

RELATIONSHIP BETWEEN THE INCIDENCE OF NEONATAL HYPERBILIRUBINEMIA AND GESTATIONAL AGE AS A RISK FACTOR

Camelia Saleh, Sri Hastuti Andayani, Sri Wahyu Herlinawati, Siti Nur Riani

Universitas YARSI, Indonesia

Email: Cameliasalba15@gmail.com

Abstract

Neonatal hyperbilirubinemia (NH) or neonatal jaundice is characterized by elevated serum levels of total bilirubin in the blood and yellow color of the baby's skin, sclera, and mucous membranes. Neonatal hyperbilirubinemia can cause mild-moderate-severe neurological disorders, up to death, if left untreated. The incidence of neonatal hyperbilirubinemia (NH) in Indonesia in 2016 reached 51.47% of cases where 33.3% of the total NH cases were related to prematurity. The purpose of this study is to determine the incidence of NH in RSAB Harapan Kita. This research is a type of quantitative analytical research with a cross-sectional approach. The study population is babies born at RSAB Harapan Kita for the period January 2022 – December 2022. Using a random sampling technique with the slovin formula and a margin of error of 5%, a sample of 315 patients met the inclusion and exclusion criteria. Furthermore, statistical analysis was carried out using the chi-square test. As many as 158 (50.2%) babies born at RSAB Harapan Kita experienced NH with the most results of female babies (54.4%), aged 24-48 hours (48.1%), low birth weight (57%), and premature gestational age (67.7%). Bivariate analysis of the association of gestational age with NH incidence has a significance value of <0.001 which proves a significant association. Conclusions: There is a significant association between preterm gestational age and NH incidence.

Keywords: Gestational Age, Mother and Child, Neonatal Jaundice, Neonatal Hyperbilirubinemia, Prematurity, Relationship

INTRODUCTION

Neonatal hyperbilirubinemia (NH) or neonatal jaundice is a condition in which serum levels of total bilirubin in the blood increase and cause clinical manifestations of yellow appearance on the skin, sclera, and mucous membranes of infants under 28 days old (Kusumaningsih et al., 2023). The appearance of yellow color is caused by the accumulation of bilirubin in body tissues, one of which is caused by the liver of premature babies who are not fully mature. There are 2 forms of bilirubin, namely conjugated and unconjugated bilirubin. Unconjugated bilirubin is hydrophobic and circulates in the blood by binding to albumin where it is carried to the liver and conjugated with glucuronic acid by the uridine diphosphate-glucuronosyltransferase (UGT) enzyme located in the smooth endoplasmic reticulum (Prasantini, 2020).

Conjugated bilirubin is water-soluble, then it will be excreted into bile and enter the gastrointestinal tract, where conjugated bilirubin will undergo metabolism by the normal intestinal flora and excreted in feces (Ansong-Assoku et al., 2018).

If the liver is immature, then this process can be inhibited. Neonatal hyperbilirubinemia is classified as physiological NH & pathological NH, physiological NH is mild and can heal by itself generally arising >the first 24 hours of life, while pathological NH can be fatal if not treated immediately, generally arising <24 hours of life (Ansong-Assoku et al., 2018).

There are 359 babies affected by neonatal pathological hyperbilirubinemia (NH) out of every 100,000 live births worldwide. About 24% of infants affected by NH die, while 13% develop long-term, mild, moderate, to severe neurological disorders (Hansen, 2021).

In 2016, the incidence of NH in Indonesia reached 51.47% of cases (Hikmah et al., 2023), of which 33.3% of the total NH cases were related to prematurity. (Risksedas, 2018) In research conducted at the neonatal intensive care unit (NICU) of Dr. Soetomo Hospital, the incidence rate of NH is related to several risk factors, including 57.4% related to cases of prematurity (Auliasari et al., 2019).

Based on the introduction, it is known that gestational age is related to NH disorders, so this study was conducted to determine the incidence rate of NH at RSAB Harapan Kita, to determine the gestational age of patients with NH at RSAB Harapan Kita, and to determine the relationship between gestational age and the incidence rate of NH at RSAB Harapan Kita for the period January 2022-December 2022.

