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SIGNIFICANT FACTORS INFLUENCING HYPERBILIRUBINEMIA AT SANTO YUSUF MOTHER AND CHILD HOSPITAL, NORTH JAKARTA USING BINARY LOGISTIC REGRESSION

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ABSTRACT

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Hyperbilirubinemia is a problem that often occurs in newborns. The cause of hyperbilirubinemia is multifactorial, including maternal, perinatal, or environmental factors that can be risk factors in newborns. Hyperbilirubinemia that occurs in infants is usually due to high bilirubin levels. High bilirubin can be a poison that causes brain damage, so hyperbilirubinemia must be treated appropriately so as not to cause chronic complications. This study aims to identify significant factors affecting hyperbilirubinemia in infants at Santo Joseph Mother and Child Hospital, North Jakarta, using binary logistic regression. This research was conducted for the first time at Santo Joseph Mother and Child Hospital. Factors that are thought to influence are gestational age, birth weight, childbirth, breastfeeding, and infection status. The results showed that the significant factors affecting hyperbilirubinemia in infants were the process of childbirth, milk feeding, and infection status. Based on the odds ratio value for each variable, it can be concluded that babies with abnormal birth processes have a risk of hyperbilirubinemia of 2.9628 times greater than babies with normal births. Meanwhile, formula-fed infants have a risk of hyperbilirubinemia of 4.2854 times less than breastfed babies. Furthermore, infants affected by infection have a risk of developing hyperbilirubinemia of 5.5752 times greater than infants who do not get infection.

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1. INTRODUCTION

Hyperbilirubinemia, better known as jaundice, is an increase in the amount of bilirubin that accumulates in the blood when total serum bilirubin levels are greater than or equal to 5 mg/dL and are characterized by jaundice, which is yellow staining seen in the skin, sclera of the eyes, nails and mucosa due to the buildup of unconjugated bilirubin in the tissues [1], [2]. Hyperbilirubinemia is a problem that often occurs in newborns [3], [4]. Hyperbilirubinemia often occurs in full-term infants, around 60% and about 80% in infants less than months [2], [5], [6].

The cause of hyperbilirubinemia is multifactorial, which includes maternal, perinatal, or environmental factors that can be risk factors in newborns [7], [8]. Most cases of hyperbilirubinemia are harmless. However, because bilirubin can be toxic, all newborns should be monitored for signs of severe hyperbilirubinemia that can cause brain damage [9], [10]. Therefore, hyperbilirubinemia must be treated appropriately and seriously so as not to cause chronic complications. Based on data at RSIA Santo Yusuf, North Jakarta, in 2021, 298 cases of hyperbilirubinemia in infants were obtained, and there was an increase in 2022 to 318 patients.

Seeing that the incidence of hyperbilirubinemia at RSIA Santo Yusuf tends to increase, analysis is needed to determine the factors that affect hyperbilirubinemia in infants. The binary response model is a model that functions when the variable data used are nominal, multinomial, and continuous variables. There are 3 types of binary response models that are often used, namely linear probability model (LPM), probit model, and logit model. The probit model and the same logit model are used to analyze the relationship between one response variable and several predictor variables, but in the probit model, the predictor variable used is continuous, while in the logit model, the predictor variable is used discretely.

Logistic regression in statistics is also called the logistic model or logit model; according to Hosmer and Lemeshow, logistic regression is a method used to determine the relationship between predictor variables and response variables that have two categories (dichotomy) or more than two categories (polychotomy) [11]. Regression analysis is an analytical technique that explains the form of relationships between two or more, especially relationships between variables that contain cause and effect. Logistic regression analysis consists of binary logistic regression, multinomial logistic regression, and ordinal logistic regression.

Binary logistic regression is a data analysis method that analyzes the relationship between one or more predictor variables with dichotomous or binary response variables [11]. The point is that in binary logistic regression, the data on the response variables is binary (0 and 1). These binary numbers describe two categories of data that contradict each other, such as successful or failed events, disease or not, death or life, and others. Compared to other statistical methods, binary logistic regression has several advantages. The advantages of binary logistic regression are used to model the relationship between response variables and binary predictor variables, can be used to predict the probability of an event occurring on response variables consisting of only two categories, and can produce models that are easy to interpret and can be used to make accurate predictions.

