemia in neonates in the Perinatology Ward, Wangaya Hospital, Denpasar.

The value of the independent variables asphyxia, breastfeeding practice, and gestational age was less than α. It was concluded that the incidence of asphyxia, breastfeeding practice, and gestational age had a significant relationship with neonatal hyperbilirubinemia in Perinatology Ward, Wangaya Hospital, Denpasar from May 2020 until May 2021.

DISCUSSION

As seen in Table 2, most neonates with hyperbilirubinemia were males (54.2%). This was consistent with the previous findings from Rompis et al. (2015), who discovered more male neonates with hyperbilirubinemia than females (n = 32, 59.2% for males). Meanwhile, Aditya et al. found that the number of male neonates did not differ significantly from females (n = 63, 50.8%). Males neonates were also the most affected by hyperbilirubinemia (53%) in a study conducted by Yasadipura (2020).

Most of the neonates with hyperbilirubinemia in this study were born by spontaneous delivery - non-instrumental/caesarian deliveries (50.8%). This was in line with the observations of a 2017 study conducted by Rohani et al. comparing the neonates delivered spontaneously (54.3%) and other neonates who had a cesarean section, vacuum, or forceps (45.7%) deliveries. A research published in 2014 by Faqih et al. discovered that the proportion of neonates with hyperbilirubinemia in spontaneous deliveries was higher than the proportion in instrumental/caesarean deliveries, 37.8% and 32.7%, respectively.

Based on the finding, most of the mothers of neonates with hyperbilirubinemia had no history of the disease (76.3%). Yasadipura et al. (2020) also supported this finding, as they discovered a higher prevalence of hyperbilirubinemia in neonates whose mothers had no history of the maternal disease (54%).

Table 2 revealed that 33 (55.9%) of the 59 neonates with hyperbilirubinemia had full-term gestational age at Wangaya Hospital in Denpasar. Hyperbilirubinemia was more common in preterm neonates, occurring in 22.7% of full-term neonates and 53% of preterm neonates. This finding was consistent with Faqih et al. (2014), which discovered that of 195 neonates...
with jaundice, 130 neonates (66.7%) had a gestational age of ≥37 weeks, while the incidence of jaundice was higher in preterm infants (80%) than full-term infants (60%). A study conducted by Cholifah in 2017 also found that the incidence of hyperbilirubinemia in preterm neonates (44.4%) was higher than that of full-term neonates (3.9%). Yasadipura et al. (2020) also found a higher incidence of hyperbilirubinemia in preterm neonates (34.7%) vs. 18.6% in full-term neonates.

Based on birth weight, it was known that the majority of neonates with hyperbilirubinemia had normal birth weight (50.8%). The incidence of hyperbilirubinemia in neonates with LBW was 44.6% (n=29), while the incidence of hyperbilirubinemia in neonates who were not LBW was 23.2% (n=30) out of 129 participants who had no LBW. This finding was similar to Cholifah et al. (2017), who found hyperbilirubinemia in 5 neonates with low birth weight (31.2%) and four neonates with normal birth weight (3.3%).

Another study conducted in 2017 by Rohani et al. also found a higher proportion of hyperbilirubinemia in neonates with LBW (n=44, 57.9%) vs. neonates with normal birthweight (n=37, 30.8%).

In this study, most neonates with hyperbilirubinemia had no asphyxia (61%). However, neonatal hyperbilirubinemia in neonates with asphyxia was 47.9% (n=23), while the proportion of non-asphyxiated neonatal hyperbilirubinemia was 24.6% (n=36). The results of this study were similar to Rohani et al. (2017), reporting that the majority of neonates with hyperbilirubinemia were neonates who had no asphyxia (54.3%), with the proportion of neonatal hyperbilirubinemia in asphyxiated neonates was 53.6%, and the proportion of neonatal hyperbilirubinemia without asphyxia was 34.6%.