RESEARCH METHODS

The type of research used is quantitative analytical observational research with a cross sectional approach (Mann, 2003). The population of infants with NH diagnosis recorded at RSAB Harapan Kita for the period January 2022-December 2022 is 1431. The study sample was taken by random sampling method from populations that met the inclusion criteria and exclusion criteria and calculated using the slovin formula so that 315 samples were obtained. Furthermore, analysis of data using the chi-square method was carried out. Data were analyzed univariately and bivariately (Sgro et al., 2011). Univariate analysis was conducted to see the incidence rate of neonatal hyperbilirubinemia, the characteristics of respondents, and see the description of the mother's gestational age, while bivariate analysis was carried out to see the relationship between gestational age and the incidence rate of neonatal hyperbilirubinemia.

RESULTS AND DISCUSSION

Univariate Analysis

The results of the analysis presented in table 2.1 showed that based on the inclusion and exclusion criteria, 158 (50.2%) neonatals with NH, and 157 (49.8%) neonatals without NH diagnosis were obtained in this study.

Table 1 Frequency Distribution of Neonatal Hyperbilirubinemia Patients

| Diagnosis | Frekuensi | Persentase |
|-------------------------|------------------|-------------------|
| Neonatal Hiperbilirubin | 158 | 50.2% |
| Undiagnosed | 157 | 49.8% |

The results of the analysis presented in table 1 show that based on the sex of infants affected by NH, the majority of which are women, 85 (54.4%) female babies experience NH compared to men, which is 73 (45.6%).

Table 2 Frequency Distribution of NH Infant Sex

| Gender | Frekuensi | Persentase |
|---------------|------------------|-------------------|
| Female | 85 | 54.4% |
| Male | 73 | 45.6% |

The results of the analysis presented in table 2.3 are classified by day, pathological NH generally occurs <24 hours, while physiological NH occurs after 24 hours and peaks on days 3 to (Ansong-Assoku et al., 2018). The majority of infants (48.1%) had elevated total bilirubin levels on total bilirubin on days one to two, 46 (29.1%) had an increase on days three and four, 33 (20.9%) infants had an increase over day four, and 3 (1.9%) infants had elevated total bilirubin before 24 hours.

Table 3 Frequency Distribution of NH Infant Age During Bilirubin Examination

| Infant Age | Frekuensi | Persentase |
|-----------------------|------------------|-------------------|
| <24 hour (<1 days) | 3 | 1.9% |
| 24-48 hour (1-2 days) | 76 | 48.1% |
| 48-96 hour (3-4 days) | 46 | 29.1% |
| >96 hour (>4 days) | 33 | 20.9% |

The gestational age of the mother is divided based on the risk of pregnancy and productive age, productive age refers to the age of 20 years to 35 years, risky age refers to young pregnancies, namely at the age of under 20 years, while high-risk pregnancy refers to pregnancy at the age of over 35 years (Williams et al., 2021). The results of the analysis presented in table 4 show that the majority of mothers, namely 123 (77.8%) mothers, were in the range of 20 years to 35 years. 33 (20.9%) mothers were over 35 years old. 2 (1.3%) mothers under 20 years old.

Table 4 Frequency Distribution of Age of Mothers with NH infants

| Mother's age | Frekuensi | Persentase |
|---------------------|------------------|-------------------|
| < 20 years old | 2 | 1.3% |
| 20– 35 years old | 123 | 77.8% |
| > 35 years old | 33 | 20.9% |

The results of the analysis presented in table 1.5 show that based on the majority of NH infants with blood type O + as many as 67 (42.4%), as many as 43 (27.2%) blood type A +, 36 (22.8%) blood type B +, and as many as 12 (7.6%) babies with blood type AB +, no babies with negative blood type (-) were obtained.