Research on binary logistic regression analysis has been conducted by several researchers. [12] examined binary logistic regression analysis to determine stillbirth factors or the birth of lifeless babies who have reached 20 weeks gestation in East Aceh Regency. The results showed that infection during pregnancy most influenced the occurrence of stillbirth. Furthermore, [13] researched the risk factors for hyperbilirubinemia in neonates in the perinatology room of RSUD Wangaya, Denpasar City. The results show that the risk factors that affect the incidence of hyperbilirubinemia in neonates treated in the perinatology room of RSUD Wangaya are gestational age or gestational age and breast milk.

Based on the previous description and previous research, in this study the authors are interested in conducting binary logistic regression analysis to determine the factors that influence hyperbilirubinemia in infants at RSIA Santo Yusuf. Previously, research on the factors affecting hyperbilirubinemia had been conducted in several hospitals, but this study was conducted at RSIA Santo Yusuf for the first time. In this study, the response variable valued 1 states hyperbilirubinemia and valued 0 states not affected by hyperbilirubinemia and predictor variables as factors that are thought to influence are gestational age, birth weight, childbirth process, milk feeding, and infection status.

2. RESEARCH METHODS

This study used a binary logistic regression analysis method, with the data used being secondary data, namely hyperbilirubinemia data in infants taken from the medical records of patients from RSIA Santo Yusuf, North Jakarta from June 2022 to November 2022 consisting of 484 baby samples. The variables used were response variable (Y) which were cases of hyperbilirubinemia in infants. The predictor variables (X) were predicted to be affected are gestational age, birth weight, delivery process, milk feeding, and status exposure to infection. Selection of predictor variables based on previous research on hyperbilirubinemia includes **[14]** stating that factors such as labor process, oxytocin induction, and neonatal sex can contribute to hyperbilirubinemia and **[15]** stating hyperbilirubinemia is influenced by various factors such as not normal labor process, hypothermia, and breastfeeding.

Table 1. Research Variables

Variable	Description	Description
Y	Hyperbilirubinemia	0 : Not hyperbilirubinemia 1 : Hyperbilirubinemia
X_1	Gestational age	0 : Aterm (≥37 weeks) 1 : Preterm (<37 weeks)
X_2	Baby birth weight	0 : Normal (2500-4000 gram) 1 : Low (<2500 gram)
X_3	Labor process	0 : Normal (per vaginal) 1 : Not normal (per abdominal)
X_4	Milk feeding	0 : Formula 1 : Breast milk
X_5	Infection status	0 : No 1 : Yes

The steps taken in this study are as follows:

1. Describe the data of each variable using descriptive statistical analysis.
2. Estimate an initial binary logistic regression model. According to **[16]**, the logistic regression model with predictor variables $x_1, x_2, \dots, x_k$ is

$$\pi(\mathbf{x}) = \frac{\exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k)}{1 + \exp(\beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k)} \tag{1}$$

with $\mathbf{x}$ vector variable predictor $(x_1, x_2, \dots, x_k)$, k the number of predictor variables, $\pi(\mathbf{x})$ probability of success occurrence if given the value of the observation vector for the predictor variable $\mathbf{x} = (x_1, x_2, x_3)$, β_0 model intercept parameters, dan $\beta_1, \beta_2, \dots, \beta_k$ is a logistic regression parameter.

3. Estimate logistic regression model parameters. Parameter estimation in the logistic regression model is carried out using the Maximum Likelihood Estimation (MLE) method. To simplify logistic regression estimation, the likelihood function is transformed from likelihood to ln-likelihood.

$$L(\boldsymbol{\beta}) = \ln\big(l(\boldsymbol{\beta})\big) = \ln \prod_{i=1}^{n} \pi(\mathbf{x}_i)^{y_i}(1 - \pi(\mathbf{x}_i))^{1-y_i} \tag{2}$$

$\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{ik})$ is the ith observation data of the predictor variable vector $\mathbf{x} = (x_1, x_2, \dots, x_k)$, and y_i is the ith observation data of respon variabel y, for $i = 1, 2, \dots, n$

4. Test the significance of parameters simultaneously using the G test to determine the overall effect of predictor variables on response variable **[17]**.