This study indicated partial breastfeeding predominated the breastfeeding practice (67.8%). However, the proportion of neonatal hyperbilirubinemia in neonates who received full breastfeeding was 50% (19 out of 38), while in neonates who were given partial breastfeeding was 25.6% (40 of 156 participants). Huang et al. (2021) also reported that 181 out of 601 subjects receiving full breastfeeding had hyperbilirubinemia, while only 98 out of 419 subjects with partial breastfeeding experienced hyperbilirubinemia. Studies by Wijaya et al. (2019) found that 33 full-breasted subjects (76.7%) had hyperbilirubinemia.
According to the findings of this study, which included 194 newborns, 29 LBW neonates developed hyperbilirubinemia. The p-value of 0.002 obtained from the statistical analysis was less than the alpha value (α = 0.05), indicating a significant association between birth weight and the occurrence of hyperbilirubinemia in neonates. This was consistent with the findings of a 2017 study by Devi et al., who discovered a connection between birth weight and newborn hyperbilirubinemia with a p-value of 0.011. Another study performed in 2015 by Imron et al. discovered a relationship between low birth weight and hyperbilirubinemia (p = 0.000, OR value of 2.182). The findings of Auliasari et al. (2019) showed a significant relationship (p = 0.032) between birth weight and the incidence of newborn jaundice. This case-control research yielded an OR value of 0.346, indicating that birthweight < 2500 gram increases the risk of neonatal jaundice by 3.46 times higher than birthweight > 2500 gram. Yasapidura et al. (2020) also presented the relationship between LBW and hyperbilirubinemia. Normal birth weight and low birth weight neonates are both at risk of neonatal jaundice. The maturity and function of low birth weight neonates are not yet maximized compared to normal birth weight neonates. The suboptimal bilirubin elimination causes jaundice via the immature liver. As a result, bilirubin accumulates and creates a yellow hue on the skin's surface.

The results of this study were in line with several other studies. This study found a relationship between the incidence of asphyxia and neonatal hyperbilirubinemia, similar to Rohani et al. (2017), reporting a p-value of 0.015 between asphyxia and the incidence jaundice in neonates. Saptanto et al. (2016) found a significant relationship between asphyxia and the incidence of pathological hyperbilirubinemia (p=0.004). Of the 74 neonates with hyperbilirubinemia, 68.9% of neonates experienced pathological hyperbilirubinemia. Aynalem et al. (2020) stated that asphyxia was associated with the incidence of hyperbilirubinemia in preterm neonates with a p-value = 0.0001.0

Asphyxia causes hepatic hypoperfusion that interferes with hepatocyte bilirubin uptake and metabolism, leading to increased unconjugated bilirubin production beyond its capacity. Thus, it can cause neonatal jaundice. Furthermore, neonatal jaundice caused by asphyxia may also be intensified by suboptimal liver function during the neonatal period, interfering with the bilirubin glucuronidation process. Any disturbance in liver function due to hypoxia, acidosis, or a lack of glucose can cause increased unconjugated bilirubin levels in the blood.

Based on the findings of statistical tests, a p-value of 0.003 was obtained, which was less than the alpha value (α = 0.05), indicating that there was a significant relationship between breastfeeding practices and the incidence of hyperbilirubinemia in neonates. This was consistent with the findings of Wijaya et al. (2018), which found breastfeeding to be associated with the incidence of hyperbilirubinemia with a p-value of 0.001. The similar results were found by Huang et al. (2021) with a p-value of 0.033. Neonates with inadequate breastmilk intake during breastfeeding had not enough milk reach their intestines to process bilirubin elimination from the body. This occurs in preterm babies whose mothers do not produce enough breastmilk.

### Table 5. Relationship between Breastfeeding and Hyperbilirubinemia.

<table>
<thead>
<tr>
<th>Breastfeeding Practices</th>
<th>Hyperbilirubinemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Full Breastfeeding</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Partial Breastfeeding</td>
<td>40</td>
<td>116</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>135</td>
</tr>
</tbody>
</table>

### Table 6. Relationship between Gestational Age and Hyperbilirubinemia.

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Hyperbilirubinemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Preterm</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Aterm</td>
<td>33</td>
<td>112</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>135</td>
</tr>
</tbody>
</table>

### Table 7. Relationship between Delivery Mode and Hyperbilirubinemia.

<table>
<thead>
<tr>
<th>Delivery Mode</th>
<th>Hyperbilirubinemia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Normal vaginal delivery</td>
<td>30</td>
<td>52</td>
</tr>
<tr>
<td>Instrumental/ Caesarian</td>
<td>29</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>135</td>
</tr>
</tbody>
</table>