Table 5 Frequency Distribution of NH Infant Blood Types

| Blood hood | Frekuensi | Persentase |
|-------------------|------------------|-------------------|
| A+ | 43 | 27.2% |
| AB+ | 12 | 7.6% |
| B+ | 36 | 22.8% |
| O+ | 67 | 42.4% |

Baby weight is divided into macrosomia (>4500 grams), normal (2500 grams – 4500 grams), low birth weight (<2500 grams), very low birth weight (<1500 grams), and low weight very extreme (<1000 grams) (William W *et al.*, 2021). The results of the analysis presented in table 1.6 show that based on the weight of NH babies born as many as 90 babies (57%) experienced low infant weight. 68 babies (43%) were of normal weight. No macrosomia baby, very low birth weight, or low weight is very extreme.

Table 6 Frequency Distribution of NH Birth Weight

| Weight | Frekuensi | Persentase |
|-----------------|------------------|-------------------|
| Normal | 68 | 43% |
| Low Weight Loss | 90 | 57% |

The results of the analysis presented in table 6 show that based on gestational age, the majority of NH infants are preterm, as many as 107 babies or 67.7% are in preterm compared to 51 or 32.3% of term babies.

Table 7 Frequency Distribution of Gestational Age of Mothers of NH Infants

| Gestational Age | Frekuensi | Persentase |
|------------------------|------------------|-------------------|
| Aterm | 51 | 32.3% |
| Preterm | 107 | 67.7% |

The results of the analysis presented in table 7 showed that based on the method of delivery, as many as 149 babies or 94.3% of NH babies were born by caesarean section, compared to 8 or 5.1% of babies born vaginam.

Table 8 Frequency Distribution of NH Infant Delivery Methods

| Method | Frekuensi | Persentase |
|-------------------|------------------|-------------------|
| Pervaginam | 16 | 10.2% |
| Caesarean section | 141 | 89.8% |

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Bivariate descriptive analysis was performed to determine the relationship between gestational age, maternal blood type, and differences between infant and maternal blood types with the incidence rate of neonatal hyperbilirubinemia using the *Chi-square test*.

Table 9 Relationship of Gestational Age with Neonatal Incidence of Hyperbilirubinemia

| Variable | Neonatal hiperbilirubnemia | | | | Total | % | *P Value |
|----------|----------------------------|------|--------|------|---------|-----|----------|
| | NH | | Not NH | | | | |
| Age | | | | | (N=315) | | |
| Gestasi | N=158 | % | N=157 | % | | | |
| Pre-term | 107 | 67,7 | 20 | 6,3 | 127 | 100 | <0.001 |
| Aterm | 51 | 32,3 | 137 | 43,5 | 188 | 100 | |

Based on the results of *the chi-square* test, the relationship between gestational age and the incidence of neonatal hyperbilirubinemia has a significance value of <0.001 (<0.05), which means that there is a significant relationship between gestational age and the incidence of neonatal hyperbilirubinemia at RSAB Harapan Kita for the period January 2022-December 2022. So hypothesis (1) in this study is proven.

Univariate Discussion

From the results of table 2, it was found that the maoyoritas value of infants who had neonatal hyperbilirubinemia was 54.4% of female babies compared to male babies who experienced NH by 45.6%. This result is not in line with research Perdani & Azhali, (2019), where the results found that the serum bilirubin level value of male neonates was higher by 14.3 mg / dL compared to 12.6 mg / dL female neonates ($p < 0.01$). Conversely, research conducted by Yuliawati & Astutik, (2018) showed that there was no relationship between sex and the incidence of neonatal jaundice ($p = 0.441$), this finding is in line with research (Baz, El-Agamy and Ibrahim, 2021) where the link between the incidence of male neonates more often than female neonates was not found to be significant ($p = 1,000$).

On research Kasemy et al., (2020) High bilirubin levels and the incidence of NH in male neonates are associated with G6PD enzyme deficiency. The Y chromosome owned by men affects the slow rate of maturation of the enzyme Yuliawati & Astutik, (2018), where in this study, G6PD enzyme deficiency is an exclusion criterion. According to the researchers, the cause of the insignificance of the results of this study analysis can be caused by the G6PD enzyme deficiency factor as an exclusion criterion in this study.