$$G = -2 \ln \left(\frac{\left(\frac{n_1}{n}\right)^{n_1} \left(\frac{n_0}{n}\right)^{n_0}}{\prod_{i=1}^{n} \hat{\pi}_i^{y_i} (1 - \hat{\pi}_i)^{(1-y_i)}} \right) \tag{3}$$

n_0 : the number of valuable observations $Y = 0$ or $n_0 = \sum_{i=1}^{n}(1 - y_i)$
n_1 : the number of valuable observations $Y = 1$ or $n_1 = \sum_{i=1}^{n} y_i$
n : the total number of observations or $n = n_0 + n_1$
$\hat{\pi}_i$: probability of succes of the ith observation, $i = 1, 2, 3, \dots, n$

y_i : ith observation value of response variable y

5. Test the significance of individual parameters using the Wald test to determine the effect of each predictor variable on the response variable.

$$W_j = \left(\frac{\hat{\beta}_j}{SE(\hat{\beta}_j)}\right)^2, j = 1, 2, \dots, k \tag{4}$$

$\hat{\beta}_j$: estimated value of the jth parameter and $SE(\hat{\beta}_j)$: standard estimate of error for the jth parameter

6. Estimate a second binary logistic regression model, determine parameter estimation, and perform significance tests. This step continues to be carried out until all predictor variables have a significant effect on the response variable so that the final regression model is obtained.

7. Perform a model conformity test to find out whether the model is suitable or not.

$$\hat{C} = \sum_{h=1}^{g} \frac{(O_h - n'_h\bar{\pi}_h)^2}{n'_h\bar{\pi}_h(1-\bar{\pi}_h)} \tag{5}$$

with $\hat{C}$ statistical value of Hosmer and Lemeshow test, h is 1, 2, …, g, O_h Number of samples of successful events in the hth group, $\bar{\pi}_h$ average estimated probability of success of the hth group, and n'_h Total sample of the hth group.

8. Interpret the model using the *odds ratio*.

$$\psi = \frac{\frac{\pi(1)}{1-\pi(1)}}{\frac{\pi(0)}{1-\pi(0)}} = \frac{e^{\beta_0+\beta_j}}{e^{\beta_0}} = e^{\beta_j} \tag{6}$$

odds ratio when the predictor variable x_j changing categories are $\psi_j = e^{\beta_j}$ or $\ln(\psi) = \ln(e^{\beta_j}) = \beta_j$.

9. Make conclusions from the results of the analysis that has been done.

3. RESULTS AND DISCUSSION

3.1 Data Description

Data description is done using descriptive statistical analysis. Descriptive statistics for hyperbilirubinemia variables describe how many infants have hyperbilirubinemia and don't have hyperbilirubinemia.

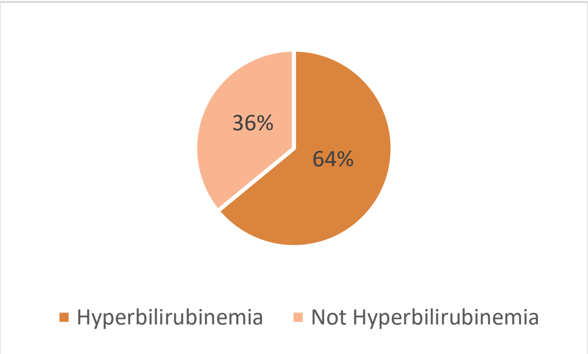

Figure 1. Description of Hyperbilirubinemia Data in Infants

Based on **Figure 1** shows that infants affected by hyperbilirubinemia by 36% (or as many as 174 babies) and infants who did not develop hyperbilirubinemia by 64% (or as many as 310 babies). This shows that babies who are not affected by hyperbilirubinemia are more than babies who are affected by hyperbilirubinemia. Hyperbilirubinemia is one of the causes of death in newborns. Therefore, identification of associated factors can facilitate early diagnosis, and reduce subsequent complications.

Table 2. Description of Gestational Age Category Data

Status of hyperbilirubinemia	Category of Gestational age		Total
	Aterm	Preterm	
Not hyperbilirubinemia	273 56.4%	37 7.6%	310 64%
Hyperbilirubinemia	160 33.1%	14 2.9%	174 36%
Total	433 89.5%	51 10.5%	484 100%

Based on Table 2 shows that the majority of babies born during aterm gestation accounted for 89.5% (or 433 babies) of the 484 infant samples used in this study. The length of pregnancy is one of the things that causes the baby to get hyperbilirubinemia. The growth of organs of babies born prematurely has not functioned like a mature baby, therefore many premature babies have difficulty living outside the mother's womb and complications are easier.