### Table 8. Multivariate Analysis with Logistic Regression Test Step 1.

<table>
<thead>
<tr>
<th>Variables in the Equation</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>Df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight</td>
<td>0.368</td>
<td>0.466</td>
<td>0.625</td>
<td>1</td>
<td>0.429</td>
<td>1.445</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1.085</td>
<td>0.382</td>
<td>8.045</td>
<td>1</td>
<td>0.005*</td>
<td>2.958</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>1.335</td>
<td>0.418</td>
<td>10.205</td>
<td>1</td>
<td>0.001*</td>
<td>3.798</td>
</tr>
<tr>
<td>Gestational Age</td>
<td>1.194</td>
<td>0.488</td>
<td>5.986</td>
<td>1</td>
<td>0.014</td>
<td>3.300</td>
</tr>
<tr>
<td>Constant</td>
<td>-6.054</td>
<td>1.364</td>
<td>19.696</td>
<td>1</td>
<td>0.0001*</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Significance if p<0.05.
As per Table 6, there were 26 preterm neonates (13.4%) with hyperbilirubinemia. The statistical test findings yielded a value of \( p = 0.0001 \), which is less than the alpha value (\( \alpha = 0.05 \)), indicating a significant relationship between gestational age and the incidence of hyperbilirubinemia in neonates. This was consistent with Faiqah S’s 2014 study, which observed a significant relationship between gestational age and hyperbilirubinemia with a \( p \)-value of 0.013.14 Cholifah et al. (2017) discovered a connection between gestational age and hyperbilirubinemia with a \( p \)-value of 0.0001.9 Case-control study conducted by Auliasari et al. found a significant relationship between preterm gestational age and the incidence of neonatal jaundice \( (p = 0.028, OR 3.077) \), indicating that preterm neonates had a higher risk of 3,077 than full-term neonates.10 Devi (2017) also discovered a significant relationship between gestational age and the incidence of hyperbilirubinemia \( (p<0.0001) \).16

Prematurity is related to unconjugated hyperbilirubinemia in neonates. Preterm neonates have lower hepatic uridine diphosphate glucuronyl transferase (UDPGT) activity, resulting in lower conjugated bilirubin. Furthermore, there is an increase in hemolysis attributed to the short lifespan of erythrocytes in preterm babies, resulting in a higher level of unconjugated bilirubin in the blood.3,5,6,8,9,10,11

According to the research findings, the mode of delivery had no significant relationship with neonatal hyperbilirubinemia \( (p=0.110) \). This finding was in accordance with Aditya et al. (2020), that observed no significant relationship between cesarean delivery and neonatal hyperbilirubinemia \( (p=0.239) \).11 Faiqah (2014) research yielded a \( p \)-value of 0.652 that showed no significant relationship between the mode of delivery and the incidence of neonatal hyperbilirubinemia.14 Wijaya et al. obtained similar results in their case-control study. With a \( p \)-value of 0.134, there was no relationship between the mode of delivery and the incidence of hyperbilirubinemia. Rohanti et al., in 2017, discovered that there was no relationship between mode of delivery and the incidence of hyperbilirubinemia \( (p = 0.607) \).8 This study’s findings were consistent with previous results, which might be attributable to a similar sample to the study by Aditya et al., namely a higher proportion of births with instrumental/ Caesarian, similar gestational age, and birth weight. This study only used small size subjects. Thus, further research with a larger subject is needed to confirm these results.

CONCLUSIONS

In summary, some factors were significantly related to neonatal hyperbilirubinemia, namely birth weight, asphyxia, breastfeeding practice, and gestational age. The mode of delivery was found to be not related to neonatal hyperbilirubinemia. Health personnel is expected to provide counseling for pregnant women and the general public about the risk factors for neonatal hyperbilirubinemia to take prompt preventative measures. Furthermore, additional studies with a larger sample and more diversified data are still needed to acquire more reliable results.

ETHICS IN PUBLICATION

This study was approved by the Health Research Ethics Committee of Wangaya General Hospital, Denpasar, Bali, before the study was conducted with the number registered: 057/VII.8/KEP/RSW/2021.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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AUTHORS CONTRIBUTION

All authors contributed to this research and publication.

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