From the results of the study, table 2 showed that the majority or as many as 76 babies (48.1%) experienced an increase in NH on the first to second day. These results are in line with research Van der Geest et al., (2022) which states that the majority of neonatal population samples experiencing NH will experience a yellow manifestation after 24 hours. This theory is also in line with research Thielemans et al., (2021) which stated a significant association between an increase in neonatal bilirubin levels at 48 hours of neonatal life and the incidence of NH ($P = 0.009$)

The results of the analysis presented in table 2.4 show that the majority of mothers with children diagnosed with NH are in the range of 20 years to 35 years, namely as many as 123 mothers or 77.8%. These results are consistent with research Isa et al., (2022), which states the mother's age >25 years is a risk factor for NH exposure.

From the results of table 9 research, it was found that the majority of neonatal blood types with NH were "O", as many as 67 neonates or 42.4% had NH, and as many as 43 neonates or 27.2% had blood type "A". This finding is in line with

research Lake et al., (2019), where neonates with blood type "O" are associated with an incidence of NH as much as 2.38x compared to blood type "A" [COR = 2.38; 95% CI (1.05-5.4)].

Based on the results of research on shows that based on the weight of NH babies born as many as 90 babies or 57% of babies fall into the low infant weight group. This result is in line with research Auliasari et al., (2019) where 42.4% of low birth weight babies experienced NH ($p = 0.032$). This finding is also in line with research (Yasadipura, Suryawan and Sucipta, 2020) found a significant link between low birth weight and the incidence of NH ($p = 0.042$).

Based on the results of the study in table 2.7 shows that based on gestational age, the majority of NH babies are preterm, as many as 107 babies or 67.7% are in preterm compared to 51 or 32.3% term babies. These results are in accordance with research Sprong et al., (2023), where NH age is associated with prematurity ($p = 0.003$).

Based on the results of the frequency study in table 2.8, it was found that based on the method of delivery, as many as 149 neonates or 94.3% of neonates with NH were born by caesarean section, compared to 8 or 5.1% of neonates born vagiman. This result is in line with research Yu et al., (2022) where there is a significant relationship between the method of cesarean delivery and the incidence of NH ($p < 0.001$).

Bivariate Discussion

In this study, which was conducted at RSAB Harapan Kita for the period January 2022-December 2022, an analysis was carried out between the relationship between gestational age and the incidence of neonatal hyperbilirubinemia using the square-test. The registered population was 1431 NH births and using the slovin formula with *a margin of error of 5%* (0.05), a sample size of 315 NH babies was obtained. Sample selection is determined by the simple random sampling method according to inclusion and inclusion criteria. The results of the analysis proved that the relationship between gestational age and the incidence of neonatal hyperbilirubinemia had a significance value of $p = <0.001$ (<0.05). This value indicates that there is a significant relationship between gestational age and the incidence of neonatal hyperbilirubinemia at RSAB Harapan Kita for the period January 2022-December 2022. The results of the study stated that hypothesis (1) was proven. This finding is in line with research (Anggie Auliasari et al., 2019) which states that the relationship between prematurity and the incidence of neonatal jaundice at Dr. Soetomo Hospital is 3,077 times greater than neonates born with term gestational age. The value is based on the OR obtained which is 3.077. This theory is in line with Sprong et al., (2023) where NH age is associated with prematurity ($p = 0.003$). Neonatal hyperbilirubinemia is associated with decreased activity of the hepatic uridine diphosphat glucoronyl transferase (UDPGT) enzyme that occurs in neonatal prematurity, in addition to increasing the lysis of red blood cells in neonatal also plays a role (Auliasari et al., 2019) (Kasemy et al., 2020).

CONCLUSION

From the results of the chi-square test in the study, a significance value of $p = <0.001$ (<0.05) was obtained this value proves a close relationship between

gestational age and NH, proving the hypothesis The results of the study can help increase knowledge by describing the neonatal state of hyperbilirubinemia in 2022 and prevention of risk factors can be done more effectively.

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