Table 3. Description of Birth Weight Data

Status of hyperbilirubinemia	Baby Weight Born		Total
	Normal	Low	
Not hyperbilirubinemia	251 51.8%	59 12.2%	310 64%
Hyperbilirubinemia	146 30.2%	28 5.8%	174 36%
Total	397 82%	87 18%	484 100%

Based on Table 3 showed that babies with normal birth weight were 82% (or as many as 397 babies) and babies with low birth weight were 18% (or as many as 87 babies). The relationship between birth weight of babies with hyperbilirubinemia is because the more normal birth weight, the bilirubin levels owned are also normal, otherwise if the condition of birth weight is not normal it will cause abnormal bilirubin. Babies with low birth weight usually have problems with immature liver function so that the bilirubin that the baby has is abnormal.

Table 4. Description of Labor Process Data

Status of hyperbilirubinemia	Labor process		Total
	Normal	Not Normal	
Not hyperbilirubinemia	134 27.7%	176 36.3%	310 64%
Hyperbilirubinemia	41 8.5%	133 27.5%	174 36%
Total	175 36.2%	309 63.8%	484 100%

Based on Table 4 showed that babies with normal delivery process amounted to 36.2% (or as many as 175 babies) and babies with abnormal labor process amounted to 63.8% (or as many as 309 babies). Babies with abnormal labor process, especially by vacuum extraction and forcep extraction methods, tend to cause closed bleeding in the head, such as caput sudccadenaum and cepalhematoma which are risk factors for hyperbilirubin in infants.

Table 5. Description of Milk Feeding Data

Status of hyperbilirubinemia	Milk Feeding		Total
	Breast Milk	Formula	
Not hyperbilirubinemia	105 21.7%	205 42.3%	310 64%
Hyperbilirubinemia	117 24.2%	57 11.8%	174 36%
Total	222 45.9%	262 54.1%	484 100%

Based on **Table 5** showed that infants given formula milk amounted to 54.1% (or as many as 262 babies) and infants who were breastfed amounted to 45.9% (or as many as 222 babies). *Hyperbilirubinemia* due to breast milk the cause is still unknown but is thought to arise due to the inhibition *of Uridine Diphosphoglucuronic Acid Glucuronyl Transferase* (UDGPA) by the results of progesterone metabolism in the breast milk of some mothers.

Table 6. Description of Affected Infection Status Data

Status of hyperbilirubinemia	Infection		Total
	No	Yes	
Not hyperbilirubinemia	249 (51.4%)	61 (12.6%)	310 (64%)
Hyperbilirubinemia	67 (13.8%)	107 (22.1%)	174 (36%)
Total	316 (65.3%)	168 (34.7%)	484 (100%)

Based on **Table 6** showed that infants who were not infected were 65.3% (or as many as 316 babies) and infants affected by infection amounted to 34.7% (or as many as 168 babies). Infections that are often experienced by newborns are usually often caused by the type of delivery that causes the occurrence of types of infections such as cephal hematoma, if this infection has occurred the baby will more easily experience elevated bilirubin levels.

3.2 Estimating an Initial Binary Logistic Regression Model

This subsection discusses estimating of an initial binary logistic regression model that contains all predictor variables. The steps used to obtain the initial binary logistic regression model are estimating parameters and testing significance with the help of Rstudio software.

Table 7. Parameter Estimation of Initial Logistic Regression Model

Predictor variables		Parameter	Parameter estimation
Notation	Name		
X_1	Gestational age	β_1	-0.7134
X_2	Baby birth weight	β_2	-0.1811
X_3	Labor process	β_3	1.0832
X_4	Milk feeding	β_4	-1.3960
X_5	Infection status	β_5	1.8301
Constant		β_0	-1.2424

Furthermore, the significance test of the parameters of the initial binary logistic regression model was carried out to determine the effect of parameter estimation significantly on the model with complete predictor variables.

3.2.1 Test the significance of parameters simultaneously

Parameter significance tests are simultaneously performed to determine the significance of the overall influence of predictor variables on response variable. The hypotheses used are as

H_0 : $\beta_1 = \beta_2 = ... = \beta_5 = 0$ (The predictor variables together have no effect on the response variable)
H_1 : there is at least one $\beta_j \neq 0$, for $j = 1, 2, \ldots, 5$ (There is at least one predictor variable that affects the response variable)

Table 8. Simultaneous Significance Test Result of Initial Model Parameters

G-value	Chi-square value	*p-value*
144.87	11.071	0.000

In **Table 8** it can be seen that the value $G > \chi^2_{(0.05;\,5)}$ and *p-value* of $0.000 < 0.05 = \alpha$, then H_0 is rejected. This means that there is at least one predictor variable that affects the response variable.

3.2.2 Test the significance of individual parameters

Individual significance tests are carried out to determine the influence of each predictor variable on the response variable. The hypotheses used are:

H_0 : $\beta_j = 0$, for $j = 1, 2, \ldots, 5$ (the *j*th predictor variable has no effect on the response variable)
H_1 : $\beta_j \neq 0$, for $j = 1, 2, \ldots, 5$ (the *j*th predictor variabel effect the response variable)

Table 9. Significance Test Result of Initial Model Parameters Individually

Predictor variables		Parameter estimation	*Std. error*	Wald	*p-value*	Conclusion
Notation	Name					
X_1	Gestational age	-0.7134	0.4207	2.8756	0.0899	Not Rejected
X_2	Baby birth weight	-0.1811	0.2971	0.3716	0.5422	Not Rejected
X_3	Labor process	1.0832	0.2556	17.9175	0.000	Rejected
X_4	Milk feeding	-1.3960	0.2339	35.6214	0.000	Rejected
X_5	Infection status	1.8301	0.2349	60.6993	0.000	Rejected

In **Table 9** it is seen that H_0 rejected for the variables predictors of childbirth (X_3), milk feeding (X_4), and infection status (X_5). This means that the predictor variables have an effect on the response variable.

3.3 Estimating the Final Binary Logistic Regression Model

From Table 4.8, the factors that significantly affect the model are the process of childbirth (X_3), feeding (X_4), and infection status (X_5). Therefore, it is necessary to establish a second logistic regression model to find out that these variables are appropriate in the binary logistic regression model.

Table 10. Final Binary Logistic Regression Model Parameter Estimation

Predictor variables		Parameter	Parameter estimation
Notation	Name		
X_3	Labor process	β_3	1.0861
X_4	Milk feeding	β_4	-1.4552
X_5	Infection status	β_5	1.7183
Constant		β_0	-1.2752

Furthermore, the parameter significance test of the second binary logistic regression model was carried out to determine the effect of predictor variables X_3, X_4, and X_5 significantly on the final model with variable respon. Based on The American Academy of Pediatrics (AAP) which states that hyperbilirubinemia has many significant factors that can occur in newborns including babies who experience bleeding during pregnancy or delivery, exclusive breastfeeding, babies who have infections, cephalohematomas or significant bruising, and babies born prematurely or with low weight. The three predictor variables are included in the significant factor of hyperbilirubinemia.

3.3.1 Test The Significance Of Parameters Simultaneously

Parameter significance tests are simultaneously performed to determine the significance of the overall influence of predictor variables on response variable. The hypotheses used are as

H_0 : $\beta_3 = \beta_4 = \beta_5 = 0$ (The predictor variables together have no effect on the response variable)
H_1 : there is at least one $\beta_j \neq 0$, for $j = 3, 4, 5$ (There is at least one predictor variable that affects the response variable)

Table 11. Final Model Parameter Significance Test Result Simultaneously

G-value	Chi-square value	*p-value*
140.52	7.815	0.000

In **Table 11** it can be seen that the value $G > \chi^2_{(0.05;\,3)}$ and *p-value* of $0.000 < 0.05 = \alpha$, then H_0 is rejected. This means that there is at least one predictor variable that affects the response variable.

3.3.1 Test the significance of individual parameters

Individual significance tests are carried out to determine the influence of each predictor variable on the response variable. The hypotheses used are:

H_0 : $\beta_j = 0$, for $j = 3, 4, 5$ (the *j*th predictor variable has no effect on the response variable)
H_1 : $\beta_j \neq 0$, for $j = 3, 4, 5$ (the *j*th predictor variabel effect the response variable)

Table 12. Final Model Parameter Significance Test Result Simultaneously

Predictor variables		Parameter estimation	*Std. error*	Wald	*p-value*	Conclusion
Notation	Name					
X_3	Labor process	1.0861	0.2519	18.5902	0.000	Rejected
X_4	Milk feeding	-1.4552	0.2307	39.7878	0.000	Rejected
X_5	Infection status	1.7183	0.2248	58.4259	0.000	Rejected

In **Table 12** it is seen that H_0 it is rejected for X_3, X_4 dan X_5. This means that the predictor variables have an effect on the response variable.

Labor process (X_3), milk feeding (X_4), and status of infection (X_5) are predictor variables that affects hyperbilirubinemia in infants at RSIA Santo Yusuf, North Jakarta. From **Table 10** the final binary logistic regression model is

$$\hat{\pi}(\mathbf{x}) = \frac{\exp(-1.2752 + 1.0861X_3 - 1.4552X_4 + 1.7183X_5)}{1 + \exp(-1.2752 + 1.0861X_3 + 1.4552X_4 + 1.7183X_5)}.$$

3.4 Goodness of Fit Test

Goodness of fit test is used to determine whether there is a difference between the observation results and the prediction results which means the model is suitable or not. Goodness of fit test can be obtained from the Hosmer and Lemeshow tests. The hypotheses used are:

H_0 : There is no difference between the results of observations and the results of model predictions
H_1 : There is a difference between the results of observations and the results of model predictions

Table 13. Model Goodness of Fit Test with Hosmer and Lemeshow Test

$\hat{C}$*-value*	**Chi-square value**	***p-value***
3.0722	15.5073	0.9297

In **Table 13**, it can be seen that the statistical value of Hosmer and Lemeshow test value. $\hat{C} < \chi^2_{(0.05;\,8)}$ and *p-value* of $0.9297 > 0.05 = \alpha$, then H_0 is not rejected. This means that there is no difference between the observations and the predictions of the model.

3.5 Interpretation of Parameter Coefficients

Interpretation of parameter coefficients is carried out to determine the tendency or relationship between the predictor variable and the response variable and show the effect of changes in the value of the variable concerned. To interpret the coefficients of logistic regression parameters, it is used odds ratio values.

Table 14. Odds Ratio Value

Variable	Odds ratio
Labor process (X_3)	2.9628
Milk feeding (X_4)	0.2333
Status affected by infection (X_5)	5.5752

Odds ratio in **Table 14** can be interpreted the parameters in the final model as follows:

1. Babies with abnormal birth processes have a risk of hyperbilirubinemia of 2.9628 times greater than babies with normal births.
2. Formula-fed infants have a risk of hyperbilirubinemia of $\frac{1}{e^{-1,4556}} = 4.2854$ times smaller than breastfed babies.
3. Infants affected by infection have a risk of hyperbilirubinemia of 5.5752 times greater than infants who do not get infection.

Thus, babies with abnormal labor and infection each have a positive influence on the occurrence of hyperbilirubinemia in infants, while babies who are routinely breastfed have a negative influence on the occurrence of hyperbilirubinemia in infants. These results are different from previous studies conducted by Wijaya and Suryawan (2019), which examined risk factors that affect the incidence of hyperbilirubinemia in neonates in the perinatology room at Wangaya Hospital, Denpasar City. In the results of their study, it was found that the factors that influence the incidence of hyperbilirubinemia in neonates in the perinatology room at Wangaya Hospital are gestational age and breastfeeding.

4. CONCLUSIONS

Based on the results and discussion, it can be concluded:

1. The final binary logistic regression model is

$$\hat{\pi}(\mathbf{x}) = \frac{\exp(-1.2752 + 1.0861X_3 - 1.4552X_4 + 1.7183X_5)}{1 + \exp(-1.2752 + 1.0861X_3 - 1.4552X_4 + 1.7183X_5)}.$$

2. The significant factors that affect hyperbilirubinemia in infants at RSIA SantoYusuf, North Jakarta are the process of childbirth (X_3), breastfeeding (X_4), and status affected by infection (X_5). Based on the model obtained, the odds ratio value can be interpreted as follows, babies with abnormal birth processes have a risk of hyperbilirubinemia of 2.9628 times greater than babies with normal births. Meanwhile, formula-fed infants have a risk of hyperbilirubinemia of 4.2854 times less than breastfed babies. Furthermore, infants affected by infection have a risk of developing hyperbilirubinemia of 5.5752 times greater than infants who do not get infection.

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